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Review

A Scoping Review of Dietary Factors Conferring Risk or Protection for Cognitive Decline in APOE ε4 Carriers

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Abstract

Alzheimer's disease (AD) is a progressive and fatal neurodegenerative disease. The strongest genetic risk factor for sporadic AD is carriage of the ε4 allele of the Apolipoprotein E (APOE) gene. Strategies to slow the progression of AD, including dietary interventions, may be modified by the pathogenic effect of this polymorphism. Our objective in this review was to determine the extent and quality of the literature investigating how dietary factors and interventions interact with the APOE ε4 genotype to impact cognitive decline in AD. To that end, we performed a systematic scoping review of published English-language articles involving human subjects. We found evidence suggesting that adherence to a Mediterranean diet may reduce cognitive decline among APOE ε4 carriers, whereas ketogenic agents appear to be ineffective. Diets high in saturated fats may be particularly harmful for APOE ε4 carriers. We identified several topics, including the use of ω-3 fatty acid and antioxidant supplements, for which additional high level evidence is needed.

Key words: Cognition, Apolipoprotein E, Alzheimer's disease.

Introduction

Sporadic Alzheimer's disease (AD) is a progressive neurodegenerative disease and the leading cause of dementia. AD is characterized by memory loss, impaired language, executive dysfunction, mood and other behavioral changes. These cognitive losses lead to functional impairment, dependence on others for care, and ultimately death. AD affects 5.8 million people in the United States, including 32% of individuals older than age 85 (1). Both environmental and genetic factors contribute to AD risk. The strongest genetic risk factor for the development of AD and the age of onset is the Apolipoprotein E (APOE) genotype (2–4). APOE is the major lipid-carrying protein synthesized in the central nervous system (CNS), and has a role in systemic and brain lipid metabolism (5). APOE is found in three isoforms in humans that are differentiated by only one or two single nucleotide polymorphisms: ε2, ε 3, and ε4. APOE ε3 is the most common allele, whereas APOE ε4 confers increased risk for AD and is found in 13.7% of the population. APOE ε2 is protective against AD and is found in 8.4% of the population (6). APOE ε4 occurs more frequently in equatorial populations and risk attributed to the gene may be affected by ethnicity, although there may be confounding sociocultural factors (7–9). APOE ε4/ε4 has been proposed to be a "thrifty" genotype, given its higher incidence in populations with sporadic food availability (10). APOE ε4 reduces brain glucose metabolism as measured by FDG-PET (11, 12) and reduce levels of expression of glucose transporters in neurons (13). This suggests that APOE isoform can affect metabolism in the CNS, a possible contributing mechanism to neurodegenerative disease.

Testing for APOE ε4 in clinical settings is discouraged due to limited impact that the results have on treatment recommendations and prognosis (14). However, education, counseling, and careful in-person disclosure of APOE ε4 status to cognitively intact individuals in a clinical research setting does not result in psychological harm (15, 16). The literature is inconsistent on whether providing this information can motivate APOE ε4 positive patients to improve their lifestyle choices that might reduce AD risk; one study found no significant impact of learning APOE ε4 genotype on diet or exercise habits (16), whereas another found that after disclosure APOE ε4 carriers consume a healthier diet that improved hyperlipidemia (17). In spite of the consensus that routine testing for APOE ε4 is premature, direct-to-consumer genetic testing for APOE ε4 has become widely accessible and inexpensive, and interest in preventative strategies for cognitive decline in APOE ε4 carriers has grown (18, 19).

In this scoping review, we sought to determine—in a systematic manner—which dietary factors and interventions are of utility for individuals carrying an APOE ε4 genotype. Dietary interventions to prevent dementia in APOE ε4 carriers have been previously reviewed (5), but not with a systematic approach. Scoping reviews use systematic, reproducible methods, but unlike meta-analysis they do not address a narrow or quantitative question, rather they aim to describe the literature relevant to broad, complex, or under-studied topics. The scoping review format was used here because our question was exploratory, and scoping reviews allow for a wider range of study types to be included.

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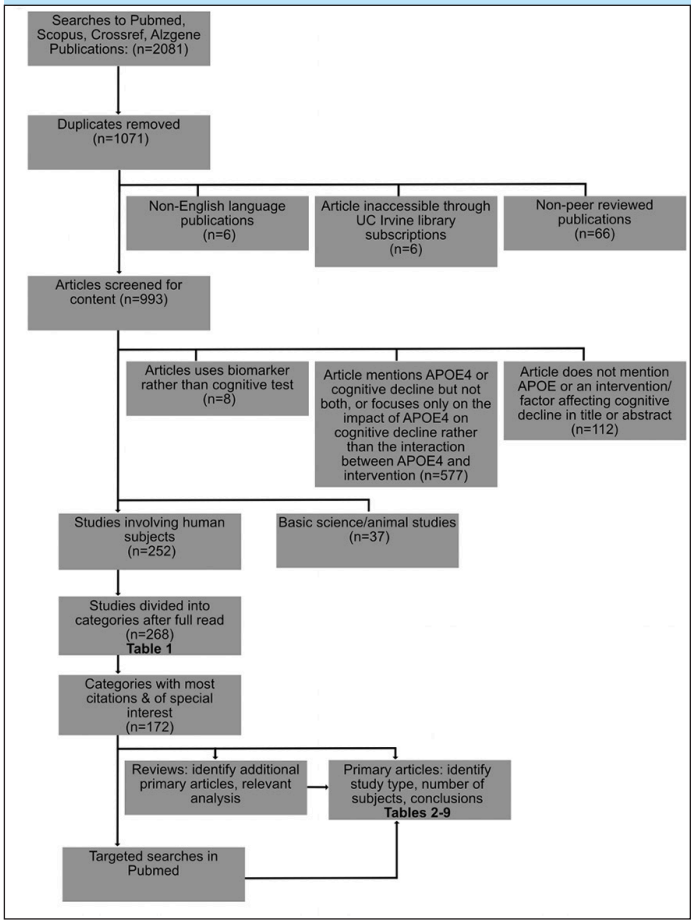
Methods

Review strategy

This review was conducted in two parts. First, we performed a scoping systematic review to identify interventions conferring risk or protection for cognitive decline that have been examined for interactions with APOE ε4 genotype. A scoping review uses transparent methods to identify and analyze the literature relevant to a topic, with the goal of presenting a descriptive overview of a potentially large and diverse body of literature (20). Compared to a quantitative systematic review, which extracts data and thoroughly assesses the quality of each study, scoping reviews address broader research questions, including a variety of methods and study types, and can be used to determine the extent of the current literature, summarize findings and trends, and identify deficiencies in existing scientific knowledge. The PRISMA ScR checklist was followed throughout the search and manuscript preparation (21) (Figure 1). Our scoping review was followed by targeted searches of the topics identified focusing on diet.

Figure 1. Flow chart depicting search strategy and inclusion criteria



Scoping review search

Sources included in the scoping review included all English-language peer-reviewed articles from any publication year, primary or review, discussing how APOE ε4 impacts the effect of an intervention or risk factor on cognitive decline in human subjects. This search was performed on April 9th 2020.

The following databases were searched: pubmed, scopus, crossref, and alzgene. Databases were searched with the following terms: “APOE4 prevent cognitive decline”, “APOE4 intervention cognitive decline”, “APOE4 therapy cognitive decline”, “APOE4 treatment cognitive decline”, and “APOE4 interaction cognitive decline”. Alzgene was searched for “APOE2/3/4”. The total number of discovered titles was 2081. After duplicates were removed, 1071 unique titles remained. These abstracts were screened by two authors (GF or NG) to determine eligibility according to the following exclusion criteria: not English language, not a peer-reviewed article, not accessible through UC Irvine services or library subscriptions. Only 6 out of 1071 articles could not be accessed. Nine hundred ninety-three articles met the criteria and the full text was screened for content according to the following exclusion criteria: article does not mention APOE ε4, cognitive decline, or the interaction between APOE ε4 and a dietary factor, does not use a cognitive test or dementia conversion as an outcome, or article focuses on basic science or animal studies rather than clinical/human subject studies. Two hundred fifty-two articles met all inclusion criteria; these articles were divided into categories according to the APOE4-interacting factor examined in each study. These categories were coded as pertaining to dietary, behavioral, unmodifiable, or medical interventions by GF and NG.

Targeted review search

Six categories pertaining to diet were selected for targeted review, based on number of citations and overlap with other included categories (for example, fish, Mediterranean diet, and ω-3 fatty acids) (Table 1). The following sources were used to develop the list of publications included in targeted reviews: first, the citations found in the scoping review were reviewed in full. Second, any additional relevant citations referenced in the publications identified in the scoping review were included. Finally, targeted searches were performed for some topics at reviewers’ discretion, in order to ensure full coverage and that relevant citations were not missed. These searches were performed only in Pubmed, and included the following keywords: “’APOE’ and ‘saturated fat’ and ‘cognitive’”, “’APOE’ and ‘dietary cholesterol’ and ‘cognitive’“, “’APOE’ and ‘Mediterranean diet’ and «cognitive’”, “’ketosis APOE’, ‘Ketogenic APOE’, “’APOE’. The same criteria was used for determining eligibility in these searches as listed above for scoping review results. These searches were performed between April 11th and August 1st of 2020.

Table 1. Scoping review search results pertaining to diet

APOE genotype Interacting Factor	Number of citations (initial search)	Primary articles (initial search)	Primary articles (including additional searches)
Antioxidants and Ginkgo biloba	10	10	17
ω-3 fatty acids	17	7	12
Fish consumption	3	3	3
Mediterranean diet	2	2	6
Dietary cholesterol and saturated fat	9	3	6
Ketogenic diet/ketogenic agents	3	0	6
Homotaurine	3		Not reviewed
B vitamins	2		Not reviewed
Anserine	1		Not reviewed
Carnitine	1		Not reviewed
Kynurenine	1		Not reviewed

Data charting process

For each study identified in the targeted review, the following variables were charted: whether the study was observational or a randomized controlled trial, number of subjects included, average age of subjects, patient diagnosis, cognitive test used, qualitative record of whether the intervention/risk factor examined had an effect on cognitive decline, and whether that effect was modified by the presence of APOE ε4. Some studies, with longitudinal, cohort, or cross-sectional observational designs included individuals of various diagnoses, in these instances "various" or "various longitudinal" was indicated in the diagnosis column. Some studies did not list all cognitive tests used or listed an extensive battery of tests used to produce a cognitive Z score; in these cases, "testing battery" was indicated in the cognitive test column.

Results

Overall search results

Our search returned a total of 252 articles that examined the role of APOE genotype and another factor on cognitive decline in a clinical context. These articles were broken into categories (Figure 1). All articles were assigned to at least one category, and some articles were used in multiple categories, thus the total of 268 listed in the table is higher than the total search results. Forty-four topics were identified, with ten pertaining to diet (Table 1). Six diet-related categories were reviewed in the following results sections (Tables 2-6).

Antioxidants

Oxidative damage may increase risk for cognitive decline (22), and antioxidant supplementation may counteract these effects in cognitively impaired individuals (23, 24). Several studies have shown greater oxidative damage in brain tissue in APOE ε4 carriers (25, 26), possibly due to decreased antioxidant activity (26). We identified five observational studies assessing the risk associated with low antioxidant levels and twelve studies investigating the benefits of antioxidant supplementation (Table 2), including four RCTs and one non-randomized clinical trial. All of these studies investigated the interaction between APOE ε4 and antioxidants in affecting cognitive decline.

Four retrospective studies (two case-control, two cross sectional) investigating potential harmful effects of low antioxidant levels were identified. One case-control study showed that lower levels of total antioxidant, lower activity of the antioxidant enzymes catalase and glutathione peroxidase, and higher levels of (Cu-Zn) superoxide dismutase, a part of an enzymatic antioxidant defense system, were found in AD participants compared to controls, a pattern that was also observed in APOE ε4 carriers with AD compared to non-APOE ε4 carriers with AD and controls, suggesting that APOE ε4 carriers are at greater risk with low antioxidant levels (27). Another case-control study found that LOAD patients who were APOE ε4 non-carriers showed pronounced 25OHD (vitamin D) deficiency, but the same was not true of APOE ε4 carriers (28). A cross-sectional study found that low retinol (vitamin A) and high α-tocopherol (vitamin E)/retinol ratio was associated with greater risk, with both APOE ε2 and APOE ε4 carriers showing greater α-tocopherol/retinol compared to APOE ε3 (29). Another cross-sectional study showed that only in cases of low cognitive support (defined as the most demanding cognitive tasks, such as allowing only for a short encoding time for episodic memory tasks) there was a significant association between vitamin B12 levels and APOE ε4 with respect to free recall (30). A similar association was found between folate and APOE ε4, however it was not significant (30). Thus, the majority of studies suggest that low antioxidant levels, with the exception of vitamin D, pose a greater risk of cognitive decline for APOE ε4 carriers.

Of the twelve studies exploring the possible benefits of antioxidant supplementation, five were trials. A RCT of one year supplementation with H2-infused water in MCI patients

Table 2. Studies investigating risk of low antioxidant levels or benefit of antioxidant supplementation for cognitive decline among APOE4 carriers

Study	Study Type	Number of Patients	Avg Age	Patient Diagnosis	Antioxidant	Test/Measurement Used	Risk Observed in Primary Outcome	Risk in APOE Subgroup Analysis
Kharrazi 2008	Obs Case-control	n=182	73.2, 75	Various	Total antioxidant status	MMSE, NINCDS/ADRDA	Yes	APOE4 > non-carriers
Dursun 2016	Obs Case-control	n=196	57, 61, 73, 74, 76	Various (Ctrl, MCI, AD groups)	Vitamin D	CDR; MMSE	No	No interaction
Bunce 2004	Obs Cross-sectional	n=167	82.81	Various	Vitamin B12, folate	Free recall of semantically unrelated words; Free and cued recall of organizable words	Yes	APOE4 > non-carriers
Huang 2018	Obs Cross-sectional	n=1754	65.31	Cognitively healthy	α-tocopherol/retinol	MoCA	Yes	Independent of genotype, more prevalent in APOE4
Miller, 2016	Longitudinal cohort	n=382	75.5	Various	25-OHD	CDR, Uniform Data Set Neuropsychological Battery, DSM-III, Spanish and English Neuropsychological Assessment Scales	Yes	Controlled
Study	**Study Type**	**Number of Patients**	**Avg Age**	**Patient Diagnosis**	**Antioxidant**	**Test/Measurement Used**	**Significant Benefit Observed in Primary Outcome**	**Benefit in APOE Subgroup Analysis**
Nishimaki 2018	RCT	n=73	73.97, 74.45	MCI	H2 infused water	ADAS-cog	No	APOE4
Snitz 2009	RCT	n=3069	79	Dementia-free and MCI	Ginkgo biloba	MMMSE, ADAS-Cog, neuropsychology battery, TICS	No	No Interaction
Petersen, 2005	RCT	n=769	72.9	aMCI	Vitamin E	MMSE, ADAS-cog, CDR, ADCS Mild Cognitive Impairment Activities of Daily Living Scale, Global Deterioration Scale, neuropsychological battery	No	No
Aisen, 2009	RCT	n=409	76.3	Mild to moderate AD	Folate, vitamin B6, vitamin B12	ADAScog, MMSE, CDR-SOB, ADCS-ADL, NPI, QOL-AD	No	No
Yasuno 2012	CT	n=663	72.7, 73	Dementia-free	ω-3 fatty acids, lycopene, Ginkgo biloba	Set- dependent activity; CCR; category fluency test; WAIS-R	Yes	APOE4 > non-carriers
Engelhart 2002	Prospective cohort	n=5395	67.7	Dementia-free	Beta carotene, flavonoids, vitamin C, vitamin E	DSM-III-R; NINCDS-ADRDA criteria	Yes (vitamin C and vitamin E only)	No interaction
Maddock 2015	Prospective cohort	n=4848	~50	Various	High vitamin D	Immediate and delayed word recall	Yes	Beneficial for E4 homozygotes
Dai 2008	Prospective cohort	n=1836	71.6, 71.7, 72.1	Dementia-free	Vitamin C, vitamin E, beta carotene	CASI; CERAD; DSM-IV; NINCDS-ADRDA	Yes (drinking fruit and vegetable juices)	Non-significant: APOE4 > non-carriers
Noguchi-Shinohara 2018	Prospective longitudinal 1	n=349	72.2	Dementia-free	Vitamin C (women)	MMSE; CDR; DSM-III-R	Yes	APOE4 > non-carriers
					Vitamin E (men)		Yes	APOE4 < non-carriers
Goodwill 2018	Prospective longitudinal	n=252	59.8	Various	High vitamin D	CERAD; CVLT-II, verbal fluency; TMT-B	Yes	No Interaction
Morris 2002	Prospective longitudinal	n=815	73.3	Dementia-free	Vitamin E from food	Clinical evaluation	Yes (vitamin E from food only)	Only non-carriers

Abbreviations: Obs; observational study, MMSE; mini-mental status examination, MoCA; Montreal Cognitive Assessment, CDR; Clinical Dementia Rating, DSM-III; Diagnostic and Statistical Manual of Mental Disorders, AD; Alzheimer's disease, MCI; mild cognitive impairment, aMCI; amnestic subtype of mild cognitive impairment, SPMSQ; Short Portable mental Status Questionnaire, DSM; Diagnostic and Statistical Manual of Mental Disorders, ADAS-Cog; Alzheimer's Disease Assessment Scale-Cognitive Subscale, CCR; category cued recall, WAISR; Wechsler Adult Intelligence Scale-Revised, CERAD; Consortium to Establish a Registry for Alzheimer's Disease, CVLT; California Verbal Learning Test, TMT; Trail Making Test, CASI; Cognitive Abilities Screening Instrument, MMMSE; modified mini mental status examination, TICS; Telephone Interview for Cognitive Status.

Table 3. Studies investigating interaction between APOE4 and omega 3 fatty acids or fish consumption in cognitive decline

Study	Study type	Number of patients	Avg Age	Diagnosis	Form of ω-3 fatty acid or fish consumption	Cognitive test	Benefit observed in primary outcome	Benefit in APOE subgroup analysis
Stonehouse 2013	RCT	n=176	33	Cognitively healthy	DHA supplementation	Computerized mental performance assessment system	Yes	Greater effect in APOE4 males
Quinn 2010	RCT	n=295	76	AD	DHA supplementation	ADAS-Cog, CDR sum of boxes	No	Non-carriers
van de Rest 2008	RCT	n=302	70	Cognitively healthy	EPA-DHA supplementation	5-test battery	No	APOE4-attention
Yasuno, 2012	Trial	n=663	72.7, 73	Dementia-free	ω-3 fatty acid supplementation	Set- dependent activity; CCR; category fluency test; WAIS-R	Yes	APOE4>non-carriers
Ronnemaa 2012	Prospective cohort	n=2009	50	Longitudinal (various)	PUFA levels	Demenita diagnosis	No	No interaction
Samieri 2011	Prospective cohort	n=1228	74	Non-institutionalized	EPA and DHA plasma levels	Test battery including MMSE	No	APOE4
Kroger 2009	Prospective cohort	n=633	81	Dementia-free	DHA levels, Mercury levels	MMSE, dementia diagnosis	No*	No interaction
Whalley 2008	Prospective longitudinal**	n=120	64	Dementia-free	Erythrocyte membrane ω-3 fatty acid levels	MMSE, RPM, AVLT, UCOT, DSST	Yes	Non-carriers
Kivipelto 2008	Longitudinal retrospective	n=1449	57	Longitudinal (various)	PUFA consumption from spreads	DWRT, DSST/ WAIS, WFT	Yes	APOE4>non-carriers
Laitinen 2006	Longitudinal retrospective	n=1449	50	Longitudinal (various)	PUFA consumption from spreads	MMSE, dementia diagnosis	Yes	APOE4
Beydoun 2007	Prospective cohort	n=2251	57	Longitudinal (various)	Plasma ω-3 fatty acid levels	DWRT, DSST, WFT	Yes	No interaction
Laurin 2003	Cross sectional and prospective	n=65	76	Cross sectional (various) and prospective (unimpaired at start of study)	ω-3 fatty acid levels	MMMSE, dementia diagnosis	No***	No****
Huang 2005	Prospective Cohort	n=2233	71	Cognitively healthy	Fatty fish 2x/ week	MMSE, TICS, IQcode, dementia diagnosis	Yes	Non-carriers
Barberger-Gateau 2007	Prospective cohort	n=8085	>65	Non-demented	Weekly fish, ω-3 fatty acid	Dementia diagnosis	Yes	Non-carriers
Daiello 2015	Retrospective Cohort	n=819	75	Cognitively healthy, MCI, AD	Fish oil supplements	ADAS-Cog, MMSE	Yes	Cognitively healthy non-carriers
van de Rest, 2016	Longitudinal retrospective	n=915	81	Longitudinal (various)	Fish in diet, fish oil supplements	21-test battery	Yes	APOE4
Samieri 2018	Retrospective cohort meta-analysis	n=23,688	74	Various	Fish consumption	In person interviews, telephone battery	Yes	No interaction
Danthiir 2014	Cross-sectional	n=390	73	Cognitively healthy	Current and childhood fish consumption	Cognitive test battery	No	No interaction

Abbreviations: Obs; observational study, RCT; randomized controlled trial, AD; Alzheimer's disease, MMSE; mini-mental status examination, CCR; category cued recall, WAISR; Wechsler Adult Intelligence Scale-Revised, WAIS; Wechsler Adult Intelligence Scale, DSST; Digit Symbol Substitution Test, WFT; Word Fluency Test, MMMSE; modified mini mental status examination; RPM; Raven's Progressive Matrices, AVLT; Auditory-Verbal Learning Test, UCOT; Universal Cognitive Aptitude Test, TICS; Telephone Interview for Cognitive Status, IQcode; Informant Questionnaire on Cognitive Decline in the Elderly, ADAS-Cog; Alzheimer's Disease Assessment Scale-Cognitive Subscale, CDR; Clinical Dementia Rating. *However, dementia risk reduction was observed in individuals in the highest quartile of mercury concentration and also had high DHA, suggesting high fish consumption. **Cognition was assessed both at age 11, 64, 66, 68. ***In prospective analysis, higher levels of EPA, DHA, omega 3 and PUFAs were found in patients with dementia or cognitive impairment. ****APOE4 carriers with dementia had lower levels of n-6 and total PUFAs than controls. Non-carriers with dementia had higher levels of DHA. Subgroup analysis performed only in the cross-sectional analysis, not prospective.

found no significant difference in ADAS-cog score between the H2-group and the control, however a secondary analysis showed a significant improvement in two tasks among APOE ε4 carriers including APOE ε4 carriers with MCI (31). Snitz et al. conducted a RCT in which 1524 participants were administered 120 mg of ginkgo biloba or placebo twice a day. No benefit was observed in either cognitively normal or MCI participants (32). A secondary subgroup analysis performed no genotype interaction (32). A RCT from Petersen et al. in which 769 MCI participants were given 2000 IU of

vitamin E, 10 mg of donepezil, or placebo daily over a three year period found that neither vitamin E nor donepezil had significant effect on progression from MCI to AD. Secondary analysis showed no effect among APOE ε4 carriers for vitamin E versus placebo, however, donepezil appeared to decrease progression to AD among ε4 carriers (Petersen, 2005). Aisen et al. randomized 409 participants with mild to moderate AD to antioxidant supplements (5 mg folate, 25 mg vitamin B6, and 1 mg vitamin B12) or placebo for 18 months. The primary analysis found no difference in the rate of change of ADAS-cog between treatment groups; secondary analyses showed no difference among APOE genotypes (Aisen, 2009). An open-label uncontrolled clinical trial by Yasuno et al. investigated the effects of supplementation with a combination of antioxidants in dementia-free participants over three years. They found that cognitive function was improved, with this effect being stronger in APOE ε4 carriers compared to non carriers (33).

Eight observational studies investigating the potential benefits of antioxidant supplementation were identified in addition to the controlled trials. Each of the seven prospective studies found at least a partial benefit of antioxidant supplementation. A cohort study found that greater supplementation of vitamin C and E were associated with a decreased risk of AD, and that this association was independent of APOE genotype (34). Another study found that vitamin D levels greater than 25nmol/L in midlife were associated with greater performance on tasks involving executive function later in life; secondary analysis showed no significant differences between APOE genotypes (35). Two studies found that antioxidant intake from foods was associated with reduced risk for AD (36, 37). In subgroup analyses, Morris et al. found that vitamin E intake through food was beneficial for APOE ε4 non-carriers only (36). Dai et al. found that fruit and vegetable juices high in polyphenols delayed the onset of AD in all APOE genotypes, though the association was stronger in APOE ε4 carriers compared to non-carriers. Maddock et al. found that both high and low levels of vitamin D (with ranges consisting of <25, 25-49, 50-74, and ≥75 nmol/l) were associated with decreased memory function after adjustment for number of APOE ε4 alleles, but that high levels were beneficial only for APOE ε4 homozygotes (38). A study by Noguchi-Shinohara et al. found that high levels of vitamin C were associated with reduced risk of cognitive decline in APOE ε4 women while higher levels of vitamin E were associated with reduced risk of decline in men who are non-carriers (39). A single retrospective study found that beta-carotene supplementation may be protective against cognitive decline for APOE ε4 carriers (40).

In spite of the majority of observational studies pointing towards antioxidant benefit for APOE ε4 carriers, individual antioxidants had mixed results. Studies investigating beta carotene (34, 40–42), vitamin C39, vitamin E34, Ginkgo biloba (33), and vitamin D35, indicated a benefit while others proved to be ineffective with no APOE ε4 interaction (32, 36, 39). The benefit of Ginkgo biloba seems dubious, as the only study showing that it may benefit APOE ε4 carriers used it in combination with ω-3 fatty acids and lycopene (33), and a high quality randomized controlled trial (RCT) showed no benefit (32).

Vitamin D in particular has contradictory results in three observational studies. One study showed benefit of higher levels (35) especially in APOE ε4 carriers. Another study showed that high levels were only beneficial for APOE ε4 homozygotes and were detrimental for APOE ε4 heterozygotes and non-carriers (38). A third small study showed that low levels of vitamin D were not associated with MMSE or age of onset in APOE ε4 carriers or non-carriers (28). Another showed that vitamin D deficiency was associated with accelerated decline in episodic memory and executive function after controlling for APOE ε4 (43). Previous work indicates that APOE ε4 carriers and APOE ε4 mouse models have higher levels of vitamin D, suggesting that APOE modulates vitamin D status (44). Further study is warranted to clarify how APOE modulates vitamin D levels and what effect this has on cognition.

In summary, the literature on antioxidant supplementation has produced mixed results, but several studies suggest that the APOE ε4 allele is associated with decreased levels of antioxidants and that antioxidant supplementation may be associated with decreased rate of cognitive decline, especially for APOE ε4 carriers. The benefit of individual antioxidants for APOE ε4 carriers requires further investigation.

ω-3 fatty acid supplementation

APOE ε4 carriers on average have lower plasma levels of DHA than non-carriers (45). We identified three RCTs, one trial without a randomized control group, and eight observational studies that investigated APOE genotype interaction with ω-3 fatty acid supplementation or higher levels of ω-3 fatty acids with an outcome of cognitive function (Table 3).

The evidence from the RCTs that ω-3 fatty acid supplementation would help prevent cognitive decline in APOE ε4 carriers was weak. A study investigating cognitive performance in healthy, cognitively young (18-45 years old) patients found significant benefit of DHA supplementation for episodic and working memory overall. No interaction between APOE ε4 genotype and treatment was found. Although a treatment x APOE ε4 x sex interaction was found, multiplicity is a concern in the interpretation of these statistical comparisons. While male APOE ε4 carriers and non-carriers had improvement with supplementation, the effect size was greater in male APOE ε4 carriers. Similarly, attention was significantly improved in male APOE ε4 carriers whereas it was not improved in male non-carriers45. A RCT of DHA supplementation in older individuals (average 76 years old) with mild/moderate AD revealed no benefit on the primary cognitive outcomes, but a pre-planned exploratory analysis found that APOE ε4 non-carriers had a significantly lower decline in cognition with DHA, whereas there was no effect in APOE ε4 carriers (47). Another randomized controlled trial of docosohexanoic acid (DHA) and eicosapentaenoic acid (EPA) supplementation was conducted in 2008 in cognitively healthy adults over 65 years old. The primary outcome was a neuropsychological test battery, which revealed no significant difference between EPA-DHA supplement and control. A pre-planned secondary analysis of a five-test battery revealed

Table 4. Studies investigating APOE4 and Mediterranean diet in cognitive decline

Study	Study type	Number of patients	Avg Age	Diagnosis	Cognitive test	Benefit observed in primary outcome	Benefit in APOE subgroup analysis
Solomon 2018	RCT	n=1175	69	At-risk older individuals	Neuropsychological Test Battery	NA	APOE4**
Martinez-Lapiscina 2014	RCT	n=522	67	Various*	MMSE, CDT	Yes	No interaction
Martinez-Lapiscina 2013	RCT	n=268	67	Various*	Test battery including MMSE	Yes	No interaction
Valls-Pedret 2015	RCT	n=447	66	Cognitively healthy	8-test battery including MMSE	Yes	No interaction
Keenan 2020	Obs Prospective cohort	n=7756	70	Dementia-free	Test battery including MMMSE	Yes	No interaction
Gardener 2015	Obs Prospective cohort	n=527	69	Cognitively heathy	Test battery	Yes	APOE4

Abbreviations: Obs; observational study, RCT; randomized controlled trial, MCI; mild cognitive impairment, MMSE; mini-mental status examination, CDT; Clock Drawing Test. *Inclusion criteria stated that participants must have a cardiovascular risk factor but no previous cardiovascular incidents and no other chronic conditions. Average subject MMSE was 27-28 suggesting subjects were generally cognitively healthy. ** Within group analysis (intervention vs no intervention); no significant interaction of randomization group x time x APOE.

that APOE ε4 carriers improved in attention after EPA-DHA supplementation (48), although none of the other cognitive domains were significantly improved and therefore the conclusions that can be drawn are limited.

One clinical trial did not include a randomized controlled group, but instead used patients with no treatment from the same community dwelling as controls, a study design subject to bias (33). The study reported that there was significant benefit overall after 3 years of ω-3 fatty acid supplementation as well as lycopene and ginko biloba. In subgroup analysis, there was a positive effect for both APOE carriers and APOE ε4 non-carriers, but the effect size was greater for APOE ε4 carriers.

Among the clinical trials of ω-3 fatty acid supplementation, three were limited to patients who were cognitively healthy and one was limited to patients who were diagnosed with AD. Of the trials examining patients who were cognitively healthy, two found a greater positive impact on cognitive decline for APOE ε4 carriers upon subgroup analysis (33, 45) and one found benefit only in APOE ε4 carriers (48) in cognitive testing batteries. In the RCT limited to cognitively impaired patients, a positive effect was found for non-carriers only on subgroup analysis of cognitive testing (47).

In addition to RCTs assessing the efficacy of DHA supplements, we identified seven observational studies (one of which was associated with two publications) that assessed poly-unsaturated fatty acid (PUFA) consumption through surveys or plasma levels of ω-3 fatty acids. One of these studies included a prospective portion and a cross-sectional portion, but only the cross-sectional portion was used for secondary analysis of groups separated by APOE genotype (49). Out of four prospective cohort studies, higher ω-3 fatty acid levels were associated with reduced cognitive decline in the primary analysis in two studies (50, 51). There was no significant effect in the primary analysis in four studies (49, 52–54). Secondary subgroup analyses of APOE ε4 carriers and non-carriers were performed in five of these prospective studies; three studies found no interaction between APOE and ω-3 fatty acid levels (50, 52, 54) in the effect on cognitive decline, one found a benefit only for non-carriers (51), and one found benefit only for carriers (53). One retrospective study with two associated publications showed that moderate consumption of PUFA from spreads (butter, margarine) reduced the risk of dementia in the primary analysis; in subgroup analysis this effect was observed only in APOE ε4 carriers (55, 56). One small cross-sectional study found no benefit of higher ω-3 fatty acid levels and no difference in secondary analysis of APOE genotypes (57).

Two observational studies were limited to cognitively healthy patients only; one of these found benefit in cognitive testing for non-carriers only in subgroup analysis (51) and the other found no positive effect and no APOE genotype interaction (52).

Overall, the literature we identified on the efficacy of ω-3 fatty acid supplementation for preventing cognitive decline was mixed. While six studies showed some benefit for APOE ε4 carriers, four studies showed either no benefit and no genotype interaction or benefit only for APOE ε4 non-carriers. Some of this inconsistency may be explained by defects in ω-3 fatty acid absorption and trafficking caused by APOE ε4 (58, 59). A study in rodents has found that long-term, high-dose DHA supplementation in APOE ε4 mice can prevent cognitive decline (60), Suggesting that especially high doses of ω-3 fatty acids may be required for APOE ε4 carriers to derive cognitive benefit.

Fish consumption

A major dietary source of ω-3 fatty acid is fish consumption. We identified two prospective, three retrospective, and one cross-sectional observational study examining the effect of fish consumption on cognitive decline (Table 3). Both of the prospective studies were conducted in patients who were cognitively healthy at the start of the study and measured fish consumption using surveys. Both observed reduced cognitive decline with higher fish consumption in the primary analysis, but in secondary analysis found that only APOE ε4 non-carriers benefited (61, 62).

Retrospective multivariate meta-analysis of five cohort studies revealed that higher fish intake was associated with slower decline in both cognition and memory, and found no interaction with APOE genotype (63). Of the studies we identified, one retrospective study showed that fish oil

Table 5. Studies investigating risk of dietary cholesterol or saturated fats for cognitive decline among APOE4 carriers

Study	Study Type	Number of Patients	Avg Age	Patient Diagnosis	Type of dietary fat	Test/Measurement Used	Risk observed in primary outcome	Risk in APOE subgroup analysis
Ylilauri 2017	Obs Prospective cohort	n=2497	53	Dementia-free	Cholesterol	Dementia diagnosis, MMSE, TMT, VFT, SRT, VRT	No	No
An 2019	Obs Prospective cohort	n=2514	59	No neuropsychiatric problems	Cholesterol	MoCA, SDMT, AVLT, LMT, DSF, WMS-RC	No	No
Salerno Kennedy 2007	Obs Cross-sectional	n=20	57.7	Various	Cholesterol	MMSE, PWLT, LDCT SCWT	Yes	No interaction
Laitinen 2006, Eskelinen 2008	Obs Prospective cohort	n=1449	50.4	Unspecified	Saturated fat	MMSE, dementia diagnosis	Yes	APOE4 only
Luchsinger 2002	Obs Prospective cohort	n=980	75	Cognitively healthy	Saturated fat	Dementia diagnosis	Yes	APOE4 only
Hanson 2015	RCT	n=20	70	MCI, normal cognition	Saturated fat	Neurocognitive battery	Yes	APOE4 carriers without impairment perform worse, APOE4 with impairment perform better

Abbreviations: Obs; observational study, MMSE; mini-mental status examination, TMT; Trail Making Test, VFT; Verbal fluency test, SRT; Simple Reaction Time, VRT; Visual Reaction Time, MoCA; Montreal Cognitive Assessment, SDMT; Symbol Digit Modalities Test, AVLT; Auditory-Verbal Learning Test, LMT; Letter Memory Test, DSF; Digit Span Forwards, WMS-RC; Wechsler Memory Scale-Revised in China, PWLT; Picture Word Learning Test, LDCT; Letter Digit Coding Test, SCWT; Stroop Colour Word Test.

Table 6. Studies investigating benefit of ketosis for cognitive decline among APOE4 carriers

Study	Study Type	Number of Patients	Avg Age	Patient Diagnosis	Test/ Measurement Used	Ketogenic intervention	Significant Benefit Observed in Primary Outcome	Benefit in APOE Subgroup Analysis
Morrill 2019	CS	n=1	71	Mild AD	MoCA	Diet	Yes	NA
Stoykovich 2019	CS	n=1	68	Mild AD	MoCA	Diet	Yes	NA
Brown 2018	CS	n=1	38	MCI	MoCA	Diet	Yes	NA
Reger 2004	RCT	n=20	74.7	Probable AD or aMCI	ADAS-Cog, MMSE, SCWIT	Ketogenic agent	Yes	No
Henderson 2009	RCT	n=152	76	Mild to moderate AD	ADAS-Cog, MMSE, ADCS-CGIC	Ketogenic agent	Yes	No
Henderson 2020	RCT	n=413	76	Mild to moderate AD	ADAS-Cog11 ADCS-CGIC	Ketogenic agent	No	No

bbreviations: CS; Case study, RCT; Randomized Controlled Trial, MCI; Mild Cognitive Impairment, AD; Alzheimer's Disease, MoCA; Montreal Cognitive Assessment, ADAS-Cog; Alzheimer's Disease Assessment Scale-Cognitive Subscale, MMSE; mini-mental status examination, SCWIT; Stroop Colour Word Interference Task, ADCS-CGIC; Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change.

supplements were associated with less frequent occurrence of dementia but only in APOE ε4 non-carriers (64), and one small cross-sectional study showed no association of current or childhood fish consumption with better performance on cognitive testing overall or for either genotype (in fact, higher current fish consumption predicted worse performance on cognitive speed tests) (65). One retrospective study found no benefit overall, but in secondary analysis found that fish in the diet, but not fish oil supplements, improved cognitive testing in APOE ε4 carriers only (66). Overall, the evidence suggests that fish consumption may be beneficial for preventing cognitive decline in the general population, but less effective in APOE ε4 carriers. These results are consistent with findings showing that fish consumption has a more positive association with plasma EPA and DHA levels in APOE ε4 non-carriers than in APOE ε4 carriers (67).

Mediterranean diet

Mediterranean diet traditionally includes olive oil, legumes, unrefined cereal, fruit, vegetables, fish, moderate consumption of dairy and wine, and low consumption of meat, and has been found to reduce risk of AD (68). Six studies, including four RCTs, were identified that included analyses of APOE genotype interaction with the effect of Mediterranean diet on cognitive decline (Table 4). All of the studies showed benefit overall in preventing cognitive decline in the primary analysis. Three RCTs showed no APOE genotype interaction (69–71). One RCT that included Mediterranean diet as part of a multidomain intervention included only older patients at high risk, with cardiovascular risk factors and average or below average cognition, showed that cognitive outcomes improved significantly only for APOE ε4 carriers in secondary within group analysis (72). Both prospective cohort studies (73, 74)

found a benefit of Mediterranean diet intervention overall; one showed benefit only for APOE ε4 carriers (73) on sub-analysis whereas the other showed no interaction (74). Among studies limited to cognitively healthy participants, one observational study (73) found benefit only for APOE ε4 carriers, one observational and one RCT found general benefit with no APOE interaction (71, 74).

In conclusion, all the studies we reviewed showed either cognitive improvement or reduction in cognitive decline with Mediterranean diet among APOE ε4 carriers, and one study showed benefit exclusively in these individuals.

Dietary saturated fat and cholesterol

APOE is a lipid transport protein and it has long been observed that APOE isoforms differentially affect the body's response to a diet rich in saturated fats (75). We identified three observational studies (two prospective cohort and one cross-sectional) that investigated the effect of dietary cholesterol on cognition and interaction with APOE genotype (Table 5). All of these studies were conducted in middle-aged subjects (average age 53, 59, 57.7). Two studies performed in dementia-free patients found that amount of egg and dietary cholesterol consumption was not associated with cognitive decline, regardless of APOE genotype (76, 77). One cross-sectional study including patients at risk for dementia (first-degree blood relatives of AD patients) found that intake of cholesterol was significantly higher in subjects with altered cognitive performance as measured by a neurocognitive battery, but there was no difference between APOE ε4 carriers and non-carriers (78).

Two well-powered observational studies (one of which produced two publications) with over 900 participants each showed that consumption of saturated fat increased risk of cognitive decline, and on subgroup analysis this risk was found to be more profound in APOE ε4 carriers (55, 79, 80) (Table 5). One study was limited to cognitively healthy older adults (80), and the other was a longitudinal study examining cognition; at the start of the study middle-aged subjects were cognitively intact, with some subjects becoming cognitively impaired at the follow-up time point 21 years later (55). One pilot RCT was identified involving cognitive testing following a single 800 calorie high fat (50%) meal. In a sample of 19 cognitively healthy and 27 MCI patients, following a high calorie, high fat meal, APOE ε4 non-carriers with no pre-existing cognitive decline performed worse than their baseline, whereas APOE ε4 carriers and APOE ε4 non-carriers with cognitive impairment performed better than baseline (81).

Ketogenic diet

While the available evidence may suggest overall that a long-term diet rich in saturated fat is detrimental to cognitive health of APOE ε4 carriers, there have been several reviews (82–85) and primary articles (86–92) on the efficacy of the ketogenic diet or ketogenic supplements for preventing cognitive decline in APOE ε4 carriers and non-carriers. The ketogenic diet is rich in fats, with very low carbohydrates. A study on the feasibility of the ketogenic diet for patients with dementia found that although there was a high dropout rate in the patients with advanced dementia in part due to caregiver burden, milder patients less frequently dropped out, achieved ketosis and showed improved cognitive performance by an average of 4.1 points on the ADAS-cog (93).

Three case studies were identified that each investigated a single APOE ε4 carrier patient with mild cognitive impairment or AD (86–88) who showed cognitive benefit after being on the ketogenic diet (Table 6). To our knowledge, no properly powered observational or RCTs have investigated the efficacy of the ketogenic diet specifically for APOE ε4 carriers to date.

Four RCTs have examined the efficacy of ketogenic compounds or supplements for improving cognition in patients with mild cognitive impairment and dementia. One found no significant benefit for cognition in APOE ε4 carriers or non-carriers using the caprylic triglyceride formulation AC-1204 (92). Another study by the same group using a slightly different formulation, AC-1202, found a significant benefit only for APOE ε4 non-carriers (89, 90. Finally, one study found that a single supplement of medium chain triglycerides acutely increased β-hydroxybutyrate levels in blood and enhanced cognitive performance only for APOE ε4 non-carriers (91). Ketogenic supplements appear to have no benefit for APOE ε4 carriers in well-powered studies.

Discussion

We performed a systematic search of the literature on dietary factors that may interact with the APOE ε4 genotype to have an impact on cognitive decline. We reviewed six dietary factors, including three with multiple RCTs. Mediterranean diet appeared to be effective for reducing cognitive decline in individuals of all APOE genotypes, and fish consumption showed consistent benefit across several well-powered observational studies, whereas ω-3 fatty acid supplementation was associated with mixed results and weak evidence of benefit. Ketogenic agents were not beneficial for APOE ε4 carriers. Several high-quality randomized studies investigating antioxidants and Ginkgo biloba showed no evidence of effectiveness. There were no randomized studies but some well-designed and powered observational studies investigating dietary saturated fat; this evidence indicated that consuming a diet high in saturated fat is detrimental for APOE ε4 carriers. Limited studies showed weak and mixed results for the effectiveness of low dietary cholesterol in preventing cognitive decline in APOE ε4 carriers.

Our results are largely in agreement with the Lancet's 2020 report on dementia prevention, intervention, and care for the general population, which recommends a Mediterranean diet but suggests that there is not yet sufficient evidence to recommend dietary supplements for the prevention of cognitive decline (94).

While APOE ε4 carriers are at increased risk for cognitive decline, they are also at increased risk for cardiovascular disease, and the effect of dietary factors on both of these disease

processes must be considered. Consumption of dietary saturated fat has a greater effect on APOE ε4 carriers' plasma lipid levels, which may compound their high risk of heart disease due to high plasma LDL at baseline (95, 96). Likewise, while ω-3 fatty acids may lower plasma LDL levels in APOE ε4 non-carriers, LDL levels increase with ω-3 fatty acid levels in APOE ε4 carriers (97–99). Thus, a possible source of caution in recommending ω-3 fatty acid supplementation could be additional cardiovascular risk factors. High serum LDL is also correlated with cerebral amyloidosis (100), possibly contributing to Alzheimer's disease pathology. Therefore, the risk of a diet resulting in high LDL for APOE ε4 carriers is compounded by both possible cognitive decline and heart disease. In contrast, consumption of eggs and cholesterol are not particularly detrimental for cognition in APOE ε4 carriers. This is consistent with reports that reducing dietary saturated fat may be more effective than dietary cholesterol for attenuating hyperlipidemia (101).

The ketogenic diet has recently become popular as a weight loss strategy and has been investigated in several case studies for effect on cognitive decline. Strong evidence indicates that ketogenic supplements do not prevent cognitive decline in APOE ε4 carriers with mild cognitive impairment. It is possible that ketogenic diet may be more effective than ketogenic agents at promoting ketosis; this may explain why case studies of dietary interventions show benefit for APOE ε4 carriers whereas RCTs of ketogenic agents do not. However, case studies are a low level of evidence and this diet must be investigated further before it can be recommended to APOE ε4 carriers. It should be noted that in contrast to many other dietary interventions, studies identified testing the efficacy of ketogenic agents and ketogenic diet were all limited to patients with MCI/mild AD, and further investigation in pre-symptomatic patients may reveal different results.

Gaps in the current knowledge of how dietary interventions differentially affect people of different APOE genotypes remain. Randomized controlled trials assessing the effectiveness of diets low in saturated fat or cholesterol would be helpful to determine the effectiveness of these interventions. The literature on APOE genotype interaction with supplemental homotaurine, B vitamins, Anserine, Carnitine, or Kynurenine is nascent; future prospective RCTs could help to determine their effectiveness. Although the body of literature on ω-3 fatty acids in APOE ε4 is robust, it would benefit from studies weighing the cost of increased plasma LDL in APOE ε4 carriers against the benefit for cognitive decline. Possibly due to ω-3 fatty acid trafficking deficiencies, APOE ε4 carriers require higher doses of ω-3 fatty acid supplementation to raise CSF levels (102, 103); future trials should confirm whether high doses over a long time course can consistently reduce cognitive decline in among APOE ε4 carriers.

Limitations

This scoping review was limited in several ways. The initial scoping review search was very broad and included reviews and primary articles. The results of the targeted reviews were also heterogeneous, with a wide variety of study designs, levels of evidence, diagnostic populations, statistical methods, and measurements of cognitive function. Quantitative meta-analysis was not performed in this review, results were qualitative and coded either beneficial, harmful, or no effect on cognition with greater effect or less effect in APOE ε4 carriers. A future quantitative systematic review would be beneficial in several of the topics identified. Additionally, while some animal and basic science studies were referenced for context, our search criteria focused on human subjects research. More thorough systematic review of basic science and animal studies may provide insight into mechanisms of the effects observed in humans and provide pre-clinical assessment of efficacy for new therapies. Assessment of study quality and bias was limited in this review, as the main objective was to describe the range/scope of literature addressing APOE genotype interactions with cognitive decline interventions, rather than critical appraisal of the quality of each individual study.

Conclusions

The available evidence suggests that a Mediterranean diet is potentially beneficial for avoiding cognitive decline in APOE ε4 carriers. We hope that this scoping overview of the current state of the literature will help better inform APOE ε4 carriers and their clinicians of the breadth and strength of the current literature on dietary factors intended to prevent cognitive decline in this at-risk population. While there is still much research to be done, there is hope that these simple and relatively safe lifestyle modifications could impact the personal and public impact of cognitive decline.

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