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Vitamin E and Alzheimer's disease

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Vitamin E and Alzheimer's disease: what do we know so far?

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Abstract: Vitamin E has been proposed as a potential clinical intervention for Alzheimer's disease (AD) given the plausibility of its various biological functions in influencing the neurodegenerative processes associated with the condition. The tocopherol and tocotrienol isoforms of vitamin E have multiple properties including potent antioxidant and anti-inflammatory characteristics, in addition to influences on immune function, cellular signalling and lowering cholesterol. Several of these roles offer a theoretical rationale for providing benefit for the treatment of AD-associated pathology. Diminished circulating concentrations of vitamin E have been demonstrated in individuals with AD. Reduced plasma levels have furthermore been associated with an increased risk of AD development while intake, particularly from dietary sources, may limit or reduce the rate of disease progression. This benefit may be linked to synergistic actions between vitamin E isoforms and other micro-nutrients. Nevertheless, randomised trials have found limited and inconsistent evidence of vitamin E supplementation as an effective clinical intervention. Thus, despite a strong rationale in support of a beneficial role for vitamin E for the treatment of AD, the evidence remains inconclusive. Several factors may partly explain this discrepancy and represent the difficulties of translating complex laboratory evidence and dietary interactions into clinical interventions. Methodological design limitations of existing randomised trials and restrictions to supplementation with a single vitamin E isoform may also limit the influence of effect. Moreover, several factors influence individual responsiveness to vitamin E intake and recent findings suggest variation in the underlying genetic architecture attenuates vitamin E biological availability and activity which likely contributes to the variation in clinical responsiveness and the failure of randomised trials to date. Importantly, the clinical safety of vitamin E remains controversial and warrants further investigation.

Keywords: vitamin E, Alzheimer's disease, tocopherols, tocotrienols, antioxidants

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that accounts for up to 80% of dementia cases.¹ It is clinically characterised by the insidious onset of episodic memory impairment that evolves over time and is associated with subsequent decline in other cognitive domains that diminish functional ability.² Its histopathological hallmarks include neurofibrillary tangles (NFTs), amyloid plaques and loss of neuronal synapses in the brain.³ AD represents a major global disease burden with an estimated 50 million people currently living with dementia, a figure expected to increase threefold by 2050 with associated global economic costs expected to double to US\$2 trillion by 2030.^{4,5} As such, prevention and treatment interventions for AD are paramount, given an estimated 9.2 million deaths could be prevented by 2050 if AD onset was delayed by one year.⁶

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It is widely accepted that AD pathology begins decades before the appearance of clinical manifestations; changes may be present up to 30 years before the onset of symptoms.⁷ Advances in neuro-imaging modalities and the ongoing development of biomarkers from cerebrospinal fluid (CSF) offer some aid to predicting the development of AD in those with mild cognitive impairment (MCI) when combined with validated clinical tests.⁸

However, existing therapeutic options are largely limited to delayed disease progression and ease of symptom burden, albeit without modification of disease-course.⁹ This has resulted in greater focus on the development of alternative interventions to delay or prevent onset that have included dietary and antioxidant measures.¹⁰ Vitamin E has been studied extensively, primarily due to its potent antioxidant properties and the biological plausibility of its potential role in combatting the pathological processes of AD. However, its use as an effective clinical intervention remains controversial.

This review will assess the current evidence for the role of vitamin E as a treatment option in the context of AD. A literature search of Medline, a major article database, was conducted using the keywords “Alzheimer Disease” AND “Vitamin E” OR “tocopherols” OR “tocotrienols”. The keywords were searched in all possible combinations. Original journal articles that were written in English and published prior to 1st March 2019 were retrieved. All studies incorporating cell, animal and human evidence were included in addition to review articles to achieve a comprehensive search of the topic and to retrieve the maximum number of articles possible. A total of 341 articles were retrieved.

Pathogenesis of AD

Several theories have proposed the onset and progression of AD as a corollary of the uncertainty of the pathogenic mechanisms that lead to disease and the likely overlapping contributions they make to the phenotype observed. Since the characteristic “plaques” and “tangles” of AD were first reported by Alois Alzheimer in 1907, the role of amyloid and tau protein deposits have remained central to AD pathogenesis.¹¹ The amyloid cascade hypothesis postulates that excessive accumulation of senile plaques, composed of amyloid-beta (A β) protein, directly induces the clinical manifestations of AD through neurodegeneration mediated by inflammation, immunological mechanisms and the effects of free radical species.¹² A β is a beta-sheet protein derived from the amyloid beta precursor protein (A β PP)

molecule through the activity of β and γ -secretase.¹³ Importantly, expression of the ApoE4 allele reduces elimination of A β and is associated with increased AD risk.¹⁴

Similarly, the accumulation of intra-cellular NFTs have been implicated in AD pathology.¹⁵ NFTs consist of hyper-phosphorylated tau-protein, an important component of the neuronal cytoskeleton. Significantly, an increased quantity of NFTs is inversely associated with cognitive impairment and is more closely correlated with dementia severity than A β plaques.¹⁶ Furthermore, hypercholesterolaemia has been associated with AD pathology through its association with the amyloid pathway, although its precise role remains uncertain.¹⁷ Laboratory studies have shown higher cholesterol levels are associated with increased proteolysis of A β PP and A β production through secretase enzyme activity.¹⁸ Dysfunctional cholesterol metabolism has also been associated with its accumulation in the brains of AD patients.¹⁹ However, the clinical application of this remains controversial as evidence from randomised trials indicates that cholesterol-reducing statins have no effect on validated measures of cognition.²⁰ Despite the obvious implications of the amyloid cascade theory, several concerns have questioned the assumption of direct causality, including the failure of therapeutic interventions targeting the amyloid pathway to provide clinical benefit²¹ and an extensive body of evidence suggests the pathological processes of AD are complex and multifactorial.²²

The mitochondrial cascade hypothesis of AD pathogenesis postulated that genetic variation influences the impact of age-related mitochondrial changes which upon reaching a threshold value initiate a pathological cascade, including the amyloid pathway.²³ In addition, critical mitochondrial dysfunction may precipitate other cellular and molecular changes associated with AD including synaptic degeneration, production of free radical species and neuro-inflammation.^{24,25} The processes of neuro-inflammation have been reported as an early event in AD, perhaps occurring before the appearance of A β deposits.²⁶ In vitro studies have demonstrated elevation of multiple interleukins (ILs), tumour necrosis factor- α (TNF- α) and granulocyte macrophage colony stimulating factor (GM-CSF) in AD murine models early in the disease process.²⁷ Additionally, elevated levels of inflammatory cytokines have been detected in the brain and CSF of AD patients.²⁷

While it is likely each of these mechanisms contribute to AD pathogenesis, oxidative stress (OS) represents a common underlying theme. The role of OS in disease is

characterised by the generation of reactive oxygen species (ROS) through the metabolism of oxygen within the mitochondria that manifests as structural and functional alterations in various biomolecules.²⁸ Multiple indicators of OS are significantly elevated in AD with detectable oxidative effects on lipids, proteins, nucleic acids and sugars.^{29,30} Importantly, cerebral glucose metabolism is reduced early in the AD process and may be accompanied by metabolic dysregulation and increased production of ROS.³¹

Several factors render the brain particularly vulnerable to the effects of ROS including its high oxygen demand and consumption, the proportion of polyunsaturated fats in neural tissues and the relative scarcity of endogenous antioxidants to address this high metabolic demand.³² Interestingly, AD-associated mitochondrial defects beyond the central nervous system represent characteristic features of a systemic disease.³³ This is supported by factors such as diabetes mellitus, obesity and physical inactivity as potential risk factors for AD development.³⁴ In addition, strong associations have been reported between vascular risk factors and AD development, with A β protein deposition found within vessels early in the disease course.³⁵ As such, there is a strong rationale in support of systemic antioxidant therapy as a preventative or therapeutic intervention for AD with particular support for vitamin E in accordance with its biological activities.^{36,37}

Basis of vitamin E as a clinical intervention in AD

Biological properties of vitamin E

Vitamin E is a collective term that describes a family of eight naturally-occurring homologues with potent antioxidant properties. The group is composed of four tocopherols and four tocotrienols, each of which has an α , β , γ and δ isoform. All eight congeners are differentially distributed within food sources such as vegetable oils, grains and various nuts and seeds³⁸ and α -tocopherol is the primary isoform normally found within vitamin E supplements.³⁹ The recommended dietary allowance for α -tocopherol is currently 15 mg/day in adults with a recommended upper intake level of 1000 mg/day for supplemental vitamin E as the highest dose unlikely to result in haemorrhage - however, high-doses (>1000 mg/day) have been used in a number of studies of vitamin E supplementation to date.³²

Plasma levels of vitamin E are dependent upon the absorption, distribution and excretion rates of each isoform. All eight homologues have lipophilic properties and are absorbed from

the intestine following ingestion in micelles formed by pancreaticobiliary secretions.³² The plasma half-life of α -tocopherol is estimated at 20 hrs, which is considerably longer than that of other isoforms, particularly the tocotrienol congeners.⁴⁰ This is significant in that α -tocopherol is therefore the predominant isoform found in tissues whereas the other congeners are metabolised and more quickly removed.⁴¹ Additionally, important interactions have been previously reported between various isoforms including antagonistic interactions between plasma α and γ -tocopherol.⁴²

Biological functions of vitamin E

Vitamin E has a broad range of biological functions that vary according to the relevant isoform. The tocopherol and tocotrienol sub-groups possess varying properties and functions linked with the level of chemical saturation in their molecular structures with tocopherols having phytyl side-chains, while tocotrienols possess three carbon-carbon double bonds.³² However, as a collective group, the potent antioxidant capabilities of vitamin E are well known and each of the eight tocopherol and tocotrienol congeners are considered free-radical scavengers.⁴³ The antioxidant capacity results from the presence of a hydroxyl group on the aromatic ring of tocopherols that quenches free radicals through hydrogen atom donation.⁴⁴

The various vitamin E isoforms enact a key role in the protection of cell membranes, rich in highly unsaturated fatty acids, from oxidative damage.⁴⁵ Several studies have shown that different isoforms are differentially located within the cell membrane and that this may influence their biological activity in the lipid membrane.^{46,47} In vivo studies have reported that the antioxidant activity of α -tocopherol is superior to other tocopherol congeners, followed in potency by the β , γ and δ isoforms, respectively.⁴⁸ While the effectiveness of α -tocopherol has also been reported through in vitro evidence, it has been suggested that its relative laboratory efficacy may be dependent upon experimental conditions.⁴⁹ Tocotrienols may exhibit more potent antioxidant activities than tocopherols due to their shorter side-chains enabling easier incorporation into the cell membrane and the presence of their unsaturated side-chain.⁵⁰ However, it has been suggested that α -tocopherol retains a superior in vivo role in neuroprotection due to its relatively greater bioavailability and preferential retention by tissues.⁵¹ Similar to tocopherols, the δ -tocotrienol isoform demonstrates reduced antioxidant potency compared to the other tocotrienol congeners.⁴⁸

Importantly, the scope of vitamin E activity extends beyond its antioxidant capabilities and includes other neuro-protective, anti-inflammatory and cholesterol-reducing properties, in addition to influencing gene expression and potentially ensuing AD pathology.⁵⁰

Several studies have demonstrated the beneficial effects of vitamin E supplementation on various markers of inflammatory stress, cellular signalling and immune function in humans and its influence on AD-associated pathology.^{52,53} Additionally, studies in murine AD models have identified associations between vitamin E deficiency and increased expression of genes associated with AD progression including those involved in the regulation of apoptosis, neuro-transmission and A β metabolism.⁵⁴ Similarly, vitamin E has been shown to confer a protective effect against hyper-phosphorylated tau protein.⁵⁵ The enzyme-inhibiting activity of various tocopherol and tocotrienol isoforms also incorporates several AD-associated enzymes, including cyclo-oxygenases (COX), which contribute to neuro-inflammation and OS.⁵⁶ The activity of both sub-groups have also been associated with reduced A β production through inhibiting secretase enzyme activity.³⁹

Comparison of tocopherol and tocotrienol isomers

Tocopherols are a necessary constituent of physiological neuronal activity with high levels of the vitamin E transfer protein (α -tocopherol transfer protein, α -TPP) found in the cerebellum.⁵⁷ Its importance is emphasised by a loss-of-function mutation within the α -TPP gene that results in a rare condition known as ataxia with vitamin E deficiency (AVED)⁵⁸ and several studies have also reported potential benefits of α -tocopherol in other neurodegenerative disorders: for example, increasing duration (years) of vitamin E supplement use has been inversely correlated with amyotrophic lateral sclerosis (ALS) rates while a meta-analysis found a protective influence from moderate-high intake of vitamin E in participants with regards to their risk of developing Parkinson's disease.^{59,60}

In contrast, research on tocotrienols has been limited, although not all are believed to be essential for normal physiological function and there is no evidence to date for any genetic mutations that alter tocotrienol metabolism and result in clinically significant sequelae.⁶¹ However, tocotrienols are an important vitamin E sub-group with biological functions that differ from tocopherols, with stronger antioxidant and anti-inflammatory effects according to some measures.¹⁷ Tocotrienols influence the mevalonate pathway by

suppressing hydroxyl-methyl-glutaryl co-enzyme A (HMG-CoA) reductase resulting in cholesterol-lowering and anti-inflammatory properties that influence AD pathology.⁶² These findings have been reported for several tocotrienol isoforms including the δ congener which suppresses the action of HMG-CoA reductase at the transcriptional level.^{63,64} However, combined supplementation with α -tocopherol has been shown to attenuate these inhibitory effects with a dose-dependent relationship in hamster models.⁶⁵ This study furthermore found that α -tocopherol supplementation alone may act as a stimulant to HMG-CoA activity and therefore demonstrate hypercholesterolaemic activity.⁶⁵ Such interactions highlight the importance of a thorough understanding of the interactions between isoforms and the appropriate selection of congeners in interventional studies.

AD and vitamin E: human studies

Plasma, serum and CSF concentrations of vitamin E in AD

A large number of case-control studies have previously evaluated vitamin E levels in the plasma, serum and CSF of patients with AD (Table 1). An early study reported reduced vitamin E levels in a small number of AD patients compared with cognitively intact controls.⁸³ Many studies have since replicated these findings and have been summarised in a 2014 meta-analysis.⁸⁴ This study reviewed the plasma status of several micro-nutrients in AD and reported diminished vitamin E levels in AD patients compared with cognitively intact controls and concluded this was not as a consequence of patient malnourishment.⁸⁴ Similar findings were reported in the sensitivity analysis of a 2017 case-control study that found no correlation between AD severity and plasma vitamin E levels, suggesting diminished plasma antioxidant status may result from early disease pathology rather than as a consequence of reduced vitamin E intake.⁷⁷

The most recent meta-analysis conducted by Mullan and colleagues (2018) evaluated 51 studies comparing the plasma nutrient status in AD participants compared to cognitively intact controls.⁸⁵ This study reported that vitamin E was the most extensively studied dietary plasma antioxidant and concluded that vitamin E levels are 11% lower in AD patients compared to cognitively normal subjects⁸⁵ corroborating the findings from a previous smaller meta-analysis of 17 studies.⁸⁶

In addition to diminished plasma vitamin E levels in AD, a meta-analysis of 116 studies reported significantly reduced levels in the central nervous system of participants with AD and suggested nutrient status of the brain

Table 1 Cross-sectional studies investigating vitamin E levels in AD patients

Study (Publication year)	Isoform(s)	Population cases	Results
Significant associations:			
Zaman et al (1992) ⁶⁶ Jimenez-Jimenez et al (1997) ⁶⁷	Unspecified α -tocopherol	10 AD 44 AD	Lower serum vitamin E levels compared with controls. Lower vitamin E levels in both serum and CSF compared with controls.
Sinclair et al (1998) ⁶⁸ Foy et al (1999) ⁶⁹	α -tocopherol α -tocopherol	25 AD 79 AD	Lower plasma vitamin E levels compared with controls. Lower plasma vitamin E levels compared with controls.
Bourdel-Marchasson et al (2001) ⁷⁰ Polidori et al (2002) ⁷¹	α -tocopherol α -tocopherol	20 AD 35 AD	Lower plasma vitamin E levels compared with controls. Lower plasma vitamin E levels and increased lipid peroxidation compared with controls.
Mecocci et al (2002) ⁷² Rinaldi et al (2003) ⁷³	α -tocopherol α -tocopherol	40 AD 63 AD, 25 MCI	Lower plasma vitamin E levels and increased oxidative damage markers compared with controls. Lower plasma vitamin E levels compared with controls.
Baldeiras et al (2008) ⁷⁴ Mangialasche et al (2012) ⁷⁵	α -tocopherol α -, β -, γ -, δ -tocopherols & α -, β -, γ -, δ -tocotrienols	42 AD, 85 MCI 168 AD, 166 MCI	Lower plasma vitamin E levels and increased oxidative damage markers in both AD and MCI compared with controls. Lower plasma vitamin E levels across all isoforms in AD and MCI cases compared with controls.
Giavarotti et al (2013) ⁷⁶ Mullan et al (2017) ⁷⁷	α -tocopherol α - and γ -tocopherols	23 AD 251 AD	Lower plasma vitamin E levels and increased oxidative stress markers compared with controls. Lower plasma levels of both vitamin E isoforms compared with controls.
No significant associations:			
Schippling et al (2000) ⁷⁸ Ryglewicz et al (2002) ⁷⁹	α -tocopherol α -tocopherol	29 AD 26 AD	No significant differences between vitamin E levels in plasma and CSF compared with controls. Patients with vascular dementia had significantly lower plasma vitamin E levels than AD patients.
Charlton et al (2004) ⁸⁰ Mas et al (2006) ⁸¹	α -tocopherol α -tocopherol	15 AD 100 AD	No significant difference in plasma vitamin E levels compared with controls. No significant difference in plasma vitamin E levels compared with controls.
von Arnim et al (2012) ⁸²	α -tocopherol	74 MCI	No significant associations between plasma vitamin E levels and dementia.

Note: Detection method for all studies was high-performance liquid chromatography.

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

parallels that of the systemic circulation.⁸⁷ One cross-sectional study was notable for its measurement of tocotrienol isoforms: 521 subjects were recruited including 168 AD, 166 MCI cases and 187 cognitively intact controls.⁷⁵ The study reported significantly diminished plasma vitamin E levels for each isoform in those with AD compared to controls and low tocopherol and tocotrienol levels were associated with increased risk of both MCI and AD.⁷⁵

Despite a substantial body of evidence in support of reduced vitamin E levels in AD, a relatively small number of case-control studies have reported no significant differences in plasma levels compared with cognitively normal

controls (Table 1). Although these studies were of limited sample size, they were supported by findings from a larger Mendelian randomised study which included data from two genome-wide association studies of vitamin E (n=7,781) and AD cases and controls (17,007 AD cases and 37,154 controls) that found no association between circulating vitamin E levels and AD.⁸⁸

Prospective studies of vitamin E concentrations and subsequent AD risk

Several prospective cohort studies have also investigated plasma vitamin E levels and the subsequent risk of

developing AD (Table 2). In 2010, a prospective study assessed plasma levels of all eight vitamin E isoforms in 232 subjects aged at least 80 years from the Kungsholmen Project with a six-year follow-up.⁸⁹ Individuals with total plasma tocopherols, tocotrienols or vitamin E in the highest tertile had a reduced risk of incident AD compared with participants in the lowest tertile. The authors suggested that any neuro-protective effects may result from the combination of vitamin E isoforms rather than specifically to any individual congener.⁸⁹

Another prospective study evaluated vitamin E status and magnetic resonance imaging (MRI) with regard to MCI conversion to AD.⁹⁰ Data from 253 participants including 81 AD, 86 MCI cases and 86 cognitively intact controls revealed lower absolute values for all vitamin E isomers in both the AD and MCI subjects compared to controls. The authors suggested the combination of vitamin E measures and MRI scanning was superior to imaging alone in predicting MCI conversion to AD, with 95% sensitivity after one-year follow-up.⁹⁰

Similar findings were reported from the Cardiovascular Risk Factor, Aging and Dementia (CAIDE) study,⁹¹ which analysed data from 140 cognitively intact participants with a follow-up time of 8 years. Elevated values of both tocopherol and tocotrienol isoforms were associated with a reduced risk of “cognitive impairment”, defined as the development of either MCI or AD.⁹¹

Evaluation of vitamin E intake and AD risk

Associations between vitamin E intake through supplementary or dietary sources and the risk of developing AD have also been extensively investigated (Table 3). A prospective study investigated vitamin E supplementation

and incident AD in a population of 633 individuals with a mean 4.3-year follow-up and reported that none of the 27 subjects taking vitamin E supplements developed AD in contrast to the predicted incidence of 3.9.⁹² Similarly, the prospective Cache County Study reported that individuals taking vitamin E supplements in addition to multivitamins containing vitamin C had reduced AD risk.⁹³ However, the study found no significant benefit from use of vitamin E supplements alone.⁹³ A more recent study published in 2017 reported that vitamin E supplementation was associated with decreased risk of cognitive decline in a cohort of 560 AD patients from the Canadian Study of Health and Aging although, no significant association was detected between vitamin E intake and AD risk specifically.⁹⁴

Several prospective studies of vitamin E dietary intake also reported beneficial effects associated with reduced AD risk. One study evaluated 815 cognitively normal elderly individuals with a mean follow-up time of 3.9-years and found that increased vitamin E intake from dietary sources was associated with a lower risk of developing AD, although the benefit was limited to those not carrying the ApoE4 risk allele.⁹⁵ Interestingly, this study suggested that vitamin E supplementation from non-dietary sources was not significantly associated with diminished AD risk.⁹⁵ Similar findings in a study of 5,395 participants reported that high dietary intake of both vitamin E and vitamin C was associated with a reduced risk of developing AD.⁹⁶ This effect was greatest among smokers and was independent of the ApoE4 risk allele.⁹⁶ Furthermore, Morris and colleagues found that subjects with higher dietary intake of vitamin E had a lower incidence of AD and that plasma α - and γ -tocopherol levels were independently associated with AD risk.⁹⁷ Finally, the

Table 2 Studies investigating cross-sectional levels of vitamin E and subsequent risk of AD development

Study (Publication year)	Isoform(s)	Study population	Follow-up	Results
Mangialasche et al (2010) ⁸⁹	α -, β -, γ -, δ -tocopherols & α -, β -, γ -, δ -tocotrienols	232 cognitively normal elderly participants	6 years	Higher total tocopherol, total tocotrienol and total vitamin E plasma levels were associated with a reduced risk of AD development.
Mangialasche et al (2013) ⁹⁰	α -, β -, γ -, δ -tocopherols & α -, β -, γ -, δ -	81 AD, 86 MCI, 86 Control	1 year	AD and MCI participants had lower plasma vitamin E levels. Combination of plasma vitamin E and MRI was superior to MRI alone in predicting conversion of MCI to AD.
Mangialasche et al (2013) ⁹¹	α -, β -, γ -, δ -tocopherols & α -, β -, γ -, δ -	140 cognitively normal elderly participants	8.2 years	Elevated serum tocopherols and tocotrienols were associated with reduced risk of cognitive impairment (MCI and AD).

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

Table 3 Epidemiological studies investigating associations between vitamin E intake and risk of AD

Study (Publication year)	Vitamin E source	Study population	Mean follow-up	Results
Significant association:				
Morris et al (1998) ⁹²	Supplements	633 cognitively-intact elderly	4.3 years	None of the vitamin E supplement users developed AD (predicted incidence of 3.9).
Zandi et al (2004) ⁹³	Supplements	4,740 elderly	3 years	Use of combined vitamin E and vitamin C supplementation was associated with decreased AD incidence.
Basambombo et al (2017) ⁹⁴	Supplements	5,269	5.2 years	Use of vitamin E and/or vitamin C supplements was associated with reduced AD risk.
Morris et al (2002) ⁹⁵	Dietary	815 elderly	3.9 years	High vitamin E intake from foods was associated with decreased risk of incident AD in ApoE4 negative persons. Vitamin E supplementation was not significantly associated with AD risk.
Engelhart et al (2002) ⁹⁶	Dietary	5,395	6 years	High dietary vitamin E intake was associated with reduced risk of AD. This effect was greatest in smokers.
Morris et al (2005) ⁹⁷	Dietary	1,041	3.9 years	High dietary vitamin E intake was associated with reduced AD incidence. α - and γ -tocopherol had independently associated with delayed cognitive decline.
Devore et al (2010) ⁹⁸	Dietary	5,395	9.6 years	High dietary intake of vitamin E at baseline was associated with a modest reduction in AD risk over follow-up.
No significant associations:				
Masaki et al (2000) ⁹⁹	Supplements	3,385 elderly male	10 years	No reduction in AD risk was detectable in those taking vitamin E supplements. Supplement use was associated with better cognitive performance at 10-year follow-up.
Luchsinger et al (2003) ¹⁰⁰	Supplements and dietary	980 elderly	4 years	Neither supplemental or dietary vitamin E intake were associated with decreased AD risk.
Gray et al (2008) ¹⁰¹	Supplements	2,969 elderly	5.5 years	Supplemental vitamin E and/or vitamin was not associated with a reduction in AD risk.

Abbreviations: AD, Alzheimer's disease.

prospective population based Rotterdam Study included 365 participants with AD and identified a modest reduction in risk over the longer term in participants from the highest tertile of dietary vitamin E intake compared with those in the lowest tertile, independent of any supplement use and other potential confounders.⁹⁸

However, several studies failed to detect associations between either dietary intake or vitamin E supplementation and AD. The Honolulu-Asia Aging Study analysed data from 3,385 men who reported taking vitamin E and vitamin C supplements at baseline in addition to measuring AD prevalence ten-years later.⁹⁹ Although the study identified a protective effect of vitamin E with vascular dementia, no association with AD risk was noted.⁹⁹ The analysis of 980 individuals within the Washington Heights-Inwood Columbia Aging Project concluded that neither supplementary nor dietary intake of vitamin E, alone or in combination, significantly attenuated AD risk.¹⁰⁰ A prospective study of 2,969 individuals followed-up over a mean 5.5 years found

no association between AD risk and the use of vitamin E supplements, with or without vitamin C.¹⁰¹

While these prospective studies provide limited evidence for the benefits of vitamin E supplementation, they nevertheless suggest that a high intake from dietary sources may confer some benefit in reducing the risk of developing AD compared to those with lower intake.

Randomised clinical trials of vitamin E supplementation

Several randomised trials have investigated the efficacy of vitamin E as a potential therapeutic intervention for AD (Table 4). The first of these was published over 20 years ago and was a double-blind, randomised multi-centre clinical trial which compared the effectiveness of selegiline (a selective monoamine oxidase inhibitor) and α -tocopherol (2000 IU/day), individually or in combination, with a placebo in 341 subjects with moderate AD for 2 years.¹⁰²

Several outcome measures were considered including time-to-death, institutionalisation, functional ability and dementia severity. The study concluded that vitamin E and selegiline slow the progression of moderate AD both independently and as a combination therapy compared with placebo but with no additive benefit of the combined regimen.¹⁰²

A larger double-blind study was undertaken several years later and compared the effects of 2000 IU/day of vitamin E, donepezil or placebo daily for 3 years in 769 subjects with the amnesic subtype of MCI.¹⁰³ Although the authors did not specify the vitamin E isoform used in supplementation, no significant difference in the rate of conversion to AD was found at any point during follow-up in the group receiving vitamin E and only minimal effects on secondary measures of cognition were detected compared with those receiving placebo.¹⁰³

In a small trial, 57 AD participants were randomised (33 completed the study) to receive either vitamin E (800 IU/day) or placebo for six-months and markers of OS and cognitive function were assessed.¹⁰⁴ Among those randomised to receive vitamin E, two sub-groups were identified: (1) those who had lower measures of OS and retained their cognitive function and (2) those with no significant changes in OS levels who demonstrated marked cognitive decline throughout the six months of the study.¹⁰⁴ This cognitive decline was greater in the latter sub-group compared with the group of participants who received placebo.

Another double-blind, randomised clinical trial (The TEAM-AD VA Cooperative Randomised Trial) investigated supplementation of α -tocopherol (2000 IU/day) and/or memantine compared to placebo in 613 patients with mild-to-moderate AD.¹⁰⁵ The study reported that α -tocopherol supplementation alone resulted in slower functional decline compared with the placebo group.¹⁰⁵ Unexpectedly, the combination of α -tocopherol and memantine demonstrated less benefit than α -tocopherol supplementation alone, although a convincing rationale for this was lacking. Furthermore, evaluation of the α -tocopherol safety data suggested no significant increase in mortality in contrast to an earlier meta-analysis.^{105,107}

More recently, the double-blind PREADViSE study (2017) evaluated the effects of low-dose vitamin E (400 IU/d, unspecified isoform) and/or selenium versus placebo in 7,540 cognitively intact elderly men.¹⁰⁶ The study found that neither vitamin E nor selenium, individually or in combination, offered any benefit in delaying the

onset of AD.¹⁰⁶ Of note, Naeini and colleagues investigated the effects of combined vitamin E and vitamin C supplementation for 1 year versus placebo in elderly individuals with MCI in a double-blind, randomised trial.¹⁰⁸ Although supplementation offered some improvement in selected measures of oxidative stress, there were no detectable benefits in cognition.¹⁰⁸ A further small trial investigating the effects of supplementation with vitamin E and other nutrients similarly found reductions in measures of OS with treatment but no derived clinical benefit.¹⁰⁹

Failure of vitamin E as a clinical intervention so far

Since Harman first postulated the “free radical theory of ageing” in 1956, the potential implications for providing “chemical means of prolonging effective life” has received significant attention.¹¹⁰ Nevertheless, evidence in support of vitamin E providing clinical benefit against AD remains inconsistent and inconclusive. Despite substantial evidence of increased OS in AD aetiology and reduced circulating vitamin E levels, the findings from clinical trials investigating vitamin E as an intervention have yet to match the expectation.

This translational discrepancy is not uncommon among studies investigating the role of OS in disease and its implication in pathogenesis and potential therapeutic approaches.¹¹¹ Indeed, several studies have shown that antioxidant supplementation is ineffective or possibly even harmful.¹¹² In the context of vitamin E and AD, the failure of clinical trials may be due to general weaknesses in the studies investigating OS or limitations of studies specific to this area. A major and controversial limitation includes determination of the most appropriate OS markers.^{113,114} Consequently, it has been suggested that disease specific proteins or combinations of markers in large-scale panels should be considered for monitoring therapeutic response and predicting outcomes.¹¹⁵ In the specific context of AD, the use of myeloperoxidase (MPO), *trans*-4-hydroxy-2-nonenal (HNE) or several advanced glycation end products (AGEs) resulting from glycoxidation have been suggested as potentially useful OS markers.¹¹⁵

However, several factors may reflect the translational difficulties from laboratory to clinical evidence in the existing vitamin E studies in AD. While increased OS and reduced plasma vitamin E levels have been associated with AD, a weakness of many vitamin E supplementation

Table 4 Randomised trials investigating vitamin E supplementation as a treatment for AD

Study (Publication year)	Study population	Isoform	Dose	Duration	Primary outcome measures	Results
Sano et al (1997) ¹⁰²	341 AD cases	α -tocopherol	2000 IU/day	2 years	ADCS; MMSE; Blessed-Dementia Scale	Slowed AD progression with α -tocopherol and/or selegiline compared with placebo group.
Petersen et al (2005) ¹⁰³	769 MCI cases	Not specified	2000 IU/day	3 years	15 cognitive tests including MMSE	No significant difference between progression to AD in group treated with vitamin E compared with placebo group.
Lloret et al (2009) ¹⁰⁴	33 AD cases	α -tocopherol	800 IU/day	6 months	MMSE; Blessed-Dementia Scale	Cognition maintained in one sub-group treated with α -tocopherol while cognition decreased sharply in a second.
Dysken et al (2014) ¹⁰⁵	613 AD cases	α -tocopherol	2000 IU/day	2 years	MMSE; ADCS-ADL Inventory	Slowed functional decline in AD in patients receiving α -tocopherol compared with placebo.
Kryscio et al (2017) ¹⁰⁶	7,540 cognitively normal men	Not specified	400 IU/day	6 years	MIS; CERAD test-battery	No significant effects on AD prevention detected. No evidence of increased mortality with vitamin E treatment.

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; ADCS, Alzheimer's Disease Assessment Scale; MMSE, Mini-Mental State Examination; ADCS-ADL, Alzheimer's Disease Cooperative Study/Activities of Daily Living; MIS, memory impairment screen; CERAD, Consortium to Establish a Registry for Alzheimer's disease.

trials has been their failure to measure antioxidant and nutritional levels at baseline. As such, an unknown proportion of participants may not have had sufficiently depleted vitamin E levels upon study entry and therefore the likelihood of observing any beneficial effects of vitamin E on primary outcome measures in these individuals may have been reduced.²² The requirement of low baseline levels for supplementation to cause an efficacious increase in plasma levels has been highlighted in non-vitamin E studies and suggests that supplementation is beneficial only in the setting of deficient or insufficient nutrient status.¹¹⁶

In addition, differences in study design between randomised trials may explain, in part, the inconsistent findings to date. For example, a study by Lloret and colleagues consisted of a relatively small number of participants with a lower vitamin E dose and shorter duration while in the study by Sano et al there were large differences in baseline Mini-Mental State Examinations between the placebo and vitamin E groups.^{102,104} It also remains unclear whether the duration of intervention in these studies is sufficient for the detection of clinical effects. A 2017 Cochrane review concluded that only the study by Dysken and colleagues (which found that that vitamin E slows functional decline in AD) was of moderate quality and that future trials were likely to counter its findings of a lack of support for the beneficial effects of vitamin E in AD.¹¹⁷

Importantly, a major limitation of trials to date may have been the choice of intervention. While two studies (Petersen et al and Kryscio et al) failed to specify which vitamin E isoform was used, the remaining studies have focused solely on α -tocopherol. There is support that supplementation with a single vitamin E isoform (aside from questions of dose and duration) is a less than optimal approach. Firstly, there is sufficient evidence for the biological activity of the other vitamin E isoforms to warrant their investigation in randomised trials.^{17,61} There have been no trials to date investigating tocotrienol supplements. Secondly, the administration of high-doses of α -tocopherol alone may inhibit the absorption of other tocopherol and tocotrienol isoforms, leading to a damaging biochemical imbalance rather than clinical benefit.²²

Furthermore, existing epidemiological studies suggest that dietary sources of vitamin E are more effective in reducing the risk of developing AD than supplementation alone. It is therefore likely that this benefit can be attributed to synergistic interactions which are obscured in trials that investigate supplementation with only a single isoform.¹¹⁸ It is worth noting that dietary vitamin E

consumption is more likely to reflect long-term intake than supplement use which may offer partial explanation as to why diet-based sources seem more effective than supplementation in reducing associated AD risk.¹¹⁹

There is also evidence to suggest that the combination of vitamin intake is influential. Vitamin C plays an important role in the reduction of vitamin E after it has been oxidised by free radicals and therefore in maintaining its antioxidant capabilities in tissues.^{120,121} It is possible that α -tocopherol radicals can themselves induce lipid peroxidation in the context of inadequate co-antioxidant (including vitamin C) levels, particularly in settings of increased oxidative stress or where α -tocopherol levels have been increased alone.^{122,123} The possibility of α -tocopherol exhibiting pro-oxidant activity under such circumstances is supported by a small randomised trial which found increased plasma oxidant activity in patients receiving vitamin E supplementation compared with placebo.¹²⁴ It may therefore be important to consider the effects of supplementation with other vitamins in combination with vitamin E to maximise antioxidant efficacy. This is supported by studies that have shown that vitamin E contributes only a relatively small proportion to overall serum antioxidant capacity.^{105,125}

Consideration of the complex bioavailability of vitamin E is important as it is influenced by several factors. The intestinal absorption of vitamin E can vary significantly depending on the food source and its composition of tocopherol or tocotrienol isomers and other nutrients.¹²⁶ It has been shown that various dietary compounds, including sterols, can reduce intestinal absorption of vitamin E.¹²⁷ Furthermore, there is large variation between individuals in the availability of high-density lipoproteins (HDLs) which are necessary for vitamin E integration into the central nervous system.¹²⁸ There is evidence to suggest this may explain the apparently higher maximum plasma levels of vitamin E in women compared to men.¹²⁹

Several other variables, including age, smoking status and obesity, have also been associated with variation in vitamin E bioavailability, with reduced plasma levels reported in those over 80 years of age although this may be partially attributable to comorbid illness and diminished food intake.¹³⁰ Low α -tocopherol levels have also been demonstrated in smokers, while obesity has been inversely correlated with plasma α -tocopherol levels^{131,132} although potential confounding through variation in dietary patterns and nutrient intake may exist.¹³¹ Such variations may have important consequences for determining which individuals

are likely to benefit from vitamin E intervention. This concept is augmented by the recent identification of 28 genetic polymorphisms that have been shown to influence vitamin E absorption, metabolism and bioavailability.^{133,134} These genetic variants have been proposed as a rationale that explains the substantial individual variability of vitamin E bioavailability and responsiveness of randomised trial participants.¹³³ Improved understanding of the genetic architecture that underpins vitamin E bioavailability and bioactivity will enable personalised and more effective recommendations of vitamin E intake.¹³⁵ Such factors may also clarify responder status in vitamin E supplementation studies and warrants further consideration.¹⁰⁴

While vitamin E is an essential micronutrient and has been internationally incorporated into many guidelines for dietary intake, its safety as a clinical intervention remains controversial.¹³⁶ Significantly, it has been reported to have a modifying effect on platelet function and may therefore theoretically increase the risk of clinically significant bleeding.¹³⁷ One meta-analysis found that supplementation with low-dose vitamin E increased the risk of haemorrhagic stroke amongst study participants.¹³⁸ These effects may be important in the setting of individuals taking other anticoagulant or antiplatelet agents including aspirin. Increased risk of prostate cancer has also been linked with vitamin E supplementation.¹³⁹ Similar concerns have been raised by several meta-analyses which concluded that vitamin E supplementation may lead to increased overall mortality.^{107,112} However, the conclusions of such meta-analyses have been questioned and different analytical approaches have produced contradictory results.^{140,141} Therefore, the potential adverse effects of vitamin E remain an important clinical consideration and should be explored in future studies.

Several reviews that provide an overview to various aspects of the relationship between vitamin E and AD already exist.^{39,61} However, this narrative review is broader in scope with a flexible structure which has allowed the authors to be more exploratory and current in their approach that considers the use of vitamin E as a potential therapeutic for the treatment of AD. This review reflects certain points based on the authors' experience and uses a specified strategy that details how the literature was searched (keywords), time limits of searches, and bibliographic databases accessed. The methodological approach described provides a reference point in time from which future narrative reviews may focus on new literature, thereby limiting redundancy.

Conclusions

In spite of a strong rationale for the role of vitamin E as an effective intervention for AD, the existing clinical evidence remains inconclusive. This review has presented findings from cross-sectional studies that reported significantly lower plasma and CSF levels of vitamin E in those with AD. Additionally, reduced plasma vitamin E status has been associated with increased future risk of developing AD. Epidemiological studies have offered mixed results with regards to vitamin E supplementation but have suggested that intake of high levels of vitamin E from dietary sources may be beneficial. However, clinical trials to date have investigated only the α -tocopherol isoform and have several limitations including failure to measure antioxidant and nutritional levels of participants at baseline. Therefore, there is insufficient evidence to accept or reject the premise that vitamin E is an effective clinical intervention for delaying or preventing the onset of AD and further research is necessary. Importantly, investigation of the underlying genetic architecture with regard to responder status to vitamin E supplementation is warranted, given it is a likely significant contributor to the failure of clinical trials to date.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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