Vitamin E levels, cognitive impairment and dementia in older persons: the InCHIANTI study

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Abstract

There is conflicting evidence that antioxidants contribute to maintaining cognitive function in elderly subjects. We investigated whether vitamin E plasma levels are related to the presence of dementia and cognitive impairment in a population-based cohort study conducted in Italy. A total of 1033 participants aged at least 65 years received clinical and neuropsychological examinations, donated blood for vitamin E analysis and had their diets assessed. Participants with plasma vitamin E levels in the bottom tertile had a significantly higher probability of being demented (OR 2.6, 95% CI 1.0–7.1) and also of suffering from cognitive impairment (OR 2.2, 95% CI 1.2–4.2) compared to those in the highest vitamin E tertile after adjustment for age, gender, education, lipid levels, energy intake, vitamin E intake, and smoking. This study supports the notion that higher vitamin E plasma levels might provide significant protection against cognitive impairment and dementia in elderly subjects.

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1. Introduction

During the 20th century advances in public health and medicine greatly reduced the risk of death in children and younger adults, raising the life expectancy from about 45 to about 80 years. It is estimated that now about 15% of the subjects in the total population of the industrialized countries are aged 65 years and older, and their number is growing rapidly. Unfortunately, many older subjects are prevented from enjoying these gained years of life due to the burden of chronic diseases and disability. Cognitive impairment and dementia, whose incidence and prevalence sharply increase with aging, are among the principal threats to a healthy and active life expectancy in old age. About 6% of subjects older than 65 years are demented [30] with Alzheimer’s disease being the most common form of dementia, which affects 47% of the people who reach 85 years of age [28,39]. Cognitive impairment not severe enough to fulfill the criteria for dementia affects between 10% and 24% of the subjects aged 65 years and over [14,52].

The number of elderly subjects who will suffer from cognitive impairment and dementia will further increase in the near future, as a consequence of the progressive aging of the...
population. Therefore, strategies to prevent or postpone the onset of cognitive impairment and slow down its progression in older persons are urgently needed. The discovery of new strategies requires the identification of factors that may confer protection against cognitive decline and dementia. Among them, micronutrients, and particularly antioxidant vitamins, such as vitamin E, are receiving a great deal of attention. Antioxidant vitamins may have neuroprotective properties not only because they reduce oxidative stress, a mechanism that probably plays an important role in cognitive impairment and dementia [13], but also because they influence intracellular mechanisms, for example increasing the rate of protein degradation by lysosomes in human astrocyte glial cells [33]. Therefore, these nutrients play an important role in the maintenance of integrity and function of the central nervous system.

The relationship between vitamin E and cognitive impairment still remains controversial. Lower vitamin E blood levels have been associated with poor cognitive function and dementia still remains controversial. Lower vitamin E blood levels have been associated with poor cognitive function and dementia [41]. Moreover, subjects suffering from dementia, both Alzheimer disease and vascular dementia, have lower plasma levels of vitamin E [8,59]. Interestingly, recent longitudinal studies report a lower risk of developing cognitive impairment or dementia among subjects with higher vitamin E intake or consuming vitamins E and C supplements [15,34,36,37]. However, other studies failed to confirm these associations [20,25,26,40]. Finally, in a randomized controlled trial conducted in Alzheimer’s patients with mild to moderate disease, treatment with 2000 IU vitamin E each day for 2 years significantly reduced the occurrence of primary outcomes, including death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia. In general, treatment with vitamin E slowed the progression of the disease [44].

The objective of this study was to investigate the relationship between plasma levels of vitamin E and cognitive impairment and dementia in a large sample of older subjects enrolled in InCHIANTI, a prospective cohort study conducted in the Chianti geographic area (Tuscany, Italy).

2. Methods

2.1. Study sample

InCHIANTI is an epidemiological study performed in two Italian towns located in the Chianti countryside: Greve in Chianti (11,709 inhabitants; rural area) and Bagno a Ripoli (village of Antella, 4704 inhabitants; just outside the urban area of Florence). The study population used for the analysis presented here consisted of a random sample of the population aged 65 years and older living in the two catchment areas. A detailed description of the design and data collection method of the InCHIANTI study has been previously published [16]. All subjects underwent a careful clinical examination and a detailed interview. A proxy was interviewed when the subject was unable to provide the required information.

Functional status was assessed by means of the Activities of Daily Living scale (ADL) [27] and the Instrumental Activities of Daily Living scale (IADL) [29]. Smoking habits were categorized as “never”, “former” and “current smoker”.

The study protocol was approved by the Istituto Nazionale per la Ricerca e Cura dell’Anziano—National Institute for Research and Care of the Elderly (INRCA) ethical committee. All subjects received an extensive description of the purposes and known risks of the study procedures, and all gave their informed consent.

2.2. Evaluation of cognitive status

Impaired cognitive function and dementia were ascertained using a two stage screening procedure. During the home interview, participants were first evaluated using the Mini Mental State Examination (MMSE) [18]. Additionally, participants who reported difficulty in performing ADLs or IADLs were asked questions aimed at understanding whether the cause of abnormality was cognitive impairment. Those with a score >26 were considered non-demented, while those with a score ≤21 were considered possibly demented and directly scheduled for the second stage screening procedure. The participants with a MMSE score between 22 and 26 received additional neuropsychological tests assessing memory (paired words test) [58], concentration/attention (digit test from the Weschler adult intelligence test) [57] and visuo-spatial ability (the Caltagirone drawings) [11]. The education-adjusted normative data for these tests exist for the Italian population. If based on these additional tests the memory of the participant was considered normal, he or she was reattributed a full score on the MMSE memory items. Analogously, we reattributed 5 points to the item “subtract seven five times from 100” and 1 point to the “pentagon drawing” when the performance in additional tests assessing analogous neuropsychological functions was considered normal. After this procedure we reanalysed the MMSE score. The participants for whom the new score was >26 were considered “not demented”, while those for whom the newly calculated score remained between 22 and 26 were scheduled for the second stage screening.

The second stage screening was performed by geriatricians and a psychologist with long standing clinical experience in the evaluation of older patients with cognitive impairment. A diagnosis of “dementia syndrome” independent of the etiology was established using a standard evaluation protocol based on the DSM IV criteria [2]. Of the 1155 participants aged 65 years and older, 82 (7.1%) were affected by dementia syndrome. Differential diagnosis between degenerative dementia, mainly represented by Alzheimer’s disease, and vascular or mixed dementia, was based only on clinical data [55]. Since neuroimaging was not available in all subjects, these data were not taken into account for the diagnosis. Demented subjects with a history of progressive cog-
nitive decline and not having focal neurological signs at the neurological exam were considered to suffer from degenera-
tive dementia. Those with a history of stepwise deterioration and/or stroke and/or focal neurological signs were considered to have vascular or mixed dementia. Forty-one subjects had Alzheimer’s disease and 41 had vascular or mixed dementia.

For this analysis we divided the study population into three
groups: (1) participants with normal cognitive functions (i.e. MMSE score ≥23, no diagnosis of dementia and no disabil-
ity attributable to cognitive impairment) (n = 807); (2) partic-
pants with cognitive impairment but not demented (i.e. those with a MMSE score <23 and/or any degree of disability in ADLs or IADLs that was judged to be related to impaired cognitive function) (n = 168); and (3) participants affected by a dementia syndrome (n = 58).

2.3. Quantification of vitamin E

Vitamin E (α-tocopherol) plasma concentration was mea-
sured by reverse-phase high performance liquid chromatog-
raphy (HPLC) as previously described [31]. Briefly, 100 μl of plasma were mixed with 100 μl ethanol; after vortexing, tocopherol was extracted into 500 μl hexane containing 0.02% butylated hydroxyl toluene (BHT) (Sigma, St. Louis, MO). Tocotrienol (a gift from Hoffman La Roche, Nutley, NJ), was added to the mixture as an internal standard. Samples were cen-
trifuged at 800 rpm for 5 min at 4 °C. The supernatant was collected and dried under a stream of nitrogen gas, and reconsti-
cted in 100 μl of methanol. Tocopherols were separated by HPLC using a 3 μm C18 reverse phase column (Perkin-
Elmer, Norwalk, CT). The mobile phase, delivered at a flow
rate of 1.0 ml/min, consisted of 1% water in methanol, con-
taining 10 mmol/l lithium perchlorate. Samples were injected with an autosampler, 1100 series, Hewlett-Packard. Eluted peaks were detected at an applied potential of +0.6 V by a LC 4B amperometric electrochemical detector (Biosana-
lytical System, West Lafayette, IN). Peaks were integrated with a ChemStation software (Hewlett-Packard). Tocopherol (α-tocopherol) concentration was expressed in μmol/l. Re-
producibility and accuracy of the procedure employed was tested by analyzing representative samples in triplicate from a sample provide by the American Association for Labora-
tory Accreditation, Washington, DC, USA containing known concentration of α-tocopherol. Intra- and inter-batch coeffi-
cients of variation were 3% and 4.2%, respectively.

2.4. Assessment of dietary intake

The food frequency questionnaire used in the InCHIANTI study was the instrument developed and used by the Italian sites of the European Prospective Study into Cancer and Nu-
trition (EPIC) study [42]. EPIC is a multicenter project con-
ducted in nine European Countries to study the relationship between diet and cancer.

The EPIC food frequency questionnaire provides a de-
tailed assessment of food consumption during the previous

year through a large number of structured and pre-coded questions. Originally, the questionnaire was conceived to be self-administered. However, in a pilot study we realized that in older subjects this method of administration provides am-
biguous results, mainly due to misunderstanding of questions. Thus, in the InCHIANTI study, the EPIC questionnaire was administered by the interviewers. The information provided by the questionnaire was transformed into average daily in-
take of macro- and micronutrients, including vitamin E, by custom software that uses for reference the table of food com-
position for epidemiological study in Italy, edited by the Eu-
ropean Institute of Oncology in 1998 [43]. The variables used in this study were: total energy and vitamin E, all expressed as daily intake.

2.5. Statistical analysis

Data are presented as mean ± S.E. or percentage. When two groups were involved, mean values were compared using the unpaired t-test, the Mann–Whitney test ANOVA, or a chi-square test, as appropriate. Multiple groups were com-
pared with ANOVA and specific contrasts were obtained by the Tukey post hoc test. Correlation between variables was assessed using the Pearson correlation coefficient. Plasma α-
tocopherol levels were categorised into tertiles, using as cut-
-off thresholds 26.0 and 32.9 μmol/l. The odds ratios and their
95% confidence interval of having a “dementia syndrome” and of having “cognitive impairment without dementia” com-
pared to “normal cognitive status” associated with being in
the lowest tertile and the intermediate tertile versus the high-
est tertile of vitamin E plasma status were evaluated using a polichotomous logistic regression model adjusted for con-
founders (SAS procedure CATMOD). The statistical analysis was performed using SAS version 8.1 (Cary NC, 1999).

3. Results

Of the 1299 subjects aged 65 years and older originally
sampled, 1155 (88.9%) agreed to participate in the study. Plasma levels of α-tocopherol were available in 1036 partici-
pants. Only three subjects were taking vitamin E supplements at a dose (300 mg daily) that is sufficient to significantly in-
crease plasma and tissue levels [10] and they were excluded. Therefore, the final sample included 1033 subjects. As ex-
pected, women outnumbered men (56% versus 44%). In com-
parision with men, women were older (76.1 versus 74.6 years;
\(p < 0.001\)) and had higher plasma levels of total cholesterol (5.8 mmol/l versus 5.4 mmol/l; \(p < 0.0001\)) and α-tocopherol (30.9 μmol/l versus 28.7 μmol/l; \(p < 0.001\)). Triglyceride lev-
els were similar in men and women (1.47 mmol/l versus 1.43 mmol/l). Total energy and vitamin E intake were higher in men than in women (2169 kcal/day versus 1703 kcal/day and 6.6 mg/day versus 5.8 mg/day; \(p < 0.001\), respectively). On average, men had received more years of formal education than women (6.2 versus 4.7 years; \(p < 0.001\)).
The demographic and biological characteristics of the whole sample and of the three groups according to their cognitive status are reported in Table 1. Demented subjects were older and had received less years of formal education compared to the other groups. Participants affected by dementia had lower total energy intake, vitamin E intake, plasma total cholesterol and vitamin E plasma levels. In our sample, 22 subjects were diagnosed as having degenerative dementia, and 36 with mixed or vascular dementia. The higher prevalence of mixed and vascular dementia is due to the fact that blood samples were not available in 19 patients with degenerative dementia compared to 4 patients with vascular or mixed dementia. One patient with vascular dementia was excluded since he was using vitamin E supplements. Vitamin E levels were not different in subjects with degenerative dementia compared to those with vascular or mixed dementia (25.7 ± 0.8 μmol/l versus 25.4 ± 0.7 μmol/l, respectively).

Vitamin E plasma levels were strongly correlated with total cholesterol and triglycerides levels (r = 0.58 and 0.49, p < 0.0001, respectively) and weakly correlated with vitamin E intake (r = 0.1, p < 0.002).

Compared to participants in the highest vitamin E tertile, those in the lowest tertile had a significantly higher risk to be demented or to have cognitive impairment than having normal cognitive function (Fig. 1, model A). After adjusting for age and education, the strength of the association between plasma vitamin E levels and cognitive impairment or dementia was reduced, but in both cases it remained statistically significant (Fig. 1, model B).

Finally, in the multivariate model fully adjusted for age, gender, lipid levels, education, total energy intake, vitamin E intake, and smoking, participants in the bottom tertile of vitamin E plasma levels were at significantly higher risk not only of being demented (OR 2.6, 95% CI 1.0–7.1) but also of having impaired cognitive function (OR 2.2, 95% CI 1.2–4.2) compared to those in the highest vitamin E tertile (Table 2 and Fig. 1, model C).
Moreover, vitamin E status depends not only on vitamin E intake, but it may also be influenced by other factors, including lifestyle, e.g. exercise [11] and smoking habit [51] and levels of other nutrients in the diet, such as lipids [24] and vitamin C [21] which may influence the absorption and metabolism of vitamin E. Therefore, dietary intake may not precisely reflect blood levels that are more directly associated with tissue's levels [10]. In other studies, plasma levels of vitamin E were reported without adjustment for lipids, i.e., cholesterol and triglyceride levels. Since vitamin E is carried in the bloodstream by lipoproteins, changes in lipid concentration should always be considered [50]. In addition, some of the studies used small samples and a significant proportion of the subjects were taking vitamin E supplements, a behavior that may be associated with having more health problems or having a healthier lifestyle than subjects who do not take supplements [37]. As we already mentioned, in the InCHIANTI study population, the use of high dose vitamin E supplementation was limited to three subjects, who were excluded from the present analysis. Finally, most of the studies did not consider the smoking habits of their subjects. Recent evidence, however, suggests that vitamin E metabolism is altered among smokers compared with non-smokers [51]. Therefore, smoking should be included as potential confounder.

Vitamin E deficiency primarily causes neurologic dysfunctions, although the underlying mechanisms remain unclear [46,47]. In this study, we observed that cognitively normal older subjects have higher plasma levels of vitamin E than cognitively impaired individuals independent of several confounders, suggesting that vitamin E is important in maintaining brain function and cognition. These findings are supported by several experimental studies showing that vitamin E prevents β-amyloid-induced cell insult and death among cells from rat’s hippocampus [5], and delays the progression of neurological impairment mediated by high levels of amyloid in transgenic mice expressing the human variant of the amyloid precursor protein [23]. The neuroprotective action of vitamin E, in particular of d-α-tocopherol, the predominant form in food and tissue, and the highest in biological activity, may be accounted for by its action at different levels.

Several studies have examined the relationship between vitamin E dietary or supplemental intake and cognitive functions or dementia. Some of these studies have shown a significant association between antioxidant vitamins E and C intake and cognitive status [15,36,37], but others did not confirm this association [25,26,40]. The differences observed among studies may have originated to some extent from methodological weaknesses. In fact, some studies measured only dietary intake. Interestingly, recent longitudinal studies (3 to 6 years) have reported that subjects with high baseline intake of vitamin E had lower risk of developing AD or cognitive decline than those with low vitamin E intake [15,36,37]. Dietary information was collected using a food frequency questionnaire, which may be susceptible to recall bias, and without obtaining plasma levels, which often do not correlate well with dietary intake. This might be due, at least in part, to the fact that estimated dietary vitamin E intake includes not only α-tocopherol intake but is the sum of a variety of tocopherols and tocotrienols contained in foods.

### 4. Discussion

In this population-based epidemiological study, we found that vitamin E plasma levels were associated with the presence of cognitive decline and dementia in community-dwelling older persons living in the Chianti area, near Florence, Italy. Subjects with vitamin E plasma levels in the lowest tertile showed about a fivefold higher probability to be affected by dementia and a twofold higher probability to suffer from cognitive impairment compared with those individuals who had the highest levels of vitamin E. The probability of having dementia and cognitive impairment remained significantly higher in those individuals with the lowest vitamin E plasma levels even after adjustment for age, gender, education, lipid levels, smoking habit, and total energy and vitamin E intake.

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### Table 2

Polychotomous logistic regression model relating low vitamin E plasma levels to cognitive impairment and dementia in older subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dementia vs. normal cognitive function odds ratio (95% CI)</th>
<th>Cognitive impairment vs. normal cognitive function odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest vitamin E tertile</td>
<td>2.6 (1.0–7.1)</td>
<td>2.2 (1.2–4.2)</td>
</tr>
<tr>
<td>Intermediate vitamin E tertile</td>
<td>1.5 (0.5–3.9)</td>
<td>2.1 (1.2–3.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.2 (1.1–1.3)</td>
<td>1.1 (1.0–1.2)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>0.6 (0.5–0.7)</td>
<td>0.6 (0.5–0.7)</td>
</tr>
</tbody>
</table>

The model was adjusted for gender, lipid levels, total energy and vitamin E daily intakes and smoking habit.

Age and low education were the only two factors beyond plasma vitamin E levels that predicted both cognitive impairment and dementia.

Moreover, vitamin E status depends not only on vitamin E intake, but it may also be influenced by other factors, including lifestyle, e.g. exercise [11] and smoking habit [51] and levels of other nutrients in the diet, such as lipids [24] and vitamin C [21] which may influence the absorption and metabolism of vitamin E. Therefore, dietary intake may not precisely reflect blood levels that are more directly associated with tissue's levels [10]. In other studies, plasma levels of vitamin E were reported without adjustment for lipids, i.e., cholesterol and triglyceride levels. Since vitamin E is carried in the bloodstream by lipoproteins, changes in lipid concentration should always be considered [50]. In addition, some of the studies used small samples and a significant proportion of the subjects were taking vitamin E supplements, a behavior that may be associated with having more health problems or having a healthier lifestyle than subjects who do not take supplements [37]. As we already mentioned, in the InCHIANTI study population, the use of high dose vitamin E supplementation was limited to three subjects, who were excluded from the present analysis. Finally, most of the studies did not consider the smoking habits of their subjects. Recent evidence, however, suggests that vitamin E metabolism is altered among smokers compared with non-smokers [51]. Therefore, smoking should be included as potential confounder.

Vitamin E deficiency primarily causes neurologic dysfunctions, although the underlying mechanisms remain unclear [46,47]. In this study, we observed that cognitively normal older subjects have higher plasma levels of vitamin E than cognitively impaired individuals independent of several confounders, suggesting that vitamin E is important in maintaining brain function and cognition. These findings are supported by several experimental studies showing that vitamin E prevents β-amyloid-induced cell insult and death among cells from rat’s hippocampus [5], and delays the progression of neurological impairment mediated by high levels of amyloid in transgenic mice expressing the human variant of the amyloid precursor protein [23]. The neuroprotective action of vitamin E, in particular of d-α-tocopherol, the predominant form in food and tissue, and the highest in biological activity, may be accounted for by its action at different levels.

One widely accepted biological function of vitamin E is related to its antioxidant properties and ability to prevent the peroxidation of lipids in blood and biological membranes. This activity may be very important in the brain tissue, which appears to be more vulnerable to oxidative damage than other tissues due to its characteristic high rate of oxygen and energy consumption, and prominent composition of polyunsaturated fatty acids, which are more susceptible to free radical damage. In addition, the brain’s level of several antioxidant enzymes is low, and concentration of metals, in particular iron, is high [17]. Oxidative stress has been involved in the pathogenesis of Alzheimer’s disease (AD) [12]. Free radical generation in AD is associated with the accumulation of β-amyloid [22] and impaired functioning of mitochondrial oxidative phosphorylation [4]. Oxidative stress may also be important in mediating vascular cognitive impairment through different...
mechanisms, including lipoprotein oxidation, a pivotal event in atherosclerosis [48], endothelial dysfunction and end organ damage in hypertension [6], an important risk factor for ischemic stroke. Moreover, higher vitamin E levels are associated with better outcome after ischemic stroke in animal models [54]. Several lines of evidence, however, suggest that the neuroprotective effect of vitamin E may be also mediated through non-antioxidant mechanisms, including preserving endothelial cell function [9], inhibiting platelet aggregation and serotonin release [49], and modulating protein kinase C signal transduction [7]. In fact, vitamin E has molecular roles that affect signal transduction pathways in biochemical processes involving synthesis of neurotransmitters and expression of pro-inflammatory molecules [3]. Inflammation is another important factor associated with cognitive impairment in old age, particularly with AD [35, 56]. Arachidonic acid, in addition to being an important component of membrane’s fatty acid composition, is an important source of eicosanoids, including prostaglandins. Vitamin E has been shown to attenuate damage in the inflamed tissue by modulating the release of arachidonic acid and prostaglandin synthesis [19, 38].

Some limitations of this study should be acknowledged. This is a cross-sectional study and therefore a cause and effect relationship between lower plasma levels of vitamin E and the presence of cognitive impairment can be suggested but not demonstrated. Due to the study design, it is equally possible that vitamin E levels decreased before the onset of the disease, i.e. a low level of vitamin E reduced the antioxidant defenses of the brain and therefore facilitated the onset and progression of conditions associated with an increased oxidative stress, such as dementia, as well as that vitamin E levels decreased after the onset of cognitive impairment and dementia as a consequence of both an increased generation of free radicals and a lower intake of foods containing vitamin E. We measured plasma levels of vitamin E, since the measurement of brain levels is not possible in human subjects. Several studies, however, have shown that supplementation with vitamin E increases its concentration in blood and the central nervous system, and furthermore, the animal brain incorporates vitamin E in a dose–response manner when plasma levels increase [32, 53]. Therefore, quantification of blood levels is a reasonable proxy of brain levels.

On the other hand, our research has several methodological strengths compared with previous studies, i.e. the population-based design, the clear differentiation between dementia and cognitive impairment, the availability of two indexes of vitamin E status, that is dietary intake and plasma levels, and the exclusion of subjects taking vitamin E supplements thus allowing to elucidate the role of vitamin E from dietary sources.

In conclusion, our data clearly show that lower vitamin E plasma levels are associated with higher probability not only to have dementia but also cognitive impairment. This suggests that a generous intake of vitamin E to reach plasma levels on the top end of the normal human plasma range (19 to 35 mmol/l) might provide significant protection against the occurrence of cognitive impairment and dementia in elderly subjects, and supports the importance of additional clinical trials with vitamin E in this area.

We plan to verify our findings in the ongoing longitudinal follow-up as soon as data become available.

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