VITAMIN E INTAKE AND CARDIOVASCULAR DISEASES IN THE EPIC-POTSDAM STUDY

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24HR	24-hour dietary recall
AI	Adequacy Intake
AMI	Acute Myocardial Infarction
AP	Angina pectoris
ATBC	The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
BMI	Body-mass-index
DBP	Diastolic blood pressure
CAD	Coronary arterial disease
CHAOS	Cambridge Heart Antioxidant Study
CHD	Coronary heart disease
CI	Confidence intervals
CPS-II	Cancer Prevention Study-II
CSFII	Continuing Survey of Food Intakes by Individuals
CV	Cardiovascular
CVD	Cardiovascular diseases
DRI	Dietary Reference Intake
EPOZ-Study	The Epidemiologic Study of Cardiovascular Risk Indicators
EPIC-Potsdam	European Prospective Investigation into Cancer and Nutrition-Potsdam
EU	European Union
FFQ	Food-Frequency-Questionnaire
FP	Food pattern
FPs	Food patterns
FP-VE	Food pattern rich in vitamin E
FP-AO	Food pattern rich in antioxidants
FS	Finnish Cohort Study
γ-CEHC	γ-Tocopherol Metabolite GTM 2,7,8-trimethyl-2-(β-carboxy-ethyl)-6-hydroxychroman
GeNuS	German Nutrition Survey
GISSI	GISSI Prevenzione trial
HATS	HDL-Atherosclerosis Treatment Study
HDL	High density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation Study
HOPE-TOO	Heart Outcomes Prevention Evaluation Study-The Ongoing Outcomes
HPFS	Health Professionals Follow-up Study
HR	Hazard risk
IHD	Ischemic heart disease
IWHS	Iowa Women's Health Study
LIXIAN-1	Lixian Nutrition Intervention
LIXIAN-2	Lixian Nutrition Intervention 2
LDL	Low-density-lipoproteins
MA	Metanalysis
MI	Myocardial infarction
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
MRC/BHF	Heart Protection Study Collaborative Group
MRFIT	The Multiple Risk Factor Intervention Trial
NHANES	National Health and Nutrition Examination Surveys
NHS	The Nurses' Health Study

NSS	Nutrition Status Surveys
Oxi-LDL	Oxidized-low-density-lipoproteins
PS	Physician' Health Study
PPP	Primary Prevention Trial
PUFA	Polyunsaturated fatty acids
RCT	Randomized clinical trial
RCTs	Randomised control trials
RDA	Recommendation Dietary Allowance
RNOS	Reactive-nitrogen-oxide-species
ROS	Reactive-oxigen-species
SBP	Systolic blood pressure
SHHS	Scottish Heart Health Study
SPACE	Secondary prevention with antioxidants of cardiovascular disease in Endstage renal disease
ST	Stroke
SU.VIMAX	Supple´mentation en Vitamines et Minéraux Antioxydants
TIA	transient ischemic attack
UK	United Kingdom
WACS	Women's Antioxidant Cardiovascular Study
WHS	Women's Health Study
WHR	Waist-to-hip ratio
ZS	The Zutphen Study

1. INTRODUCTION

The possible role of vitamin E in the cardiovascular diseases (CVD) was initially proposed in the "antioxidant hypothesis of atherosclerosis" [1], which postulated "that suboptimal levels of principal antioxidant micronutrients are hitherto underrated risk factors for CVD". This hypothesis was based on the properties of antioxidant micronutrients against reactive-oxygen-species (ROS) [2-4]. The main rationale for the association between vitamin E and the prevention of atherosclerosis, and consequently CVD, is based on the idea that some components of vitamin E prevent oxidation of low-density-lipoprotein (LDL) -cholesterol and the fatty streak formation.

In view of this, proposals have been aimed to elucidate the complex contribution of vitamin E to atherosclerosis that finally may be benefit in order to reduce the incidence and mortality of CVD. Therefore, the objective of this study is to examine the relationship between the vitamin E intake and the risk for CVD, specifically myocardial infarction (MI), stroke (ST) and transient ischemic attack (TIA) events, among a population from the European Prospective Investigation into Cancer and Nutrition-Potsdam (EPIC-Potsdam) cohort study taking into account the intake of vitamin E in two manners, as a single-nutrient and together with other known antioxidants.

1.1 Cardiovascular diseases and public health relevance

1.1.1 Definition and global epidemic

CVD are all pathological conditions involving the cardiovascular system (heart, blood vessels and pericardium) and including coronary heart disease (CHD) i.e. heart attack or MI,

cerebrovascular disease i.e., ST, raised blood pressure i.e., hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure [5].

According to the World Health Organization (WHO), CVD is the number one cause of world-wide mortality. In 2005 an estimated 17.5 million people died from CVD, 30 % of all global deaths. Just about 13.3 million of these deaths were due to MI and ST [6]. Chronic diseases, including CVD and diabetes, account for 60% of global mortality, and 80% of them come from low and middle-income countries. In spite of the increment of expectation of life due to the improvement of living conditions and the development of pharmacological industry, the CVD mortality remains as the major health burden among developed countries, this could be due to uncontrollable cardiovascular risk factors among an aging population. In reference to low- and middle-income countries they are showing an increment of the CVD mortality. The "westernisation" of lifestyles and urbanization of these countries could be underlying reasons of this pattern. Worldwide projections have suggested ischemic heart disease as one of the three leading causes in the coming decades [7, 8].

The Federal Statistical Office from Germany reported that CVD were the leading cause of death in Germany in 2006 (43.7% deaths). More men died due to acute myocardial infaction (AMI), ischemic heart disease (IHD) and subsequent MI, but more women died due to ST, hypertensive diseases, other forms of heart diseases and diseases of arteries, arterioles and capillaries [9].

1.1.2 Impact of cardiovascular diseases in Europe on the economy

In the EU the cost of CVD during 2003 represented €169 billion. In the two million deaths from CVD in 2003 was spent €24.4 billion of the total cost of cardiovascular disease, and represented a loss of 2.18 million working years. Germany and the UK had over half of all EU CVD costs. Their expenditure took up 15 and 17.1 % respectively of the two countries' healthcare budgets [10]. For 2002 in Germany the cost of CVD was 35.4 billion, for

hypertension disease 8.1 billion, cerebrovascular disease 7.8 billion, IHD and MI 7 billion, and heart failure 2.5 billion [9]. Increment in trends of CVD means the growth of health spending in governments and also a descent of productivity due to time off work. Individual and family health care cost must be joined to economy impact [5]. Under this panorama CVD will continue being relevant in public health.

1.1.3 Cardiovascular diseases, atherosclerosis and antioxidants

The relationship between atherosclerosis and CVD is largely accepted. Studies, from basic science and experimental to clinical interventions, have long been done. These studies have led to the understanding of the mechanism of atherosclerosis and their multiple risk factors, including dietary risk factors.

Proposals on the aetiology of the CVD, such as the Steinberg's LDL hypothesis [11] (which itemizes on the lipid peroxidation theory [12] and on the fundamental level of inflammatory cell-cell interactions in the Ross' response-to-injury hypothesis [13]), the Jackson's Cytokine Hypothesis [14], and the tocopherol-mediated lipid peroxidation [15, 16] may complement the antioxidant hypothesis of arteriosclerosis. On the other hand, the concept of tocopherol-mediated lipid peroxidation may be also contradictory with the antioxidant hypothesis of arteriosclerosis [17].

In cell cultures and animal studies, α-tocopherol has been shown to reduce the LDL oxidation and to opposse the atherosclerotic process [18-20]. A large body of evidence suggests that oxidised-LDL is more atherogenic than native LDL not only because of its contribution to fatty streak formation, but also by the activation of an inflammatory response [21, 22].

Ever since D. Harman proposed the free-radical theory of aging in the 1950s, free-radical damage has been associated with diverse pathologies including atherosclerosis [23]. All

metabolic processes in the human body continually generate considerable amounts of ROS, which are potentially dangerous, and can bring in operation the defence strategies known as the “antioxidative defence system”. Numerous pathological processes have been involved with oxidative stress, which is defined as any imbalance of pro-oxidants over antioxidant defence potentials and that may be mediated by regular metabolites or by exogenous radicals [3, 24]. In fact, vitamin and micronutrient antioxidants act as part of the non-enzymatic antioxidant defence system.

1.2 Vitamin E, properties and relevance of vitamin E

1.2.1 From chemical structures to physiological implications

In 1926 the term “vitamin E” was adopted by Barnett Sure to represent a food factor “X” that was discovered by H.M. Evans and L.S. Bishop and found to be an essential nutrient for rat reproduction. At same time Mattill´s research group had identified also this essential nutrient “factor” in their investigation of the diet milk effect on reproduction. Subsequently, both teams of research suggested antioxidant properties of the tocopherols. Shortly thereafter Fenholz E. characterized the chemical structure of alpha-tocopherol and Karrer P. synthesised dl-α-tocopherol [25-27].

In regard to the vitamin E definition, according to the nomenclature policy for vitamins and nutrients developed by the International Union Nutrition Sciences Committee on Nomenclature, “the term vitamin E should be used as the generic descriptor for all tocol and tocotrienol derivatives exhibiting qualitatively the biology activity of the alpha-tocopherol” [28]. Vitamin E is composed of eight naturally occurring components, 4 forms of tocopherol and 4 forms of tocotrienol, α, β, γ, and δ respectively, and all have chain-breaking antioxidant activity. All components contain a molecular ring (chroman ring), a side chain (16 Carbon atoms) which is called the phytyl tail for tocopherols and unsaturated tail for tocotrienols, and an active group on the chroman ring which is called the hydroxy group. These forms differ in

the number of methyl groups substituted on the chroman ring and in the saturation of the isoprenoid side chain. Furthermore, all components of vitamin E have different stereoisomer forms, but only the RRR- stereochemistry in the side chain is maintained by humans [29]. The α-form has all three available sites filled, while α- and γ-forms have two methyl groups but in different positions, and the δ-form has only one. Among all isomers of vitamin E, the RRR-α-tocopherol is by far the most abundant lipid-soluble antioxidant in humans, and it is present in cellular and sub-cellular membranes. The RRR-α-tocopherol is the major lipid-phase antioxidant compound of the vitamin E group. Its biological activity depends on a free hydroxyl group in position 6 of the chromane ring [30]. In regards to γ-tocopherol, the unsubstituted C-5 position appears to make the γ-tocopherol able to trap reactive-nitrogen-oxide-species (RNOS) [31] and also a more stable and more efficient antioxidant for food lipids, (i.e. inhibition of rancitidy and prolongation of shelf-life of processed food) [32]. In addition, tocotrienols are characterized as having a shorter and rigid lipophilic tail that confers to be distributed uniformity within the fatty layer of the cell membrane [33].

1.2.2 Vitamin E against atherosclerosis

1.2.2.1 Antioxidant *vs*. Prooxidant function

Vitamin E, especially the α-tocopherol form, is a chain-breaking antioxidant that reacts with free radicals (notably peroxil radical) and a single oxygen, to protect polyunsaturated fatty acids (PUFA) against peroxidation. On the other hand, the α-tocopherol under certain conditions may actually act as prooxidant via the tocopheroxyl radical, called the tocopherol-mediated-lipid peroxidation [15]. In this respect, the γ-tocopherol has less prooxidant activity than does the α-tocopherol because its chemical structure makes it a more stable phenolic radical [34]. With regards to the tocotrienols, they may be more efficient radicals scavengers in biomembranes than corresponding tocopherols [35].

1.2.2.2 Non-antioxidant functions

Investigations have reported evidences on the alternative functions of vitamin E on the atherosclerosis, which may not be described inside its antioxidant role [36]. Although all forms of vitamin E exert non-antioxidant functions, γ-tocopherol is more effective than α-tocopherol in anti-inflammatory effects, reducing oxidative DNA damage, increasing dismutasa activity, and scavenging peroxynitrite [31]. Table 1 shows a compilation of these non-antioxidant functions.

Table 1. Non-antioxidant functions of vitamin E

Function	Evidence
Anti-inflammatory	The release of IL-1β from lipopolysacharide-activated monocytes Inhibiting monocyte-endothelial adhesion Inhibition of inflammatories cytokines and chemikines (monocyte chemotactic protein 1 and IL-8 in human aortic endothelial cells) Diminution smooth muscle cell proliferation Inhibition of the aggregation of platelets Production of collagen α1(I) in human fibroblasts and in the livers of C57BL/6 mice Inhibition of protein kinase C activity and then inhibit smooth muscle cell proliferation (α, β, and δδ-tocopherol)
Regulator the expression of genes involved in growth, apoptosis, and inflammation	Activator protein 1 (AP-1), α-tropomyosin, collagenase, cytokine interleukin-1- β, glycoprotein IIB, and intercellular adhesion molecule 1 (ICAM-1) Inhibition of CD36 scavenger receptor expression Modulation of α-tocopherol-transfer-protein expression
Modulation of immune response	Inhibition of cyclooxygenase activity in macrophages and epithelial cells, leading to decrease in prostaglandin E2 levels (γ- tocopherol)
Detoxification of nitrogen dioxide	Nitration of γ-tocopherol
Detoxification of xenobiotics	Induction of some citocromos P450 by activation of a nuclear pregnane X receptor-driver reporter gene, leading to decrease efficacy of xenobiotics.

Compiled from literature in references [2, 31, 36, 37].

1.2.3 Vitamin E metabolism

All components of vitamin E appear to be absorbed by the gastrointestinal tract. The hepatic α-tocopherol transfer protein, together with the tocopherol-associated proteins, selects α-tocopherol for incorporating it into the plasma lipoproteins. This leads to ejection of other tocopherols into the bile, and thus backs into the gastrointestinal tract. Although the tocopherol-associated proteins has a much lower affinity to other tocopherols and tocotrienols, it appears that the tocopherol-associated proteins is responsible for higher concentrations of these non-α-tocopherol forms in some human tissues [38]. The final products of all forms are conjugated and eliminated via the bile or urine. Whilst all of the other non-α-tocopherol forms of vitamin E are degraded fast, the α-tocopherol is the compound of vitamin E with the highest biological activity. The α-tocopherol is kept longer into the circulation, and its concentration levels depend more on plasma lipid concentration than on an age-related absorption efficacy. In contrast, the γ-tocopherol is degraded faster and the amount found in urine was about 10 times higher than the excreted α-tocopherol. Both α-tocopherol and γ-tocopherol excretions are not affected by age changes [39]. Higher concentrations of γ- and δ-tocopherol, and tocotrienols can be present in the fecal matter. Their concentrations are higher in fecal matter when compared to those in plasma (i.e., fecal/plasma ratio of γ-tocopherol= 6.3; fecal/plasma ratio of α-tocopherol=1.9) [40].

Many aspects of the vitamin E metabolism are yet unclear. However, evidence suggested that other non-α-tocopherol forms have a metabolism quite different from αα-tocopherol form. With regard to the γ-tocopherol, concentrations of γ- tocopherol in human tissues (e.g. muscle, skin, brain, vein and adipose) are higher than those in human plasma. The γ-tocopherol is degraded to γ-CEHC, a potent natriuretic factor, and excreted into urine [31]. Contrary to the fact that all forms of vitamin E cannot be interchanged in the body [29], new findings appear to suggest that γ-tocopherol might be able to transform into α-tocopherol in the body [32].

1.2.4 Vitamin E and antioxidant network

It is known that antioxidant nutrients are often highly correlated and may have interactive and synergistic effects. Experimental evidences and models suggest the existence of an antioxidant network system among ubiquinols, glutations, phenolics, ascorbic acid, carotenoids and compounds of vitamin E [41, 42]. Table 2 summarizes some findings in regard to the interaction among vitamin E, other antioxidants and the so-called co-antioxidants.

Table 2. Interaction among nutrients

	TYP OF ACTION	DESCRIPTION	REF.
β-carotene	Antioxidant	singlet oxygen quenching	[43]
β-carotene and α-tocopherol	Antioxidant	tocopherol inhibits the breakdown of carotenoids	[44]
β-carotene and free radical	antioxidant/prooxidant	lipid oxidation: scavenge oxy-radicals and terminates free radical reactions	[45]
Ascorbic acid on α-tocopherol	coantioxidant	Tocopheroxyl radical is repaired to form α-tocopherol	[46]
Ascorbic acid on β-carotene	coantioxidant ?	β-carotene cation is repaired to form β-carotene	[47]
Ubiquinols	antioxidant/oxidant	tocopheroxyl radical is repaired to form α-tocopherol	[48]
α-tocopherol	antioxidant/oxidant	ubisemiquinone is repaired to form ubiquinol	[49]
α-tocopherol on glutathione–dependent enzime	coantioxidant ?	Protection of glutathione-dependent enzimes	[50]
Phenolics	coantioxidant	tocopheroxyl radical is repaired to form α-tocopherol	[51]

1.3 Assessing of vitamin E intake

1.3.1 Correlations with biological measures

The α-tocopherol is the predominant form of vitamin E maintained in human plasma and has more biological activity. Therefore, both dietary and biological assessments have been chiefly focused on it. A variety cut-offs in plasma for the deficiency of vitamin E have been used mainly due to the diverse methods applied for lipid-adjustment. German Dietary Association considers plasma values of α-tocopherol from 12 to 46 μM as a normal range and plasma values of α-tocopherol >30 μM as desirable values [30], others had considered plasma α-tocopherol <16 μM or <22 μM as deficient status [52, 53].

With regard to the Dietary Reference Intake (DRI) the table 3 shows values for adults from USA and Germany. These recommendations for vitamin E intake are based on the α-tocopherol only. The Recommendation Dietary Allowance (RDA) values used in USA are higher than Adequacy Intake (AI) used in Germany.

Table 3. Dietary Reference Intake for vitamin E

MEASURE	
Recommended Dietary Allowance (RDA), USA [29]	
Adults	
>19 years	15 mg/day of α-tocopherol
Adequate Intake (AI), Germany [30]	
Adults, men	
19-24 years	15 mg TE/day
25-50 years	14 mg TE/day
51-64 years	13 mg TE/day
>65 years	12 mg TE/day
Adults, women	
19-24 years	12 mg TE/day
25-50 years	12 mg TE/day
51-64 years	12 mg TE/day
> 65 years	11 mg TE/day
Pregnant	13 mg TE/day
Lactanting	17 mg TE/day

Dietary methods for estimating dietary nutrients, such Food Frequency Questionnary (FFQ), dietary history and 24-hour dietary recall (24HR), are considered to provide an accurate estimate of intake for vitamin E. In fact, validity studies reported that these dietary methods have sources of error in common, i.e. use of the same food composition, underreporting (fats and energy) and over reporting (healthy foods) [54, 55]. Table 4 shows correlations between vitamin E intake and blood values from some validation studies. These correlations were reported between -0.07 and 0.60 and being higher when supplement contribution was accounted into. Age, sex, smoking status, Body-Mass-Index (BMI), waist-to-hip ratio (WHR), waist circumference, type of employment, presence of fat dietary, alcohol consumption, total energy intake, and blood lipid content have been related to the intake of vitamin E and/or its bioavailability in blood [56-64].

Table 4. Summary of correlations between vitamin E intake and biomarkers

FIRST AUTHOR, YEAR	BIOMARKER	QUESTIONNAIRY	CORRELATION COEFFICIENT
Malekshak AF et al, 2006 [65]	all		
	serum α-tocopherol[1]	FFQ	0.06
	serum α-tocopherol	24HR	0.10
Brunner E et al, 2001 [66]	men[2]		
	plasma α-tocopherol	FFQ	-0.02
	women		
	plasma α-tocopherol	FFQ	-0.07
White E et al, 2001 [67]	women		
	serum α-tocopherol	FFQ	0.06
	serum α-tocopherol	SUPPL	0.60
	women		
	serum γ-tocopherol	FFQ	-0.09
Various investigators, 1997 [68]	men		
	plasma α-tocopherol[3]	HD	0.42
	plasma α-tocopherol	24HR	0.26
	women		
	plasma α-tocopherol	HD	0.31
	plasma α-tocopherol	24HR	0.42
Ocke MC et al, 1997 [69]	men		
	serum α-tocopherol	FFQ	0.24
	serum α-tocopherol	FFQ[3]	0.33
	women		
	serum α-tocopherol	FFQ	0.15
	serum α-tocopherol	FFQ[3]	0.13
Boeing H et al, 1997 [70]	all		
	α- and γ-tocopherols[4]	FFQ	0.14
Jacques PF et al, 1993 [71]	all		
	plasma α-tocopherols[5]	FFQ + SUPPL	0.53
	all		
	plasma α-tocopherols[5]	FFQ	0.35
Ascherio A et al, 1992 [72]	men[6]		
	plasma α-tocopherol	FFQ	0.51
	women		
	plasma α-tocopherol	FFQ	0.41
	men[6]		
	plasma γ-tocopherol	FFQ	-0.51
	women		
	plasma γ-tocopherol	FFQ	-0.42
Bolton-Smith C et al, 1991 [73]	men[7]		
	serum α-tocopherol		
	smokers	FFQ	0.27
	non-smokers	FFQ	0.32
Willet WC et al, 1985 [74]	all		
	α-tocopherol plasma	FFQ	0.12

[1] adjusted for cholesterol level. [2]adjusted for total energy intake and cholesterol level. [3] adjusted for total energy intake. [4]adjusted for sex and smoking status. [5]adjusted for age, sex, total energy intake and plasma cholesterol concentrations. [6]adjusted for age, BMI, plasma cholesterol and plasma triglycerides. [7]adjusted for total energy intake, BMI, serum cholesterol and serum triacylglycerol. FFQ=Food-Frequency-Questionnary;HD=history dietary; S-FFQ=Semiquantitative-Food-Frequency-Questionnairy; SUPPL= estimated from supplement intake; 24HR=24 hours-recall

1.3.2 Food sources of vitamin E

Most vegetable oils are main sources of vitamin E, but also other planted-based foods provide good amounts of vitamin E. Table 5 shows main food sources of vitamin E classified by content of vitamin E expressed as α-tocopherol equivalents (based on the rat fetal resorption assays). All compounds of vitamin E occur naturally in foods, but in varying amounts and predominant form. Larger amounts of α-tocopherol are present in vegetables oils such as olive, wheat germ, cottonseed, safflower and sunflower, sunflower products such as margarine and seeds, vegetables (dried fruits and condensed tomato products), nuts (almonds, filberts, peanuts and brazil nuts), cereal grains (breakfast cereal and wheat germ), fish body oils, baked products (cake and cookies) and snack products (corn and potato chips). Among the richer γ-tocopherol food sources are vegetable oils such as corn, peanut, sesame, apricot, cottonseed, soybean and walnut; margarines (from soybean and corn), salad dressings (French, Italian, mayonnaise), nuts (pistachios and peanut butter), seeds (sesame and lima), cereal grains (corn and cereal-based snack products) and baked products (cake mixes, cookies, chocolate chips and chocolate products). Food sources of tocotrienols include vegetables oils such as palm and coconut, cocoa butter, macadamia, cereal grains (wheat bran, wheat, oats, rye, rice bran, breakfast cereal), fresh corn, soybean and mushroom [75-77].

Table 5. Foods with high content of vitamin E

VERY HIGH >30.0 α-TE/100 g	HIGH 15-30.0 α-TE/100 g	MODERATE TO LOW 1-15 α-TE/100 g	LOW < 1.00 α-TE/100 g
Fats and oils: safflower and sunflower. Grains: wheat germ. Margarine: light and soft.	Fats and oils: canola, palm and soybean. Vegetables: spinach. Nuts: almonds and brazil nut, sunflower, soya, sesame, lima. Cereal grain: wheat bran, wheat, oats, corn, rye, rice bran, breakfast cereal, corn fresh, wheat germ. High oil products, snack products: sunflower seeds.	Fats and oils: butter and margarine. Grains: corn, oat bran, rice, wheat bran and flour. Vegetables (green):brocoli, sparagus, brusels sprouts, celery, parsley, lettuce, and peppers. Other vegetables: cabbages, carrots, mustard, tomato, vegetable juice. Fruits: olives green, peaches, avocados and apple red deliciosus. High oil product, frosting chocolate and vanilla, cake mixes, breakfast cereals. Nuts: peanut, pistachio and peanut butter. High oil products, snack products: corn and potatoes chips. Others: hen eggs, seafood.	Fats and oils: coconut and lard. Dairy products. Bread. Vegetables (yellow): squashes and zucchini. Legumes (grains): lentils, beans, and lupins. Vegetables: mushroom, cauliflor, onions and potatoes. Fruits and vegetables: dried fruits, condesed tomato products and apple. Mushroom. Nuts: macadenia. High oil products: candy, chocolate. Low-fat or fat-free products.

Adapted from values in [76].

Table 6 compiles data on the contribution of five aggregated food groups to vitamin E in the diet from different populations. Almost these percentages of contribution to vitamin E were done following Block calculation [78]. In USA sources of vitamin E come from refined and pre-cooked foods, predominantly γ-tocopherol forms [79, 80]. In contrast with the USA, the food sources of vitamin E in Spain predominantly come from the plant-based foods, more α-tocopherol forms [81, 82]. In Germany vegetable food sources of vitamin E are different from those in the USA and Spain, but foods rich in α-tocopherol forms are predominant [83]. Either geographic or "westernization" culture appears to be an influence in the choice of sources of vitamin E.

Table 6. Main food sources of vitamin E and % of contribution

DESCRIPTION	FOOD GROUPS	% CONTRIBUTION TO VITAMIN E
USA, CSFII, 1994-1996 [79] (5056 men)	Ready-to-eat-cereal	9.48
	Cakes, cookies, pies, doughnuts	8.28
	Beef	6.86
	White bread	6.68
	Oils and salat dressing	5.75
USA, CSFII, 1994-1996 (4703 women)	Ready-to-eat-cereal	9.02
	Cakes, cookies, pies, doughnuts	8.24
	Oils and salat dressing	6.82
	Beef	6.29
	White bread	5.05
USA, NHANES II, 1976-1980 [80] (11 658 adults)	Fats and oils	20.2
	Vegetables	15.1
	Meat, poultry, and fish	12.6
	Dessert	9.9
	Breakfast cereals	5.3
SPAIN, 2004 [81]	Vegetable oils	40.0
	Fruits non-citrus	10.0
	Nuts and seeds	8.0
SPAIN, 2000 [82]	Added fats	33.8
	Fruits fresh	12.9
	Fish	8.9
	Cereals	8.5
	Vegetables	6.1
GERMANY, 1998 [83] (men)	Vegetables fats	>30.0
	Breads	10.5
	Vegetables	7.5
	Fruit	6.0
	Confectionary	5.0
GERMANY, 1998 (women)	Vegetables fats	>31.0
	Breads	9.7
	Vegetables	9.0
	Fruit	8.2
	Juices	5.2

1.4 Epidemiological evidences of relationship between vitamin E intake and cardiovascular diseases

A systematic review focalizes on observational studies on the topic of vitamin E intake and risk of cardiovascular disease by the author has been done [84]. In summary, the idea of a

possibly beneficial effect of vitamin E intake on cardiovascular disease largely bases on analyses from cohort studies. In contrast, supplementation with vitamin E had no effect on CVD incidence in most of the RCTs conducted so far. Observational studies with material biological showed divergent results and any of those studies were designed to relate the intake of vitamin E. In the next sections evidences of cohort studies and RCTs are shown.

1.4.1 Cohort studies

Nine prospective cohort studies have reported analyses of the association between vitamin E intake from food and/or supplements and CVD (MI and/or ST) events (fatal and/ or non-fatal). Main features and results are shown in table 7. In brief, the following cohorts accounted for an inverse association between vitamin E intake from dietary sources and/or supplementation, and CVD incidence or mortality: Health Professionals Follow-up Study (HPFS) [85], Iowa Women's Health Study (IWHS) [86, 87], Scottish Heart Health Study (SHHS) [88], Cancer Prevention Study II (CPS-II) [89], Physicians' Health Study (PS) [90], Nurses' Health Study (NHS) [91], Finnish Cohort Study (FS) [92]. These studies reported a 5% reduction of CHD risk among men from dietary vitamin E intake (SHHS) [88], a 32% reduction of CHD risk among men from dietary vitamin E intake (FS) [92], a 40% reduction of CHD risk among men from dietary and supplemental vitamin E intake (HPFS) [85], a 34% reduction of major CHD risk among women from dietary and supplemental vitamin E intake (NHS) [91], a 62% reduction of CHD risk among women from dietary vitamin E intake (IWSS) [86], a 65% reduction of CHD risk among women from dietary vitamin E intake (FS) [92], a 0% to 14% reduction of IHD risk among women users of vitamin E, vitamin C and/or vitamin A without multivitamins or plus multivitamins (CPS-II) [89], and a 59% reduction of CHD mortality among men who took vitamin E supplements more than 4 years (a secondary analysis within PS) [90]. A total of four analyses addressed the relationship between vitamin E intake and ST events with a 60% reduced ST mortality associated with higher dietary vitamin E intake within the IWHS [87] and a 15% reduced ST incidence among women who took vitamin E-containing multivitamins for more than 5 years within the CPS-II [89]. Contrary to these results, both the ATBC analysis [93] and ZS cohort [94] did not find a significant relation between vitamin E intake and risk of ST.

1.4.2 Metaanalysis of cohort studies and pooling of cohort studies

Three MAs of cohort studies reported a significant inverse association between increased vitamin E intake from diet and supplements and CVD, 4% to 44% reduction of CVD (table 8) [95-97]. The pooling analysis of primary data of 9 cohort studies was carried out in the Pooling Project of Cohort Studies on Diet and Coronary Disease. After adjustment for age and energy intake, a lower risk of CHD incidence at higher intakes of dietary vitamin E was found. After adjustment for the other potential confounders, this association persisted in women, but not in men. On the other hand, vitamin E supplementation was associated with reduced CHD incidente (table 9) [98].

Table 7: Observational studies of dietary and supplemental vitamin E intake and cardiovascular events

Study	Features	Outcomes (# events)	Main findings Relative Risk (95%, p values)	Variables included multivariable model	Inverse association to CVD
The Health Professionals Follow-up Study (HPFS), USA 1986 (Rimm EB, 1993) [85]	n=39 910 subjects Sex=100%men A=40-75 Fup-time=4.0 y	CHD (667)	Dietary and supplemental VEI: 0.60[0.44-0.81, p=0.01]	age, energy intake, smoking status, alcohol consumption , history of HYP, parental history of MI before 65 years of age, aspirin use, profession, BMI, physical activity and intakes (VE, VC, carotene)	Yes
	n=43 738 subjects Sex=100%men A=40-75 Fup-time=8.0 y	ST (328)	Dietary and supplemental VEI: 1.25[0.88-1.78, p>0.2]	same variables of the previous analysis plus calendar time and except intakes (VE, VC, carotene)	No
Iowa Women's Health Study (IWHS), USA 1986 (Kushi LH, 1996) (Yochum LA, 2000) [86, 87]	n=34 486 postmenopausal Sex=100%women A=55-69 Fup-time=6.0 y	CHD (242)	Dietary VEI: 0.38[0.18-0.80, p=0.004]	age, energy intake, BMI, WHR, pack-years of cigarette smoking, HYP, DIA, use of estrogen-replacement therapy, physical activity, alcohol intake, marital status and education	Yes
	n=34 486 postmenopausal Sex=100%women A=55-69 Fup-time=11.0 y	ST (215)	Dietary VEI: 0.40[0.20-0.80, p=0.008]	same variables of the previous analysis plus intakes of cholesterol, saturated fat, fish, VC, carotenoids, dietary fiber and whole grains	Yes
Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC), Finland 1986 (Hirvonen T, 2000) [93]	n=26 497 subjects Sex=100%men A=50-69 Fup-time=6.1 y	CEI (731) SAH (83) ICH (95)	For CEI, dietary VEI: 0.86[0.70-1.06, p=0.25] For SAH, dietary VEI: 0.81[0.44-1.50, p=0.55] For ICH, dietary VEI: 0.64[0.36-1.15, p=0.15]	age, cigarettes smoked/day; smoking/years, supplementation group, serum total cholesterol, HDL-cholesterol, SBP and DBP, BMI, height, history of DIA, CHD, alcohol intake and education	No
Scottish Heart Health Study (SHHS), UK 1984 (Todd S, 1999) [88]	n=11 629 subjects Sex=49.5%men A=44-55 Fup-time=7.7 y	CHD (393)	Among men, dietary VEI: 0.95[0.68-1.31, p=0.05]	age, serum total cholesterol, SBP, smoking, energy intake, DIA, BMI, the Bortner personality score, TGC, HDL-cholesterol, fibrinogen, physical activity and alcohol consumption	Yes, only men

Cancer Prevention Study II (CPS-II), USA 1982 (Watkins ML, 2000) [89]	n=1,063 023 subjects Sex=42.7%men A= >30 Fup-time= 7.0 y	IHD (9058) ST (4482)	For IHD mortality women users of VE, VC and/or VA: 0.86[0.80-0.92, p=0.005]. For IHD mortality women users of VE, VC and/or VA plus multivitamins: 0.82[0.76-0.88, p=0.01]. For ST mortality women users of VE, VC and/or VA plus multivitamins ≥5 years: 0.81[0.67-0.98; p=0.05].	age, exercise, education level, BMI, vegetable intake, smoking status, history of CHD, ST, DIA, cancer, HYP, aspirin use, diuretic use, liquor, wine, beer, or coffee consumption, marital status, race, employment and estrogen replacement status	Yes, only women but not specific to VE
Physicians' Health Study (PS), USA 1982 (Muntwyler J, 2002) [90]	n=83 639 subjects Sex=100%men A=44-67 Fup-time= 5.5 y	CVD (1037) CHD (608)	For CVD mortality: 0.92[0.70-1.21, p=NA] For CHD mortality: 0.88[0.61-1.27, p=NA] For CHD mortality among who took VE supplements ≥4 years: 0.41[0.19-0.85, p=NA]	history of HYP, HYCHOL and DIA, current and past smoking, alcohol intake, physical activity, BMI, complementary vitamins, and randomization status	Unclear
The Nurses' Health Study (NHS), USA 1980 (Stampfer MJ, 1993) [91]	n=87 245 healthy subjects Sex=100%women A=34-69 Fup-time=8.0 y	Major CHD (552)	Dietary and supplemental VEI: 0.66[0.45-0.78, p<0.001]	Age and smoking status	Yes
			Among users of VE supplements ≥2 years: 0.59[0.38-0.91, p=NA]	age and smoking status, BMI, alcohol intake, menopausal status, postmenopausal hormone use, vigorous activity, regular use of aspirin, HYP, high cholesterol level, DIA, energy intake, use of vitamin and multivitamin supplement	Yes
Finnish Mobile Clinic Study (FS), Finland 1966-1972 (Knekt P, 1994) [92]	n=5133 subjects Sex=53.54%men A=30-69 Fup-time=12-16 y	CHD (244)	Among men, dietary VEI: 0.68[0.42-1.11, p=0.01]. Among women, dietary VEI: 0.35[0.14-0.88, p<0.01]	age, smoking, serum total cholesterol, HYP, BMI and energy intake	Yes, both sex
The Zutphen Study (ZS), The Netherlands 1960 (Keli SO,1996) [94]	n=552 subjects Sex=100%men A=50-69 Fup-time=15 y	ST (42)	Dietary VEI: 1.64[0.54-4.97, p=0.30]	age, SBP, serum total cholesterol, energy intake, lifetime cigarette smoking exposure until 1970, fish consumption in 1970 and alcohol consumption (10 years)	No

A=age range; BMI=body-mass-index; DIA=diabetes; DBP=diastolic blood pressure; CEI=cerebral infarction; CHD=coronary heart disease; CVD=cardiovascular disease; Fup-time=years of follow-up; HYP=hypertension; HYPCHOL=hypercholesterolemia; ICH=intracerebral hemorrhage; IHD=ischemic heart disease; n=number of participants; NA=not applied; Out=outcomes; RR=relative risk; SAH=subaracnoid hemorrhage; SBP=systolic blood pressure; ST=stroke; TGC=triglycerides; VA=vitamin A; VE=vitamin E; VEI=vitamin E intake; VC=vitamin C; WHR=waist-to-hip ratio

Table 8. Metaanalysis and pooled analysis of cohort studies involving dietary and/or supplemental vitamin E intake and risk for cardiovascular disease

	METAANALYSIS OF COHORT STUDIES		
Reference	**Studies included**	**Features**	**Odds ratio (95%CI)**
(Asplund K, 2002) [97]	NHS, HPFS, ZS, IWHS, FS, The Nutrition Status Surveys, Established Populations for Epidemiologic Studies of the Elderly (EPESE), Shangai Survey, and The Rotterdamm Study	n=82 379 IC=1957	0.74 [0.66-0.83] P value significant
(Marchioli R, 1999) [96]	NHS, HPFS, IWHS, and FS	n=166 774 IC=1705	0.64 [0.56-0.73] P value significant
Reference	**Studies included**	**Features**	**RR for the highest vs. lowest percentile of intake (95%CI, p values)**
(Law MR, 1998) [95]	NHS, HPFS, IWHS, and FS	n=166 774 IC=1705	0.88 [0.81-0.96,p=0.003]
	POOLING ANALYSIS (Knekt P, 2004) [98]		
Type of analysis	**Studies included**	**Features**	**Pooled RR for the highest vs. lowest quintile of intake (95%CI, p values)**
Dietary intake	Adventist Health Study (AHS), Atherosclerosis Risk in Community Study (ARIC), Alpha-Tocopherol, Beta-Carotene, Cancer Prevention Study (ATBC-only placebo arm), Finnish Mobile Clinic Examination Survey (FMC), Glostrup Population Study (GPS), HPFS, IWHS, NHS,and Västerbotten Intervention Program (VIP).	n= 156 949 IC= 2908 MC= 1124	0.84[0.71-1.00, p=0.17]*
Dietary and supplemental intake	Alpha-Tocopherol, Beta-Carotene, Cancer Prevention Study (ATBC, only placebo arm), HPFS, IWHS, and NHS.	n= 227 243 IC= 3036 MC= 1364	0.95[0.81-1.12, p=0.85]*
Suplemental intake	Alpha-Tocopherol, Beta-Carotene, Cancer Prevention Study (ATBC, only placebo arm), HPFS, IWHS, and NHS	n= 227 243 IC= 3036 MC= 1364	0.87[0.78-0.97, p=0.02]****

FS=Finnish Mobile Clinic Study; HPFS=The Health Professionals Follow-up Study; IC=incidence cases; IWHS=Iowa Women's Health Study; MC=mortality cases; n=number of persons; NHS=The Nurses' Health Study RR=relative risk; ZS=The Zutphen Study *Model adjusted for age, energy intake, smoking status, body-mass-index, physical activity, education, alcohol intake, history of diabetes, hypercholesterolemia, hypertension, postmenopausal hormone use among the women and quintiles of intake of energy-adjusted saturated fatty acids, cholesterol, flavonoids, folate with supplements, vitamin B-6 with supplements, and cereal fiber. **Model among subjects who consumed VE supplements in amounts of <25 mg/d in comparison with nonusers adjusted for age, energy intake, smoking status, body-mass-index, physical activity, education, alcohol intake, history of diabetes, hypercholesterolemia, hypertension, postmenopausal hormone use among the women.

1.4.3 Randomized clinical trials

Thirteen RCTs and four systematic reviews including metanalysis of RCTs evaluated the effect of vitamin E supplementation on CV events. The majority of RCTs did not confirm an effect of vitamin E supplementation on CVD (table 9 and 10). However, three primary prevention trials reported statistically significant results: the Women's Health Study (WHS), Lixian Nutrition Intervention trial (LIXIAN-2) and the Alpha Tocopherol Beta Carotene trial (ATBC). The WHS noted a reduction of CVD mortality risk (2 to 41%) in women who took 600 IU of natural vitamin E every other day during 10.1 years of follow-up [99]. A 58% of reduction of cerebrovascular disease mortality was observed among men who had been randomized to multivitamin and mineral supplementation that included 60 IU of α-tocopherol within the LIXIAN-2 trial [100, 101]. The ATBC noted a 14% of reduction for subarachnoid hemorrhage incidence but a significant increment for both intracerebral hemorrhage and cerebral infarction among men who had been randomized to 50 mg of dl-α-tocopherol supplementation [102].

Three further studies, designed as secondary prevention studies, showed a beneficial effect of vitamin E supplementation on CVD outcomes: Women's Antioxidant Cardiovascular Study (WACS) [103], Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) [104] and Cambridge Heart Antioxidant Study (CHAOS) [105]. The WACS found marginally significant reduction only in secondary outcomes (21% in ischemic ST and 10% in the combination of MI, ST and CVD deaths) among women at high risk who took 600 IU of natural vitamin E every other day during 9.4 years. Within the WACS a significant reduction (11%) of the primary endpoint (MI, ST, coronary revascularization, or CVD deaths) among women with prior CVD was also observed [103]. Within the SPACE trial a significant 54% reduction of major CVD events and 65% reduction of non-fatal MI was observed among subjects at high risk who had been assigned randomized to take 800 IU of α-tocopherol [104]. Similarly, among subjects at high risk who had been assigned to take 400 or 800 IU of α-tocopherol in the CHAOS trial, the risk for major CVD event and nonfatal MI was reduced by 47% and 77% respectively [105].

Table 11 displays main results of the four metanalyses [97, 106-108]. Briefly, in contrast with results from observational studies, metanalyses of RCTs suggest no beneficial effect of vitamin E supplementation.

Table 9. Summary of primary prevention randomized clinical trials of vitamin E supplementation and cardiovascular diseases

Study	Location and subjects randomized	Design	Main findings Relative risk[95%CI, p values]	Inverse Association to CVD
SU.VI.MAX **1994** (Hercberg S, 2004) [109]	France; n=12741; Sex=39.5%men; A=30-60; Fup-time=7.5 y; IC= 271	DB, PC, 2 groups:combination of VC, VE, selenium, and zinc, or placebo; D-VE= 30 mg; Out= major fatal and nonfatal ICD events, and cancer	ICD: 0.97[0.77-1.20, p=0.80] ICD men: 0.82[0.71-1.20, p=0.54] ICD women: 1.17[0.67-2.05, p=0.57]	No
PPP **1993** (de Gaetano G, 2001)[110]	Italy, multicentre; n=4495 at high risk for CVD; Sex=42%men;A=57-72;Fup-time=3.6 y; IC=109; MC=48	OL, PC, 2x2: aspirin /VE; D-VE= 300 mg, α-toc synthetic; Out= Main combined endpoint: CV death, nonfatal MI and nonfatal ST	Main combined endpoint: 0.71[0.48-1.04, p=ns]	No
WHS **1991** (Lee IM, 2005) [99]	USA; n=39 876 healthy; Sex=100%women; A ≥45; Fup-time=10.1 y; IC= 999	DB, PC, 2x2:VE, aspirin, or both, or placebo; D-VE=600 IU/every other day, natural-source; Out=major CVD events(nonfatal MI, nonfatal ST, or CVD death) and cancer	Major CVD events: 0.93[0.82-1.05, p=0.26] MI incidence: 1.01[0.82-1.23, p=0.96] Nonfatal ST: 0.98[0.82-1.17, p=0.82] CVD mortality: 0.76[0.59-0.98, p=0.03]	Yes, only secondary outcomes
LIXIAN-1 **1986** (Blot WJ, 1993)[100]	China, multicentre; n=29 584 health at risk to cancer; Sex=45%men;A=40-69; Fup-time=5 y; MC=523(CvD)	OL, no true PC, 2x4: groups with different combinations of nutrients, one arm included VE plus BC and selenium; D-VE=30 mg, synthetic; Out=cancer, CvD, and other deaths	CvD: 0.90[0.76-1.07, p=ns] CvD women: 0.96[p=ns] CvD men: 0.86[p=ns]	No
LIXIAN-2 **1985** (Blot WJ, 1995) (Mark SD, 1996) [101, 111]	China, multicentre; n=3318 with esophageal dysplasia; Sex=44%men;A=40-69; Fup-time=6 y; MC=57(CvD)	OL, no true PC, 2 groups: multivitamin and minerals, or placebo. VE included; D-VE=60 IU, dl-α-toc; Out= cancer, CvD, and other deaths	CvD: 0.63[0.37-1.07, p=0.08] CvD men: 0.42[0.20-0.93, p=0.02] CvD women: 0.93[0.44-1.98, p=0.85]	Yes, only men
ATBC **1985-1988** (Virtamo J, 1998) [112]	Southwestern Finland, multicentre; n=27 271 heavy smokers; Sex=100%men; A=50-69; Fup-time=6.1 y; IC=2111; MC=907	DB, PC, 2x2: VE, BC, or both vitamins, or placebo; D-VE=50 mg, dl-α-toc synthetic=55 IU; Out=Major coronary events: nonfatal AMI and fatal CHD	Major coronary events: 0.96[0.88-1.04, p=ns] Fatal CHD: 0.92[0.81-1.05, p=ns] Nonfatal AMI:1.01[0.88-1.10, p=ns]	No
ATBC **1985-1988** (Leppala JM, 2000) [102]	Southwestern Finland, multicentre; n=28 519 heavy smokers ST free at baseline; Sex=100%men; A=50-69; Fup-time=6.0 y; IC=1057; MC=160	DB, PC, 2x2: VE, BC, or both vitamins, or placebo; D-VE=50 mg, dl-α-toc synthetic=55 IU; Out= First-on-trial subtypes of ST: SAH, ICH, and CEI	SAH incidence: 1.50[0.97-2.32, p=0.07] SAH mortality: 2.81[1.37-5.79, p=0.005] ICH incidence: 1.04[0.72-1.51, p=0.84] ICH mortality: 1.64[0.93-2.90, p=0.09] CEI incidence: 0.86[0.75-0.99, p=0.03] CEI mortality: 1.50[0.97-2.32, p=0.07]	Yes, only CEI

A=age range; α-toc= alpha-tocopherol; AO=antioxidant; ATBC=Alpha-Tocophero, Beta-Carotene Cancer Prevention Study; BC=beta carotene; CEI=cerebral infarction; CHD=coronary heart disease; CV=cardiovascular; CVD=cardiovascular disease; CvD=cerebrovascular disease; DB=double-blind; D-VE=dose of vitamin E, typ of vitamin E; Fup-time=follow-up time; IC=incidence cases; ICH=intracerebral hemorrhage; ICD=ischemic cardiovascular disease; IHD=ischemic heart disease; LIXIAN-1=Lixian trial in general population; LIXIAN-2=Lixian dysplasia trial; MI=myocardial infarction; MC=mortality cases; n=number of participants; ns=no statistical significant; OL=open label; Out=outcomes; PC=placebo-controlled; PCA=progression of carotid atherosclerosis; PVD=peripheral vascular disease; PPP=The Primary Prevention Project; SAH=subarachnoid hemorrhage; ST=stroke; SU.VI.MAX=Supple´mentation en Vitamines et Minéraux Antioxydants; VE=vitamin E; VC=vitamin C; WHS=Women's Health Study; 2x2=2x2 factorial desing comparing placebo, agent A, agent B, and combinations of agent A and agent B

Table 10. Summary of secondary prevention randomized clinical trials of vitamin E supplementation and CVD

Study	Location and subjects randomized	Design	Main findings, Relative Risk [95%CI, p values]	Inverse association to CVD
WACS 1995-1996 (Cook NR,2007) [103]	USA; n=8171 at high risk; Sex=100%women; A ≥40; Fup-time=9.4 y; IC= 1450	DB, PC, 2x2x2:VE, BC, VC, or placebo; D-VE=600 IU/every other day, natural-source; Out= Combined of MI, ST, coronary revascularization, or CVD death	Combined CVD event: 0.94[0.85-1.04, p=0.23] Ischemic ST: 0.79[0.62-1.01, p=0.06] MI, ST and CVD deaths: 0.90[0.78-1.03, p=0.08] Combined CVD event with prior CVD: 0.89[0.79-1.00, p=0.04]	Yes, only secondary outcomes
SPACE 1997 (Boaz M, 2000) [104]	Israel, multicentre; n=196 hemodialysis patients; Sex=69%men; A=55.6-73.2; Fup-time=519 days; IC=48; MC=23(CVD causes)	DB, PC, 2 groups: VE or placebo; D-VE=800 IU, α-toc natural; Out= Combined endpoint of CVD: MI, ischemic ST, PVD, unstable AP	Combined CVD: 0.46[0.27-0.78, p=0.014] CVD mortality: 0.61[0.28-1.30, p=0.25] Nonfatal MI: 0.35[0.10-1.24, p=0.08] Fatal MI: 0.26[0.06-1.17, p=0.10]	Yes
HATS 1995-1997 (Brown BG, 2001) [113]	n= 160 with coronary disease; Sex=87%men; A=younger than 70 y; Fup-time=3 y; IC=25; MC=2	DB, PC, 2x2 : simvastatin plus niacin, or AO including VE, or both treatment, or placebo; D-VE=800 IU, d- α-toc; Out= Changes in arteriogram and composite CV events: deaths from coronary causes, nonfatal MI or ST, and revascularization	Composite CV event for AO: 1.38, p=0.38 Composite CV event for both treatment: 0.64, p=0.40	No
MRC/BHF 1994 (Group of HPS Collaborative, 2002) [114]	UK, multicentre; n=20 536 at high risk:DM, CAD, PVD; Sex=75.3%men; A=40-80; Fup-time=5.0 y; IC=2110/1270/4618/865	DB, PC, 2x2= placebo vs. combination of VE, BC and VC; D-VE= 600 mg synthetic; Out= major coronary events (nonfatal MI and death from CHD), fatal CHD, major vascular events (major coronary events, ST, coronary or non-coronary revascularisations), and nonfatal ST	Major coronary event: 1.02[0.94-1.11, p=0.7] Major vascular event: 1.0[0.94-1.06, p>0.9] Nonfatal and fatal ST: 0.99[0.87-1.12, p=0.8]	No
HOPE 1994 (Yusuf S, 2000) [115]	Multinacional[1]; n=9541 at high risk; Sex=73.3%men; A=59-73; Fup-time=4.5 y; IC=1511; MC=670 (CV causes)	DB, PC, 2x2 = Ramipril, VE, both, or placebo; D-VE=400 IU, natural; Out= composite outcome of nonfatal MI, nonfatal ST, and CV mortality	Composite: 1.05[0.95-1.16, p=0.33] CV mortality: 1.05[0.90-1.22, p=0.54] Nonfatal MI: 1.02[0.90-1.15, p=0.74] Nonfatal Stroke1.17[0.89-1.13, p=0.13]	No
HOPE-TOO 1994 (Lonn E, 2005) [116]	Multinacional; n=9541 at high risk; Sex=75%men; A=59-73; Fup-time=7 y; IC=1907; MC=957 (CV causes)	DB, PC, 2x2 = Ramipril, VE, both, or placebo; D-VE=400 IU, natural; Out= composite outcome of nonfatal MI, nonfatal ST,and CV mortality, and cancer.	Composite: 1.04[0.96-1.14, p=0.34] CV mortality: 1.02[0.91-1.10, p=0.79] All heart failure: 1.13[1.01-1.26, p=0.03]	No
GISSI 1993 (Gruppo Italiano, 1999) [117]	Italy, multicentre; n=11 324 post-MI; Sex=80.3%men; A=49-70; Fup-time=3.5 y; IC=1500/1155; MC=639(CV causes)	OL, PC, 2x2=VE, PUFA, both, or placebo; D-VE=300 mg, synthetic=330 IU; Out=2 combined endpoints: All-cause death, nonfatal MI and nonfatal ST; and CV death, nonfatal MI and nonfatal ST	All-cause deaths, nonfatal MI and nonfatal ST: 0.89[0.77-1.03, p=ns] CV death, nonfatal MI and nonfatal ST: 0.88[0.75-1.04, p=ns]	No
CHAOS 1992 (Stephens NG, 1996) [105]	UK, single centre; n=2002 CAD; Sex=84.4%men; A=53-71; Fup-time=1.5 y; IC=105; MC=50	DB, PC; D-VE=800 or 400 IU, α-toc natural; Out= Major CV events: combined nonfatal MI and CV death, and nonfatal MI	Major CV event: 0.53[0.34-0.83, p=0.005] Nonfatal MI: 0.23[0.11-0.47, p<0.001] CV mortality: 1.18[0.62-2.27, p=0.61]	Yes
ATBC subgroup 1985 (Rapola JM, 1997) [118]	Southwestern Finland, multicentre; n=1862 smokers, previous MI; Sex=100%men; A=50-69; Fup-time=5.3 y; IC=424; MC=234	DB, PC, 2x2: VE, BC, or both vitamins, or placebo; D-VE=50 mg, dl-α-toc synthetic=55 IU; Out=Major coronary events: nonfatal MI and fatal CHD	Major coronary events: 0.97[0.80-1.19, p=ns] Nonfatal MI: 0.89[0.67-1.20, p=ns] Fatal CHD: 1.05[0.80-1.37, p=ns]	No

[1] Two-hundred and sixty-seven hospitals, physician offices and clinics in Canada, the United States, Mexico, Europe and South America. A=age range; α-toc= alpha-tocopherol; AO=antioxidant; ASAP=Antioxidant Supplementation in Atherosclerosis Prevention ATBC=Alpha-Tocophero, Beta-Carotene Cancer Prevention Study; BC=beta carotene; CEI=cerebral infarction; CHAOS=Cambridge Heart Antioxidant Study; CHD=coronary heart disease; CV=cardiovascular; CVD=cardiovascular disease; CvD=cerebrovascular disease; DB=double-blind; D-VE=dose of vitamin E, typ of vitamin E; Fup-time=follow-up time; GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico; HATS=The HDL-Atherosclerosis Treatment Study; HOPE=The Heart Outcomes Prevention Evaluation Study; HOPE-TOO= The Heart Outcomes Prevention Evaluation Study-the Ongoing Outcomes; IC=incidence cases; ICH=intracerebral hemorrhage; ICD=ischemic cardiovascular disease; IHD=ischemic heart disease; MI=myocardial infarction; MC=mortality cases; MRC/BHF= Heart Protection Study Collaborative Group; n=number of participants; ns=no statistical significant; OL=open label; Out=outcomes; PC=placebo-controlled; PCA=progression of carotid atherosclerosis; PVD=peripheral vascular disease; SAH=subarachnoid hemorrhage; SPACE=Secondary Prevention with Antioxidants of cardiovascular disease in endstage renal disease; ST=stroke; VE=vitamin E; VC=vitamin C; WACS=Women's Antioxidant Cardiovascular Study; WHS=Women's Health Study; 2x2=2x2 factorial desing comparing placebo, agent A, agent B, and combinations of agent A and agent B

Table 11. Summary of metanalysis results of randomised clinical trials

Reference	Studies included	Analysis results
Shekelle PG, 2004 [107]	7 studies: ATBC sub-group, CHAOS, HOPE, MRC/BHF, GISSI, HATS, and SPACE.	VES alone vs. placebo, RRR for fatal MI= 0.97[0.74-1.27] VES plus AO vs.placebo, RRR for fatal MI= 1.02[0.77-1.37] VES alone vs. placebo, RRR for non fatal MI= 0.72[0.51-1.02] VES plus AO vs. placebo, RRR for non fatal MI= 0.99[0.89-1.10]
Eidelman RS, 2004 [106]	7 studies: LIXIAN-1, ATBC, CHAOS, GISSI, HOPE, PPP and MRC/BHF	OR for all CVD event=0.98[0.94-1.03] OR for nonfatal MI=1.00[0.92-1.09] OR for nonfatal ST=1.03[0.93-1.14] OR for CVD mortality=1.00[0.94-1.05]
Vivekananthan DP, 2003 [108]	6 studies: ATBC, HOPE, PPP, GISSI, MRC/BHF and CHAOS.	OR for CVD mortality=1.0[0.94-1.06]; p=0.94 OR for CVA mortality=1.02[0.92-1.12]; p=0.71
Asplund K, 2002 [97]	4 studies: ATBC, LIXIAN-1, PPP and ASAP.	OR for CVD mortality=0.98[0.88-1.04]

ASAP= Antioxidant Supplementation in Atherosclerosis Prevention study; ATBC= Alpha Tocopherol Beta Carotene trial; AO=other antioxidant vitamins; CVA=cerebrovascular accident; CHAOS= Cambridge Heart Antioxidant Study; GISSI= GISSI Prevenzione trial; HATS= HDL-Atherosclerosis Treatment Study; HOPE= Heart Outcomes Prevention Evaluation Study; LIXIAN-1= Lixian Nutrition Intervention general population trial; MI=myocardial infarction; MRC/BHF= Heart Protection Study Collaborative Group; OR=odds ratio; PPP= Primary Prevention Trial; RRR= relative risk ratio; ST=stroke; VES=vitamin E supplementation

1.5 What do we eat? Single nutrients vs. dietary patterns

Under the assumption that a specific nutrient has an independent relationship with a disease, nutrient-based analysis have been done by means of categorization and dosage of nutrient intake. On the other hand, under the hypothesis of existence of an integrated system, or to explain multiple and variety interrelations among nutrients and foods, or the premise “men eat foods, but do not nutrients”, dietary scores or pattern have been built. With regarding to the relationship between vitamin E intake and cardiovascular disease, almost observational studies that analyzed this association showed the categorization of vitamin E intake in relation to the risk for cardiovascular events (tables 7 and 8). In studies of intervention, the supplementation of vitamin E was dosed (tables 9 and 10). Up to date a dietary pattern exclusively rich in vitamin E linked to cardiovascular events has been not yet reported. Furthermore, dietary patterns rich in antioxidant including vitamin E have been reported, but not in relation to CVD. In the table 12 is compiled some findings in regarding to antioxidant scores. One of them was assessed in a control-study [119], and the rest were assessed in cohort studies [120-123]. Only one showed no association between the antioxidant score and outcome .

Table 12. Proposed score of antioxidants

FIRST AUTHOR, YEAR	DESCRIPTION OF SCORE	OUTCOMES	ANTIOXIDANT INTAKE ASSOCIATED TO
Okamoto K and Horisawa R, 2006 [119]	AO intake score: summation of tertile scores from soy products, green yellow-vegetables, fruits, boiled rice and tea intakes.	SAH	↓ RR for SAH
Zhang J et al., 2006 [120]	Composite AO intake score: summation of ranking scores from vitamin C, vitamin E, β-carotene and selenium.	Hip fracture risk	↓ RR for hip fracture among smokers
Wright ME et al., 2004 [121]	Composite AO index: summation of PCA scores from flavonoids, carotenoids and vitamin E, plus vitamin C and selenium.	Lung cancer risk	↓ RR for lung cancer
Laurin D et al., 2004 [122]	Combined AO index: summation of Z score of β-carotene, vitamin C, vitamin E, and flavonoids.	Dementia risk	No association
Van Hoydonck PG, 2002 [123]	Oxidative balance score: vitamin C, β-carotene and iron. The lowest oxidative balance score group: smokers with a diet relatively high in AO and/or low in PRO. The highest oxidative balance score group: smokers with a diet relatively low in AO and/or high PRO. The intermediate oxidative balance score group: smokers with a diet either low AO and low PRO or high AO and high PRO.	All-cause, cancer and CVD mortality risk	↓ RR for all-cause and total cancer mortality

AO=antioxidant; CVD=cardiovascular disease; PCA=principal component analysis; PRO=pro-oxidant; RR=relative risk; SAH=subarachnoid hemorrhage

Epidemiological evidences about a posible role of antioxidants have been reported. A meta-analysis have suggested that high dietary intake of flavonols from a small number of fruits and vegetables, tea and red wine may be associated with a reduced risk from CHD mortality [124]. On the other hand, flavonols and flavones are not associated with the risk for ST [125-127]. Results of The Pooling Project of Cohort Studies on Diet and Coronary Disease from nine major cohort studies suggest that higher intake of vitamin C including supplementation is associated with lower CHD rates [98]. Most cohort studies had reported that higher intake of β-carotene is inversaly related to CVD [128]. A recent analysis reported that serum beta-carotene and vitamin C concentrations were positively correlated with consumption of both fruit and vegetables [129]. Another metanalysis of cohort studies confirmed the relation between higher antioxidants intake and prevention of CHD risk [130].

1.6 Aims and research questions

This study investigates the relationship between the dietary vitamin E intake and the risk of CV events, specifically MI, ST and TIA, in the EPIC-Potsdam cohort study. The aims are to give answers to the following questions:

– Which food groups are the main sources of vitamin E? How much of them explain the estimated vitamin E intake?
– Is there a relationship between vitamin E and CV events? Is there an inverse association with the risk for CVD?
– Does a food pattern rich in vitamin E represent the dietary vitamin E intake? Does a food pattern rich in antioxidants, i.e. vitamin E, vitamin C, flavonoids and beta-carotenoids, represent the dietary antioxidant intake?
– Does a food pattern rich in vitamin E has an inverse association with the risk for CV events?
– Does a food pattern rich in antioxidants, i.e. vitamin E, vitamin C, flavonoids and beta-carotenoids, has an inverse relationship with CV events?
– Which socio-demographic, anthropometric and dietary factors are associated with both dietary vitamin E intake and CV events?

2 MATERIAL AND METHODS

2.1. The EPIC-Potsdam Study

2.1.1 The EPIC-Study and the EPIC-Potsdam Study, a general description

The EPIC-Study is an ongoing large multi-center prospective cohort study designed to investigate relationships between diet and cancer as well as other chronic diseases. The EPIC-Study was initiated in 1992 and is coordinated by the International Agency for Research on Cancer (IARC) of the WHO in Lyon, France. The study includes over half a million participants, men and women, generally aged 35-70 years, and from 23 centers located in 10 European countries (Greece, Spain, Italy, France, Germany, Netherlands, United Kingdom, Denmark, Sweden, and Norway). The german contribution to EPIC-Study compilated about 53,000 participants from two centers, Potsdam and Heidelberg [131].

The EPIC-Potsdam study was also designed to contribute to the investigation into the diet and chronic disease in general such as MI, diabetes and ST. The recruitment phase in EPIC-Potsdam Study was from August 1994 to September 1998 and was based on addresses from general population registries. Details about the recruitment procedures have been reported previously. In brief, a total of 27,548 subjects (10,904 men and 16,644 women) were recorded and the participation rate was 22.7%. A first comparison with a reference population showed that the EPIC-Potsdam cohort population had more favorable socio-economic status and health-related indicators than the reference population [132, 133] Therefore, this was noted that the EPIC-Potsdam participants have a chance to maintain in the study during the follow-up time.

2.1.2 Baseline examination

Data collection included questionnaires, interviews and physical examinations as listed in table 13. It was organized in the following way: self-administrated questionnaires for optical reading with immediate computerized check for completeness; PC-guided, menu-controlled interactive interviews to clarify information immediately with the participant; immediate double data input of physical examinations.

Table 13. EPIC-Potsdam cohort study instruments and requested type of exposure variables

INSTRUMENT	EXPOSURE VARIABLES
Self-administered questionnaires	
Food Frequency questionnaire	Frequency and quantity of food consumption, use of sauce and fat, regular use of supplements.
Lifestyle questionnaire	Family status, education, educational attainment, occupational status, physical activity at work, history of alcohol consumption, Women: age at menache, regularity and length of menstrual cycle, menopause, number of children, breast feeding, oral contraception use, hormone replacement therapy, pregnancy.
PC interviews	
PC-guided, menu-controlled interactive interview	Occupation, smoking history, physical activity in winter and summer, weight history, subjective health situation, medical anamnesis, surgery, diet, reproductive history, including pregnancies, use of medication during the previous 4 weeks.
Physical examinations	
Anthropometry	Height, weight, waist and hip circumference, sitting height, skinfold measurements, chest breadth and depth.
Blood pressure measurements	Three blood pressure readings with 2-min intervals by automatic devices (Boso oscillomat®), pulse rate.

2.1.2.1 Dietary assessment

In EPIC, the assessment of dietary intake was divided into two parts, the main study assessing the habitual dietary intake by means of the self-administered FFQ and the calibration study assessing short-term dietary intake of the previous day by means of a 24HR. The FFQ assessed the usual food and nutrient intakes of participants during the 12 months prior to the examination. Details on the validity and reproducibility of the questionnaire have been

previously published [70, 134-137]. The FFQ included 148 single food items and questions on specific aspects of diet, such as food preparation methods. Photographs and standard portion sizes were used to support the estimation of portion sizes. Frequency of intake was measured using 10 categories, ranging from “never” to “five times per day or more”. The information on portion sizes and frequency of food intake was used to calculate the amount of each food item consumed per day, on average. Subsequently, the food items of the FFQ were aggregated into 49 separate food groups by Schulze et al (see Appendix 1) [138].

2.1.2.2 Assessment of other characteristics

2.1.2.2.1 Socio-demographic, lifestyle and medical history

Information about socio-demographic features such as family status, education level and occupation, lifestyle factors such as smoking and drinking habits, physical activity, weight history, subjective health and life situation, and also medical history such as medical anamnesis, surgical history, diet, reproductive history in women including pregnancies, and the use of medication during the previous 4 weeks was obtained by means of either self-administered questionnaires or personal computer-assisted interviews. The assessment followed the EPIC protocol for quality control [139].

2.1.2.2.2 Anthropometry

Data on body weight, height, waist and hip circumference, sitting height and skinfold measurement of the participants were collected following instructions of the anthropometric EPIC protocol for quality control [139]. BMI was calculated as body weight in kg divided by the square of body height in m.

2.1.3 Follow-up and case ascertainment

The EPIC-Potsdam follow-up is based on a combination of methods including local registries and active follow-up through study participants and their next of kin. In order to classify cardiovascular events the 10th Revision of the International Statistical Classification of Diseases was used (ICD Codes: I21, I211, I212, I213, I229, I609, I619, I630, I632, I634, I635, I639, I64, I640 and G45) [140]. By the end of April 2006, 2740 cardiovascular events (i.e., MI, ST and TIA) has been reported to the EPIC-Potsdam database. Having set the censored date to April 2006 and after exclusion of non-verified cases by medical diagnostic certification or dead certificates, 550 cases with verified diagnoses remained and were available for this analysis. Of those, 197 were MI, 201 were ST and 152 were TIA. Subjects with a diagnosis before and/or after the censoring date were not included.

2.2 Study design

For the present analysis, 25,765 subjects from EPIC-Potsdam cohort study without prevalent CVD were used, 10,085 men and 15,680 women.

2.2.1 Exclusion criteria

To identify a specific relationship between vitamin E intake and the risk for CV event some previous exclusion criteria were applied:

- subjects with incomplete dietary assessment,
- subjects with incomplete non-dietary information, and
- subjects with no follow-up time.

In total 1,851 subjects were excluded.

2.2.2 Outcomes: case ascertainment and verified-cases

For the analysis, the following fatal and non-fatal CV events as outcomes were separately considered:

- 185 MI (ICD-10th codes: I21, I211, I212, I213, and I22),
- 179 ST (ICD-10th codes: I609, I619, I630, I632, I634, I635, I639, I64, and I640), and
- 138 TIA (ICD-10th code: G45).

All CV events were considered, for subjects who had more than one outcome event, only the first event occurred in the follow-up time was considered. In total, there were 484 fatal and non-fatal CV events.

As the number of deaths was small, non-fatal and fatal events were analyzed together. The end of the follow-up was determined by either the occurrence of any CV event (verified MI, ST or TIA fatal and non-fatal event) or censoring (last complete follow-up).

2.2.3 Definition of nutrient variables

Food intake was recorded and dietary instruments have previously been defined in the section **2.1.2.1**. Values for nutrients were derived from the German Food Code and Nutrient Date Base [141].

The present analysis concentrates on vitamin E intake that was calculated as α-tocopherol equivalent (α-TE, mg), following the German References for Nutrient Intake. For comparison purpose the vitamin E intake as α-tocopherol was also calculated, following the USA References for Nutrient Intake. The α-TE is a measure that takes into account the

weighted intake of α-, β-, γ- and δ- tocopherol as well as α- and β-tocotrienol, as follow: α-TE = α-tocopherol + 0.5β-tocopherol + 0.1γ-tococopherol + 0.03δ-tocopherol + 0.3α-tocotrienol + 0.05β-tocotrienol [29].

The vitamin E content on each food group of the study participants was computed by multiplying the frequency of intake, portion size and vitamin E content. The total intake of vitamin E estimate of the study participants was defined as the sum of the vitamin E content in all 49 food groups [138]. In the same way the total nutrient intake was computed for the following nutrients:

- vitamin C as mg of ascorbic acid,
- β-carotenoid as mg equivalent,
- and flavonoids (quercetin, epicathechin, luteolin, kaempferol, myricetin, genistein, cyanidin, delphinidin, malvidin, peonidin, and petunidin) as mg.

These nutrients were considered in this analysis.

2.3. Statistical analysis

All statistical analyses were conducted with the SAS System® for Windows™ release 8.00 (SAS Institutes Inc., Cary, North Carolina, USA) applying descriptive and analytic methods described in the following. A p value <5% was considered statistically significant, exceptions are specified.

2.3.1 Descriptive analysis

To describe the general characteristics of population the following analyses were done:

- continuous ordinal variables: arithmetic mean and standard deviations, and
- ordinal, nominal and dummy variables: relative frequencies.

Differences by gender were tested for significance. For non-normal distributed variables gender comparisons were performed by means of Mann-Whitney U test. For categorical variables gender comparisons were performed by means of Pearson's X^2 test. Comparisons between categorized variables (quintiles) were performed by linear trend regression for continuous variables and by Pearson's X^2 test for categorical variables. Significance levels of linear trends were based on F-tests. Linear trends were evaluated by assigning ordinal scores to each successive quintile and treating the variable as continuous in the regression model. Correlations among variables were evaluated by Pearson's correlation coefficients.

2.3.2 Energy adjustment and categorization

The distribution of dietary intake of vitamin E was checked for normality. Data transformations applied to achieve approximately normal distributed dietary variables [142]. However, in this analysis both logarithm and square root transformations did not result in an approximate normal distribution of the vitamin E intake. It is known that lipid vitamins such vitamin E and carotenoids are correlated to total energy intake, therefore, it was assumed that the relationship between vitamin E intake and total energy intake is linear. Thus, using the following methodology a standardized distribution of the vitamin E intake was obtained. In order to control some influence of total energy intake on the estimated vitamin E intake an adjustment for total energy intake by the residual method was done. The energy-adjusted vitamin E intake variable was defined as residuals derived from a linear regression model of total vitamin E intakes on their total energy intakes of the individuals. This new variable, energy-adjusted-vitamin E intake (mgTE*kJ/day), was normally distributed and stands for the differences between each individual's actual intake and the intake predicted by their total energy intake [143, 144]. It has been suggested that adjustment for total energy intake reduces measurement error in FFQ [145] and improves stability in multivariate models [146]. Additional, residuals were ranked on the basis of quintiles using the SAS macro %dummy (data, continuous variable, number of categories).

Similar pre-treatment analyses to other nutrients such vitamin C, flavonoids, and beta carotenoids were applied.

2.3.3 Stepwise linear regression deriving food groups to explain the variance in the vitamin E intake

For identifying food groups explaining most of the variance in the vitamin E intake a stepwise regression was conducted. Based on regression analysis, a dependent variable is predicted by independent variables. The stepwise selection method allowed the choice of predictive independent variables depending on their contribution to explanation of variance of the dependent variable. The stepwise selection method is a combination of the forward and backward selection methods, testing at each stage for independent variables to be included or excluded into the model. The stepwise process finishes when none of the variables outside the model has an *F* statistic significant at the level of significance to entry, i.e. $p < 0.05$ and every variable in the model is significant at the level of significance to stay in the model, i.e. $p < 0.15$. In this analysis, the total vitamin E estimated from all foods was defined as the dependent variable and the contents of vitamin E intake for each one of the 49 food groups compiled by Schulze et al [138] were used as independent variables. The percentage of variance of vitamin E intake explained by each food group was given by the coefficient of determination (R^2). This was the statistical criterion to define the contribution of each food group for explaining the variance of vitamin E intake. The food group with the highest R^2 is named the first contributor, and all contributors represent the best set of food group predictors of vitamin E intake. Food groups which explain at least 60% of variance in vitamin E intake were considered to be the best set of predictors.

To describe major sources of vitamin E in the EPIC-Potsdam cohort the average percentage contribution to vitamin E intake in each food group was examined. A ranked list of the contribution of food groups to vitamin E intake was generated based on procedures described by Block et al [78]. The percentage contribution to absolute vitamin E intake in each food group was compared to their R^2 derived by stepwise linear regression model. In this analysis

for comparison purpose both non-adjusted vitamin E intake and energy-adjusted-vitamin E intake were examined.

2.3.4 Stepwise linear regression deriving fat components to explain the variance in the vitamin E intake

In order to obtain the best set of fat components related to vitamin E intake, a similar method described in the previous section **2.3.3** was done. Energy-adjusted vitamin E intake was the dependent variable and intakes from fat contributors such as glycerol, cholesterol, saturated fat, PUFA, monounsaturated fats and the ratio of PUFA/saturated fat were defined as independent variables.

2.3.5 Reduced rank regression model deriving food groups rich in antioxidants

Reduced rank regression model has been introduced as a linear multivariate reduction method which can be used in nutritional epidemiology as a method to build dietary pattern [147]. It summarizes a reduced rank regression model:

– first, multiple responses are regressed to multiple predictors,

– and secondly, some latent variables or factors are generated explaining as much response variation as possible linearly.

Response variables were selected by a priori-criterion that these variables are known as antioxidants and they have also a possible effect to prevent cardiovascular disease (disease-related antioxidants): vitamin E, vitamin C, β-carotenoid, and flavonoids. In this analysis, flavonoids were defined as the sum of residuals from quercetin, epicathechin, luteolin, kaempferol, myricetin, genistein, cyanidin, delphinidin, malvidin, peonidin, and petunidin intakes regressed on total energy intake. Based on the 49 food groups defined by Schulze et al [138], in this analysis vegetables (raw and cooked vegetables, cabbage, and vegetarian

dishes), fruits (fresh and canned fruit, and fruit juice) and dairy products (low- and high-fat dairy products) were grouped together (see Appendix 1 and 2). Total intake of each one of the resulting 43 food groups were considered as predictors, then 43 predictors were included in this model. For this analysis, only three factors (response and predictor) were considered an appropriate pre-specified number of factors to generate.

The reduced rank regression method implemented in PROC PLS is an attempt to derive factors to predict the responses linearly. Response and predictor factors were generated in which either response or predictor variables were reflected. The first factor obtained by reduced rank regression was retained for subsequente analysis because it explains the largest amount of variation among response variables (Appendix 3, SAS program).

2.3.6 Constructing food patterns (FPs)

Following methodologies previously used by Schulze et al [148] and Schulz et al [149] two FPs were derived, one FP rich in vitamin E and the other one FP rich in antioxidants.

To construct the FP rich in vitamin E, the top ten food groups which explained most variance in energy-adjusted vitamin E obtaining by a linear regression model (described previously in section **2.3.3**) were taken into account. The intake of these food groups was standardized with mean zero and one unit standard deviation. The FP rich in vitamin E is the sum of standardized intake of the top ten food groups, five food groups being directly associated with the vitamin E intake and five food groups being indirectly associated with the vitamin E intake. For food groups showing a negative parameter estimate in the linear regression model, a negative algebraic sign was assigned to the corresponding food groups in the calculation of the food pattern variable.

Firstly, in order to construct the FP rich in antioxidants, the best set of food groups which explain most variance of the response factors was derived using a linear regression model (Appendix 3). The first response factor was regressed to the 43 food groups and then by stepwise selection method the top twelve food groups which explain more variance in the first response factor were retained. Secondly, the total intake of these food groups was standardized with mean zero and one unit standard deviation. The FP rich in antioxidants is defined as the sum of standardized intake of the top twelve food groups, six food groups being directly associated with the selected response factor and six food groups being indirectly associated with the selected response factor. For food groups showing a negative parameter estimate in the linear regression model, a negative algebraic sign was assigned to the corresponding food groups in the calculation of the FP variable.

Participants were categorized based on the quintiles of FP rich in vitamin E and also on the quintiles of FP rich in antioxidants using the SAS macro %dummy (data, continuous variable, number of categories). A higher score indicated that the individual ate foods directly associated with the FP more frequently than a person with a lower score. Pearson's correlation coefficients among FP rich in vitamin E, FP rich in antioxidants, non-adjusted and energy-adjusted-vitamin E intake and the other nutrients variables were calculated.

2.3.7 Cox's Proportional Hazard Model

In the analysis of survival data, the Cox's model is a well-recognised statistical technique. It is a semiparametric model that does not require a particular probability distribution to represent survival times and is considered as a robust method. Cox's proportional hazard model is based on the assumption that the hazard function for a subject depends on the values of the covariates and the value of the baseline hazard. In the Cox's model, the method of maximum partial likelihood is used to estimate the parameters which are estimated without specifying the baseline hazard function $\lambda_0(t)$. The Cox's model is represented as (1),

Equation= $\lambda_i(t) = \lambda_0(t) \exp \{ \beta_1 x_{i1} + ... + \beta_i x_{ip} \}$ (1),

where $\lambda_i(t)$ is the **hazard function** for the ith subject, $\lambda_0(t)$ is the baseline hazard function, and β_1 ,…, β_p are unknown lineal regression parameters associated with the explanatory variables. The **hazard function** is the probability that an individual will experience an event within a small time interval, given that the individual has survived up to the beginning of the interval. It is computed as the number of failures per time units in the respective interval, divided by the average number of surviving cases at the mid-point of the interval [150].

In order to evaluate the association between either vitamin E intake or food patterns and risk of cardiovascular outcomes, hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox's proportional hazard modelling within the framework of the counting process were calculated. In the counting process, the subject's age was used as the primary time variable and a subject remains at-risk during the following time interval, entry time t_0 defined as the subject's age at recruitment and exit time t_1 defined as the subject's age at diagnosis of cardiovascular outcomes or censoring date. Providing input data to PROC PHREG (SAS/STAT®, v.8) in counting process format allows to adapt time-dependent covariates and discontinuous intervals of risk. Then an extension of the Cox regression model handle to time-dependent variable was done [151].

In the proportional hazard Cox's model, the chi square goodness-of-fit value is computed as a function of the log-likelihood for the model with all covariates and the log-likelihood of the model in which all covariates are set to zero. If this X^2 value is significant, we reject the null hypothesis and assume that the independent variables are significantly related to survival times. Goodness-of-fit was also tested by the log-likelihood ratio test examining the change in the -2 logL statistic from the full to the reduced model according to the change in the degrees of freedom of the models [150].

To determine whether Cox's regression models adequately described the data, some model diagnostics were done. To test proportional hazard assumption, a diagnostic based on weighted Schoenfeld residuals was run. For each covariate in the model, a smoothed plot of

(vector of weighted Schoenfeld residuals *plus* coefficient β_p) versus the difference (t_1-t_0) was done. A zero slope indicates that the coefficient is not varying with time [151].

The significance of linear trends across quintiles of either vitamin E intake or FP was tested by assigning each participant the median value for the quintile and modelling this value as a continuous variable.

In addition, the association between either vitamin E or simplified dietary patterns and risk for CV outcomes was performed into the following groups: age categories, users of vitamin E supplements and non-users of vitamin E supplement, smokers and non-smokers, subjects with high and low intakes of PUFA/saturated fat ratio. Evaluation of outliers influence was also tested by evaluation of residuals.

2.3.8 Covariates of the multivariate model

In order to identify variables that could be included into the multivariate model, three different evaluations were done:

- For each defined outcome, a logistic regression, using all potential independent variables and cardiovascular risk factors, was done to predict the event.
- The known factors associated with vitamin E were regressed on energy-adjusted-vitamin E intake using linear regression model and stepwise selection.
- All potential cardiovascular risk factors and known factors associated with vitamin E were independently tested in Cox regression models.

These results were compared. Two aspects were taken into account to select covariates included in the multivariate model: reports of previous epidemiologic studies and the reduction of multi-collinearity among variables.

The following covariates were selected: sex, education (no or primary school; more than primary school), BMI categories (<25; 25-30; >30kg/m^2), WHR (>0.8 women; >0.9 men), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, vitamin E supplementation users at baseline and follow-up (yes/no).

3. RESULTS

3.1. Baseline description

In this analysis 25,765 subjects from the EPIC-Potsdam cohort were included. The age in the population study was 50±9 years, 33.9% of the subjects were younger than 45 years, 28.4% were between 45 to 55 years, and 37.7% were more than 55 years. Within the total population, women outnumbered men by a proportion of 1.5 (15,680 women compared with 10,085 men).

3.1.1. Vitamin E intake distribution

With regard to vitamin E as α-TE, among all subjects of the EPIC-Potsdam cohort the mean (± standard deviation) was 11.69 ± 4.1 mg/d. The difference between men and women on the vitamin E intake distribution was statistically significant (non-parametric, Mann-Whitney-U-Test, $p<0.0001$). The mean and standard deviation of vitamin E intake for men was 12.53 ± 4.3 mg/d and for women was 11.15 ± 3.9 mg/d, men and women, respectively were the mean and standard deviation of vitamin E intake. An asymmetric distribution characterized the vitamin E intake, the skewness was 1.37301 and kurtosis was 4.2224. The difference between the highest and the lowest intake values for vitamin E in the population study was 52.48 mg/d (range). The percentage of relative variability of vitamin E intake data distribution around the mean was 35.08% (coefficient of variability).

A description of vitamin E intake distribution as α-TE and as energy-adjusted vitamin E is shown in the table 14. Residual scores from the regression of vitamin E intake on total energy intake were defined as energy-adjusted vitamin E intake. These residuals were normally

distributed. In the overall cohort, 65.2% of the participants were below Germans Adequate Intake for vitamin E.

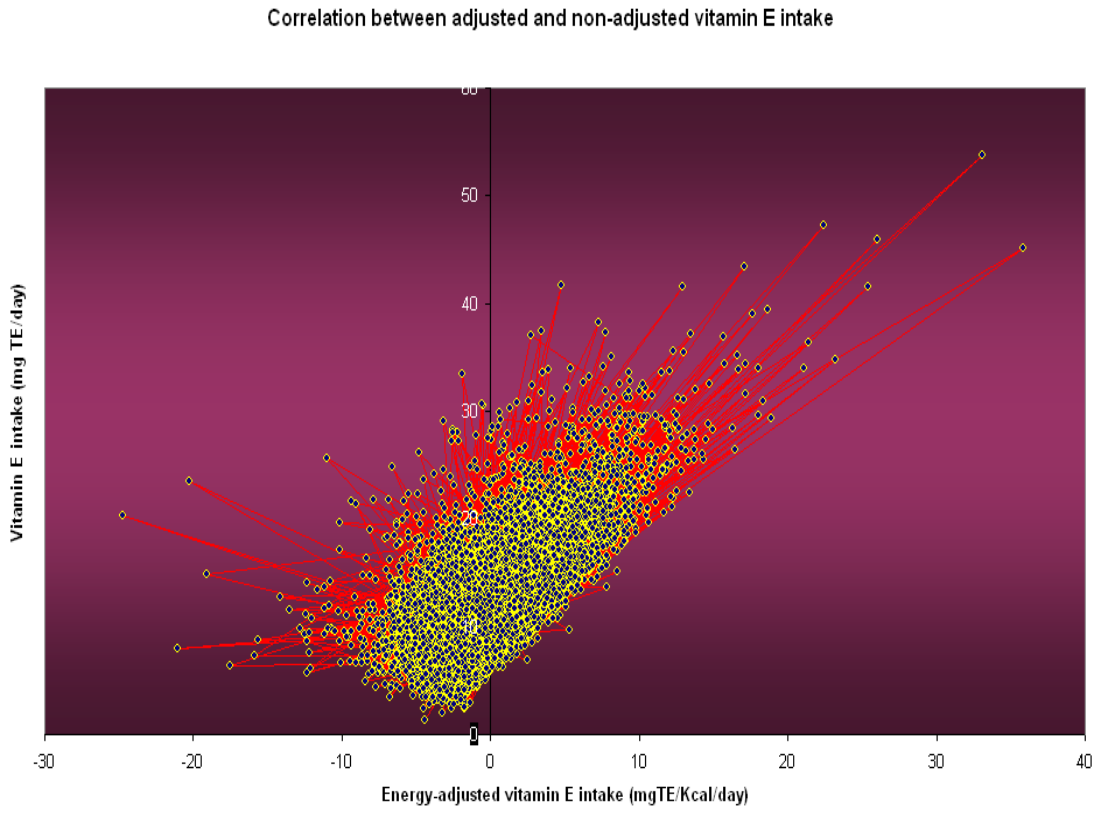
Table 14. Description of the vitamin E intake of cohort population EPIC-Potsdam (n=25765) at baseline, all and by gender

		MEAN	STANDARD DEVIATION	% BELOW AI*
α-TE(mg/d)	**ALL**	11.69	4.1	65.20
	M	12.53	4.3	64.69
	W	11.15	3.9	65.54
EA-VE (mg/d/kJ)	**ALL**	0.00	2.8	-
	M	-0.61	2.9	-
	W	0.39	2.6	-

*acording to German reference [30]. AI=Adequate Intake; EA-VE=energy-adjusted vitamin E intake; M=men; α-TE =alpha-tocopherol equivalent; W=women

For all participants, mean (± standard deviation) of energy-adjusted vitamin E intake was 0.00 (± 2.8) mg/d/kJ. Scores of energy-adjusted vitamin E intake were distributed from -17.4 to 38.87, median was negative (-0.23) and the mode was -2.99166. The energy-adjusted vitamin E intake distribution showed a skewness of 0.9 and a kurtosis of 6.2. Figure 1 shows raw and energy-adjusted vitamin E intake distributions for the whole cohort study. Differences by gender were found, mean (± standard deviation) of the energy-adjusted vitamin E intake for men was -0.61 (± 2.9) mg/d/kJ and for women was 0.39 (± 2.6) mg/d/kJ.

Figure 1.



3.1.2. General characteristics of the study population across energy-adjusted vitamin E intake

Table 15 shows the EPIC-Potsdam cohort study characteristic across quintiles of energy-adjusted vitamin E intake. Higher quintiles of energy-adjusted vitamin E intake were associated with lower age. In the fifth quintile of energy-adjusted vitamin E intake approximately 38% were younger than 45 years. Women predominated in higher scores of energy-adjusted vitamin E intake. Subjects with a higher education, non-current smoking habits, lower and intermediate alcohol consumption, more time in sport activity and users of vitamin E supplements were in the highest scores of energy-adjusted vitamin E intake. With regard to BMI, the highest percentage of obesity (>30kg/m^2) was found among subjects of the highest quintile of energy-adjusted vitamin E intake. The lowest quintile of energy-adjusted vitamin E intake showed more subjects with higher level of WHR (women>0.8;men>0.9) and more subjects who also had either SBP>140 mmHg or DBP>90 mmHg.

Table 16 shows the EPIC-Potsdam cohort study characteristics across quintiles of energy-adjusted vitamin E intake by gender. The percentage of men who were older than 55 years increased across quintiles of the energy-adjusted vitamin E intake, whereas the percentage of women who were younger than 45 years old increased across quintiles of the energy-adjusted vitamin E intake. More men with either SBP>140 mmHg or DBP>90 mmHg had lower scores of energy-adjusted vitamin E intake. In contrast, more women with SBP>140 mmHg had lower scores of energy-adjusted vitamin E intake. Among men the use of vitamin E supplementation was associated with higher scores of energy-adjusted vitamin E intake, but not in women. In view of gender, the WHR and prevalence of diabetes, hypertension and hyperlipidaemia did not associate with energy-adjusted vitamin E intake. All other characteristics were similar to the overall cohort.

Table 15. General features of cohort population in EPIC-Potsdam (n=25765) across quintiles of energy-adjusted vitamin E intake at baseline*

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	
EA-VE	-3.41±1.4	-1.37±0.3	-0.24±0.3	1.03±0.4	3.97± 2.3	**P values**
Age categories, %						
<45year	31.59	33.53	33.30	33.28	37.71	<.0001
45-55 years	31.17	28.80	28.14	27.91	26.20	
>55 years	37.24	37.67	38.56	38.81	36.10	
Gender, men %	60.62	37.69	33.61	31.38	32.41	<.0001
Education, secondary school and higher, %	58.04	61.93	62.29	62.12	61.79	<.0001
BMI, %						
< 25 kg/m^2	40.79	42.41	42.96	42.75	42.71	0.0142
25-30 kg/m^2	41.98	40.87	39.74	40.02	39.05	
>30 kg/m^2	17.23	16.73	17.29	17.23	18.25	
WHR, %						
W>0.8/M>0.9	63.50	53.93	52.15	52.46	52.85	<.0001
Time of sport activity, (%)						
>2 hours/week	19.10	21.29	22.49	23.25	24.65	<.0001
Smoking status, (%)						
Current smoker	30.58	22.14	17.99	16.90	15.99	<.0001
Alcohol consumption, %**						
Lower	32.78	42.27	44.69	46.30	47.55	<.0001
Intermediate	31.36	37.34	39.08	38.62	38.99	
Higher	35.86	20.40	16.22	15.08	13.47	
Vit-E suppl, %	14.94	19.52	20.32	21.17	20.49	<.0001
SBP, %						
>140 mmHg	29.01	23.10	22.88	22.81	22.10	<.0001
DBP, %						
>90 mmHg	31.05	26.47	25.40	24.57	24.91	<.0001
Diabetes, %	4.60	5.22	5.47	5.55	5.24	0.2130
Hyperlipidaemia, %	28.29	27.54	29.30	29.15	28.37	0.2702

*continuous variables: means ± standard deviation; categorical variables:percentage. **alcohol consumption categories: Lower: W=abstiners or <5 g/d, M= <10g/d; Intermediate: W=5-15g/d, M=10-30g/d; Higher: W=>15g/d, M= >30g/d. BMI=Body-Mass-Index; DBP=diastolic blood pressure; EA-VE=energy-adjusted vitamin E; M=men; n=number of persons; SBP=systolic blood pressure;Vit-E suppl=vitamin E supplementation; W=women;WHR=waist-to-hip-ratio

Table 16. General features of cohort population in EPIC-Potsdam (n=25765) across quintiles of energy-adjusted vitamin E intake at baseline, by gender*

		Q1	Q2	Q3	Q4	Q5	
EA-VE (n)	M	-4.31±1.6 (2016)	-2.1± 0.4 (2016)	-0.80 ± 0.4 (2016)	0.57 ± 0.5 (2016)	3.59 ± 2.2 (2016)	**P values**
	W	-2.60 ± 1.1 (3135)	-0.97 ± 0.3 (3135)	0.06 ± 0.3 (3135)	1.28 ± 0.4 (3135)	4.20 ± 2.4 (3135)	
Age categories,%							
<45year	M	28.46	25.83	23.85	23.75	24.84	<.0001
45-55 years		33.07	30.39	32.33	29.05	30.94	
>55 years		38.47	43.78	43.83	47.20	44.22	
	W	38.04	38.87	8.39	37.98	43.59	
		28.95	26.63	27.23	26.15	24.52	<.0001
		33.00	34.50	34.38	35.87	31.89	
Education, secondary school and higher, %	M	58.01	66.39	69.31	69.31	66.44	<.0001
	W	55.84	57.49	58.99	58.83	60.04	0.0089
BMI, %							
< 25 kg/m^2	M	33.07	29.70	28.66	26.47	29.45	0.0024
25-30 kg/m^2		48.88	52.45	52.95	55.63	51.71	
>30 kg/m^2		18.05	17.85	18.39	17.90	18.84	
	W	53.64	50.35	51.08	48.60	49.30	0.0142
		31.63	31.82	32.88	33.90	32.84	
		14.73	17.83	16.04	17.51	17.86	
WHR, %							
>0.9	M	77.88	76.04	75.15	76.64	75.74	0.3092
>0.8	W	41.47	40.48	40.61	42.01	41.80	0.6431
Time of sport Activity, %							
>2 hours/week	M	18.39	22.01	23.40	23.70	24.64	<.0001
	W	19.16	20.79	21.40	23.60	24.94	<.0001
Smoking status, %							
Current smoker	M	37.23	25.93	23.15	20.33	18.94	<.0001
	W	24.90	18.24	16.71	15.08	14.54	<.0001
Alcohol consumption, %**							
Lower	M	22.46	29.95	35.40	37.68	41.94	<.0001
Intermediate		30.44	41.05	44.72	45.81	42.98	
Higher		47.10	29.00	19.88	16.51	15.07	
	W	46.21	48.34	48.69	50.26	49.78	<.0001
		29.11	33.99	37.02	35.33	37.31	
		24.68	17.67	14.29	14.41	12.91	
Vit-E suppl, %							
	M	11.55	14.97	14.92	18.34	17.35	<.0001
	W	20.44	22.03	21.72	22.51	22.16	0.3207
SBP, %							
>140 mmHg	M	35.75	35.99	35.10	34.11	31.23	0.0092
	W	17.47	15.75	17.03	18.62	17.38	0.0536
DBP, %							
>90 mmHg	M	38.72	37.73	37.33	36.34	34.66	0.0822
	W	19.99	19.16	19.61	19.80	20.15	<.0001

*continuous variables: means ± standard deviation; categorical variables:percentage. **alcohol consumption categories: Lower: W=abstiners or <5 g/day, M= <10g/day; Intermediate: W=5-15g/day, M=10-30g/day; Higher: W=>15g/day, M= >30g/day. BMI= Body-Mass-Index; DBP=diastolic blood pressure; EA-VE=energy-adjusted vitamin E intake; M=men; n=number of persons; SBP=systolic blood pressure;Vit-E supl=vitamin E supplementation; WHR=waist-to-hip-ratio; W=women

With regard to dietary characteristic of the EPIC-cohort, table 17 shows main dietary features related to vitamin E intake. In the overall cohort the mean (± standard deviation) of total energy intake was 8913.98 (± 2903.84) kJ/d. A significant difference by gender for the total energy intake was found. The mean contribution of carbohydrates, protein, and fat to the total energy intake were 41.5, 15.0, and 43.6 % in men and 46.0, 14.5, and 39.2% in women. The mean (± standard deviation) of Basal Metabolic Rate was 6.47 (± 0.98) kcal/d, and also difference among men and women was found, 7.49 (± 0.65) kcal/d and 5.81 (± 0.44) kcal/d, men and women respectively. Except for PUFA/saturated fats ratio, the other fat components of the diet showed a statistically significant difference by gender. Men had a higher consumption of PUFA, saturated and monounsaturated fats, cholesterol and glycerol than women. The mean (± standard deviation) of the PUFA/saturated fatty acids ratio in all subjects was 0.45 (± 0.15).

Table 17. Main dietary features related to vitamin E intake in the cohort population EPIC-Potsdam (n=25765) at baseline, all and by gender*

DAILY ENERGY AND NUTRIENT INTAKE	ALL	MEN	WOMEN
Total energy intake, kJ/d	8913.98 ± 2903.84	10310.19 ± 3024.93	8015.81 ± 2431.14
Carbohydrate contribution,%	45.45 ± 6.39	43.87 ± 6.39	46.46 ± 6.18
Protein contribution, %	14.62 ± 2.24	14.54 ± 2.19	14.67 ± 2.26
Fat contribution, %	35.51 ± 5.45	35.21 ± 5.64	35.71 ± 5.32
Alcohol contribution, %	4.41 ± 4.86	6.38 ± 5.67	3.15 ± 3.76
BMR, kcal/d	6.47 ± 0.98	7.49 ± 0.65	5.81 ± 0.44
PUFA, g/d	14.61 ± 6.09	16.68 ± 6.62	13.28 ± 5.31
Saturated fats, g/d	34.11 ± 14.57	38.94 ± 15.95	31.00 ± 12.67
MONO, g/d	28.67 ± 11.64	33.37 ± 12.81	25.65 ± 9.69
Cholesterol, mg/d	0.31 ± 0.13	0.35 ± 0.14	0.28 ± 0.11
Glycerol, mg/d	5.59 ± 2.04	6.40 ± 2.22	5.07 ± 1.72
PUFA/ saturated ratio	0.45 ± 0.15	0.45 ± 0.15	0.45 ± 0.15
Fiber, mg/d	21.65 ± 22.53	23.12 ± 23.98	20.76 ± 21.59

*means ± standard deviation. BMR=Basal metabolic Rate; MONO=monounsaturated fats; PUFA=polyunsaturated fats; PUFA/saturated ratio=ratio of polyunsaturated fatty acids/ saturated fatty acids

3.1.3. Vitamin E and fat

Fat contribution to total energy intake was correlated to vitamin E intake, i.e., Pearson´s correlation; r=0.89, p<0.0001. Table 18 shows the contribution of different types of fats to vitamin E intake as α-TE and energy-adjusted vitamin E in different models. Main fat contributors to α-TE were PUFA, monounsaturated fatty acids and glycerol, whereas main fat contributors to energy-adjusted vitamin E were PUFA and monounsaturated fatty acids (model 1 for α-TE and energy-adjusted vitamin E). The inclusion of the PUFA/saturated fat ratio in the model 2 influenced only the model where the energy-adjusted vitamin E was the dependent variable. The PUFA/saturated fats ratio, PUFAs and glycerol showed a positive contributions to vitamin E, however glycerol had the lowest regression coefficient. The 39.84% of the variability in the energy-adjusted vitamin E intake was explained by the PUFA/saturated fats ratio, even though PUFA and saturated fats were excluded of the Model 2. In addition, the PUFA/saturated fats ratio increased across quintiles of the energy-adjusted vitamin E intake, and approximately 72% of subjects in the higher quintile of the energy-adjusted vitamin E intake were in the higher tertile of PUFA/saturated fats ratio.

Table 18. Parameter estimates and percentage of the R^2 in models with fat components relate to vitamin E intake

	Model 1		Model 2		Model 1		Model 2	
Dependent variable	**α-TE**		**α-TE**		**EA-VE**		**EA-VE**	
Independent variables	**Parameter estimates**	**R^2**	**Parameter estimates**	**R^2**	**Parameter estimates**	**R^2**	**Parameter estimates**	**R^2**
PUFA/saturated ratio	-	-	1.8484	0.08	-	-	2.4712	39.84
PUFA, g/d	0.3993	80.50	0.3505	80.50	0.4785	30.63	0.4132	11.29
MONO fats, g/d	-0.2452	1.45	-0.2415	1.45	-0.1537	24.56	-0.1488	4.57
Saturated fats, g/d	-0.1010	0.65	-0.0831	0.65	-0.0374	0.18	-0.0135	0.02
Cholesterol, mg/d	-10.6863	0.82	-10.6090	0.82	-1.8127	0.03	-0.0135	0.03
Glycerol, mg/d	3.2744	1.08	3.2677	1.18	0.2818	0.05	0.2729	0.03

Model 1: the independent variables are the following fat components: PUFA, MONO, saturated fats, cholesterol and glycerol. Model 2: the independent variables are the fat components of the model 1 plus the ratio of PUFA/saturated fatty acids. α-TE=alpha-tocopherol equivalents; EA-VE=energy-adjusted vitamin E; MONO=monounsaturated fatty acids; PUFA=polyunsaturated fatty acids; PUFA/saturated ratio=ratio of polyunsaturated fatty acids/ saturated fatty acids; R^2=the square of the coefficient of determination as percentage

3.1.4. Vitamin E and antioxidants

Mean and standard deviation of vitamin C, beta-carotene, flavonols (quercentin and kaempferol), flavones (luteolin) and anthocyanidins (cyanidin, delphinidin, malvidin, peonidin, and petunidin) from the cohort population and their distributions across quintiles of energy-adjusted vitamin E are shown in table 19. With exception of myricetin, all antioxidants described a significant increment across quintiles of vitamin E as energy-adjusted vitamin E.

Table 19. Antioxidant intakes of cohort population in EPIC-Potsdam (n=25765) across quintiles of the energy-adjusted vitamin E at baseline*

	mean±std (n=25765)	**Q1 (n=5153)**	**Q1 (n=5153)**	**Q1 (n=5153)**	**Q1 (n=5153)**	**Q1 (n=5153)**	
EA-VE		-3.41±1.4	-1.37±0.3	-0.24±0.3	1.03±0.4	3.97± 2.3	<.0001
Vitamin C (mg/d)	125.79±61.1	102.55±48.8	111.77±49.8	121.95± 53.3	133.95±58.2	158.71±75.4	<.0001
Beta-carotene (mE/d)	2.61±1.4	2.01±0.9	2.21±0.9	2.49±1.1	2.79± 1.2	3.55±1.9	<.0001
Quercetin (mg/d)	5.59±4.5	4.73±4.7	5.07±4.1	5.38±4.2	5.86±4.3	6.90±4.8	<.0001
Kaempferol (mg/d)	2.40±3.0	2.13±3.1	2.22±2.8	2.29±2.7	2.51±2.9	2.85±3.1	<.0001
Myricetin (mg/d)	0.83±1.05	0.87±1.3	0.83±1.0	0.80±0.9	0.82±0.9	0.86±0.9	0.2288
Luteolin (mg/d)	0.13±0.1	0.08±0.1	0.10±0.1	0.12±0.1	0.14±0.1	0.21±0.2	<.0001
Cyanidin (mg/d)	0.89±1.2	0.65±0.9	0.76±1.0	0.87±1.0	0.98±1.2	1.18±1.4	<.0001
Delphinidin (mg/d)	0.52±0.7	0.37±0.5	0.45±0.6	0.52±0.7	0.55±0.7	0.63±0.9	<.0001
Malvidin (mg/d)	2.03±0.5	1.56±2.0	1.83±2.2	2.04±2.4	2.15±2.4	2.58±3.3	<.0001
Peonidin (mg/d)	0.33±0.5	0.25±0.3	0.30±0.3	0.34±0.4	0.36±0.4	0.44±0.6	<.0001
Petunidin (mg/d)	0.41±0.6	0.30±0.4	0.37±0.4	0.42±0.5	0.44±0.5	0.54±0.7	<.0001

*mean±standard deviation. EA-VE=energy-adjusted vitamin E; n= number of persons

Table 20 shows the Pearson´s correlation coefficient matrix among antioxidants. The vitamin E had direct association with vitamin C, carotenoids and flavonoids, but these were not strong associations, only carotenoids appear to have a moderate relationship. Among all flavonoids,

luteolin showed the strongest direct association with vitamin E, whereas only myricetin had an inverse association with vitamin E. With the exception of luteolin, the sum of flavonoids had stronger associations with vitamin E, vitamin C and carotenoids than each one of the flavonoids.

Table 20. Pearson´s correlation coefficient matrix of antioxidant in the cohort population EPIC-Potsdam (n=25765) at baseline

	VE	VC	CA	FLAV
EA-VE (mg/d/kJ)	1	0.36279	0.44721	0.19620
VC (mg/d/kJ)		1	0.45807	0.29704
CA (mgE/d/kJ)			1	0.26270
FLAV* (mg/d/kJ)				1
Quercetin (mg/d)	0.1794	0.27969	0.74057	0.88847
Kaempferol (mg/d)	0.08456	0.05855	0.13858	0.80310
Myricetin (mg/d)	-0.00915	0.04150	0.04958	0.73293
Luteolin (mg/d)	0.35785	0.35787	0.39204	0.16213
Cyanidin (mg/d)	0.17150	0.28379	0.22845	0.34539
Delphinidin (mg/d)	0.16024	0.25946	0.17694	0.55498
Malvidin (mg/d)	0.14963	0.25633	0.17458	0.58317
Peonidin (mg/d)	0.16065	0.26012	0.17750	0.55551
Petunidin (mg/d)	0.16065	0.25946	0.37694	0.55498

* The flavonoids is the sum of residuals from quercetin, epicathechin, luteolin, kaempferol, myricetin, genistein, cyanidin, delphinidin, malvidin, peonidin, and petunidin intakes regressed on total energy intake. CA=energy-adjusted carotenoids; EA-VE=energy-adjusted vitamin E; FLAV= sum of energy-adjusted residuals of flavonoids; VC=energy-adjusted ascorbic acid, vitamin C

3.1.5. Food sources of vitamin E

Table 21 shows the food groups contributing to vitamin E intake in the EPIC-Potsdam cohort study according to both percentages of contribution to total α-TE intake and partial R^2. According to absolute contribution to α-TE intake by Block [78] calculations, the top ranking

food sources of α-TE intake in the EPIC-Potsdam cohort were margarine, vegetable oils and fats, chips&salt sticks, cake & cookies, types of bread other than wholemeal bread, fresh fruits, juice, raw vegetables, wholemeal bread, eggs and fish. More than 70% of total α-TE came from these foods. According to the percentage of the variance contribution to the α-TE, margarine, vegetable oils and fats, and cake&cookies contributed to explain more than 68.25% of variance in the α-TE intake.

Table 21. Food groups contributing to alpha-tocopherol equivalent intake at baseline, EPIC-Potsdam cohort (n=25765)

FOOD GROUP	TOTAL FOOD INTAKE (g/d)*	ABSOLUTE CONTRIBUTION TO α-TE (g/d)*	CONTRIBUTION TO α-TE (%)	VARIANCE CONTRIBUTION TO α-TE (R^2, %)
Margarine	15.53±15.02	1.63±1.82	13.02	24.54
Vegetable oils and fats	3.52±3.43	1.22±1.32	9.95	24.24
Chips& salt sticks	2.26±5.72	0.05±0.12	9.01	<1
Cake&cookies	62.59±65.82	1.11±1.18	9.01	19.47
Types of bread other than wholemeal bread	132.45±80.59	0.83±0.52	7.54	1.34
Fresh fruits	142.58±96.60	0.62±0.44	5.52	1.32
Juice	198.28±228.91	0.52±0.67	4.81	4.26
Raw vegetables	56.92±44.86	0.48±0.45	4.14	2.52
Wholemeal bread	46.17±55.17	0.44±0.54	3.96	<1
Eggs	17.49±15.9	0.43±0.41	3.89	<1
Fish	23.87±25.85	0.43±0.52	3.65	3.71
Meat	38.57±28.18	0.40± 0.31	3.59	2.53
Cooked vegetables	36.42±22.63	0.38±0.29	3.44	<1
Nuts	3.26±8.11	0.33±0.82	2.54	6.84
Pommes frites	13.95±14.0	0.28±0.28	2.48	1.38
Sauce	16.33±14.79	0.28±0.32	2.41	<1
Cooked potatoes	83.11±48.7	0.25±0.27	2.16	<1
Confectionery&sweets	22.14±26.8	0.20±0.31	1.69	<1
Soup	40.76±38.26	0.19± 0.17	1.66	<1
Butter	8.78±12.64	0.17±0.25	1.65	1.10
Vegetarian dishes	1.43±5.77	0.01±0.05	1.58	<1
Pizza	7.10±9.99	0.18±0.25	1.58	<1
Processed meat	49.07±59.71	0.18±0.14	1.58	<1
High-fat cheese	27.75±25.29	0.16±0.145	1.42	<1
Muesli	5.50±14.9	0.15±0.41	1.28	1.11

Legumes	23.13±20.1	0.11±0.11	0.99	<1
Poultry	12.88±12.69	0.11±0.11	0.96	<1
High-fat dairy products	98.81±152.90	0.11±0.15	0.91	<1
Cabbage	13.95±13.72	0.08±0.08	0.74	<1
Low-fat dairy products	101.63±181.91	0.06±0.11	0.54	<1
Rest fats	0.29±0.77	0.06±0.17	0.50	<1
Canned fruit	17.76±24.67	0.05±0.08	0.47	<1
Pasta, rise	16.26±14.7	0.03±0.03	0.41	<1
Pudding	16.00±22.27	0.04±0.06	0.36	<1
Jam, honey	11.73±12.8	0.04±0.11	0.34	<1
Coffee	418.67±319.4	0.02±0.03	0.23	<1
Low-fat cheese	6.99±14.8	0.02±0.05	0.20	<1
Breakfast cereals	1.73±6.42	0.01±0.05	0.10	<1
Tee	270.08±369.32	0.00±0.02	0.04	<1
Mushrooms	2.00±2.37	0.00±0.05	0.03	<1
Des-coffee	40.05±143.96	0.00±0.01	0.02	<1
High-energy drink	44.86±143.08	0.00±0.00	0.02	<1
Garlic	0.13±0.45	0.00±0.00	0.00	<1
Water	437.98±444.98	0.00±0.00	0.00	<1
Low-energy drink	11.17±74.47	0.00±0.00	0.00	<1
Beer	180.71±378.82	0.00±0.00	0.00	<1
Wine	62.68±101.57	0.00±0.00	0.00	<1
Spirits	2.65±9.61	0.00±0.00	0.00	<1
Other alcoholic beverage	1.71±6.01	0.00±0.00	0.00	<1

* means±std. α-TE=alpha-tocopherol equivalents; R^2=square of the coefficient of determination as percentage

Based on the R^2 obtained by means of the regression of energy-adjusted vitamin E on the content of vitamin E of the 49 food groups, the best set of food groups which explain most of the variance of the energy-adjusted vitamin E intake was composed of the following: vegetable oils and fats, margarine, processed meat, nuts, raw vegetables, types of bread other than wholemeal bread, beer, cooked vegetables, low-fat dairy products and fresh fruits. The 80.75% of the variance in energy-adjusted vitamin E is explained by these food intake groups (Table 22). In the analysis by gender, The food group cooked vegetables is substituted with fish among men and with cake&cookies among women. The percentage of the intervariability of energy-adjusted vitamin E intake explained by these food groups was 71% and 69%, men and women respectively.

Table 22. Partial R^2 of main food groups to explain most the variance in energy-adjusted vitamin E intake at baseline, EPIC-Potsdam cohort (n=25765)

FOOD GROUP	TOTAL FOOD INTAKE (g/d)*	ABSOLUTE CONTRIBUTION TO α-TE (g/d)*	PARAMETER ESTIMATE	VARIANCE CONTRIBUTION TO EA-VE (R^2, %)
Vegetable oils and fats	3.52±3.43	1.22±1.32	1.00501	37.58
Margarine	15.53±15.02	1.63±1.82	0.79795	22.63
Processed meat	49.07±59.71	0.18±0.14	-3.83037	5.02
Nuts	3.26±8.11	0.33±0.82	0.69866	5.13
Raw vegetables	56.92±44.86	0.48±0.45	0.94778	3.90
Types of bread other than wholemeal bread	132.45±80.59	0.83±0.52	-0.59114	1.85
Beer	180.71±378.82	0.00±0.00	-1055.29	1.50
Cooked vegetables	36.42±22.63	0.38±0.29	0.89289	1.19
Low-fat dairy products	101.63±181.91	0.06±0.11	-3.83438	0.91
Fresh fruits	142.58±96.60	0.62±0.44	0.61261	1.06
High-fat dairy products	98.81±152.90	0.11±0.15	-2.95194	1.05
Cake&cookies	62.59±65.82	1.11±1.18	0.32767	1.76
Fish	23.87±25.85	0.43±0.52	0.51480	1.07
Sauce	16.33±14.79	0.28±0.32	0.82815	0.78
Muesli	5.50±14.9	0.15±0.41	0.47705	0.47
High-fat cheese	27.75±25.29	0.16±0.145	-1.4644	0.48

*means±std.α-TE=alpha-tocopherol equivalents; EA-VE=energy-adjusted vitamin E; R^2=square of the coefficient of determination as percentage

3.1.6. Food patterns

Table 23 shows a description of both the FP rich in vitamin E and FP rich in antioxidants. The FP rich in vitamin E is the sum of the standardized total intake of the following food groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low-fat and high-fat dairy products. On the one hand a positive and direct association with energy-adjusted vitamin E intake was observed in vegetable oils and fats, margarine, nuts, raw vegetables and cooked vegetables. On the other hand, processed meat, types of bread other than wholemeal bread, beer, low-fat and high-fat dairy products groups showed an inverse association with energy-adjusted vitamin E intake (Appendix 4. SAS results).

Table 23. Food patterns in the cohort population EPIC-Potsdam (n=25765), all and by gender

		MEAN	STANDARD DEVIATION	RANGE
FP-VE	**ALL**	-0.001	3.46	71.60
	M	-1.44	3.53	68.12
	W	0.93	3.08	59.48
FP-AO	**ALL**	-0.001	4.01	75.40
	M	-1.74	4.16	65.58
	W	1.12	3.49	58.29

FP-AO=food pattern rich in antioxidants; FP-VE= food pattern rich in vitamin E; M=men; W=women

FP rich in antioxidants is the sum of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat. This pattern rich in antioxidants simplifies the total intake of the top twelve food groups which explained more variance in the selected response factor from the reduced rank regression model previously described (**section 2.3.5**). The selected response factor explained 50.35% of vitamin E, 55.8% of vitamin C, 47.72% of carotenoids, and 17.39% of flavonoids. Food groups selected to build the FP rich in antioxidants explained 82.9% the variance in the selected response factor. A positive and direct association with the selected response factor was observed in fruits, vegetables, vegetable oils and fats, margarine, nuts and tea. On the other hand, processed meat, beer, types of bread other than wholemeal bread, butter, dairy products and confectionery&sweet groups showed an inverse association with the selected response factor.

Differences by gender in the both FP rich in vitamin E and FP rich in antioxidant were found. Scores of the either FP rich in vitamin E as well as the FP rich in antioxidants among men had a tendency to be negative. Among women the scores had a tendency to be positive.

Pearson's correlation coefficient matrix among antioxidant nutrients and scores of FPs in the EPIC-Potsdam study on table 24 is shown. Strong and direct associations between vitamin E intake and both FPs (rich in vitamin E and rich in antioxidants) and also between vitamin E and both scores (extracted response and extracted factor) were found. The FP rich in vitamin E had a strong, significant and direct association with the FP rich in antioxidants and carotenoids as well as the FP rich in vitamin E showed a weaked direct association with flavonoids. With regard to the FP rich in antioxidants, a direct and moderate association with carotenoids, flavonoids and vitamin C were found. Both factors, extracted response and extracted predictor, showed moderate to strong relationships with both antioxidants and scores of food patterns.

Table 24. Pearson´s correlation coefficient matrix of antioxidants (nutrients and scores) in the cohort population EPIC-Potsdam (n=25765) at baseline

	FP- VE	**FP-AO**	**FEP-RRR**	**FER-RRR**
EA-VE	0.74798	0.67718	0.70696	0.75351
VC	0.38715	0.46131	0.70291	0.77979
CA	0.54505	0.42126	0.53529	0.75318
FLAV*	0.28596	0.38820	0.41134	0.52865
FP-VE**	1	0.80991	0.71327	0.71134
FP-AO^{o}		1	0.81965	0.69833
FEP-RRR^{oo}			1	0.85199
FER-RRR^{oa}				1

*The flavonoids is the sum of residuals from quercetin, epicathechin, luteolin, kaempferol, myricetin, genistein, cyanidin, delphinidin, malvidin, peonidin, and petunidin intakes regressed on total energy intake. **Food pattern rich in vitamin E is the algebraic sum of the standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. ^{o} Food pattern rich in antioxidants is the sum algebraic of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat. ^{oo} The first extracted response factor is a latent factor extracted by reduced rank regression that explain more variation in the following antioxidants: vitamin E, vitamin C, flavonoids, and carotenoids. The first extracted predictor factor is a latent factor extracted by reduced rank regression that explain more variation in the 42 food intakes groups or predictors. CA=energy-adjusted carotenoids; EA-VE=energy-adjusted vitamin E; FEP-RRR=First extracted predictor factor by reduced rank regression; FER-RRR=First extracted response factor by reduced rank regression; FLAV=energy-adjusted sum of flavonoids; FP-AO=food pattern rich in antioxidant nutrients; FP-VE=food pattern rich in vitamin E; VC=energy-adjusted ascorbic acid, vitamin C

Pearson's correlation matrix among food groups which were chosen as components of the FPs, antioxidant nutrients and both FP rich in vitamin E and FP rich in antioxidants food patterns is shown in table 25. The following direct, strong and significant linear associations were found: for energy-adjusted vitamin E intake with vegetable oils and fats and raw vegetables; for energy-adjusted vitamin C with raw vegetables, fresh and juice fruits, and fruits together; for energy-adjusted carotenoids with vegetables oils and fats, and raw vegetables; for flavonoids with tea and fresh fruits; for the FP rich in vitamin E with vegetables oils and fats and raw vegetables; for the FP rich in antioxidants with vegetables oils and fats and all vegetables together. The following indirect, strong and significant linear associations were found: for the FP rich in vitamin E with types of bread other than wholemeal bread; for the FP rich in antioxidants with processed meat, types of bread other than wholemeal bread, beer and butter. All antioxidants and both FPs showed positive significant correlations with the following food groups: vegetable oils and fats, fruit juice, fresh fruits, raw vegetables, cooked vegetables, vegetarian dishes, cabbage, fish, vegetables group, fruits group and tea. In spite of the fact that margarine group had an inverse association with energy-adjusted vitamin C, energy-adjusted carotenoids and flavonoids, a direct association among the energy-adjusted vitamin E with both FP rich in vitamin E and FP rich in antioxidant was noted. In addition, all dairy products showed direct relationships with energy-adjusted vitamin C, energy-adjusted carotenoids and flavonoids, but showed inverse correlation with energy-adjusted vitamin E and both FP rich in vitamin E and FP rich in antioxidants.

Table 25. Pearson´s correlation coefficient among antioxidant nutrients, food patterns and food group intakes in the cohort population EPIC-Potsdam at baseline (n=25765)

	EA-VE	VC	CA	FLAV*	FP- VE**	FP-AO°
Vegetable oils and fats	0.53693 <.0001	0.29067 <.0001	0.43103 <.0001	0.24937 <.0001	0.55054 <.0001	0.42687 <.0001
Margarine	0.38451 <.0001	-0.06046 <.0001	-0.03105 <.0001	-0.07794 <.0001	0.11301 <.0001	0.16986 <.0001
Fruit juice	0.10830 <.0001	0.65938 <.0001	0.10744 <.0001	0.05423 <.0001	0.03822 <.0001	0.22018 <.0001
Fresh fruits	0.29270 <.0001	0.52166 <.0001	0.39375 <.0001	0.46520 <.0001	0.26005 <.0001	0.28356 <.0001
Canned fruits	0.07726 <.0001	0.08848 <.0001	0.09178 <.0001	-0.00481 0.4405	0.02465 <.0001	0.00595 0.3393
Raw vegetables	0.49730 <.0001	0.48272 <.0001	0.68880 <.0001	0.27174 <.0001	0.55155 <.0001	0.35304 <.0001
Cooked vegetables	0.20793 <.0001	0.19827 <.0001	0.35872 <.0001	0.11681 <.0001	0.38243 <.0001	0.15478 <.0001
Vegetarian dishes	0.12137 <.0001	0.06292 <.0001	0.15042 <.0001	0.15197 <.0001	0.16270 <.0001	0.36370 <.0001
Cabbage	0.12654 <.0001	0.15528 <.0001	0.18422 <.0001	0.06932 <.0001	0.13760 <.0001	0.11701 <.0001
Nuts	0.23777 <.0001	-0.01628 0.0090	0.03399 <.0001	0.03621 <.0001	0.28326 <.0001	0.22802 <.0001
Processed meat	-0.12976 <.0001	-0.10495 <.0001	-0.13597 <.0001	-0.12515 <.0001	-0.39039 <.0001	-0.42727 <.0001
Types of bread other than wholemeal bread	-0.16182 <.0001	-0.19227 <.0001	-0.18914 <.0001	-0.13730 <.0001	-0.44006 <.0001	-0.46267 <.0001
Chips&salt snacks	0.03639 <.0001	-0.05484 <.0001	-0.02769 <.0001	-0.00765 <.0001	-0.01943 0.0018	-0.02907 <.0001
Beer	-0.29381 <.0001	-0.21475 <.0001	-0.17610 <.0001	-0.14836 <.0001	-0.38579 <.0001	-0.40666 <.0001
High-fat dairy products	-0.04072 <.0001	0.06079 <.0001	0.07285 <.0001	0.01736 0.0053	-0.21509 <.0001	-0.15165 <.0001
Low-fat dairy products	-0.10049 <.0001	0.00476 <.0001	0.02137 <.0001	-0.00107 0.8631	-0.15163 <.0001	-0.02441 <.0001
Confectionery&sweet	-0.05160 <.0001	-0.05535 <.0001	-0.04876 <.0001	0.03756 <.0001	-0.04313 <.0001	-0.25811 <.0001
Cake&cookies	0.11595 <.0001	-0.07806 <.0001	-0.01114 <.0001	-0.03576 <.0001	-0.03668 <.0001	-0.08756 <.0001

Fish	0.17629 <.0001	0.03057 <.0001	0.06621 <.0001	0.03652 <.0001	0.03092 <.0001	0.00919 0.1401
Vegetables	0.24213 <.0001	0.18956 <.0001	0.33185 <.0001	0.17879 <.0001	0.31773 <.0001	0.43034 <.0001
Fruits	0.21077 <.0001	0.78030 <.0001	0.24882 <.0001	0.21945 <.0001	0.13219 <.0001	0.29884 <.0001
Dairy products	-0.10339 <.0001	0.04800 <.0001	0.06899 <.0001	0.01193 0.0556	-0.26850 <.0001	-0.12891 <.0001
Butter	-0.27532 <.0001	-0.08910 <.0001	-0.05864 <.0001	-0.02298 0.0002	-0.21382 <.0001	-0.45797 <.0001
Tea	0.09034 <.0001	0.05947 <.0001	0.13666 <.0001	0.56805 <.0001	0.11250 <.0001	0.31845 <.0001

*The flavonoids is the sum of residuals from quercetin, epicathechin, luteolin, kaempferol, myricetin, genistein, cyanidin, delphinidin, malvidin, peonidin, and petunidin intakes regressed on total energy intake. ** Food pattern rich in vitamin E is the algebraic sum of the standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. º Food pattern rich in antioxidant is the sum algebraic of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat. CA=energy-adjusted carotenoids; EA-VE=energy-adjusted vitamin E; FEP-RRR=First extracted predictor factor by reduced rank regression; FER-RRR=First extracted response factor by reduced rank regression; FLAV=energy-adjusted sum of flavonoids; FP-AO=food pattern rich in antioxidant nutrients; FP-VE=food pattern rich in vitamin E; VC=energy-adjusted ascorbic acid, vitamin C

For all antioxidant nutrients significant linear trends across quintiles of the both FP rich in vitamin E and FP rich in antioxidants were noted. Table 26 shows some antioxidant nutrient intakes across quintiles of both FP rich in vitamin E and FP rich in antioxidants.

Table 26. Antioxidant nutrient intakes across quintiles of the food pattern rich in vitamin E and the food pattern rich in antioxidants in the cohort population EPIC-Potsdam (n=25765) at baseline*

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	
FP-VE**	-4.59 ± 2.3	-1.49 ± 0.5	-0.00 ± 0.4	1.46 ± 0.5	4.61 ± 2.7	**P values**
α-TE (mg/day)	11.11±3.8	10.64±3.5	10.82±3.5	11.62±3.70	14.26±4.7	<.0001
Ascorbic acid intake (mg/day)	111.73±56.6	113.52±53.4	118.78±53.8	128.41±56.9	156.52±71.8	<.0001
Beta-carotenoids (mequivalent/day)	2.06±0.8	2.17±0.9	2.26±1.0	2.49±1.1	3.09±1.6	<.0001
Flavonoids intake (mg/day)	10.62±1.47	11.59±1.39	12.43±1.39	13.79±1.11	17.25±1.86	<.0001
FP-AO***	-5.66±2.8	-1.66±0.6	0.21±0.5	1.91±0.5	5.20±2.4	**P values**
α-TE (mg/day)	11.78±4.2	11.74±3.9	11.95±3.8	12.57±3.9	14.62±5.0	<.0001
Ascorbic acid intake (mg/day)	104.60±46.8	106.53±46.8	110.96±49.1	123.95±57.2	152.59±78.4	<.0001
Beta-carotenoids (mequivalent/day)	2.17±0.9	2.17±0.9	2.26±1.0	2.49±1.1	3.09±1.6	<.0001
Flavonoids intake (mg/day)	9.04±8.1	10.01±7.8	11.17±8.4	13.08±9.5	17.36±13.2	<.0001

* means ± standard deviation. ** The food pattern rich in vitamin E is the algebraic sum of the standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. *** The food pattern rich in antioxidants is the sum algebraic of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat. α-TE=alpha-tocopherol equivalents; FP-AO=food pattern rich in antioxidants; FP-VE=food pattern rich in vitamin E; n=number of persons

Food group intakes across both quintiles of FP rich in vitamin E and FP rich in antioxidants are shown on tables 27 and 28. Significant p trend values of these food groups across either FP rich in vitamin E or FP rich in antioxidants were noted. Higher scores of either FP rich in vitamin E or FP rich in antioxidants were associated with higher intakes of nuts, raw vegetables, cooked vegetables, other vegetable fats and oils, margarine, tea, and composite groups of fruits and vegetables. Contrary to this, the groups processed meat, beer, other types of breads, butter and dairy products showed indirect associations with FP rich in vitamin E and FP rich in antioxidants.

Table 27. Food intake groups across quintiles of the food pattern rich in vitamin E in the cohort population EPIC-Potsdam (n=25765) at baseline*

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	
FP-VE**	-4.59 ± 2.3	-1.49 ± 0.5	-0.00 ± 0.4	1.46 ± 0.5	4.61 ± 2.7	**P values**
Vegetable oils and fats	1.90±8.1	2.27±1.9	2.78±2.0	3.80±2.5	6.87±5.0	<.0001
Margarine	13.13±14.5	14.15±13.9	15.00±13.3	16.90±14.6	18.44±17.7	<.0001
Raw vegetables	34.89±25.0	40.73±24.3	48.11±26.9	60.67±31.8	100.21±66.3	<.0001
Cooked vegetables	27.47±16.1	29.91±16.0	34.01±17.5	38.84±18.5	51.86±31.0	<.0001
Nuts	2.08±3.9	2.15±3.7	2.37±4.4	3.10±5.7	6.58±15.3	<.0001
Processed meat	93.65±66.8	62.03±36.59	51.88±33.2	47.18±32.0	43.83±31.6	<.0001
Tpes of bread other than wholemeal bread	197.68±89.8	148.48±69.4	120.69±65.2	104.69±63.4	90.69±64.6	<.0001
Beer	449.65±654.8	185.32±294.3	113.88±211.9	84.09±180.2	70.59±163.3	<.0001
High-fat dairy products	157.59±258.2	99.37±128.1	84.53±103.7	76.52±93.9	76.02±97.9	<.0001
Low-fat dairy products	153.22±304.5	97.25±159.9	87.72±127.2	84.12±114.5	85.86±120.3	<.0001
Butter	14.40±17.1	9.40±12.2	7.53±10.8	6.30±9.8	6.28±10.0	<.0001
Tea	224.88±367.4	243.53±331.5	254.83±338.8	278.79±351.1	348.35±435.9	<.0001

* means ± standard deviation. **The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: nuts, types of bread other than wholemeal bread, raw vegetables, cooked vegetables,low- and high-fats dairy products, beer, vegetable oils and fats, margarine, processed meat. FP-VE= food pattern rich in vitamin E; n=number of persons

Table 28. Food intake groups across quintiles of the food pattern rich in antioxidant nutrients in the cohort population EPIC-Potsdam (n=25765) at baseline*

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	
FP-AO**	-5.66±2.8	-1.66±0.6	0.21±0.5	1.91±0.5	5.20±2.4	**P values**
Vegetable oils and fat	2.15±2.1	2.51±2.2	2.94±2.4	3.74±2.8	6.27±5.0	<.0001
Margarine	10.88±14.1	14.19±13.8	16.14±13.8	17.65±14.6	18.77±17.2	<.0001
Raw vegetables	40.74±31.4	45.96±31.7	51.72±34.4	60.57±39.6	85.63±63.8	<.0001
Cooked vegetables	33.09±20.4	33.81±20.0	35.11±20.6	37.32±23.3	42.78±26.8	<.0001
Vegetarian dishes	0.30±1.3	0.46±1.7	0.63±2.2	1.02±2.9	4.72±11.6	<.0001
Cabbage	12.16±12.3	13.11±12.4	13.45±12.5	14.75±14.2	16.30±16.3	<.0001
Fresh fruit	111.27±78.0	122.85±80.6	137.11±87.3	152.54±90.4	189.15±120.9	<.0001
Fruit juices	142.49± 167.7	157.30±173.9	180.33±186.8	211.65±213.6	299.61±327.9	<.0001
Canned fruit	18.45±24.3	16.96±22.7	17.06±23.7	17.68±25.2	18.63±27.2	<.0001
Nuts	2.49±4.7	2.28±4.0	2.5±5.0	2.88±5.3	6.13±15.1	<.0001
Processed meat	92.66±65.8	64.42±39.0	54.23±33.4	46.49±30.5	40.77±31.5	<.0001
Other types of breads	194.87±87.4	150.45±71.2	125.45±67.3	103.81±63.5	87.65±64.0	<.0001
Beer	453.56±654.7	200.27±303.2	118.59±221.0	74.38±158.0	56.73±133.8	<.0001
High-fat dairy products	143.66±244.9	99.08±173.9	89.99±122.2	79.68±101.3	81.48±108.9	<.0001
Low-fat dairy products	114.72±274.5	99.23±130.8	94.64±142.9	96.65±1395	103.08±140.7	<.0001
Butter	20.12±18.6	9.33±10.6	6.02±8.4	4.39±6.9	4.04±6.8	<.0001
Tea	169.48±249.8	185.33±238.01	216.21±264.6	275.87±312.6	503.49±566.2	<.0001
Derived groups						
Vegetables	86.29±16.4	93.34±16.5	100.91±17.4	113.66±20.0	149.43±29.6	<.0001
Fruits	172.21±90.0	297.12±92.4	334.50±99.3	381.87±109.7	507.39±158.0	<.0001
Dairy products	258.37±259.2	198.31±152.35	184.63±132.35	176.33±120.4	184.56±124.8	<.0001

* All continuous variables: means ± standard deviation. **The food pattern rich in antioxidants is the sum algebraic of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat.
n=number of persons; FP-AO= food pattern rich in antioxidants

3.1.7. Characterization of the EPIC-Potsdam cohort across quintiles of food patterns

In spite of the fact that the FPs have some different food components, the main features of the EPIC-Potsdam cohort population across quintiles of FP rich in vitamin E and quintiles of FP rich in antioxidants had a strikingly similar characterization and these also were similar across quintiles of energy-adjusted vitamin E intake. Tables 29 and 30 show main features of the EPIC-Potsdam study across quintiles of FP rich in vitamin E and quintiles of FP rich in antioxidants. Most young adults in the highest quintile of both patterns, FP rich in vitamin E and FP rich in antioxidants, were found. In the fifth quintile of the FP rich in vitamin E and the FP rich in antioxidants, approximately 38% were younger than 45 years. In both FPs, women predominated in the highest score, in contrast, the lowest had more men. Most people with more education (≈64%), non-current smoking habits (≈84%), lower and intermediate alcohol consumption (≈82%), more time spent in sport activity (≈29%) and users of vitamin E supplements (≈23%) were in the highest score of these patterns.

With regard to BMI, the highest percentage of underweight and normal BMI (≈45%) was found among subjects in the highest score of these patterns. Most people who had overweight and obesity were in the lowest quintile of the FP rich in vitamin E, 68.34 and 18.19 % respectively. Most overweight people were in the lowest quintile of the FP rich in antioxidants, 44.07%. The lowest score of both patterns, FP rich in vitamin E and FP rich in antioxidants, showed more subjects with higher WHR (≈67%), more subjects who reported hypertension (≈48%), and more subjects who had either SBP>140 mmHg (29%) or DBP>90mmHg (31%). In addition, more subjects who had hyperlipidaemia (29.19%) and diabetes (4.95%) were in the highest quintile of FP rich in antioxidants, but only hyperlipidaemia prevalence was statistically significant related across quintiles of the FP rich in antioxidants.

Table 29. General features of cohort population in EPIC-Potsdam (n=25765) across quintiles of the food pattern rich in vitamin E at baseline*

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	
FP-VE**	**-4.59 ± 2.3**	**-1.49 ± 0.5**	**-0.00 ± 0.4**	**1.46 ± 0.5**	**4.61 ± 2.7**	**P values**
Age categories, %						
<45year	30.49	32.51	33.05	35.67	37.71	<.0001
45-55 years	32.00	28.72	27.67	26.59	27.23	
>55 years	37.51	38.77	39.28	37.75	35.07	
Gender, men %	71.26	46.03	32.41	25.03	20.98	<.0001
Education, secondary school and higher, %	57.31	61.71	61.23	61.77	64.16	<.0001
BMI categories, %						
< 25 kg/m^2	37.26	41.63	42.58	45.04	45.12	<.0001
25-30 kg/m^2	68.34	41.35	40.38	37.71	37.65	
>30 kg/m^2	18.19	17.01	17.03	17.26	17.23	
WHR, %						
M>0.9 / W>0.8	67.96	56.78	52.18	49.25	48.79	<.0001
Time of sport activity, (%)						
>2 hours/week	19.15	19.46	21.35	23.17	27.63	<.0001
Smoking status, %						
Current smoker	29.28	21.60	18.55	18.14	16.03	<.0001
Alcohol consumption categories, % º						
Lower	34.23	43.02	46.11	45.74	44.48	<.0001
Intermediate	33.67	38.21	38.33	37.82	37.36	
Higher	32.10	18.77	15.56	16.44	18.16	
Vit-E suppl, %	14.77	18.18	19.46	21.54	22.49	<.0001
SBP, %						
>140 mmHg	30.37	24.45	23.07	22.45	19.54	<.0001
DBP, %						
>90 mmHg	32.19	27.81	25.33	24.26	22.82	<.0001
Diabetes, %	5.69	4.85	5.03	5.47	5.05	0.2821
Hyperlipidaemia, %	28.53	29.19	28.10	28.60	28.24	0.7743

*Continuous variables: means ± standard deviation; categorical variables: percentaje. **The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. ºAlcohol consumption categories= Lower=abstiners or <5 g/day women or <10g/day men, Intermediate=5-15g/day women or 10-30g/day men, Higher=>15 g/day women or >30g/day men. BMI=Body-Mass-Index; DBP=diastolic blood pressure; M=men; n=number of persons; SBP=systolic blood pressure; FP-VE=food pattern rich in vitamin E; Vit-E suppl=vitamin E supplementation; WHR=waist-to-hip-ratio; W=women

Table 30. General features of cohort population in EPIC-Potsdam (n=25765) across quintiles of the food pattern rich in antioxidant nutrients at baseline*

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	
FP-AO**	**-5.66±2.8**	**-1.66±0.6**	**0.21±0.5**	**1.91±0.5**	**5.20±2.4**	**P values**
Age categories, %						
<45year	31.69	31.07	33.46	34.78	38.42	<.0001
45-55 years	31.61	29.75	27.21	26.82	26.82	
>55 years	36.70	39.18	39.34	38.40	34.76	
Gender, men %	70.23	47.66	32.91	24.70	13.62	<.0001
Education, secondary school and higher, %	56.74	61.36	61.01	61.96	65.09	<.0001
BMI, %						
< 25 kg/m^2	39.63	41.02	41.02	43.95	45.99	<.0001
25-30 kg/m^2	44.07	41.65	40.77	38.50	36.66	
>30 kg/m^2	16.30	17.33	18.20	17.54	17.35	
WHR, %						
M>0.9/W>0.8	67.47	57.77	53.81	49.47	47.45	<.0001
Time of sport activity, (%)						
>2 hours/week	17.97	18.98	20.69	23.38	29.75	<.0001
Smoking status, (%)						
Current smoker	31.46	22.24	18.36	16.84	14.71	<.0001
Alcohol consumption categories, % º						
Lower	32.72	38.93	45.86	47.72	48.36	
Intermediate	34.14	40.50	38.15	37.38	35.22	<.0001
Higher	33.15	20.57	15.99	14.90	16.42	
Vit-E suppl, %	13.60	17.12	20.24	21.00	24.49	<.0001
SBP, %						
>140 mmHg	29.61	25.36	23.13	22.55	19.23	<.0001
DBP, %						
>90 mmHg	31.57	28.64	25.33	23.83	23.04	<.0001
Diabetes, %	4.85	5.05	5.51	5.72	4.95	0.1962
Hyperlipidaemia, %	26.84	28.82	29.42	28.39	29.19	0.0317

*Continuous variables: means ± standard deviation; categorical variables: percentaje. ** The food pattern rich in antioxidants is the sum algebraic of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat. ºAlcohol consumption categories= Lower=abstiners or <5 g/day women or <10g/day men, Intermediate=5-15g/day women or 10-30g/day men, Higher= >15 g/day women or >30g/day men. BMI= Body-Mass-Index; DBP=diastolic blood pressure; M=men; n=number of persons; SBP=systolic blood pressure; FP-AO= food pattern rich in antioxidants; Vit-E suppl=vitamin E supplementation; WHR=waist-to-hip-ratio; W=women

Tables 31 and 32 show the main population characteristics of the EPIC-Potsdam cohort study across quintiles of both FPs, the FP rich in vitamin E and the FP rich in antioxidants, by gender. As was observed in the overall cohort analysis, most men in the highest score either FP rich in vitamin E or FP rich in antioxidants were older than 55 years (over 44%), but most young adult women in the highest score in both FPs were noted (41%). A similar characterization across quintiles of the FP rich in vitamin E and the FP rich in antioxidants for education, time spent in sport and smoking status in the overall cohort and by gender was found.

More men who had overweight and obesity predominated in the highest quintile of both FPs, but among women not significant linear trend were observed. No significant linear trend across quintiles of the FP rich in vitamin E for WHR was noted, only among men a similar trend to the overall cohort across quintiles of the FP rich in antioxidants, was found.

With regard to alcohol consumption, only among men a similar trend to the overall cohort was observed. More men were higher alcohol drinkers who had lower scores of both patterns, FP rich in vitamin E and FP rich in antioxidants (43%). Among women who had intermediate alcohol consumption was observed a tendency to increase across quintiles of either the FP rich in vitamin E or the FP rich in antioxidants. With regard to the vitamin E supplementation, the highest percentage of vitamin E supplementation users were among women with the highest score of FP rich in antioxidants (25.57%). Diabetes and hyperlipidaemia prevalence showed significant trend in the gender analysis. More men who had diabetes self-reported at baseline had also the highest score of both patterns, this was not so among women. Both, men and women who had reported hyperlipidaemia at baseline were in the highest score of both patterns, FP rich in vitamin E and FP rich in antioxidants. However, the tendency in the overall cohort to decrease subjects with SBP>140 mmHg and DBP>90 mmHg across quintiles of the FP rich in vitamin E and the FP rich in antioxidants is attenuated in the gender analysis.

Table 31. General features of cohort population in EPIC-Potsdam (n=25765) across quintiles of the food pattern rich in vitamin E at baseline, by gender*

		Q1	Q2	Q3	Q4	Q5	
FP-VE (n)**	M	-6.17±2.5 (2017)	-2.98± 0.5 (2017)	-1.41 ± 0.4 (2017)	0.12 ± 0.5 (2017)	3.22 ± 2.5 (2017)	**P values**
	W	-2.85 ± 1.1 (3136)	-0.52 ± 0.4 (3136)	0.72 ± 0.3 (3136)	2.07 ± 0.4 (3136)	5.21 ± 2.7 (3136)	
Age categories,%							
<45year	M	29.90	25.63	24.24	21.81	25.14	<.0001
45-55 years		34.56	30.99	30.00	29.80	30.44	
>55 years		35.55	43.38	45.76	48.39	44.42	
	W	38.11	38.84	39.35	38.81	41.77	
		28.83	25.92	27.04	26.05	25.64	<.0001
		33.07	35.24	33.61	35.14	32.59	
Education, secondary school and higher, %	M	54.24	64.60	70.10	69.56	70.95	<.0001
	W	54.78	55.64	57.84	60.20	62.72	<.0001
BMI, %							
< 25 kg/m²	M	31.83	30.99	30.09	26.03	28.41	<.0001
25-30 kg/m²		49.43	51.71	51.56	56.02	52.90	
>30 kg/m²		18.74	17.30	18.34	17.95	18.69	
	W	51.59	51.24	50.77	50.29	49.08	0.0742
		31.63	31.82	32.88	33.90	32.84	
		17.57	16.33	16.04	16.36	17.67	
WHR, %							
M>0.9	M	77.24	76.40	76.75	76.40	74.71	0.4004
W>0.8	W	42.32	40.75	39.89	41.58	41.90	0.3025
Time of sport activity, %							
>2 hours/week	M	19.58	21.52	21.62	22.41	27.02	<.0001
	W	16.77	19.07	22.48	23.21	28.35	<.0001
Smoking status, %							
Current smoker	M	33.96	27.66	23.60	20.13	20.23	<.0001
	W	21.27	19.45	17.35	16.68	14.73	<.0001
Alcohol consumption categories, %							
Lower	M	23.90	30.89	34.31	37.98	40.36	<.0001
Intermediate		32.47	40.41	43.93	45.22	42.98	
Higher		43.63	28.71	21.76	16.81	16.66	
	W	51.47	51.34	47.70	47.83	44.93	<.0001
		31.03	33.48	37.34	34.50	36.42	
		17.51	15.18	14.96	17.67	18.65	
Vit-E suppl, %							
	M	11.85	13.49	15.82	15.96	20.03	0.0110
	W	20.06	21.49	21.21	22.58	23.53	0.3207
SBP, %							
>140 mmHg	M	35.55	35.05	32.33	36.19	33.07	0.0431
	W	17.60	16.68	16.87	18.94	16.17	0.0376
DBP, %							
>90 mmHg	M	38.32	36.34	36.49	38.08	35.55	0.2936
	W	19.93	18.59	19.48	21.36	19.36	0.0801

*Continuous variables: means ± standard deviation; categorical variables: percentaje. **The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. BMI=Body-Mass-Index; DBP=diastolic blood pressure; M=men; n=number of persons; SBP=systolic blood pressure; FP-VE=food pattern rich in vitamin E; Vit-E suppl=vitamin E supplementation; WHR=waist-to-hip-ratio; W=women

Table 32. General features of cohort population in EPIC-Potsdam (n=25765) across quintiles of the food pattern rich in antioxidant nutrients at baseline, by gender

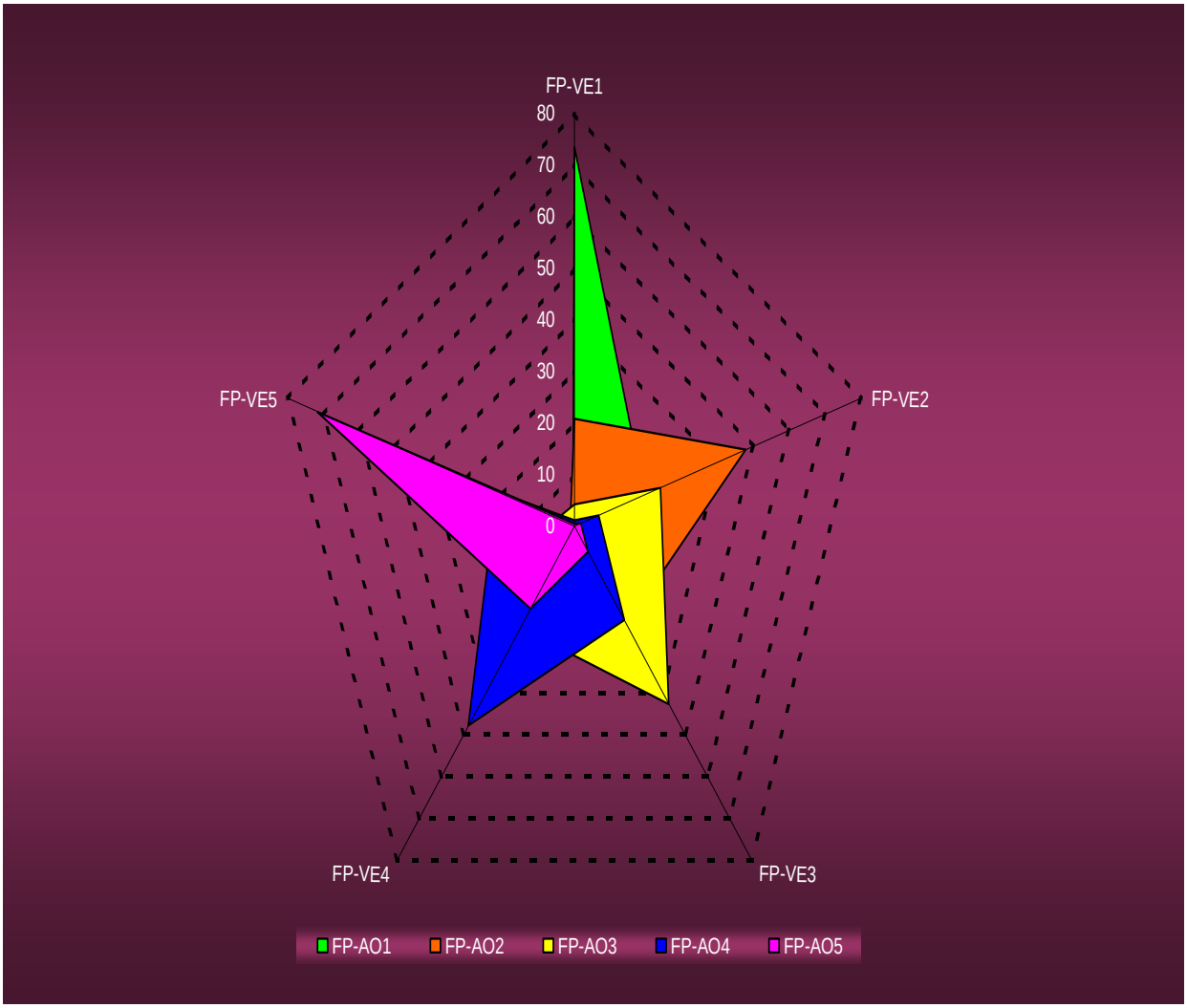
		Q1	Q2	Q3	Q4	Q5	
FP-AO (n)**	M	-6.17±2.5 (2017)	-2.98± 0.5 (2017)	-1.41 ± 0.4 (2017)	0.12 ± 0.5 (2017)	3.22 ± 2.5 (2017)	**P values**
	W	-2.85 ± 1.1 (3136)	-0.52 ± 0.4 (3136)	0.72 ± 0.3 (3136)	2.07 ± 0.4 (3136)	5.21 ± 2.7 (3136)	
Age, %							
<45year	M	29.65	25.29	24.29	23.90	23.60	<.0001
45-55 years		33.81	31.43	30.49	29.45	30.59	
>55 years		36.54	43.28	45.22	46.65	45.81	
	W	39.29	37.66	38.36	39.60	41.96	
		29.05	26.56	26.69	25.06	26.12	<.0001
		31.66	35.78	34.95	35.33	31.92	
Education, secondary school and higher, %	M	54.83	64.35	68.47	70.20	71.59	<.0001
	W	53.48	55.20	58.77	59.63	64.13	<.0001
BMI, %							
< 25 kg/m²	M	35.55	29.25	28.66	24.39	29.50	<.0001
25-30 kg/m²		48.14	54.09	52.31	54.39	52.70	
>30 kg/m²		16.31	16.66	19.04	21.22	17.80	
	W	54.46	49.59	48.85	49.84	50.22	0.0742
		29.43	33.86	33.74	33.29	32.75	
		16.10	16.55	17.41	16.87	17.03	
WHR, %							
M>0.9	M	76.98	76.02	77.54	76.51	72.33	0.0210
W>0.8	W	41.66	41.16	42.18	40.59	41.15	0.7294
Time of sport activity (%)							
>2 hours/week	M	18.49	20.87	22.31	23.00	27.47	<.0001
	W	14.89	18.24	21.97	24.17	30.61	<.0001
Smoking, (%)							
Current smoker	M	38.23	27.71	22.76	19.48	17.40	<.0001
	W	24.33	18.78	16.20	15.24	14.92	<.0001
Alcohol consumption , %º							
Lower	M	23.55	28.76	30.39	37.83	46.90	<.0001
Intermediate		32.42	40.26	46.55	46.21	39.56	
Higher		44.03	30.99	23.05	15.96	13.53	
	W	48.02	48.50	49.11	49.68	47.96	0.0007
		32.72	35.27	35.84	34.50	34.44	
		19.26	16.23	15.05	15.82	17.60	
Vit-E supl, %	M	10.91	14.28	14.03	17.50	20.43	0.0110
	W	18.53	20.92	21.33	22.51	25.57	<.0001
SBP, %							
>140 mmHg	M	33.81	36.34	34.61	35.35	32.08	0.0533
	W	16.49	16.87	19.01	17.60	16.29	0.0308
DBP, %							
>90 mmHg	M	36.54	38.32	37.68	37.38	34.85	0.1842
	W	19.10	19.83	20.22	19.58	19.99	0.8347
Diabetes, %	M	5.45	5.55	7.14	8.43	9.77	<.0001
	W	3.16	4.05	4.21	4.15	3.92	0.1903
Hyperlipidaemia, %	M	28.11	32.42	36.24	39.71	39.61	<.0001
	W	20.79	23.88	24.81	25.29	26.37	<.0001

*Continuous variables: means ± standard deviation; categorical variables: percentaje. ** The food pattern rich in antioxidants is the sum algebraic of the standardized total intake of the following food groups: fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), dairy products (low- and high-fats dairy products), types of bread other than wholemeal bread, beer, vegetable oils and fats, margarine, nuts, tea, butter, confectionery&sweet and processed meat. ºAlcohol consumption categories= Lower=abstiners or <5 g/day women or <10g/day men, Intermediate=5-15g/day women or 10-30g/day men, Higher= >15 g/day women or >30g/day men. BMI= Body-Mass-Index; DBP=diastolic blood pressure; M=men; SBP=systolic blood pressure; FP-AO=food pattern rich in antioxidants; Vit-E suppl=vitamin E supplementation; WHR=waist-to-hip-ratio; W=women.

Figure 2 shows the percentage of subjects in each quintile of the FP rich in vitamin E distributed in the quintiles of the FP rich in antioxidants. A comparison among both FPs showed that more than 70% of the subjects categorized in the highest and the lowest quintiles of the FP rich in vitamin E are also categorized in the highest and lowest quintiles of FP rich in antioxidants.

Figure 2.

Percentual comparison of derived food patterns



FP-VE1=Food pattern rich in vitamin E, first quintile; FP-VE2=Food pattern rich in vitamin E, second quintile; FP-VE3=Food pattern rich in vitamin E, third quintile; FP-VE4=Food pattern rich in vitamin E, fourth quintile; FP-VE5=Food pattern rich in vitamin E, fifth quintile; FP-AO1=Food pattern rich in antioxidants, first quintile; FP-AO2=Food pattern rich in antioxidants, second quintile; FP-AO3=Food pattern rich in antioxidants, third quintile; FP-AO4=Food pattern rich in antioxidants, fourth quintile; FP-AO5=Food pattern rich in antioxidants, fifth quintile

3.2 Incidence of cardiovascular outcomes

Table 33 shows the distribution of CV outcomes in all subjects of the EPIC-Potsdam cohort and by gender. In this analysis, the rate of people who experienced at least one cardiovascular event was 18.79% per 1000 persons during the time of follow-up. Incidence of all CV events in men was higher than women (27.38% / 13.27%). Incidence of MI in men was higher than in women (13.49% / 3.13%). However, both ST and TIA events predomined among women, 167 events in women and 150 events in men.

Table 33. Cardiovascular outcomes cases and incidence in all cohort population EPIC-Potsdam and by gender

	ALL (n=25765)		**MEN (n=10085)**		**WOMEN (n=15680)**	
	Number of events	**Incidence per 1000 %**	**Number of events**	**Incidence per 1000 %**	**Number of events**	**Incidence per 1000 %**
Myocardial infarction (MI)	185	7.18	136	13.49	49	3.13
Stroke (ST)	179	6.95	91	9.02	88	5.61
Transient ischemic attack (TIA)	138	5.36	59	5.85	79	5.04
All together, MI, ST and TIA*	484	18.79	276	27.38	208	13.27

*excluded who had more than 2 events (4 women and 5 men)

3.3 Evaluation of risk for cardiovascular outcomes

3.3.1 Association between vitamin E intake and cardiovascular outcomes

3.3.1.1 Myocardial infarction

Table 34 shows the HR and 95%CI for MI events across quintiles of energy-adjusted vitamin E intake in the overall cohort study. There was a tendency to reduce the number of MI events among all subjects across quintiles of energy-adjusted vitamin E intake, but not statistically significant (p=0.3836). Among all subjects, a statistical significant increment of the HR for MI events across quintiles of energy-adjusted vitamin E intake in multivariate model was noted.

Table 34. Hazard ratios and 95% confidence intervals for myocardial infarction events across quintiles of energy-adjusted vitamin E intake, EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=186)	46	29	39	35	36	
Person-years of follow-up	41066.24	41721.29	41516.25	41662.85	41591.08	
HR (95%CI), Model 1	1.0	0.81 (0.51-1.29)	1.16 (0.75-1.79)	1.06 (0.68-1.65)	1.12 (0.72-1.74)	0.4145
HR (95%CI), Model 2	1.0	0.87 (0.54-1.42)	1.38 (0.86-2.23)	1.37 (0.82-2.29)	1.70 (0.99-2.94)	0.0282

Model 1: adjusted for gender. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men;5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

Even though the vitamin E intake differed a statistically significant by gender (p<.0001) and the number of MI events had tended toward to increase across quintiles of energy-adjusted vitamin E intake, the analysis by gender noted that the MI events did not show an association with quintiles of energy-adjusted vitamin E intake (p=0.8744 men; p=0.3827 women).

Table 35 shows the HR and 95%CI for MI events across quintiles of energy-adjusted vitamin E intake by gender. In the same manner as among all subjects, an increment of the HR for MI closely at significant levels in the multivariate model among men was observed, but not among women.

Table 35. Hazard ratios and 95% confidence intervals for myocardial infarction events across quintiles of energy-adjusted vitamin E intake, EPIC-Potsdam cohort study, men (n=10085) and women (n=15680)

MEN	**Q1 (n=2017)**	**Q2 (n=2017)**	**Q3 (n=2017)**	**Q4 (n=2017)**	**Q5 (n=2017)**	**p values**
Number of events (n=136)	23	27	28	31	27	
HR (95%CI), Model 1	1.0	1.15 (0.64-1.95)	1.15 (0.66-2.00)	1.27 (0.74-2.17)	1.13 (0.64-1.97)	0.6696
HR (95%CI), Model 2	1.0	1.23 (0.69-2.18)	1.35 (0.74-2.47)	1.64 (0.87-3.08)	1.85 (0.93-3.70)	0.0637
WOMEN	**Q1 (n=3136)**	**Q2 (n=3136)**	**Q3 (n=3136)**	**Q4 (n=3136)**	**Q5 (n=3136)**	**p values**
Number of events (n=49)	12	6	9	8	14	
HR (95%CI), Model 1	1.0	0.49 (0.18-1.29)	0.73 (0.31-1.73)	0.62 (0.25-1.53)	1.17 (0.54-2.53)	0.6910
HR (95%CI), Model 2	1.0	0.58 (0.21-1.57)	0.93 (0.36-2.41)	0.88 (0.32-2.44)	1.77 (0.66-4.78)	0.1422

Model 1: non-adjusted. Model 2: adjusted for education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men;5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.1.2 Stroke

Table 36 shows the HR and 95%CI for ST events across quintiles of energy-adjusted vitamin E intake in overall cohort study. There was among all subjects a reduction of the number of ST events across quintiles of energy-adjusted vitamin E intake (p=0.0101), however, no significant association was observed in the different models. The number of ST events across quintiles of energy-adjusted vitamin E intake did not show a statistical significant association in the analysis by gender. Regarding the HR for ST events by gender, there was no statistically significant effect across quintiles of vitamin E intake in the multivariate models.

Table 36. Hazard ratios and 95% confidence intervals for stroke events across quintiles of energy-adjusted vitamin E intake, EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=179)	45	29	27	50	28	
Person-years of follow-up	41063.19	41722.53	41592.14	41625.49	41656.88	
HR (95%CI), Model 1	1.0	0.66 (0.41-1.06)	0.63 (0.39-1.02)	1.14 (0.76-1.72)	0.67 (0.42-1.09)	0.5194
HR (95%CI), Model 2	1.0	0.74 (0.46-1.21)	0.74 (0.44-1.26)	1.41 (0.86-2.30)	0.82 (0.46-1.48)	0.9092

Model 1: adjusted for gender. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5g/day women or <10g/day men;5-15g/day women or 10-30g/day men; >15g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.1.3 Transient ischemic attack

In table 37 the HR and 95%CI for TIA events across quintiles of energy-adjusted vitamin E intake in overall cohort study is shown. No significant relation between the number of TIA events and quintiles of energy-adjusted vitamin E intake (p=0.7472) was noted and no statistical significance either to reduce the HR for TIA events across quintiles of energy-adjusted vitamin E intake was found. The number of TIA events was not related to quintiles of energy-adjusted vitamin E intake among either men or women (p=0.8679 men; p=0.1334 women). Regarding the HR for TIA events and quintiles of energy-adjusted vitamin E intake among either men or women no statistical significant association was observed.

Table 37. Hazard ratios and 95% confidence intervals for transient ischemic attack events across quintiles of energy-adjusted of vitamin E intake, EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=138)	32	23	25	30	28	
Person-years of follow-up	41454.15	41550.49	41845.45	41485.47	41273.29	
HR (95%CI), Model 1	1.0	0.72 (0.42-1.23)	0.78 (0.46-1.33)	0.93 (0.56-1.55)	0.92 (0.55-1.54)	0.9093
HR (95%CI), Model 2	1.0	0.69 (0.40-1.22)	0.76 (0.42-1.35)	0.92 (0.51-1.66)	0.94 (0.50-1.79)	0.8072

Model 1: adjusted for gender. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5g/day women or <10g/day men;5-15g/day women or 10-30g/day men; >15g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.2 Association between the food pattern rich in vitamin E and cardiovascular outcomes

3.3.2.1 Myocardial infarction

Table 38 shows the HR and 95%CI for MI events across quintiles of FP rich in vitamin E in the overall cohort study. A tendency to diminish the number of MI events across quintiles of the FP rich in vitamin E (p=0.0082) was noted, however, no statistic significant HR for MI events across quintiles of the FP rich in vitamin E was observed. The number of MI events were not associated with quintiles of the FP rich in vitamin E among either women or men (p=0.6734 men; p=0.1831 women). Neither the crude nor the multivariate model by gender was statistically significant.

Table 38. Hazard ratios and 95% confidence intervals for myocardial infarction events across quintiles of the food pattern rich in vitamin E intake[1], EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=185)	52	34	34	43	22	
Person-years of follow-up	41289.43	41855.10	41497.10	41466.99	41449.09	
HR (95%CI), Model 1	1.0	0.83 (0.54-1.28)	1.00 (0.65-1.56)	1.47 (0.96-2.23)	0.84 (0.50-1.40)	0.7153
HR (95%CI), Model 2	1.0	0.91 (0.58-1.41)	1.13 (0.71-1.79)	1.67 (1.07-2.62)	1.02 (0.59-1.76)	0.2933

[1]The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. Model 1: adjusted for gender. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.2.2 Stroke

In the overall cohort study, the number of ST events was not associated with quintiles of the FP rich in vitamin E (p=0.4349). No relation between the HR for ST events and quintiles of the FP rich in vitamin E was noted. Analysis by gender showed that among men the number of ST events and quintiles of the FP rich in vitamin E had dependency (p=0.0552), but not among women. Table 39 shows the HR and 95%CI for ST events across quintiles of the FP rich in vitamin E by gender. There was no significant reduction of HR for ST events across quintiles of the FP rich in vitamin E among men. However, the HR for ST events among women appeared to be increased across quintiles of the FP rich in vitamin E, but only close to significance levels.

Table 39. Hazard ratios and 95% confidence intervals for stroke events across quintiles of the food pattern rich in vitamin E intake[1], EPIC-Potsdam cohort study, men (n=10085) and women (n=15680)

MEN	**Q1 (n=2017)**	**Q2 (n=2017)**	**Q3 (n=2017)**	**Q4 (n=2017)**	**Q5 (n=2017)**	**p values**
Number of events (n=91)	26	12	21	11	21	
HR (95%CI), Model 1	1.0	0.40 (0.20-0.79)	0.67 (0.37-1.20)	0.33 (0.16-0.67)	0.67 (0.38-1.20)	0.1796
HR (95%CI), Model 2	1.0	0.42 (0.21-0.85)	0.74 (0.40-1.37)	0.33 (0.15-0.71)	0.64 (0.33-1.25)	0.1816
WOMEN	**Q1 (n=3136)**	**Q2 (n=3136)**	**Q3 (n=3136)**	**Q4 (n=3136)**	**Q5 (n=3136)**	**p values**
Number of events (n=88)	14	21	15	18	20	
HR (95%CI), Model 1	1.0	1.46 (0.74-2.88)	1.05 (0.51-2.18)	1.26 (0.63-2.54)	1.45 (0.73-2.88)	0.2827
HR (95%CI), Model 2	1.0	1.63 (0.82-3.23)	1.28 (0.61-2.71)	1.57 (0.76-3.26)	2.03 (0.97-4.26)	0.0924

[1]The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. Model 1: non-adjusted. Model 2: adjusted for education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.2.3 Transient ischemic attack

Table 40 shows the HR and 95%CI for TIA events across quintiles of the FP rich in vitamin E in the overall cohort study. The number of TIA events was not related to quintiles of the FP rich in vitamin E among all subjects (p=0.4119) and among either women (p=0.6223) or men (p=0.3897). Regarding the risk for TIA, neither the gender-adjusted model nor the multivariate model was statistically significant to decrease or to increase across quintiles of the FP rich in vitamin E among all subjects and by gender.

Table 40. Hazard ratios and 95% confidence intervals for transient ischemic attack events across quintiles of the food pattern rich in vitamin E intake[1], EPIC-Potsdam cohort study, among all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=138)	30	28	34	20	26	
Person-years of follow-up	41329.75	41904.10	41443.06	41515.84	41416.08	
HR (95%CI), Model 1	1.0	0.93 (0.55-1.56)	1.15 (0.69-1.91)	0.69 (0.38-1.24)	0.92 (0.53-1.61)	0.5595
HR (95%CI), Model 2	1.0	0.90 (0.53-1.54)	1.10 (0.65-1.87)	0.65 (0.35-1.20)	0.87 (0.47-1.58)	0.4581

[1]The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products.Model 1: gender-adjusted. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals;HR=hazard ratio; n=number of persons

3.3.2.4 All cardiovascular events

Table 41 shows the HR and 95%CI for CV events across quintiles of the FP rich in vitamin E in the overall cohort study. A tendency toward reducing the HR for CV events across quintiles of the FP rich in vitamin E (p=0.0100) was observed. In the gender-adjusted model a reduction of CV events across quintiles of the FP rich in vitamin E was noted (25% reduction; p=0.0713). After adjustment for covariates an attenuation of the HR for CV events across quintiles of the FP rich in vitamin E was observed.

Table 41. Hazard ratios and 95% confidence intervals for cardiovascular events[1] across quintiles of the food pattern rich in vitamin E intake[2], EPIC-Potsdam cohort study, all subjects (n=25756)

	Q1 (n=5039)	Q2 (n=5039)	Q3 (n=5039)	Q4 (n=5039)	Q5 (n=5039)	p values
Number of events (n=484)	127	89	98	87	83	
Person-years of follow-up	41581.61	41832.75	41840.71	41704.82	41333.74	
HR (95%CI), Model 1	1.0	0.69 (0.53-0.91)	0.79 (0.61-1.04)	0.73 (0.55-0.98)	0.75 (0.56-1.00)	0.0713
HR (95%CI), Model 2	1.0	0.72 (0.55-0.96)	0.88 (0.66-1.16)	0.78 (0.58-1.04)	0.80 (0.59-1.08)	0.1922

[1]Cardiovascular events=myocardial infarction, stroke and transient ischemic attack. [2] The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. Model 1: gender-adjusted. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

Table 42 shows the HR and 95%CI for CV events across quintiles of the FP rich in vitamin E by gender. Among either men or women the number of CV events were not related to quintiles of the FP rich in vitamin E (p=0.9659 men, p=0.8941 women). However, among men the HR for CV events across quintiles of the FP rich in vitamin E decreased in the multivariate model (31% reduction, p=0.0566). No statistically significant association in women was observed.

Table 42. Hazard ratios and 95% confidence intervals for cardiovascular events[1] across quintiles of the food pattern rich in vitamin E intake[2], EPIC-Potsdam cohort study, men (n=10080) and women (n=15676)

MEN	**Q1 (n=2016)**	**Q2 (n=2016)**	**Q3 (n=2016)**	**Q4 (n=2016)**	**Q5 (n=2016)**	**p values**
Number of events (n=276)	104	59	45	39	29	
HR (95%CI), Model 1	1.0	0.73 (0.51-1.07)	0.67 (0.45-0.97)	0.65 (0.45-0.94)	0.65 (0.45-0.95)	0.0241
HR (95%CI), Model 2	1.0	0.77 (0.53-1.13)	0.73 (0.50-1.07)	0.70 (0.48-1.02)	0.69 (0.46-1.01)	0.0566
WOMEN	**Q1 (n=3135)**	**Q2 (n=3135)**	**Q3 (n=3135)**	**Q4 (n=3135)**	**Q5 (n=3136)**	**p values**
Number of events (n=208)	23	30	53	48	54	
HR (95%CI), Model 1	1.0	1.01 (0.65-1.55)	1.13 (0.74-1.72)	0.90 (0.58-1.41)	1.02 (0.66-1.57)	0.9405
HR (95%CI), Model 2	1.0	1.01 (0.65-1.56)	1.14 (0.74-1.74)	0.92 (0.59-1.43)	1.04 (0.67-1.61)	0.9993

[1]Cardiovascular events=myocardial infarction, stroke and transient ischemic attack. [2] The food pattern rich in vitamin E is the algebraic sum of standardized total intake of the following groups: vegetable oils and fats, margarine, nuts, raw vegetables, cooked vegetables, processed meat, types of bread other than wholemeal bread, beer, low- and high-fat dairy products. Model 1: non-adjusted. Model 2: adjusted for education (basic school; high education), BMI categories (<25; 25-30;>30kg/m^2), waist-to hip ratio (>0.9 men;>0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (%), hyperlipidaemia prevalence (%), alcohol intake (abstiners, <5 g/day women,<10g/day men;10-25g/day women, 10-30g/day men; >25 g/day women, >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (%). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.3 Association between the food pattern rich in antioxidant nutrients and cardiovascular outcomes

3.3.3.1 Myocardial infarction

Table 43 shows the HR and 95%CI for MI events across quintiles of the FP rich in antioxidants in the overall cohort study. Among all subjects the number of MI events decreased across quintiles of the FP rich in antioxidants (p=0.0019). Neither the gender-adjusted model nor the multivariate model showed an inverse association between the HR for MI events and quintiles of the FP rich in antioxidants, but it may appear to be a tendency to increase the risk for MI events across quintiles of the FP rich in antioxidants. In the analysis by gender no significant association was observed.

Table 43. Hazard ratios and 95% confidence intervals for myocardial infarction events across quintiles of the food pattern rich in antioxidant[1], EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=185)	53	44	38	29	21	
Person-years of follow-up	41394.59	41590.98	41800..64	41451.38	41320.12	
HR (95%CI), Model 1	1.0	1.02 (0.68-1.52)	1.06 (0.69-1.62)	0.93 (0.59-1.49)	0.77 (0.45-1.29)	0.4065
HR (95%CI), Model 2	1.0	1.08 (0.71-1.65)	1.15 (0.71-1.84)	1.05 (0.62-1.79)	0.92 (0.51-1.68)	0.9097

[1]The food pattern rich in antioxidants (vitamin E, vitamin C, beta-carotene and flavonoids) is the algebraic sum of standardized intakes of the following groups: fruits (fresh fruits, canned fruits and juice), vegetables (raw vegetables, cooked vegetables, vegetarian dishes and cabbage), dairy products (high- and low- content), tea, vegetable oils and fats, margarine, nuts, types of bread other than wholemeal bread, beer, processed meat, confectionery and butter. Model 1: adjusted for gender. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemic prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.3.2 Stroke

The number of ST events was not related to quintiles of the FP rich in antioxidants in the overall cohort study (p=0.3332). Table 44 shows the HR and 95%CI for ST events across quintiles of the FP rich in antioxidants. No relation between the HR for ST events and quintiles of the FP rich in antioxidants was found. In the analysis by gender no significant association between HR for ST and the FP rich in antioxidants was observed.

Table 44. Hazard ratios and 95% confidence intervals for stroke events across quintiles of the food pattern rich in antioxidants[1], EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=179)	37	39	44	31	28	
Person-years of follow-up	41445.65	41643.48	41814.92	41463.35	41292.82	
HR (95%CI), Model 1	1.0	1.06 (0.67-1.67)	1.24 (0.79-1.95)	0.92 (0.56-1.52)	0.89 (0.53-1.50)	0.6211
HR (95%CI), Model 2	1.0	1.19 (0.75-1.92)	1.48 (0.90-2.44)	1.10 (0.63-1.93)	1.09 (0.60-1.99)	0.8154

[1]The food pattern rich in antioxidants (vitamin E, vitamin C, beta-carotene and flavonoids) is the algebraic sum of standardized intakes of the following groups: fruits (fresh fruits, canned fruits and juice), vegetables (raw vegetables, cooked vegetables, vegetarian dishes and cabbage), dairy products (high- and low- content), tea, vegetable oils and fats, margarine, nuts, types of bread other than wholemeal bread, beer, processed meat, confectionery and butter. Model 1: gender-adjusted. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.3.3 Transient ischemic attack

In table 45 the HR and 95%CI for TIA events across quintiles of the FP rich in antioxidants in the overall cohort study is shown. The number of TIA events was related to quintiles of the FP rich in antioxidants among either all subjects (p=0.0082) or men (p=0.0288), but not among women (p=0.1148). In all subjects, a 31% reduction of HR for TIA events across quintiles of the FP rich in antioxidants was found, but large confidential intervals and bordeline "*p* values" were observed. No significant findings by gender were found.

Table 45. Hazard ratios and 95% confidence intervals for transient ischemic attack events across quintiles of the food pattern rich in antioxidant[1], EPIC-Potsdam cohort study, all subjects (n=25765)

	Q1 (n=5153)	Q2 (n=5153)	Q3 (n=5153)	Q4 (n=5153)	Q5 (n=5153)	p values
Number of events (n=138)	30	43	20	19	26	
Person-years of follow-up	41083.08	41713.58	41554.32	41642.88	41614.97	
HR (95%CI), Model 1	1.0	1.37 (0.85-2.21)	0.63 (0.35-1.14)	0.62 (0.34-1.12)	0.88 (0.51-1.54)	0.1540
HR (95%CI), Model 2	1.0	1.25 (0.77-2.04)	0.54 (0.29-1.00)	0.50 (0.26-0.97)	0.69 (0.36-1.32)	0.0582

[1]The food pattern rich in antioxidants (vitamin E, vitamin C, beta-carotene and flavonoids) is the algebraic sum of standardized intakes of the following groups: fruits (fresh fruits, canned fruits and juice), vegetables (raw vegetables, cooked vegetables, vegetarian dishes and cabbage), dairy products (high- and low- content), tea, vegetable oils and fats, margarine, nuts, types of bread other than wholemeal bread, beer, processed meat, confectionery and butter. Model 1: gender adjusted. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.3.3.4 All cardiovascular events

Table 46 shows the HR and 95%CI for CV events across quintiles of the FP rich in antioxidants in the overall cohort study. The number of CV events was associated with quintiles of the FP rich in antioxidants (p=0.0059). The gender-adjusted model showed a statistical significant reduction (27%) of the HR for all CV events across quintiles of the FP rich in antioxidants, but after multivariate adjustment this association was attenuated.

Table 46. Crude and adjusted hazard ratios and 95% confidence intervals for cardiovascular events[1] across quintiles of the food pattern rich in antioxidant[2], EPIC-Potsdam cohort study, all subjects (n=25756)

	Q1 (n=5151)	Q2 (n=5151)	Q3 (n=5151)	Q4 (n=5151)	Q5 (n=5152)	p values
Number of events (n=484)	122	117	89	79	77	
Person-years of follow-up	41581.61	41832.75	41840.71	41704.82	41333.74	
HR (95%CI), Model 1	1.0	0.91 (0.70-1.18)	0.74 (0.56-0.99)	0.72 (0.54-0.96)	0.73 (0.54-0.99)	0.0108
HR (95%CI), Model 2	1.0	0.95 (0.73-1.25)	0.80 (0.59-1.09)	0.76 (0.55-1.06)	0.80 (0.56-1.13)	0.1071

[1]Cardiovascular events=myocardial infarction, stroke and transient ischemic attack. [2] The food pattern rich rich in antioxidants is the algebraic sum of standardized intakes of the following groups: fruits (fresh fruits, canned fruits and juice), vegetables (raw vegetables, cooked vegetables, vegetarian dishes and cabbage), dairy products (high- and low- content), tea, vegetable oils and fats, margarine, nuts, types of bread other than wholemeal bread, beer, processed meat, confectionery and butter. Model 1: gender-adjusted. Model 2: adjusted for gender, education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

Neither men nor women showed a statistical significant association between the number of CV events and quintiles of the FP rich in antioxidants (p=0.7855 men, p=0.8780 women). Table 47 shows the HR and 95%CI for CV events across quintiles of FP rich in antioxidants by gender. Among men the HR for CV events across quintiles of the FP rich in antioxidants was decreased. There was a 45% of reduction for CV events in the multivariate model across quintiles of the FP rich in antioxidants (p=0.0100). Contrary to men, no statistically significant model among women was identified.

Table 47. Hazard ratios and 95% confidence intervals for cardiovascular events[1] across quintiles of the food pattern rich in antioxidant[2], EPIC-Potsdam cohort study, men (n=10080) and women (n=15676)

MEN	**Q1 (n=2016)**	**Q2 (n=2016)**	**Q3 (n=2016)**	**Q4 (n=2016)**	**Q5 (n=2016)**	**p values**
Number of events (n=276)	58	50	68	51	49	
HR (95%CI), Model 1	1.0	0.74 (0.51-1.07)	0.78 (0.54-1.12)	0.62 (0.43-0.91)	0.58 (0.39-0.85)	0.0049
HR (95%CI), Model 2	1.0	0.77 (0.53-1.14)	0.79 (0.53-1.19)	0.64 (0.41-1.00)	0.55 (0.34-0.87)	0.0100
WOMEN	**Q1 (n=3136)**	**Q2 (n=3136)**	**Q3 (n=3136)**	**Q4 (n=3136)**	**Q5 (n=3136)**	**p values**
Number of events (208)	54	27	48	36	43	
HR (95%CI), Model 1	1.0	0.97 (0.64-1.47)	0.81 (0.53-1.25)	0.79 (0.51-1.22)	0.77 (0.50-1.20)	0.2451
HR (95%CI), Model 2	1.0	1.01 (0.66-1.55)	0.90 (0.56-1.43)	0.87 (0.54-1.42)	0.88 (0.53-1.47)	0.5359

[1]Cardiovascular events=myocardial infarction, stroke and transient ischemic attack. [2] The food pattern rich rich in antioxidants is the algebraic sum of standardized intakes of the following groups: fruits (fresh fruits, canned fruits and juice), vegetables (raw vegetables, cooked vegetables, vegetarian dishes and cabbage), dairy products (high- and low- content), tea, vegetable oils and fats, margarine, nuts, types of bread other than wholemeal bread, beer, processed meat, confectionery and butter. Model 1: non-adjusted. Model 2: adjusted for education (basic school; high education), BMI categories (<25; 25-30; >30kg/m^2), waist-to hip ratio (>0.9 men; >0.8 women), smoking status (non-smoker and ex-smoker status; current), diastolic blood pressure (>80mmHg), systolic blood pressure (>140 mmHg), sport activity (>2 hour/week), diabetes prevalence (yes/no), hyperlipidaemia prevalence (yes/no), alcohol intake (abstiners or <5 g/day women or <10g/day men; 5-15g/day women or 10-30g/day men; >15 g/day women or >30g/day men), tertiles of PUFA/saturated fat intake ratio, VE supplementation users at baseline and follow-up (yes/no). CI=confidence intervals; HR=hazard ratio; n=number of persons

3.4 Other analysis

In sub-analyses by age categories, smoking status, vitamin E supplementation, PUFA/saturated fats ratio there was no statistically significant association between these variables and CV outcomes. The exclusion of subjects in both extreme percentiles of energy-adjusted vitamin E did not change previous findings. The evaluation of Schoenfeld residuals of predictors suggest that the proportionality assumption was violated.

4. DISCUSSION

4.1 Vitamin E and cardiovascular risk, comparison with previous studies

The present study analysed the relationship between vitamin E intake and risk of CVD based on 27,576 participants from the EPIC-Potsdam study over a mean follow-up time of 8.1 years. In summarizing the EPIC-Potsdam population characteristics and vitamin E intake, individuals with high vitamin E intake compared to those with low vitamin E intake were more likely to be women, to have a higher educational, non-smokers habits, lower and intermediate alcohol consumption, to spend more time in sport activity and to use vitamin E supplements. In contrast, the lowest intake of vitamin E was noted among subjects who had higher WHR and over normal range of blood pressure (SBP and DBP), and more likely also to report diabetes and hyperlipidaemia.

In this study, the intake of vitamin E in the overall cohort as well as by sex was higher than the dietary vitamin E intake reported by the German Nutrition Survey (GeNuS) [152] and the NHANES 1999-2000 [153]. The EPIC-Potsdam population would be characterized as well-nourished population but in deficit of vitamin E intake according to DRI for Germans (see Table 3). In the overall cohort from EPIC-Potsdam 66.5% of the subjects did not reach the DRI for vitamin E taking into account only food sources. This finding is similar to another German report. In the GeNuS non users of vitamin supplementation showed 66.5% and 68.6%, men and women respectively, below the DRI for vitamin E. In adittion, these percentages below the DRI for vitamin E dropped among the regular users of vitamin E supplements, minus 6.4% among men and minus 8.6% among women [152].

For 1998 the GeNuS reported that 38% of men and 48% of women add vitamin and/or mineral supplements to their usual diet [152], and also a recent report shows that 27,6% of German people are vitamin and/or mineral supplements users being predominantly women

who take supplements [154]. In US according to the NHANES III, the prevalence of dietary supplement usage reachs about 40% [155]. In the present study 9.1% of the overall cohort reported to take vitamin E supplementation at baseline or at one point during the follow-up being also predominant among women with healthy behaviours. This frequency of vitamin E supplementation is in accordance with those found in the MONICA study [156].

The characterization of the EPIC-Potsdam population across dietary vitamin E intake quintiles in this study is in agreement with lifestyle patterns previously reported as healthy lifestyle pattern associated with supplementation usage [157, 158].

The author's review of prospective cohort studies, meta-analyses and pooling projects of cohort studies which have evaluated vitamin E intake and CVD among adult population suggests a possible protective effect of the vitamin E intake on CVD, specifically CHD and ST (5% to 65% reduction) [84]. As was showed in the Section **1.4** (tables 7-8), after adjustment for known and potential risk factors, the inverse association between vitamin E intake and risk of CVD remained statistically significant in most but not all of those reviewed studies. In the present study from EPIC-Potsdam, known CVD risk factors as age, BMI, WHR, smoking status, education level, alcohol consumption, blood presure levels, sport activity, diabetes and hyperlipidaemia were linearly related to dietary vitamin E intake. The influency of these factors on vitamin E had been previously mentioned (Section **1.3)**. But contrary to results from observational studies (tables 7-8) and against all expectations, seeing the distribution of these risk factors across quintiles of vitamin E intake, in this study from EPIC-Potsdam an increment of the risk for MI in the overall cohort associated with higher intake of vitamin E was found ($p=0.0282$), but the risk for either ST or TIA events was not associated with dietary intake of vitamin E.

The paradoxical properties of vitamin E as anti- and pro-oxidant would partially explain both the increment of the risk for MI associated with higher intake of dietary vitamin E and the non association between vitamin E and the risk for ST and TIA [31, 159-161]. This was also observed in the HPFS, an inverse association with MI was found but not with ST [162, 163].

An explanatory hypothesis suggests that each CV event is affected in different manner depending of the types of fats [164]. Moreover, a previous report from EPIC-Potsdam study showed that classical risk factors may explain more ST events than TIA events [165]. In the present study it appears that any potential association between vitamin E intake and ST could be attenuated by including different types of ST together in the analysis. Among observational and RCTs studies which have analyzed the relation between vitamin E intake and ST and were also described in the Section **1.4**, only the IWHS showed 60% reduction for ST linked to dietary intake [166] and the LIXIAN-1 reported about 58% reduction of cerebrovascular linked to a mix supplementation including vitamin E [101, 111], but an increment of subarachnoid hemorrhage is linked to vitamin E supplementation in the ATBC [102].

Prospective studies on vitamin E intake and the risk for CVD, all which were previously described on Section **1.4** and also the present study from EPIC-Potsdam, did not only differ in their exposure variable (vitamin E intake from either dietary sources and /or from supplements) but also used different assessment methods to derive vitamin E intake. Almost all of those have been based on data collection by different well-known questionnaires which had been tested in advance, proving a reasonable validity and reliability; however, disadvantage of nutritional data collection methods cannot be taken away. First, self-reported nutritional questionnaires may cover information on the diet of any given period in the past, but their answers are likely to be strongly influenced by the immediate past, and information on the day-to-day variation and the seasonal fluctuation of foods (e.g. fruits and vegetables) and nutrients cannot be obtained [167, 168]. Furthermore, because the information is based on an individual's memory and report, all collected methods have a subjective component, and an element of omission or addition of foods. Second, people tend to over-report their intake of fruits and vegetables, and underreport important sources of vitamin E from foods (i.e. fat and oil consumptions), which would underestimate vitamin E intake [144, 168-169]. In the EPIC-Potsdam study as well as in the HPFS [72, 85] and IWHS [86, 166] seem to have incorporated questions about home food processing which is known to influence the vitamin E content of the food, thus measurement error in the estimation of vitamin E intake is disminished [75].

In this analysis from the EPIC-Potsdam study, the vitamin E intake data were derived from FFQ at baseline and data on the use of vitamin supplementation were collected at baseline and

follow-up. Because the risk estimation was based on single assessment of the exposure, the present study from EPIC-Potsdam and almost all prospective studies which were described in the section **1.4** have limited ability to detect and to explain the relationship between disease and nutrient intake if diet changes over time [170]. According to Patterson et al. [171], a measure of the usage of supplement at one point in time incorporates measurement error that will attenuate measures of association. Other cohort studies have reported the elimination of the potential biased recall of both dietary vitamin E intake and VE supplement use (e.g. updating information about dietary vitamin E intake and the consumption of multivitamins and VE supplements), the NHS [172] and HPFS [162-163]. Another cohort tested the association between dietary vitamin E intake and ST by averaging the vitamin E intake in three times, the ZS [94]. In this analysis of the EPIC-Potsdam study the vitamin E supplementation data at follow-up was taken into account, but no significant difference between users and non users of vitamin E supplementation in the risk for CV outcomes was found.

In this study from EPIC-Potsdam as well as almost all cohort studies which had analyzed vitamin E intake and CVD, vitamin E intake was assessed as α-tocopherol equivalent that does not consider the contribution of all forms of vitamin E; and they did not distinguish between components of vitamin E, which seem to have a relevant role on the atherosclerotic process [173-175]. It is likely that the high bioavailability of α-tocopherol is the reason that more weight has been carried on α-tocopherol (e.g. the accuracy of dietary questionnaires are designed to compare vitamin E intake with plasma α-tocopherol concentrations) than on other non-α-tocopherol forms. Data from experimental and human studies suggested that some other non-α-tocopherol forms of vitamin E may play a protective role against cancer and CVD [31, 175-178].

4.2 Vitamin E, energy, fats and cardiovascular diseases

To summarize findings in the present study, fat contribution to total energy intake was over 35% and the PUFA intake had the higher rank, 80.5%, to explain the variance in the raw

vitamin E intake than any of the other fat components showed. After energy adjustment of the vitamin E intake, the inflation of PUFA intake as fat component relate to vitamin E intake is corrected (30.63%). When the ratio of PUFA to saturated fatty acid was included (Model 2) and the total energy intake was also adjusted, the ratio of PUFA to saturated fatty acid was the most important fat component relate to vitamin E (39.84%). Additionally, food groups known as foods rich in trans fatty acids, i.d. cake&cookies and margarine, showed an inflated contribution to vitamin E variance, 19.47% and 24.54% respectively. After the energy adjustment, these food groups reduced their contribution to vitamin E variance, specially cake&cookies (1.76%).

These results seemed to confirm the relation between energy, fatty acids sources and vitamin E. The indisputable fact is that fats supply energy and essential fatty acids, and are also the main sources of vitamin liposolubles like vitamin E [179]. Because persons who consume more total energy also tend to consume more of specific nutrients, absolute intakes of all nutrients are related to risk of diseases, and failure to adjust for energy intake can lead to misleading conclusions [143]. The adjustment for total energy intake corrects by individual differenciation of energy expenditure and compensates also error of energy intake reporting [168]. In this analysis the methodological strategy of adjustment for total energy intake by residual method appears to be adequate to remove extraneous variation due to total energy intake, specifically due to fat intake [143-144, 146, 180-183]. It has been reported that the residual method also increases the power to detect nutrient-disease associations when the exposure variables are categorized [143]. Epidemiological evidences have reported different associations between dietary fat intake and CVD [179] and almost all discrepancies result from methodological limitations like small study size, inadequate dietary assessment methods, no recollection of dietary information repeatedly during follow-up, and no proper account for total energy intake [184].

Findings from NHS reported that among women a high dietary intake of saturated fatty acids is associated with an increment of the risk for CHD, but a high dietary intake of the ratio of PUFA to saturated fat is associated with a significantly lower risk of CHD. In addition, the substitution of PUFA for saturated fat without a reduction in the total fat content of the diet substantially reduced the risk of CHD [170]. Other reports from NHS showed that a higher

intake of α-linolenic acid is protective against fatal IHD [181]. In another study neither saturated fat intake nor MUFA fat intake were statistically significant predictors of CHD, but the ratio of PUFA to saturated fat intake was inversely associated with risk of CHD [185]. On the other hand, an intervention among postmenopausal women who reduced the total fat intake and increased intakes of vegetables, fruits and grains during 8.1 years did not reduce the risk for CHD, ST, or CVD [186]. Among American Indians total fat, saturated fatty acid, and monounsaturated fatty acid intake were direct predictors of CHD mortality [187]. Among men n-3 PUFAs from both plant and seafood sources may reduce CHD risk [188]. In GISSI-Prevenzione clinical trial, long-term administration of omega-3 PUFA (1 g daily) significantly decreased the risk of overall (-20%), CV (-30%), and sudden death (-45%) [189]. A recent report from a multiethnic cross-sectional population found that higher intake of saturated and trans fats are associated with the increased subclinical atherosclerosis [190].

Other research has suggested that chronic diseases like CHD, ST, hypertension, diabetes, obesity, depression, schizophrenia, and Alzheimer's disease are characterized by low-grade systemic inflammation condition, and this condition is linked with an essential fatty acids deficient state. Essential fatty acids or PUFAs are also suggested as “endogenous polypill” to prevent CV mortality and morbidity due to having aspirin-like action, inhibit of HMG-CoA and ACE enzymes, and possess diuretic, anti-hypertensive, and β-blocker-like actions [191-193]. Although all essential fatty acid are PUFAs, not all PUFAs are essential fatty acid. PUFAs are considered precusors of pro- and anti- inflammatories molecules and it has been suggested that the balances of those components could determine the final outcome of the disease process. This paradox of PUFAs is similar to the vitamin E paradox, pro- and anti-oxidant [191].

A meta-analysis found that a 2% increase in total energy intake from trans- fatty acids was associated with a 23% increase in the incidence of CHD, and inclusively trans fatty acids appear to increase the risk of CHD more than any other macronutrient at lower levels of intake [192, 193]. On the other hand, the intake of trans- fatty acid from rumians appears to have other effects [194].

Based on all these evidences dietary recommendations support the idea that types of fats are more important than total amount of fat in determining the risk of CVD [179, 195]. Most fats and oils consumed on a regular basis are a combination of several fatty acids, not fat or oils containing only one type of fatty acid [179]. However, the ability to distinguish an effect on CV events from either vitamin E or the different fat components is limited by their high intercorrelations, i.e. high degree of statistical collinearity, because their predominant sources are the same foods [196].

Because dietary vitamin E comes from dietary fat sources and the metabolism of vitamin E is linked to fat metabolism, almost all limitations in the methodological analysis of fats, previously mentioned, may also apply to vitamin E analysis [143, 144, 197, 198]. From the author's review [84] five cohort studies which tested the association of vitamin E intake on CVD included at least one blood lipid parameter in their multivariate models (NHS, FS, ZS, SHHS, and ATBC) [88, 94, 125, 172, 199] and one analysis from IWHS included intake of cholesterol and saturated fats in the multivariate model [166].

In the present study, only the ratio of PUFA to saturated fatty acid intake into multivariate hazard risk models was introduced. The ratio of PUFA to saturated fatty acid intake is an index that contains the composition of dietary fat intake in the overall cohort and bias may occur due to the correlated measurement errors among nutrients (exposure and confounders) [168]. This analysis from EPIC-Potsdam failed to control for intake of trans fat. This may seriously confound the associations for unsaturated fats because of strong correlations between trans fat and mono- and polyunsaturated fats [197] and could partially explain the association between vitamin E and MI. In addition, a food group rich in trans fatty acid as margarine was chosen to be a part of both food pattern rich in vitamin E and food pattern rich in antioxidant. The limitation of the nutrient database for trans fatty acids was not available and therefore not able to account for trans fatty acid intake and residual confounders may not be rejected. There are also potential limitations related to the nutrient database for all components of vitamin E and larger differences in the types of fats and oils due to the manufacturing process.

With regard to alcohol intake, it is unclear, the contribution to total energy intake and the role on CVD [59, 190, 200, 201]. Alcohol consumption appears to influence the status of antioxidants including vitamin E [59, 206]. In this study from EPIC-Potsdam, the energy from alcohol intake was not able to explain variance in the vitamin E intake but lower and intermediate levels of alcohol consumption were among subjects with higher intake of vitamin E.

4.3 Vitamin E, antioxidants and derived food intake patterns

The traditional analysis of a single nutrient or food and its relationship with diseases has been described to have conceptual and methodological limitations [202-204]. On the other hand, dietary pattern has importance in the area of nutritional epidemiology to evaluate the relation between diet and the risk for diseases because of the dietary pattern are more closely related to the fact that nutrients and foods are consumed in combination, and their joint effects may best be examined by considering the whole eating behaviour [202, 205-206]. Overall, in observational studies two general approaches have been suggested to derive patterns of food intake related to CVD, specifically CHD and ST. One way is the hypothesis-oriented that is based on available scientific evidence for specific diseases, and the other is based on exploratory methods that depends on the data to derive patterns [138, 202, 205-208].

In the present study, two dietary patterns were constructed from the sum of standardized total intake of selected food groups derived of linear regression and reduced rank regression models. One is a FP rich in vitamin E and the other one is a FP rich in antioxidants, i.e. vitamin E, vitamin C, carotenoids and flavonoids. A higher score of the FP rich in vitamin E is characterized by a high intake of vegetable oils and fats, margarine, nuts, raw vegetables and cooked vegetables, and on the other, by a low intake of types of bread other than wholemeal bread, beer, processed meat, high- and low-fat dairy products. A higher score of the FP rich in antioxidants shows, on one side a high intake of fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), vegetable oils and fats, margarine, nuts and tea, and on the other, a low intake of dairy

products (low- and high-fat dairy products), types of bread other than wholemeal bread, beer, butter, processed meat and confectionery&sweet. Almost all of those food groups have been reported as component part of dietary patterns namely “fruit and vegetables” and “plain cooking” from a previous analysis of the EPIC-Potsdam study [206].

The present study as other previous reports confirms that nutrients and food groups are highly correlated [196, 202, 204, 209]. In fact, stronger correlations among antioxidant nutrients (vitamin E, vitamin C, carotenoids and flavonoids) and some food groups are noted, especially those included in the derived FPs. The correlation matrix showed the strength of association and how these FPs account for the possible cumulative or/and interactive effect among nutrient-nutrient, nutrient-food, and food-food. In the present study correlations among vitamin E, vitamin C, β-carotenoids, flavonoids and the both FPs rich in vitamin and rich in antioxidant were larger and stronger than in other food patterns from previous reports of EPIC-Potsdam study including similar food intake groups but derived by factor analysis [206].

Some food groups of those FPs have been associated with the risk for CVD in other studies. Frequent nut consumption was related to a reduction of the risk of both fatal CHD and non-fatal MI [210]. Among women higher intake of whole grain foods was associated with a lower risk of ischemic ST [211] and with decreased risk of CHD [212]. Results from prospective cohort studies showed that an increased consumption of fruit and vegetables is related to a reduction in CHD risk [213-215] and also ST risk [216]. Other findings reported a beneficial effect of whole-grain and fruit and vegetable consumption on the risks of total mortality and incident CAD but not on the risk of ischemic ST [217, 218]. On the other hand, an increment of CVD risk had been demonstrated with higher intake of dairy fats [219], butter and margarine [220]. With regard to dairy products, controversial findings have been reported [221].

Some food groups of those FPs were also a part of several dietary pattern which have been previously related to the risk for CVD. Dietary pattern analysis from prospective

observational studies suggested that plant-based dietary patterns which are rich in fruit, vegetables, and whole grains, low in meat and refined grains, and that focus on healthy sources of fats are useful for preventing CHD and ST [205]. A “prudent pattern” characterized by higher intakes of fruits, vegetables, legumes, fish, poultry, and whole grains significantly lowered CHD risk [222-224] and also ST risk [225], whereas a “western pattern” characterized by higher intakes of red and processed meats, refined grains, and sweets and desserts significantly increased CHD risk [222] and also ST risk [225]. A diet high in PUFA (high consumption of seed oils, low consumption of olive oil, processed meat, fish, eggs, and vegetables) has been related with lowest mortality rates [226]. Diets lower in carbohydrate and higher in vegetables sources of protein and fat may moderately reduce the risk of CHD [227]. A dietary pattern of nutrient-rich plant foods and high-fat fish and low in trans fatty acids was associated with decreased risk of MI [220]. A Japanese dietary pattern highly correlated with soybean products, fish, seaweeds, vegetables, fruits and green tea was associated with a decreased risk of CVD mortality [228]. A score based on 8 food and nutrient components (fruits, vegetables, whole grains, nuts and legumes, low-fat dairy, red and processed meats, sweetened beverages, and sodium) was associated with a lower risk of CHD and ST [229]. Furthermore, a frequent consumption of traditional Mediterranean food is associated with reduced CV mortality [230]. Another Mediterranean dietary score (components included vegetables, legumes, fruits, nuts, whole grains, fish, monounsaturated fat-saturated fat ratio, alcohol, and meat) was associated with reduced CVD among men but not among women [231].

With regard to FPs and population features from data of the EPIC-Potsdam study, the highest score of either FP rich in vitamin E or FP rich in antioxidants was observed predominantly among women, young adults, who were more likely to have education, non-smokers habits, lower and intermediate alcohol consumption, to spend more time in sport activity and to use vitamin E supplements. In contrast, the lowest score of either FP rich in vitamin E or FP rich in antioxidants was noted among people who had a BMI above 25 kg/m^2, SBP and DBP values over normal range and had also higher values of WHR. The characterization of the EPIC-Potsdam across both FPs was similar to vitamin E intake. All of these findings suggest that the healthy lifestyle at baseline in the EPIC-Potsdam study is related to a higher intake of micronutrient as vitamin E, vitamin C, β-carotenoids and flavonoids as well as to a dietary intake behaviour rich in plant-based foods.

The present study showed an association between FPs and all CV events, but only among men significant relationships were found. Higher intake of FP rich in vitamin E is associated with a 31% of reduction for all CV events and higher intake of FP rich in antioxidants is associated with a 45% of reduction for all CV events. In other words, a dietary pattern rich in plant-based foods and low in animal source foods seems to be linked to a reduction in CV events. The 14% of difference of risk for all CV events among both FPs seems to be linked to the effect of inclusion of fruits, tea, butter and confectionery&sweet in the FP rich in antioxidants. The FP rich in antioxidants may explain more the whole intake (nutrients and foods) than the FP rich in vitamin E or the single nutrient, i.d. vitamin E intake. These findings are agreement with the assumption of an existing antioxidant network [40, 191, 232] and suggest that any single nutrient, specially antioxidants, may be analyzed without the consideration of other nutrients when the relatioship diet-disease is evaluated.

Nutritional patterns derived from exploratory methods may be used to overcome some of the limitations of existing epidemiological studies, it is known [202, 204-205], however, bias in the interpretation of results cannot be rejected due to dietary pattern often may not be reproducible in other populations [202], or simply are caused by the play of chance due to the insufficient number of outcomes to justify associations [233]. Both linear regression by selection stepwise and reduced rank regression statistical methods can be applied to explain variation in nutrients by linear functions of food intakes and make possible the identification of food groups into a nutrient pattern or dietary intake behaviour. Selection of response variables for the reduced rank regression model is based on prior information, then the reduced rank regression allows both ways to derive food pattern, hypothesis-oriented and exploration of data. In addition, the proposed score to construct simplified measures of dietary patterns by Schulze MB [148] showed stability to describe this dietary intake behaviour.

In this analysis, although several dietary and non-dietary components significantly related to known healthful patterns were not introduced into multivariate models (eg, fiber and folate), stronger correlations with derived FPs were found. It might be to suggest that the derived FPs capture additional aspects of a nutrient intake behaviour and thus foods including in both FPs may be good markers for dietary and lifestyle factors associated with the risk of CV events.

4.4 Other perspective, from traditional biomarkers to inflammatory and genetic biomarkers

In general, the assessment of vitamin E with questionnaires may not measure the true exposure of a subject because the hypothesized effect of vitamin E on CVD is influenced by the bioavailability and bioactivity [234]. Most frequently biomarkers used to measure exposure for vitamin E intake are plasma and serum levels of α-tocopherol as is mentioned on Table 4. Other as adipose tissue α-tocopherol concentration may be a good biomarker of long-term exposure for VE which appears to be independent from the presence of disease [235, 236], however, studies which have assessed adipose tissue α-tocopherol levels did not find an association to CVD [237, 238]. Another study has assessed other cellular and urinary markers of vitamin E metabolism; perhaps it could have helped to explain some association of vitamin E intake and CVD [239]. Furthermore, other studies also assessing non-α-tocopherol forms (i.e., γ-tocopherol and the ratio α-/γ- tocopherol) found an inverse association between γ-tocopherol, but not α-tocopherol, and CVD [240-241].

One author's review had analyzed epidemiological evidences of vitamin E from biological material and its relationship with CVD, but divergent results made it impossible to mergue in a definitive conclusion [84]. There are only two prospective studies that investigated serum α-tocopherol concentrations in relation to CVD incidence or mortality using a full cohort design; one based on data from the ATBC showed an inverse association between serum α-tocopherol concentrations and CVD mortality, especifically CHD and ST; and the other one based on a population-based follow-up study in Japanese inhabitants reported that only high serum levels of β- plus γ-tocopherols had a weak tendency to be related to high hazard ratios for heart disease and IHD but not to ST, whilst other tocopherols were not significantly associated with CVD [242].

In other way, healthful diet has been associated with antioxidant biomarkers. Neuhoser et al showed that higher plasma concentrations of α-tocopherol, vitamin C and beta-cryptoxanthin are associated with an “excellent and good diet” score according to the Diet Quality Index [243], this index was also revised and positively correlated with plasma carotenoids and vitamin E [244]. Gerber et al identified plasma concentration of EPA, DHA, β-carotenoid and vitamin E as biomarkers of quality of diet, but one composite index of all of those biomarkers was a best dietary quality indicator [245]. Furthermore, indices like Healthy Eating Index, Recommended Foods Score (from 24HR) and Dietary Diversity Score for Recommended Foods were identified as stronger positive predictors of serum concentrations of α-tocopherol, vitamin C, folate and carotenoids [246].

Food groups, component of the derived FPs in this analysis, have been correlated with some biomarkers. It is worth mentioning here; vegetable and fruit intake showed positive correlation with carotenoids [247-250] and vitamin C [248, 251]; nut and seeds intake showed inverse relations with levels of C-reactive protein, interleukin-6, and fibrinogen [252]; soy foods, fruit juice, chocolate, grape seed fruit, vegetables, tea and wine are positively correlated with different types of flavonoids [253]; salad, raw vegetable, and salad dressing intake are positively associated with serum micronutrient levels of folic acid, vitamin C, vitamin E, lycopene, and alpha- and beta-carotene [254]. In addition, different associations between dietary patterns and inflammatory biomarkers have also been reported [255-257]. It seems to be likely a result of the strategy of combining different antioxidants, which protect each other and act together at different levels of the lipid production, improves lipid profile, inflammatory and oxidative status [258-264].

Based on the above mentioned, the use of valid biomarkers of exposure for vitamin E, it is also applied to other antioxidants as vitamin C, β-carotenoids and flavonoids, may increase accuracy to investigate nutrient-disease relations [72, 265-266]. Any biomarker in the present study was included. In general terms, the use of biomarkers is limited among cohort studies not only due to the availability at a reasonable cost but also other requirements as high quality assays and an appropiate interpretation of metabolism of antioxidants.

To the best of the author's knowledge, only two studies have derived dietary patterns using reduced rank regression in which are related food groups to CV outcomes, but both were associated also with known biomarks of CVD. One reported that the combination of a high intake of whole-grain bread, fresh fruit, olive oil, mushrooms, cruciferous vegetables, wine, and nuts with a low intake of fried potatoes is associated with a favorable biomarker profile (high plasma folate and vitamin B-12, but low homocysteine concentrations), and the reduction of the risk for CHD in two different German populations [267]. The other one reported that high intakes of meat, margarine, poultry, and sauce and low intakes of vegetarian dishes, wine, vegetables, and whole-grain cereals are associated with CAD biomarks (high concentrations of C-reactive protein and C-peptide and low concentrations of HDL cholesterol) and the increment of the risk for CAD among German women [268]. Furthermore, using the reduced rank regression to derive dietary pattern, another study reported that a diet high in total and saturated fat and low in fiber and micronutrients is associated with increment of subclinical atherosclerosis [256].

The weight for each antioxidant compounds varies significantly depending on the type of score constructed (Table 12). In the present study the simplified food intake pattern assigns the same weight for each selected food group, but the antioxidant content and antioxidant activity is not taken into account. Antioxidant activity is one of several factors that probably contribute to reduce chronic disease. Some studies suggest that to inquire a relationship between antioxidant and CVD both biomarkers of antioxidant content and inflammatory biomarkers are necesary to analyze [236, 269-271], others suggest that the analysis of the TAC of the diet may also be useful [272-277]. TAC is an independent predictor of plasma β-carotene concentrations [278], diets according TAC have been tested using biomarkers of inflamation [279], dietary TAC is inversely and independently correlated with plasma concentrations of high-sensitive C-reactive protein [275]. However, the antioxidant activity may not be the most important health factor for selected foods which were included in the derived FPs in this study, e.g. antioxidant activity associated with fiber is remarkably high in colon. Thus, bias by omission or inclusion of foods into the FPs cannot be rejected [276].

Finally, nutritional genomics may greatly contribute to the understanding the cellular and molecular mechanisms underlying diet-disease relationships [280]. There is evidences of

nutrient-gene and gene-environment interactions, and the gene expression patterns may be associated with many chronic diseases [281]. With regard to antioxidants, the polymorphism of P22(phox) C242T has been related to CVD and also associated with low plasma concentration of vitamin E among Chinese [282, 283], and a possible role of the Hp polymorphism in vitamin C deficiency and atherosclerosis has been also reported [284].

4.5 Strenghts and limitations

In general, an increment of the risk for MI in the overall cohort associated with higher intake of vitamin E was found. Although the paradoxal properties of vitamin E, pro- and anti-oxidant, which may explain this finding, the chance cannot be omitted being that the highest score of FP rich in vitamin E showed other tendency on the risk for CV events. Then, a generalization of results based of single vitamin E intake is inappropiate to do.

Based on results of the derived FPs, FP rich in vitamin E and FP rich in antioxidant, and the estimate relative risk for all CV events among men, it seems to be that these results partially support current recommendations for the adoption of a dietary pattern rich in plant-foods but low in fat foods from animal sources such as dairy products, butter and processed meat for protection against the occurrence of the cardiovascular events.

However, some limitations cannot be omitted in the interpretation of those results. Measurement error affects the determination not only exposure variable but also other dietary and non-dietary variables included in the multivariate models. Errors of dietary measurement are likely to be correlated because dietary intake estimation is obtained from the same instrument. As a consequence of measurement error, an important protective association would be attenuated or/and the HR in the multivariate model would be inflated, and thus it would be interpreted as under- and over-adjustment [168, 196, 285]. Other limitation is the residual confounding that results from either measurement error of covariates which are included in multivariate models or unmeasured variables [286-287]. In the present study all

variables included in multivariable Cox regression models are known to have an effect on intake of vitamin E or/and CV events, but variables as BMI and alcohol consumption showed a contrary effect to the expected on the risk for CV events. Nevertheless, some reports have noted a similar apparent cardioprotective effect of moderate alcohol intake linked to drinking pattern and type of alcohol [190, 200, 201, 288-291]. In addition, other reports showed a joint relationship of physical activity and BMI with CVD risk [292-294].

As was noted in previous reports including one based on EPIC-Potsdam data, variables which influenced the risk for ST may be different to variables influenced the risk for TIA [165, 295-297]. In this study reduced models did not show a significant change in the estimate risk for ST and TIA.

In this study another methodological limitation is a possible misclassification of the exposure variable, i.d. vitamin E intake, which results from either to consider only the dietary intake or an inapropiate categorization due to non-linearily in the dose-response relationship [298-300]. The contribution of vitamin E supplementation to total intake of vitamin E has been found to range from 3 to 6% in German population references [152, 301]. The total vitamin intake is generally higher among regular users as compared to nonusers of dietary supplements [152]. Not having information about intake of vitamin E from dietary supplements may lead to a considerable misclassification of individuals with regard to total intake and rankings of intake. Especially users of high dose of supplements who are cathegorized into the lowest quintile, whereas those belong to the highest quintile [298-299]. In spite of the fact that in the present study only dietary intake of vitamin E was evaluated, there were not difference in the estimate HR for CV outcomes among users and non users of vitamin E supplements.

It is known that the categorization in quintiles of exposure variables could add limitations to clarify the nutrient-disease relation. On the one side, the categorization makes a continuous predictor be more accurately modeled and thus it seems to yield interpretable estimates of risk. It seems to apply in nutritional exposures [180]. On the other hand, the needed dummy variables will spend more degrees of freedom than will fitting a smooth relationship, hence

power and precision of estimates will suffer due to loss of the inherent variability of exposure variable and increment the variance of the estimated hazard ratio [302-303]. In addition, frequency of events abruptly changes within two categories when the exposure variable reaches an unknown threshold level, e.g. the number of events of ST between third and fourth quintiles of energy-adjusted vitamin E (table 36). Such threshold effects are common in biological data where a drug therapy is ineffective until the dosage reaches the right level [304-307]. In this study, the extending Cox model shows limitations because the proportionality assumption was suggested to be violated. It appears to be linked to the presence of time-dependent variables, but also misclassification of exposure and covariates. Further analysis would be fitted to provide more appropiate and flexible model.

The present analysis has several strengths, nutrient intakes were estimated with a validated dietary instrument in a large, well-described cohort. Little loss to follow-up and the verification of outcomes reduced misclassified outcomes. To the author's knowledge the relation between a dietary pattern rich in vitamin E and CVD has never been reported and there is also the first report of a dietary pattern rich in antioxidant derived by reduced rank regression and its relation with CV events. The author consider that this methodology to obtain the food patterns may be actually applied.

In the present analysis, the mean of follow-up time of about 8 years was short to compile a far greater events among a healthy population. Conversely, other cohort studies with short follow-up time reported more CV events and significant associations (table 7). In this study of data from EPIC-Potsdam the statistical power could have been jeopardized due to the effect size and the variability in the outcome measure as consecuence of a too-small ratio of events per variable (<10 events) [233, 308].

In this analysis were not considered change of diets in the follow-up, disorders of nutrition and medicaments [309], this possibly introducing bias. A generalization of these findings associated with CV events appears to be limited, because a dietary pattern has a geographical and culture influence [310], and CVD has also its own sociodemographic risk factors [311].

4.6 Public health impact and future research

In fact, CVD, especially MI and ST, are considered a public health issue and according to tendency studies CVD will rise in the next decades and with it, a larger economic impact will is predictable. Several international organizations conduct a strong effort to prevention, giving priority to measures aimed at improving lifestyles as well as one of the major health determinants, nutrition.

Vitamin E has been described to have antioxidant and non-antioxidant functions, but its role on the prevention of CVD is unclear. Contradictory findings have been reported and a definitive conclusion is not able to do. Information based on dietary pattern is easier to translate into public health recommendations, thus dietary pattern continues being a suitable way to analyse diet-disease associations. In addition, an update of food content of the different forms of vitamin E (tocopherols and tocotrienols) as well as different types of fats is necesary. Further analysis could also explore a more flexible model that allows to derive the threshold level of vitamin E intake in order to define multiple cut points of dietary intake according to biological plausibility, i.e. biomarkers.

New study designs should take into account the experimental evidences of metabolism, genetic, molecular actions, and synergy; and also incorporate traditional biomarkers, inflammatory and genetic biomarkers. The inclusion of clinical imaging methods to assess the progression of atherosclerosis may also be considered. Both observational and intervention studies are required to uphold the hypothesis of a possible relation between vitamin E and CVD. Under the assumption that the possible effect of vitamin E as well as other antioxidant factors may be small, long studies with large sample sizes to produce reliable estimates are required. Nutrigenomic research may be useful to inquire in diet-disease relationships. Cohort studies may analyze multiple factors which may influence CVD risk through of the life, possibly including a family long life study.

5. SUMMARY AND CONCLUSIONS

The EPIC-Potsdam population would be characterized as a well-nourished population but in deficit of vitamin E intake. The characterization of the EPIC-Potsdam population across dietary vitamin E intake quintiles in this study seems to be according to other lifestyle patterns previously reported as healthy lifestyle pattern associated with supplementation usage. These results seemed to confirm the relation between energy, fatty acids sources and vitamin E. In this analysis the methodological strategy of adjustment for total energy intake by residual method appears to be adequate to remove extraneous variation due to total energy intake, specifically due to energy contribution by fats. In this study, individuals with high vitamin E intake compared to those with low vitamin E intake were more likely to be women, to have higher education, non-smoking habits, lower and intermediate alcohol consumption, to spend more time in sport activity and to use vitamin E supplements. In contrast, the lowest intake of vitamin E was noted among subjects who had higher WHR and over normal range of blood pressure (SBP and DBP), and more likely also to report diabetes and hyperlipidaemia.

Results of this study showed statistically significant associations between higher intake of vitamin E and increment of the risk for MI. This appears to be partially justified under consideration of the paradoxical properties of vitamin E as anti- and pro-oxidant, however, those results may be a product of chance, and also bias and methodological limitations cannot be omitted.

In the present study to derive dietary patterns both methods hypothesis-oriented and exploratory were considered, the identification of food groups related to nutrients by means of either linear regression model or reduced rank regression model, and then a simplified food pattern rich in vitamin E and another simplified food pattern rich in antioxidant were constructed. A higher score of the FP rich in vitamin E means a high intake of vegetable oils and fats, margarine, nuts, raw vegetables and cooked vegetables, but low intakes of types of bread other than wholemeal bread, beer, processed meat, high- and low-fat dairy products. As

well as a higher score of the FP rich in antioxidants means a high intake of fruits (fruit juice, fresh and canned fruits), vegetables (raw vegetables, cooked vegetables, cabbage, vegetarian dishes), vegetable oils and fats, margarine, nuts and tea, but low intakes of dairy products (low- and high-fat dairy products), types of bread other than wholemeal bread, beer, butter, processed meat and confectionery&sweet.

The highest score of either FP rich in vitamin E or FP rich in antioxidants were shown predominantly among women, young adults, who were more likely to have higher education, non-smoking habits, lower and intermediate alcohol consumption, to spend more time in sport activities and to use vitamin E supplements. In contrast, the lowest score of either FP rich in vitamin E or FP rich in antioxidants were noted among people who had a BMI above 25 kg/m^2, SBP and DBP values over the normal range and also had higher values of WHR. All of these findings suggest that the healthy lifestyle at baseline in the EPIC-Potsdam study is related to a higher intake of micronutrient as vitamin E, vitamin C, β-carotenoids and flavonoids as well as to a dietary intake behaviour rich in plant-based foods and low in animal source and refined foods.

Higher intake of the FP rich in vitamin E is associated with a 31% reduction for all CV events and higher intake of the FP rich in antioxidants is associated with a 45% reduction for all CV events. In other words, a dietary pattern rich in plant-based foods and low in animal source and refined foods seems to be related to a reduction in CV events. The difference of risk for all CV events among both FPs (14%) seems to be linked to the effect of inclusion of fruits, tea, butter and confectionery&sweet in the FP rich in antioxidants.

On one hand, an increment of the risk for MI is associated with higher intake of the single vitamin E in the overall EPIC-Potsdam cohort. On the other hand, higher intake of the FP rich in antioxidants is associated with a reduction of the risk for all CV events among men, but not among women. The FP rich in antioxidant may explain more the whole intake (nutrients or foods) than the FP rich in vitamin E and the single vitamin E intake. These findings are in agreement with the assumption of an existing antioxidant network and suggest that single

nutrients, specially antioxidants, may not be analyzed without the consideration of other nutrients when the diet-disease relationship is evaluated. In addition, this study suggests that foods included in both FPs may be good markers for dietary consumption behaviour and lifestyle factors associated with the risk of CV events.

These findings are in agreement with the assumption of a network of antioxidants and its possible protective role on the risk for CVD. Cardiovascular disease is considered the leading cause of mortality world-wide and the prevention of CVD is one aim in the public health. Then, it is necesary that succeding antioxidant research including vitamin E, all components as well, takes into account the experimental evidences of metabolism, genetic, molecular actions, and synergy of antioxidants; and also incorporate traditional biomarkers, inflammatory and genetic biomarkers, in order to have the best understanding of the relation between antioxidants and CVD.

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7. APPENDIX

1. Forty-nine food groups by Schulze MB.

NAMED GROUP	FOOD ITEMS
Wholemeal bread	Wholemeal bread,dark and wholemeal rolls
Types of bread other than wholemeal bread	Rye bread,wheat bread, mixed bread, pale rolls, crispbread, croissants
Muesli	Whole-grain breakfast cereal, muesli
Cornflakes	Cornflakes, other refined grain-based breakfasr cereal
Pasta& rice	Cooked pasta, cooked rice
Vegetarian dishes	Vegetarian dishes
Chips&salt sticks	Chips, salt sticks, cracker
Pizza	Pizza, quiche
Cake&cookies	Cake, tart, cookies
Confectionery&ice-cream	Chocolate, candy bars, pralines, sugar, ice-cream
Sweet bread spreads	Jam, honey, chocolate spread, peanut butter
Eggs	Boiled eggs,fried eggs, omelette
Fresh fruit	Apple, pear,peach, cherry, grape, strawberry, blackberry, raspberry, kiwi, pineapple, mango, banana
Canned fruit	Canned fruit
Raw vegetables	Cucumber,carrot, sprouts, papikra, tomato, onion, radish
Cabbage	Broccoli, cauliflower, red and white cabbage, kohlrabi (all cooked)
Cooked vegetables	Tomatoes, tomato sauce, sweet pepper, courgette, aubergine, spinach, carrots, asparagus, pea-carrot vegetable mix, leek, celery, (all cooked)
Garlic	Raw,fried or cooked rice
Mushrooms	Fresh mushrooms, mushroom dishes
Legumes	Green peas, green beans, pea-bean-lentil stew
Cooked potatoes	Salted potatoes, jacket potatoes, mashed potatoes, potatoes salad, dumplimg
Fried potatoes	French fries, potatoes fritters, fried potatoes
Nuts	Nuts

Low-fat dairy products	Milk or yoghurt (≤1.5% fatt), soured milk, low-fat curd cheese
High-fat dairy products	Other milk or yoghurt, curd cheese, cream
Low-fat cheese	Low-fat cheese
High-fat cheese	Other cheese
Water	Tap water, mineral water
Coffee	Coffee
Decaf coffee	Decaffeinated coffee
Tea	Black tea, green tea, fruit tea and herbal teas
Fruit juice	Citrus, apple, orange, grapefruit, grape,cherry, pineapple juice, multi-vitamin drinks
Low-energy soft drinks	Low-energy soft drinks
High-energy soft drinks	Other energy soft drinks
Beer	Beer
Wine	Wine, fruit wine, champagne
Spirits	Spirits
Other alcoholic beverages	Desset wine, liqueor,aperitif
Butter	Butter as spread and for food preparation
Margarine	Margarine as spread and for food preparation
Vegetable oils and fats	Used for food preparation as frying and dressing
Animal fast	Used for food preparation, except butter
Sauce	Ketchup, brown and white sauce, salad dressing, sauce for vegetables
Dessert	Pudding,sweet soufflé
Fish	Fish, canned fish, smoked fish
Poultry	Fried, grilled or roasted chicken or turkey
Meat	Pork,beef, hamburger, minced meat, liver, lamb, roast hare
Processed meat	Salami, cold-cut sausage, ham, fried sausage
Soup	Vegetable or potatoes stew, vegetable soup, meat or fish soup, broth, thickened soup

APPENDIX

2. Food groups in this study.

NAMED GROUP	FOOD ITEMS
Wholemeal bread	Wholemeal bread,dark and wholemeal rolls
Types of bread other than wholemeal bread	Rye bread,wheat bread, mixed bread, pale rolls, crispbrea croissants
Muesli	Whole-grain breakfast cereal, muesli
Cornflakes	Cornflakes, other refined grain-based breakfasr cereal
Pasta&rice	Cooked pasta, cooked rice
Chips&salt sticks	Chips, salt sticks, cracker
Pizza	Pizza, quiche
Cake&cookies	Cake, tart, cookies
Confectionery&ice-cream	Chocolate, candy bars, pralines, sugar, ice-cream
Sweet bread spreads	Jam, honey, chocolate spread, peanut butter
Eggs	Boiled eggs,fried eggs, omelette
Garlic	Raw,fried or cooked rice
Mushrooms	Fresh mushrooms, mushroom dishes
Legumes	Green peas, green beans, pea-bean-lentil stew
Cooked potatoes	Salted potatoes, jacket potatoes, mashed potatoes, potatoes salad, dumplimg
Fried potatoes	French fries, potatoes fritters, fried potatoes
Nuts	Nuts
Low-fat cheese	Low-fat cheese
High-fat cheese	Other cheese
Water	Tap water, mineral water
Coffee	Coffee
Decaf coffee	Decaffeinated coffee
Tea	Black tea, green tea, fruit tea and herbal teas
Low-energy soft drinks	Low-energy soft drinks
High-energy soft drinks	Other energy soft drinks
Beer	Beer
Wine	Wine, fruit wine, champagne
Spirits	Spirits

Other alcoholic beverages	Desset wine, liqueor,aperitif
Butter	Butter as spread and for food preparation
Margarine	Margarine as spread and for food preparation
Vegetable oils and fats	Used for food preparation as frying and dressing
Animal fast	Used for food preparation, except butter
Sauce	Ketchup, brown and white sauce, salad dressing, sauce for vegetables
Dessert	Pudding,sweet soufflé
Fish	Fish, canned fish, smoked fish
Poultry	Fried, grilled or roasted chicken or turkey
Meat	Pork,beef, hamburger, minced meat, liver, lamb, roast hare
Processed meat	Salami, cold-cut sausage, ham, fried sausage
Soup	Vegetable or potatoes stew, vegetable soup, meat or fish soup, broth, thickened soup

NEW DERIVED GROUPS

Fruits: **fresh and canned fruit, and fruit juice**	Apple, pear,peach, cherry, grape, strawberry, blackberry, raspberry, kiwi, pineapple, mango, banana, canned fruit, fruit juice like citrus, apple, orange, grapefruit, grape,cherry, pineapple juice, and multi-vitamin drinks
Vegetables: **raw and cooked vegetables, cabbage, and vegetarian dishes**	Cucumber,carrot, sprouts, papikra, tomato, onion, radish, broccoli, cauliflower, red and white cabbage, kohlrabi, tomatoes, tomato sauce, sweet pepper, courgette, aubergine, spinach, carrots, asparagus, pea-carrot vegetable mix, leek, celery, vegetarian dishes
Dairy products: **low- and high-fat dairy products**	All types of milk or yoghurt, soured milk, all types of curd cheese, milk cream

3. SAS program.

```
proc pls data=total nfac=3 method=rrr;
      model yresidve yresidvc yresidvac yresidflav=FG1-FG43;
      output out=outpls xscore=xfactor
                        yscore=yfactor;
run;
```

.../...

```
proc reg data=total_1;
      model yfactor_1=FG1-FG43
            / selection=stepwise;
run;
```

4. SAS results.

Stepwise Selection: Step 42

Variable ve_fg19 Entered: R-Square = 0.8912 and C(p) = 40.6175

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	42	176445	4201.07942	5018.01	<.0001
Error	25722	21534	0.83720		
Corrected Total	25764	197980			

Parameter Variable	Standard Estimate	Error	Type II SS	F Value	Pr > F
Intercept	-3.08522	0.02287	15242	18206.4	<.0001
ve_fg1	0.14365	0.01222	115.64195	138.13	<.0001
ve_fg2	-0.59114	0.01398	1496.70787	1787.75	<.0001
ve_fg3	0.47705	0.01465	887.62591	1060.23	<.0001
ve_fg4	-1.31803	0.12922	87.09972	104.04	<.0001
ve_fg5	-2.43774	0.20647	116.70313	139.40	<.0001
ve_fg6	0.73491	0.11654	33.29390	39.77	<.0001
ve_fg7	-0.24208	0.04799	21.30401	25.45	<.0001
ve_fg8	0.36604	0.02368	199.98114	238.87	<.0001
ve_fg9	0.32767	0.00543	3052.22108	3645.75	<.0001
ve_fg11	0.19429	0.05191	11.72772	14.01	0.0002
ve_fg12	0.21550	0.01475	178.80620	213.58	<.0001
ve_fg13	0.61261	0.01410	1579.42871	1886.56	<.0001
ve_fg15	0.94778	0.01545	3149.55444	3762.01	<.0001
ve_fg16	0.83142	0.07500	102.88528	122.89	<.0001
ve_fg17	0.89289	0.02144	1452.41933	1734.85	<.0001
ve_fg19	-2.10968	0.90337	4.56595	5.45	0.0195
ve_fg20	-0.24701	0.05462	17.12200	20.45	<.0001
ve_fg21	0.36069	0.02228	219.44137	262.11	<.0001
ve_fg22	0.65852	0.02199	750.93638	896.96	<.0001
ve_fg23	0.69866	0.00714	8026.19341	9586.95	<.0001
ve_fg24	-3.83438	0.05668	3830.98059	4575.94	<.0001
ve_fg25	-2.95194	0.04306	3933.86996	4698.84	<.0001
ve_fg26	-1.32096	0.12919	87.52743	104.55	<.0001
ve_fg27	-1.46448	0.04400	927.39539	1107.73	<.0001
ve_fg29	-3.29773	0.20943	207.57234	247.94	<.0001
ve_fg30	-2.21867	0.71436	8.07576	9.65	0.0019
ve_fg31	-5.00312	0.36657	155.95315	186.28	<.0001
ve_fg32	0.26876	0.00869	801.68137	957.57	<.0001
ve_fg34	-15.51550	0.62936	508.81926	607.76	<.0001
ve_fg35	-1055.29483	18.81928	2632.51427	3144.43	<.0001
ve_fg38	-74.92131	3.91939	305.91647	365.40	<.0001
ve_fg39	-0.83040	0.02568	875.60663	1045.88	<.0001
ve_fg40	0.79795	0.00350	43418	51860.7	<.0001
ve_fg41	1.00501	0.00499	33932	40530.2	<.0001
ve_fg42	0.81190	0.03471	458.12793	547.21	<.0001
ve_fg43	0.82815	0.01914	1567.01398	1871.73	<.0001
ve_fg44	-1.21256	0.09942	124.52298	148.74	<.0001
ve_fg45	0.51480	0.01137	1716.26682	2050.01	<.0001
ve_fg46	-0.28613	0.05903	19.67071	23.50	<.0001
ve_fg47	-0.14932	0.02175	39.46558	47.14	<.0001
ve_fg48	-3.83037	0.04895	5126.98991	6123.97	<.0001
ve_fg49	0.21543	0.03679	28.70968	34.29	<.0001

Bounds on condition number: 1.6516, 2055.5

All variables left in the model are significant at the 0.1500 level.

No other variable met the 0.1500 significance level for entry into the model.

Summary of Stepwise Selection

Step	Variable Entered	Variable Removed	Label	Number Vars In	Partial R-Square	Model R-Square	C(p)
1	ve_fg41			1	0.3758	0.3758	121831
2	ve_fg40			2	0.2263	0.6021	68324.0
3	ve_fg48			3	0.0502	0.6523	56461.8
4	ve_fg23			4	0.0513	0.7036	44339.4
5	ve_fg15			5	0.0390	0.7425	35128.4
6	ve_fg2			6	0.0185	0.7610	30758.2
7	ve_fg35			7	0.0150	0.7760	27223.7
8	ve_fg17			8	0.0119	0.7878	24420.2
9	ve_fg24			9	0.0091	0.7969	22280.7
10	ve_fg13			10	0.0106	0.8075	19781.6
11	ve_fg25			11	0.0105	0.8180	17292.5
12	ve_fg9			12	0.0176	0.8357	13121.9
13	ve_fg45			13	0.0107	0.8463	10600.7
14	ve_fg43			14	0.0078	0.8541	8760.82
15	ve_fg3			15	0.0047	0.8588	7652.45
16	ve_fg27			16	0.0048	0.8636	6529.44
17	ve_fg22			17	0.0044	0.8680	5480.46
18	ve_fg39			18	0.0041	0.8721	4506.40
19	ve_fg32			19	0.0039	0.8761	3577.03
20	ve_fg34			20	0.0028	0.8789	2918.97
21	ve_fg42			21	0.0024	0.8812	2360.11
22	ve_fg38			22	0.0016	0.8828	1987.06
23	ve_fg21			23	0.0011	0.8839	1735.83
24	ve_fg29			24	0.0010	0.8849	1501.92
25	ve_fg12			25	0.0007	0.8856	1337.28
26	ve_fg31			26	0.0007	0.8863	1170.47
27	ve_fg44			27	0.0007	0.8870	1017.33
28	ve_fg8			28	0.0007	0.8876	864.563
29	ve_fg5			29	0.0007	0.8883	710.014
30	ve_fg1			30	0.0006	0.8888	581.309
31	ve_fg16			31	0.0004	0.8893	479.071
32	ve_fg26			32	0.0004	0.8897	375.487
33	ve_fg4			33	0.0004	0.8901	281.015
34	ve_fg47			34	0.0004	0.8905	188.061
35	ve_fg6			35	0.0002	0.8907	147.822
36	ve_fg46			36	0.0001	0.8908	123.322
37	ve_fg7			37	0.0001	0.8909	101.749
38	ve_fg49			38	0.0001	0.8910	82.4746
39	ve_fg20			39	0.0001	0.8911	63.3654
40	ve_fg11			40	0.0001	0.8912	51.5562
41	ve_fg30			41	0.0000	0.8912	44.0709
42	ve_fg19			42	0.0000	0.8912	40.6175

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EIDESSTATTLICHE ERKLÄRUNG

Hiermit erkläre ich an Eides statt, dass ich die am Fachbereich Gesundheitswissenschaften der Technischen Universität Berlin eingereichte Dissertation mit dem Titel „Vitamin E intake and cardiovascular diseases in the EPIC-Potsdam study“ selbstständig und ohne unerlaubte Hilfe angefertigt habe, die benutzten Hilfsmittel sowie die Literatur vollständig angegeben sind und dass ich die Arbeit noch keinem anderen Fachbereich bzw. noch keiner anderen Fakultät vorgelegt habe.

Zorabel Cordero Gonzalez, Berlin, 04.07.08