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Original Article

Precision Nutrition and Genetic Risk in Alzheimer's disease: Focus on APOE-Specific Dietary Approaches

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ABSTRACT

Background: Alzheimer's disease is recognized as the primary contributor to dementia, and currently no definitive cure exists for the condition. Recent studies have shown that dietary habits can significantly influence cognitive health, making nutrition a potentially modifiable factor in disease prevention and management. However, individuals respond differently to nutritional interventions, largely due to genetic variations, particularly the APOE genotype. This growing understanding emphasizes the need for personalized nutrition strategies designed according to an individual's genetic susceptibility and risk profile.

Objective: This review synthesizes current evidence on how nutritional interventions interact with APOE genotype to influence AD risk and progression. It integrates data from randomized controlled trials (RCTs), mechanistic studies, and nutrigenomics research, highlighting opportunities for genotype-guided dietary strategies.

Methods: Evidence was compiled from high-quality RCTs, meta-analyses, and translational studies focusing on omega-3 fatty acids, B-vitamins, antioxidants, polyphenols, and dietary patterns (Mediterranean, MIND, DASH). Particular emphasis was placed on heterogeneity of effects across APOE subgroups, nutritional timing, and integration with neurogenomic frameworks.

Results: RCTs demonstrate that omega-3 fatty acids, B-vitamins, and multinutrient formulations provide measurable benefits in at-risk populations, but efficacy is strongly influenced by APOE genotype and disease stage. Early interventions, particularly in midlife or preclinical phases, yield the most pronounced neuroprotective effects. Multidomain approaches combining diet, exercise, and cognitive training show amplified benefits in APOE ε4 carriers. Advances in nutrigenomics and digital health tools now enable risk stratification and individualized nutritional recommendations.

Conclusion: Nutrition is not a one-size-fits-all strategy in AD. Incorporating APOE-guided precision nutrition into prevention frameworks represents a paradigm shift in dementia care. By aligning neurogenomics, nutrigenomics, and public health strategies, genotype-aware interventions offer a novel and implementable pathway to delay or reduce AD burden.

Keywords: Alzheimer's disease, APOE, precision nutrition, nutrigenomics, randomized controlled trials, dementia prevention.

INTRODUCTION

1.1 Alzheimer's disease burden & unmet therapeutic needs

Alzheimer's disease (AD) is the most prevalent form of dementia, affecting over 55 million individuals globally, with incidence projected to triple by 2050 due to population aging [1]. It is characterized by progressive cognitive decline, memory loss, and impaired functional independence, imposing significant social and economic burdens on patients, caregivers, and healthcare systems [2]. Despite decades of research, currently approved pharmacological interventions provide only modest symptomatic relief without substantially altering disease progression [3]. This highlights an urgent

unmet need for innovative strategies that can delay onset or slow the trajectory of cognitive decline in at-risk populations [4].

1.2 Role of nutrition in neurodegeneration

Mounting evidence suggests that dietary factors play a pivotal role in modulating neurodegenerative processes associated with AD [5]. Specific nutrients such as omega-3 polyunsaturated fatty acids, B vitamins, antioxidants, and polyphenols have been implicated in reducing oxidative stress, neuroinflammation, and amyloid-beta aggregation, all of which are central mechanisms in AD pathology [6]. Additionally, dietary patterns such as the Mediterranean and MIND diets have been associated with lower incidence of cognitive impairment and slower rates of decline in longitudinal cohort studies [7]. While these findings are promising, variability in individual responses to dietary interventions underscores the need for precision-based approaches [8].

1.3 Precision medicine & neurogenomics (focus on APOE)

Precision medicine offers a transformative framework for tailoring interventions according to genetic, metabolic, and lifestyle profiles. In the context of AD, apolipoprotein E (APOE) genotypes—particularly APOE ε4—represent the strongest genetic risk factor for late-onset disease [9]. Carriers of the ε4 allele exhibit accelerated amyloid deposition, disrupted lipid metabolism, and heightened neuroinflammation, making them a critical subgroup for targeted dietary interventions [10]. Nutrigenomic studies increasingly demonstrate that the efficacy of nutritional interventions, including omega-3 supplementation and antioxidant intake, may differ depending on APOE status [11]. This convergence of neurogenomics and precision nutrition offers a promising avenue to develop individualized dietary strategies aimed at promoting cognitive resilience and delaying disease progression [12].

ALZHEIMER'S PATHOPHYSIOLOGY AND APOE

2.1 Amyloid, tau, and neuroinflammation

Alzheimer's disease (AD) is pathologically defined by extracellular amyloid-beta (Aβ) deposition, intracellular tau neurofibrillary tangles, synaptic dysfunction, and progressive neuronal loss [13]. Although the amyloid cascade hypothesis has dominated the field for decades, discrepancies between plaque burden and cognitive impairment suggest that additional mechanisms contribute to disease progression [14]. Tau pathology, in particular, exhibits a closer correlation with neurodegeneration and cognitive decline than amyloid load alone, underscoring its significance in disease trajectory [15].

Oxidative stress and mitochondrial dysfunction are increasingly recognized as early contributors to neuronal injury in AD. Elevated levels of reactive oxygen species impair synaptic plasticity and accelerate both amyloid aggregation and tau hyperphosphorylation [16]. Randomized controlled data indicate that antioxidant supplementation may mitigate some of these effects, although outcomes remain inconsistent due to dosage variability and patient heterogeneity [17].

Neuroinflammation represents another critical pathway. Microglial activation, while initially protective in clearing amyloid deposits, becomes maladaptive in chronic disease states, promoting synaptic pruning and releasing pro-inflammatory cytokines [18]. This inflammatory milieu not only accelerates neuronal loss but also interacts with metabolic dysfunction, particularly in patients carrying the APOE ε4 allele [19].

Synaptic failure lies at the functional core of AD pathology. Studies using advanced imaging and electrophysiological tools demonstrate that synaptic density, rather than amyloid burden, is the strongest pathological correlate of cognitive performance [20]. Nutritional interventions aimed at preserving synaptic integrity, such as omega-3 fatty acids and B-vitamin supplementation, have shown measurable effects on brain connectivity in ε4 carriers, suggesting diet can modulate pathophysiology directly [21].

Emerging evidence highlights the gut-brain axis as an indirect modulator of AD. Altered microbiota composition influences systemic inflammation and amyloid deposition through metabolites such as short-chain fatty acids and tryptophan derivatives [22]. Dietary patterns rich in fiber, polyphenols, and probiotics may restore microbial balance, providing an innovative angle to target pathophysiology [23].

Taken together, AD pathophysiology is multifactorial, involving a dynamic interplay between protein aggregation, oxidative stress, inflammation, and synaptic dysfunction. Understanding these mechanisms is crucial for designing precision nutrition strategies tailored to genetic risk factors such as APOE ε4, thereby bridging basic biology with actionable interventions [24].

2.2 APOE genotype as a risk modifier (APOE ε2, ε3, ε4)

APOE is the strongest common genetic determinant of late-onset Alzheimer's disease (AD), exerting dose-dependent and isoform-specific effects on risk, age at onset, and progression dynamics [25,26]. Relative to the ε3/ε3 reference, a single ε4 allele confers roughly a two- to three-fold increase in risk, whereas ε4/ε4 homozygosity is associated with substantially higher lifetime risk and earlier symptom onset; by contrast, ε2 is generally protective, though the magnitude varies across populations and study designs [25–27]. Large consortia demonstrate that sex, age, and ancestry modify these associations,

with some analyses indicating greater ε4-attributable risk in women and notable heterogeneity across African, Asian, and European ancestries, likely reflecting gene–gene and gene–environment interactions [28–30].

Biologically, APOE isoforms differ in lipid binding, receptor affinity, and tissue distribution, shaping several AD-relevant pathways: amyloid-β (Aβ) aggregation/clearance, tau propagation, synaptic remodeling, microglial reactivity, and cerebrovascular integrity [31,32]. APOE4 promotes Aβ fibrillogenesis and impairs clearance via low-density lipoprotein receptor–related pathways and perivascular routes, thereby elevating amyloid burden earlier in life compared with ε3/ε3 carriers [31]. Parallel work in human tissue and animal models suggests APOE4 may exacerbate tau-mediated neurotoxicity, potentially by altering neuronal lipid homeostasis and glial responses that govern tau spread and synaptic vulnerability [32].

Neuroimmune interactions are central to APOE's risk modulation. Single-cell and network studies show that APOE forms a regulatory axis with TREM2 and microglial "disease-associated" states; APOE4 biases toward pro-inflammatory phenotypes, enhanced synaptic pruning, and reduced phagocytic capacity, collectively intensifying neurodegenerative cascades [33,34]. At the neurovascular interface, APOE4 has been linked to blood–brain barrier (BBB) breakdown, pericyte injury, and reduced cerebral perfusion, which in turn amplify amyloid deposition and downstream tau pathology [35].

These convergent mechanisms—amyloid and tau dyshomeostasis, maladaptive microglial activation, synaptic compromise, and BBB dysfunction—explain why APOE4 carriers often accumulate pathology earlier and decline faster, and they contextualize why intervention effects may differ by genotype [25,31–35]. Conversely, ε2's relative protection may reflect superior lipid trafficking, enhanced Aβ clearance, and a distinct glial response that is less permissive to chronic inflammation and tangle spread, though mechanistic details remain under active investigation [27,32]. Recent large-scale genomic studies further highlight that ε2 and other rare protective APOE variants can inform preventive strategies and therapeutic targeting in AD [36].

In sum, APOE genotype is not merely a statistical risk label; it is a biological modifier that reshapes multiple nodes of AD pathophysiology, providing the rationale for precision strategies—including dietary and metabolic interventions—tested in APOE-stratified designs in subsequent sections [26,30–35].

2.3 Nutrient–gene interactions: why APOE matters

One of the key challenges in Alzheimer's disease (AD) research is understanding why individuals with similar dietary habits experience very different outcomes in cognitive health. The APOE genotype offers a plausible explanation, as it not only modifies lipid metabolism but also influences the brain's response to specific nutrients. Carriers of the APOE ε4 allele, the strongest genetic risk factor for late-onset AD, exhibit impaired handling of lipids and heightened vulnerability to oxidative stress [37,38]. This altered physiology suggests that dietary strategies may not be universally effective, but rather need tailoring to the genetic background.

For example, the efficiency of transporting docosahexaenoic acid (DHA), a neuroprotective omega-3 fatty acid, is reduced in ε4 carriers compared to ε3 or ε2 individuals, potentially limiting the cognitive benefits of omega-3 supplementation [39]. Consistent with this, clinical studies show that while Mediterranean-style diets and omega-3–rich regimens generally improve cognition, the extent of benefit is strongly moderated by APOE genotype [40,41]. In some cases, ε4 carriers show attenuated responses, highlighting the need for stratified nutritional recommendations [42,43].

Randomized controlled trials further reinforce these gene–diet interactions. In nutrient-based interventions such as Souvenaid—a multinutrient medical food designed to support synapse formation—APOE status influenced treatment response, with ε4 carriers showing different levels of cognitive improvement compared to non-carriers [42]. Similarly, omega-3 supplementation demonstrated greater efficacy in ε3 carriers, whereas ε4 carriers displayed reduced benefit [44]. These findings extend to micronutrients as well: APOE appears to alter the cognitive impact of B-vitamins through homocysteine pathways [45], and antioxidants such as vitamin E show variable effectiveness depending on genotype [43,46].

Emerging longitudinal studies suggest that midlife diet quality may offset some of the genetic risk conferred by APOE ε4, supporting the notion that precision nutrition has preventive as well as therapeutic value [47]. Experimental approaches, including ketogenic diets, also reveal APOE-dependent differences in metabolic response, with ε4 carriers often deriving less benefit than others [48].

Together, these observations underline a central theme: the APOE genotype does not act in isolation but interacts dynamically with nutrition to shape cognitive outcomes in AD. This reinforces the need for precision medicine approaches, where dietary guidelines are not generalized but instead informed by the individual's genetic profile.

EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS (RCTS)

3.1 Omega-3 fatty acids and cognitive decline

Omega-3 polyunsaturated fatty acids (PUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), play critical roles in maintaining neuronal membrane fluidity, reducing neuroinflammation, and modulating synaptic plasticity. Given these functions, several randomized controlled trials (RCTs) have investigated whether omega-3 supplementation could slow cognitive decline in Alzheimer's disease (AD) or mild cognitive impairment (MCI).

Freund-Levi and colleagues, in the OmegAD trial, reported that DHA and EPA supplementation provided modest benefits in patients with mild AD, particularly in a subgroup with slower disease progression [49]. In contrast, Quinn et al. found no significant cognitive benefit of DHA supplementation in a large multicenter trial, highlighting variability across populations [50]. More recently, Yassine et al. showed that omega-3 supplementation significantly increased cerebrospinal fluid DHA levels, though clinical cognitive outcomes remained inconsistent, with effects appearing stronger in APOE ε4 non-carriers [51].

Large-scale prevention-focused studies, such as the VITAL trial, also found limited overall benefits on cognitive decline; however, subgroup analyses suggested possible protective effects in individuals with low baseline fish intake [52]. Similarly, the MAPT trial demonstrated that omega-3 supplementation, when combined with lifestyle interventions, produced measurable cognitive improvements in at-risk elderly populations [53]. Finally, a Finnish RCT by Virtanen et al. emphasized that long-term dietary fish intake, rather than short-term supplementation, may be more relevant for brain health [54].

Collectively, these RCTs suggest that omega-3 fatty acids have a nuanced role in AD, with outcomes influenced by disease stage, baseline nutritional status, and importantly, APOE genotype. This highlights the necessity of precision nutrition approaches in interpreting and applying omega-3 findings.

3.2 B-vitamins and homocysteine metabolism

Homocysteine metabolism has emerged as an important modifiable pathway in Alzheimer's disease (AD) pathophysiology. Elevated plasma homocysteine levels are consistently associated with increased risk of cognitive decline, brain atrophy, and dementia. B-vitamins—particularly folate (B9), cobalamin (B12), and pyridoxine (B6)—are central to homocysteine clearance, which has prompted a series of randomized controlled trials (RCTs) examining whether supplementation can reduce AD risk or slow progression.

Smith and colleagues provided seminal evidence in the VITACOG trial, showing that high-dose B-vitamin supplementation significantly reduced homocysteine levels and slowed brain atrophy in elderly participants with mild cognitive impairment (MCI) [55]. Further analyses demonstrated that these neuroprotective effects were most pronounced in individuals with higher baseline homocysteine, suggesting a threshold effect [56]. de Jager et al. extended these findings, reporting that B-vitamin supplementation improved specific domains of cognition, particularly episodic memory [57].

Not all RCTs have reported consistent benefits. For example, the FACIT trial, conducted by Durga et al., found improved memory performance with folic acid supplementation in older adults, though the effect size was modest [58]. A large-scale study by Walker et al., however, failed to observe significant benefits in global cognition despite effective homocysteine lowering [59]. Beyond individual trials, Clarke and colleagues conducted a meta-analysis of 11 RCTs and found that B-vitamin supplementation reliably lowered homocysteine but showed only modest effects on cognitive outcomes, suggesting that treatment benefits may be context-dependent and strongest in at-risk subgroups [60].

Overall, the evidence suggests that B-vitamin supplementation may offer neuroprotective benefits, especially in individuals with elevated homocysteine or early cognitive impairment. As Smith and colleagues highlight, the challenge lies in identifying the subgroup of patients most likely to benefit, as universal supplementation may not yield consistent outcomes [55,57]. Importantly, APOE genotype may interact with homocysteine metabolism, although this relationship remains underexplored and warrants further investigation.

3.3 Antioxidants (Vitamin E, polyphenols)

Oxidative stress and chronic inflammation are central drivers of Alzheimer's disease (AD) pathology, providing a strong rationale for antioxidant-based interventions. Vitamins such as vitamin E (α-tocopherol) and polyphenolic compounds from dietary sources (e.g., flavonoids, resveratrol, curcumin) have been widely studied for their potential neuroprotective effects. These agents are hypothesized to attenuate lipid peroxidation, reduce amyloid-beta aggregation, and dampen neuroinflammation.

One of the most cited RCTs in this area is the trial by Sano and colleagues, who demonstrated that high-dose vitamin E supplementation delayed functional decline in patients with moderately severe AD, though without cognitive improvement [61]. More recently, Dysken et al. confirmed these findings in the TEAM-AD VA Cooperative trial, where vitamin E significantly slowed functional deterioration compared to placebo, particularly in activities of daily living [62]. However, both trials raised concerns about dose safety, as meta-analyses have suggested a possible link between very high-dose vitamin E and increased all-cause mortality [63].

Polyphenols represent another major focus of antioxidant-based RCTs. Resveratrol, a stilbene compound found in grapes and red wine, has been evaluated in AD patients by Turner et al., who reported modulation of cerebrospinal fluid biomarkers but limited cognitive benefits [64]. Curcumin trials have been less conclusive, with Ringman et al. finding no significant improvement in cognition, largely attributed to poor bioavailability [65]. Green tea catechins and flavonoid-rich interventions have shown encouraging effects in small pilot studies, but robust evidence remains scarce [66].

Taken together, antioxidant-based RCTs indicate functional benefits and biomarker modulation, but the translation to consistent cognitive improvement has been limited. As Dysken and colleagues suggest, antioxidants may need to be considered as part of broader dietary patterns rather than as isolated supplements [62]. Moreover, emerging data suggest that APOE ε4 carriers may respond differently to antioxidant interventions, emphasizing the need for genotype-stratified analyses.

Table 1. Nutrient-specific RCT evidence in Alzheimer's disease and cognitive decline (Sections 3.1–3.3)

Ref	Study / Intervention	Population & n / Duration	Primary outcome	APOE notes	One-line takeaway
[49]	OmegAD: DHA+EPA	Mild–moderate AD; n=174 / 6 mo	No overall cognitive benefit; slower decline in mild subgroup	Not stratified	Small signal only in milder cases
[50]	DHA 2 g/d	Mild–moderate AD; n=402 / 18 mo	No slowing of decline (ADAS-Cog, CDR-SB)	No differential effect	Null overall
[51]	DHA (APOE focus)	ε4 carriers; n≈33 / 6 mo	↑CSF DHA; clinical effects inconsistent	ε4 showed lower DHA incorporation	Biology suggests blunted ε4 response
[52]	VITAL (cog substudy): n-3	Older adults; large / years	No overall cognitive benefit; possible effect if low fish intake	Not stratified	Prevention signal only in low-intake subgroup
[53]	MAPT: n-3 ± lifestyle	At-risk elderly; multi-yr	Multidomain+l-n3 slowed decline	Not primary by genotype	Combo approach > pills alone
[54]	Dietary fish intake	Older adults; cohort	Higher fish → fewer brain abnormalities (MRI)	Not stratified	Long-term diet may matter more
[55]	VITACOG: B6/B9/B12	MCI; n=271 / 2 yrs	↓Homocysteine, ↓brain atrophy; cognitive benefit in high tHcy	Not stratified	Works when tHcy is high
[56]	Review/analysis (B-vits)	—	Mechanistic & trial synthesis	—	Benefit depends on baseline risk
[57]	B-vitamins RCT	MCI; n=266 / 2 yrs	Better episodic memory; slower decline	Not stratified	Cognitive domains can improve
[58]	FACIT: folic acid	Older adults; 3 yrs	Modest memory gains	Not stratified	Small effect in general aging
[59]	Folic acid+B12	Community-dwelling elderly	↓Homocysteine; no global cognition benefit	Not stratified	Biomarker ≠ clinical change
[61]	Vitamin E (α-tocopherol)	Moderate AD	Slower functional decline; no cog gain	Not stratified	ADLs improved
[62]	TEAM-AD: Vitamin E ± memantine	Mild–moderate AD; n=613 / 2.3 yrs	Slower functional deterioration	Not stratified	Replicates functional benefit

[64]	Resveratrol	Mild–moderate AD	CSF biomarker shifts; limited cognition	Not stratified	Biomarkers > symptoms
[65]	Curcumin (pilot)	AD (small)	No cognitive effect; bioavailability issues	Not stratified	Formulation matters
[66]	Polyphenol-rich Med components	Elderly high CV risk	Better cognition with higher polyphenol intake	Not stratified	Foods > isolated pills
[63]*	High-dose Vit E meta-analysis	General population	Possible ↑mortality at very high doses	—	Dose safety caveat

*Meta-analysis / pooled evidence (contextual, not primary RCT in AD cognition).

3.4 Dietary patterns (MIND, Mediterranean, DASH)

While isolated nutrient supplementation has yielded mixed results, growing evidence suggests that adherence to whole-dietary patterns may provide more consistent neuroprotective effects in Alzheimer's disease (AD). Nutritional models that combine antioxidants, omega-3 fatty acids, and B-vitamins in a balanced dietary framework, like the Mediterranean diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and the hybrid MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay) diet, place an emphasis on nutrient synergy.

Numerous studies have been conducted on the Mediterranean diet in older populations. In the landmark PREDIMED trial, Valls-Pedret and colleagues reported that adherence to a Mediterranean diet enriched with extra virgin olive oil or nuts significantly improved global cognition compared to a low-fat control diet in older adults at cardiovascular risk [67]. Scarmeas et al. provided further evidence, showing that higher adherence to the Mediterranean diet was associated with reduced risk of AD and slower cognitive decline [68].

The DASH diet, originally developed for blood pressure management, has also been linked to cognitive benefits. Morris et al. demonstrated that adherence to DASH dietary principles correlated with better cognitive scores in older adults, though effects were generally weaker than those observed with Mediterranean diet adherence [69].

To address this, the MIND diet was formulated by Morris and colleagues, integrating neuroprotective components of both Mediterranean and DASH patterns while placing additional emphasis on berries and green leafy vegetables. In two prospective cohort studies, higher MIND adherence was associated with a 53% reduction in AD risk among high-adherence participants, and even moderate adherence conferred significant protection [70].

These findings emphasize that dietary patterns rich in plant-based foods, fish, nuts, and unsaturated fats — and low in red meats and processed foods — may offer greater benefits than supplementation alone. Importantly, subgroup analyses suggest that APOE ε4 carriers may particularly benefit from dietary adherence, though larger genotype-stratified RCTs are still needed to confirm this interaction.

3.5 Multinutrient formulations (souvenaid, Fortasyn Connect, etc.)

Multinutrient formulations represent a promising strategy in addressing the complex nutrient requirements of Alzheimer's disease, particularly in the early clinical stages. Unlike single-nutrient trials, these combinations are designed to target multiple pathological mechanisms simultaneously, including synaptic loss, oxidative stress, and impaired membrane function. The best-studied formulation, Souvenaid® (Fortasyn Connect), contains a mixture of omega-3 fatty acids (DHA, EPA), uridine monophosphate, choline, phospholipids, antioxidants (vitamins C, E, selenium), and B-vitamins. This combination is hypothesized to enhance synaptic membrane synthesis and function, thereby preserving cognitive performance.

Souvenaid has been tested in a number of randomized controlled studies conducted by Scheltens and associates in patients with mild AD. Their Souvenir I and II trials demonstrated improvements in memory performance compared with placebo, particularly in individuals at prodromal or mild dementia stages [71]. Similarly, Soininen et al. found that Souvenaid slowed cognitive decline over 24 months in early AD, though the benefits were not universal across all outcomes [72].

Longer follow-up studies revealed that the formulation may preserve hippocampal volume and functional connectivity in early disease stages, supporting its neuroprotective potential [73]. However, the efficacy appears stage-dependent; patients with moderate or advanced AD did not derive consistent benefits, likely reflecting irreversible neurodegeneration at later phases [74]. Importantly, subgroup analyses suggest that the APOE ε4 genotype may influence responsiveness, with some evidence that ε4 carriers show attenuated benefits compared to non-carriers, although this remains inconclusive [75].

Overall, these trials highlight that a multinutrient, systems-level approach may offer additive or synergistic effects compared to single compounds. Yet, heterogeneity in outcomes underscores the need for precision nutrition models where APOE genotype and disease stage are considered in tailoring interventions.

3.6 Heterogeneity in APOE subgroups

A consistent challenge in Alzheimer's nutrition trials is the variable response across APOE genotypes, particularly between APOE ε4 carriers and non-carriers. Several RCTs and post-hoc analyses indicate that ε4 carriers often show attenuated or differential benefits from omega-3 fatty acids, multinutrient formulations, and antioxidant interventions.

For instance, Quinn et al. (2010) observed that DHA supplementation failed to produce cognitive benefits in mild-to-moderate AD patients overall, but subgroup analyses suggested APOE ε4 status modulated treatment effects [76]. Similarly, Yassine et al. (2016) found that ε4 carriers have lower levels of DHA incorporation in plasma and cerebral fluid, which may impair its neuroprotective effectiveness [77]. These findings align with translational work by de Wilde et al. (2017), which suggested impaired brain uptake of DHA in APOE4 carriers [78].

In contrast, certain trials with multinutrient formulations like Souvenaid/LipiDiDiet indicate that ε4 status does not completely negate therapeutic response, but rather influences magnitude and domain specificity (e.g., memory vs executive function) [79]. A meta-analysis by Yassine & Finch (2020) further emphasized that personalized interventions stratified by APOE status may yield more robust and reproducible outcomes [80].

Overall, heterogeneity in outcomes highlights the significance of precision nutrition. Stratification by APOE genotype in RCTs is not just a methodological refinement but a necessity to avoid diluted effect sizes and conflicting interpretations. This highlights the urgent need for genotype-guided trial designs, ensuring that therapeutic claims are not confounded by underlying genetic risk variability.

Table 2. Dietary patterns, multinutrient formulations, and genotype heterogeneity (Sections 3.4–3.6)

Ref	Intervention / Focus	Population & n / Duration	Primary outcome	APOE notes	One-line takeaway
[67]	Mediterranean diet (RCT substudy)	Older adults at CV risk; JAMA IM	Improved global cognition vs low-fat	Not primary by genotype	Pattern beats pills
[68]	Mediterranean diet adherence	AD risk cohort	Lower AD risk & slower decline	Not reported	Strong observational support
[69]	MIND diet (cohort)	Older adults	53% ↓AD risk (high adherence)	Not reported	Neurocentric pattern promising
[70]	MIND diet (cohort)	Older adults	Slower cognitive aging	Not reported	Replicates protection
[71]	Souvenaid (Fortasyn)	Mild AD; 12 wks	Memory benefit, not global cognition	No stratification	Early-stage advantage
[73]	Souvenaid RCT	Mild AD	Preservation of hippocampal connectivity/volume	No stratification	Neuroprotective signal
[72]	LipiDiDiet (Fortasyn)	Prodromal AD; n=311 / 24 mo	Slower cognitive decline & atrophy	No definitive APOE signal	Works earlier in disease
[74]	Multi-vitamin formulation (pilot)	Moderate–late AD	Inconsistent benefits	Not stratified	Limited at later stages
[76]	DHA RCT (JAMA)	Mild–moderate AD; n=402	No overall benefit	No ε4 effect	Null trial anchors expectations
[77]	DHA RCT with ε4 focus	ε4 carriers; 6 mo	Reduced DHA brain incorporation	ε4 blunts uptake	Mechanistic basis for heterogeneity

[78]	Translational (DHA uptake)	ε4 vs non-ε4	Lower brain DHA in ε4	ε4 disadvantage	Precision nutrition rationale
[79]	LipiDiDiet (prodromal AD)	24 mo	Slower decline; domain-specific	APOE effect uncertain	Stage > genotype (so far)
[80]*	APOE × diet review	—	APOE alleles shape diet response	—	Stratify trials by genotype

*Systematic review/meta-review (contextual evidence).

PRECISION NUTRITION FRAMEWORK FOR ALZHEIMER'S

4.1 APOE-guided dietary interventions

The concept of tailoring dietary strategies based on APOE genotype has gained increasing attention in recent years. Unlike conventional "one-size-fits-all" nutritional recommendations, APOE-guided interventions recognize that lipid transport, glucose metabolism, and neuronal resilience vary substantially between carriers of different alleles. APOE ε4 carriers, for example, exhibit reduced cerebral uptake of docosahexaenoic acid (DHA), impaired cholesterol homeostasis, and heightened neuroinflammatory responses, which may explain their attenuated response to certain nutrient therapies [81,82]. In contrast, APOE ε2 carriers may benefit from enhanced synaptic plasticity and antioxidative capacity, suggesting that their nutritional requirements differ markedly [83].

Several randomized trials provide a foundation for genotype-tailored approaches. Secondary analyses of omega-3 supplementation studies reveal that APOE ε4 carriers often experience weaker cognitive benefits, whereas ε4 non-carriers maintain more favorable responses [84]. Similarly, ketogenic interventions appear to improve cognition preferentially in APOE ε4-negative individuals, highlighting the need for stratification when interpreting dietary outcomes [85]. Moreover, evidence from multinutrient formulations such as Fortasyn Connect indicates that APOE genotype moderates efficacy, with non-ε4 carriers showing greater stabilization of cognitive decline [86]. These findings collectively underscore that APOE is not merely a genetic risk marker but also a determinant of dietary responsiveness.

Moving toward clinical translation, genotype-informed nutrition offers opportunities to improve therapeutic precision. For APOE ε4 carriers, interventions may need to prioritize early life dietary optimization, higher doses or alternative delivery forms of DHA (e.g., lysophosphatidylcholine-DHA), and adjunctive anti-inflammatory dietary components [87]. For APOE ε2 and ε3 carriers, a balanced focus on maintaining vascular health and preventing metabolic dysfunction may be more relevant [88]. Importantly, ethical considerations—such as informed consent for genetic testing, equitable access to genotype-tailored diets, and cultural acceptability—must remain central as precision nutrition strategies are implemented [89].

In summary, APOE-guided dietary interventions represent a paradigm shift from generic recommendations toward truly personalized nutrition in Alzheimer's disease. While current evidence is promising, larger APOE-stratified clinical trials are needed to establish standardized dietary frameworks for clinical use.

4.2 Metabolic comorbidities (diabetes, obesity) and diet interactions

Dietary patterns such as the Mediterranean and MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay) diets are among the most consistently associated with reduced risk of Alzheimer's disease (AD) and cognitive decline. Morris and colleagues reported that higher adherence to the MIND diet correlated with markedly slower cognitive aging and a substantially lower incidence of AD in older cohorts [90,91]. Systematic reviews and meta-analyses, for example by Singh et al., reinforce that Mediterranean-style diets are associated with lower dementia risk across populations [92].

That said, benefit magnitude may vary by genotype. Scarmeas et al., in the WHICAP cohort, found that the protective association of a Mediterranean-style diet with cognitive outcomes was **attenuated** among APOE ε4 carriers compared with non-carriers [93]. A broader meta-analysis by Wu and Sun similarly observed weaker effect sizes in ε4 carriers in pooled prospective studies, suggesting a genotype–diet interaction that reduces but does not abolish benefit [94]. Conversely, the PREDIMED-NAVARRA randomized substudy (Martínez-Lapiscina et al.) reported cognitive benefits of the Mediterranean diet that were not clearly modified by APOE status, indicating that genotype–diet effects may be context- and population-dependent [95].

Mechanistically, APOE ε4–related differences in lipid handling, neuroinflammation, and blood–brain barrier transport of neuroprotective lipids provide plausible explanations for this heterogeneity. Practically, these data support broad public-health promotion of Mediterranean/MIND dietary patterns for cognitive health, while also arguing for APOE-stratified analyses in future trials to refine recommendations for ε4 carriers.

4.3 Nutritional timing (early vs late intervention)

The timing of dietary interventions has emerged as a critical factor influencing Alzheimer's disease (AD) prevention and management. Evidence indicates that nutritional strategies implemented during midlife or the preclinical stage may provide the most substantial cognitive protection, whereas interventions in later stages of AD often yield more modest outcomes. Prospective cohort studies suggest that adherence to neuroprotective dietary patterns—encompassing omega-3 fatty acids, B-vitamins, and polyphenols—decades before symptom onset is associated with preserved hippocampal integrity and delayed onset of mild cognitive impairment, particularly in APOE ε4 carriers [96]. The VITACOG trial further demonstrated that high-dose B-vitamin supplementation effectively reduced homocysteine levels and slowed brain atrophy in individuals with mild cognitive impairment, with the strongest effects observed when treatment began prior to significant cognitive decline [97,98].

In contrast, randomized trials in symptomatic AD populations, such as the LipiDiDiet study with Souvenaid, reported only modest improvements in memory and functional outcomes, highlighting the reduced efficacy of late-stage nutritional interventions [99]. Mechanistically, APOE ε4 carriers exhibit impaired transport of neuroprotective lipids and antioxidants across the blood-brain barrier in later disease stages, which may partly explain the attenuated response [100]. These findings underscore the value of a precision nutrition approach, integrating baseline biomarkers such as homocysteine, omega-3 index, and antioxidant status to guide intervention timing and composition.

By tailoring dietary strategies to individual risk profiles and disease stage, early interventions can maximize cognitive preservation, while late interventions can focus on maintaining function and slowing progression [101,102]. Overall, this evidence emphasizes that "one-size-fits-all" approaches are insufficient; stage-specific, APOE-aware nutritional interventions hold the greatest potential to modify disease trajectory and support long-term brain health.

4.4 Practical implementability (clinical and public health perspective)

Personalized nutrition approaches tailored to APOE genotype have gained momentum as a means to optimize cognitive outcomes in Alzheimer's disease (AD) prevention. Rather than applying uniform dietary recommendations, emerging work underscores the heterogeneity in metabolic responses, nutrient utilization, and cognitive trajectories among APOE subgroups.

Observational studies suggest that APOE ε4 carriers derive particular benefit from diets enriched in polyunsaturated fatty acids, antioxidants, and low-glycemic foods, whereas high saturated fat and refined carbohydrate intake appears disproportionately harmful in this group [103]. In contrast, ε2 carriers often exhibit greater resilience against metabolic stressors, though targeted support with micronutrients such as folate and vitamin D may still be advantageous [104]. Importantly, ε3 homozygotes, representing the majority, show more consistent responses across dietary interventions, serving as the reference baseline in most studies [105].

Recent randomized and mechanistic trials highlight that precision-based nutritional plans—integrating APOE genotype, lipid metabolism profiles, and neuroinflammatory markers—are feasible and effective. For instance, lifestyle-based interventions combining Mediterranean diet patterns with structured exercise and cognitive training have yielded amplified cognitive benefits in ε4 carriers, possibly by counteracting their elevated oxidative and vascular burden [106]. Similarly, targeted omega-3 fatty acid supplementation demonstrates variable efficacy across APOE genotypes, with plasma DHA transport and brain bioavailability significantly lower in ε4 carriers, necessitating higher or more bioavailable formulations [107].

Digital health tools and nutrigenomics platforms are also being developed to translate these findings into clinically actionable algorithms, enabling risk stratification and individualized dietary guidance [108]. While still in early adoption, these approaches embody the shift toward precision nutrition in AD prevention, ensuring that genotype, biomarker profiles, and lifestyle context inform recommendations.

Taken together, the integration of APOE status into personalized nutrition underscores the transition from generalized public health advice toward genetically informed dietary interventions, offering the potential for greater efficacy, adherence, and long-term brain resilience [109].

FUTURE PERSPECTIVES

5.1 Neurogenomics + Nutrigenomics Integration

Bringing neurogenomics together with nutrigenomics means moving from one-gene/one-nutrient ideas to multi-omic, APOE-aware systems that can actually predict *who* benefits from *what* diet, *when*, and *why*. Practically, that means layering: (i) genomics (APOE and polygenic risk), (ii) epigenomics/transcriptomics (cell-type–specific responses), (iii) proteomics (immune and lipid pathways), (iv) metabolomics & lipidomics (ω-3 status, one-carbon flux), (v) microbiome (diet–inflammation crosstalk), and (vi) digital dietary phenotyping + clinical biomarkers (homocysteine, ω-3 index, glycemic markers)—all fused by AI/ML into testable, individualized nutrition hypotheses for Alzheimer's disease (AD) [110–114].

Recent multi-omics maps underscore why integration matters: APOE ε4 carriers show a shared immune–inflammatory proteomic signature across diseases, implying a *systemic* vulnerability that diet could plausibly modulate—yet effects likely hinge on context (sex, vascular risk, lifestyle) [115]. Parallel synaptic multi-omics identifies lipid-handling and synapse-repair nodes in AD—giving mechanistic targets for DHA, choline/phosphatidylcholine, and antioxidant strategies to "feed" membrane remodeling and microglial resolution pathways [116]. Proteomics platforms (Olink/SomaScan) now resolve brain–CSF–plasma networks at scale, enabling nutrition-responsive biomarkers (e.g., complement, lipid carriers, neuroinflammation panels) to track target engagement in trials [117].

On the nutrition side, lipidomics/metabolomics link dietary ω-3 intake and endogenous lipid mediators to AD risk and progression, while Mendelian randomization across hundreds–thousands of metabolites begins to pinpoint causal nutrient–pathway signals relevant to cognitive decline [118,119]. Importantly, precision-nutrition consensus from NIH stresses that recommendations must incorporate genetics, age, sex, ancestry, environment, and social factors—exactly the variables that shape APOE-diet responses in AD [120]. Emerging AI-driven frameworks can learn from these layers (omics + lifestyle + biomarkers) to predict *responders* versus *non-responders*, propose genotype- and stage-specific dietary protocols, and adapt them over time using continuous biomarker feedback [121,122].

5.2 AI and machine learning in personalized diet prediction

Artificial intelligence (AI) and machine learning (ML) are rapidly emerging as transformative tools for precision nutrition in Alzheimer's disease (AD). By integrating genomic data, such as APOE status, with dietary intake records, biomarker panels, and neurocognitive outcomes, AI-driven models can identify patterns invisible to conventional statistical approaches [123]. These models offer the ability to predict which nutrient combinations—omega-3 fatty acids, B-vitamins, polyphenols—are most likely to benefit specific APOE subgroups, thereby supporting genotype-guided dietary prescriptions [124].

Recent proof-of-concept studies demonstrate the feasibility of combining multi-omics (genomics, metabolomics, microbiome) with machine learning pipelines to generate individualized nutritional risk scores [125]. Such models can stratify APOE ε4 carriers into high- and low-risk subgroups for accelerated cognitive decline, while simultaneously simulating potential intervention outcomes under different dietary regimens [126]. Importantly, these predictive frameworks not only enhance trial design by pre-selecting likely responders but also inform clinical decision-making for early preventive strategies.

Another frontier is the incorporation of digital phenotyping—continuous lifestyle data from wearable devices, smartphone applications, and electronic health records—into ML models. By linking real-time activity, sleep, and dietary logs with APOE-related metabolic signatures, dynamic AI systems can adapt recommendations over time, reflecting an individual's changing physiology and disease stage [127]. Such adaptive feedback loops may overcome the "one-time snapshot" limitation of current nutritional genomics approaches.

While promising, the clinical translation of AI-guided precision nutrition faces challenges, including limited longitudinal datasets, the need for model transparency, and ethical considerations around data privacy and equity of access [128]. Nonetheless, the integration of AI and nutrigenomics holds the potential to revolutionize Alzheimer's prevention strategies, enabling tailored interventions that evolve with the patient's genetic and lifestyle context.

5.3 Ethical, social, and economic considerations

The integration of neurogenomics and nutrigenomics into Alzheimer's disease (AD) prevention introduces several ethical, social, and economic challenges that must be carefully addressed. The disclosure of APOE genotype status, for example, has been shown to increase anxiety and alter health-related behaviors in some individuals, raising concerns about psychological impact and informed consent [129]. While genotype-guided nutrition could empower patients with actionable strategies, the risk of stigmatization, genetic discrimination, or overmedicalization must be minimized through robust counseling and ethical frameworks [130].

On the societal level, equity in access to precision nutrition remains a major barrier. Nutritional genomics services, advanced biomarker assays, and AI-guided dietary recommendations are often concentrated in high-income settings, potentially widening existing disparities in dementia care [131]. Furthermore, cultural factors shape perceptions of genetic testing and dietary interventions, meaning that ethical frameworks must adapt to diverse populations rather than apply a "one-size-fits-all" model [132].

Economic considerations are equally critical. While preventive strategies are generally more cost-effective than late-stage AD care, the scalability of personalized nutrition programs depends on balancing upfront costs of genetic testing and continuous monitoring with long-term savings from delayed disease onset [133]. Recent cost-effectiveness models suggest that targeted interventions in APOE ε4 carriers may deliver substantial public health benefit by reducing institutionalization rates, yet evidence remains preliminary [134].

Finally, data governance and privacy concerns arise as genomic and lifestyle data are increasingly digitized. Ensuring secure storage, transparent consent processes, and patient ownership of data will be key to maintaining trust and facilitating responsible clinical translation [135]. In sum, ethical foresight and equitable policies must accompany scientific progress, ensuring that precision nutrition advances not only scientific novelty but also patient dignity, accessibility, and societal benefit.

5.4 Roadmap for Clinical Translation

Moving precision nutrition for Alzheimer's disease (AD) from research into clinical practice requires a clear and coordinated roadmap. At the trial level, harmonizing endpoints across studies is essential. Cognitive tests, neuroimaging, and biomarker panels must be standardized, while results should be stratified by APOE genotype to uncover genotype-specific effects that are often masked in pooled analyses [136]. Adaptive trial designs, such as those modeled in the FINGER study and expanded internationally through the WW-FINGERS consortium, provide strong examples of how nutrition and lifestyle interventions can be systematically evaluated across diverse populations [137].

Alongside trial design, implementation requires a minimal but robust biomarker set—APOE genotype, omega-3 index, homocysteine, lipid profile, and markers of inflammation—that can be feasibly adopted in both research and clinical care [138]. Early intervention should remain the priority, focusing on midlife and individuals at genetic or metabolic risk, where preventive impact is greatest. For patients already experiencing symptomatic AD, precision nutrition may instead emphasize maintaining daily function, slowing decline, and supporting quality of life [136,138].

Finally, broader translation depends on policy alignment and healthcare integration. Global frameworks, including the WHO dementia action plan, the Lancet Commission on dementia prevention, and National Academies consensus reports, stress the importance of embedding prevention into national health strategies [138–140]. Digital health platforms, clinician education, and cost-effectiveness modeling are needed to ensure feasibility, equity, and scalability [137,139,140]. Together, these steps outline a realistic path from promising nutrigenomics research to actionable, ethically sound, and widely accessible precision nutrition strategies for AD.

CONCLUSION

Precision nutrition—anchored on APOE genotype and mechanistic biomarkers—offers a realistic, evidence-based path to improve Alzheimer's disease (AD) prevention and early-stage care. Randomized trials and cohort data show that nutrient effects (omega-3s, B-vitamins, antioxidants, multinutrient formulations) and whole-diet patterns (MIND/Mediterranean) vary by disease stage, baseline biomarker status, and importantly by APOE genotype; this heterogeneity explains much of the inconsistent trial literature and argues for genotype-stratified approaches rather than one-size-fits-all recommendations [55,72,136].

For clinical translation, the priority is clear: (1) shift emphasis toward early and at-risk populations where dietary interventions show largest signal; (2) adopt APOE-stratified, adaptive trial designs with a pragmatic biomarker core (APOE genotype, omega-3 index, homocysteine, lipids, and simple inflammatory markers) to identify true responders; and (3) test multi-component, food-first dietary strategies complemented by targeted supplements or bioavailable formulations when needed. These steps should be embedded within existing multidomain platforms (e.g., FINGER/WW-FINGERS) and aligned to policy frameworks to ensure scalability and equity [136–139].

Research priorities remain: large APOE-stratified RCTs powered for clinically meaningful cognitive and functional endpoints; mechanistic nested multi-omics to uncover responder biology; pragmatic implementation pilots that include cost-effectiveness and equity analyses; and iterative AI/ML models that refine individualized dietary prescriptions from real-world biomarker and digital-phenotype data. Together, these actions can convert promising nutrigenomic insights into ethically sound, scalable prevention and care strategies.

In sum, APOE-guided precision nutrition is not a speculative sideline but a deliverable, high-impact strategy — one that can complement pharmacotherapy, reduce dementia risk at the population level, and personalize care for those at greatest genetic vulnerability.

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