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Clinical Application of APOE in Alzheimer's Prevention: A Precision Medicine Approach

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Abstract

Population-attributable risk models estimate that up to one-third of Alzheimer's disease (AD) cases may be preventable through risk factor modification. The field of AD prevention has largely focused on addressing these factors through universal risk reduction strategies for the general population. However, targeting these strategies in a clinical precision medicine fashion, including the use of genetic risk factors, allows for potentially greater impact on AD risk reduction. Apolipoprotein E (APOE), and specifically the APOE ε4 variant, is one of the most well-established genetic influencers on late-onset AD risk. In this review, we evaluate the impact of APOE ε4 carrier status on AD prevention interventions, including lifestyle, nutrigenomic, pharmacogenomic, AD comorbidities, and other biological and behavioral considerations. Using a clinical precision medicine strategy that incorporates APOE ε4 carrier status may provide a highly targeted and distinct approach to AD prevention with greater potential for success.

Keywords

Alzheimer's disease; Alzheimer's disease prevention; apolipoprotein ε4; APOE; clinical precision medicine

Introduction

Alzheimer's disease (AD) affects more than 5.5 million people in the United States, and is estimated to affect as many as 24 million people worldwide (1). While the prevalence of AD increases 15-fold between the ages of 65 to 85, research has shown that the disease starts to develop in the brain decades before clinical symptoms become apparent (2). Recent epidemiological studies have shown that up to one-third of dementia cases may be preventable through risk factor modification, including changes in diet, activity level, and

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management of comorbidities such as diabetes, hypertension, and hyperlipidemia (3). These patient-specific lifestyle, behavioral, and treatment modifications, in addition to family history and genetic risk factor assessment, can be used to provide a highly targeted and distinct approach to AD prevention.

While the field of AD prevention continues to evolve, many interventions are based on universal risk-reduction strategies for the general population rather than a clinical precision medicine approach that incorporates individualized risk factors such as genetics. Targeting AD prevention strategies in such a way is important because it allows for optimal risk reduction by addressing risk factors for a particular individual. In the following discussion, we review examples of a clinical precision medicine AD prevention strategy, that factors in the most well-established genetic influencer on late-onset AD risk, apolipoprotein E (APOE) (4), and which may impact the effectiveness of various AD prevention interventions. We begin with an introduction to the APOE gene, followed by a discussion of the literature linking the specific APOE ε4 polymorphism to increased risk of AD. We then review the literature investigating whether APOE ε4 has been shown to modify the effectiveness of various prevention interventions for AD. From a practical clinical perspective, considering that APOE is available via direct-to-consumer testing, and also readily available to order by clinicians, its application in routine clinical care should be further explored as its use may lead to more specialized and effective prevention strategies to come.

APOE and AD Risk

APOE is a gene that codes for the apolipoprotein E protein, which is important in the transport and metabolism of lipids (5). The three major alleles of the APOE gene are ε2, ε3, and ε4. APOE ε4 carriers are at increased risk for developing AD and increased risk for developing the disease at an earlier age (6), while APOE ε2 carriers are at decreased risk for developing the disease (7). Furthermore, studies have shown that individuals with two copies of the ε4 allele are at even greater risk, and the odds ratios for developing AD based on APOE is 5 times greater in APOE ε4 homozygotes compared to heterozygotes (8). Imaging studies have further supported these findings by demonstrating that APOE ε4 carriers have higher levels of brain amyloid-β (Aβ) and lower levels of CSF Aβ42 compared to non-carriers, findings that are associated with AD pathology (9–12).

With such a strong potential for the APOE ε4 variant to affect the development of AD, and given that its frequency in the general population is estimated to range from 0.09 to 0.30 (8, 13), it is important to consider AD prevention strategies in relation to ε4 carrier status. Tailoring AD prevention strategies to ε4 carrier status in such a way is one example of how the field of AD prevention can take further steps towards more precision-based care for its patients.

Utility of APOE in the Clinical Practice of AD Prevention: Lifestyle, Nutrigenomic, Pharmacogenomic, and AD Comorbidity Considerations

In this section, we discuss research incorporating APOE ε4 carrier status into strategies for AD prevention, including considerations related to lifestyle, nutrigenomics,

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pharmacogenomics, AD comorbidities, and other biological and behavioral factors that may be impacted by ε4 carrier status.

Multi-Modal Lifestyle Considerations

Some clinical trials have demonstrated that multimodal interventions aimed at reducing AD risk, including nutrition, physical activity, cognitive engagement, and management of comorbidities improved cognitive functioning in non-impaired individuals at risk for AD (14, 15). A subgroup analysis of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial showed that there was no significant difference between the effects of lifestyle modifications on cognitive function in APOE ε4 carriers versus non-carriers (16). However, within-group analysis by ε4 carrier status demonstrated that there was greater improvement in certain measures of cognitive function in treatment versus control groups for ε4 carriers compared to non-carriers. These findings suggest that ε4 carriers may respond differently than non-carriers to certain interventions, and examination of more specialized prevention strategies based on ε4 carrier status is warranted.

Physical Activity

Physical activity is a critical aspect of AD prevention (12, 17–19). A systematic review of 16 prospective studies concluded that physical activity decreased the risk of developing AD by 45% (19). Several studies have further demonstrated a difference in response to physical activity in APOE ε4 carriers versus non-carriers (20, 21). For example, sedentary ε4 non-carriers had an odds ratio (OR) for AD of 1.77 compared to physically active non-carriers, whereas physically active ε4 carriers had an OR of 2.30 and sedentary ε4 carriers had an OR of 5.53 (20). Another study demonstrated that aerobic activity was associated with greater cognitive performance for ε4 carriers compared to non-carriers (21). Neuroimaging studies have further demonstrated that ε4 carrier status exacerbates the effect of a sedentary lifestyle on AD pathology in cognively healthy individuals (12, 22). One study demonstrated that sedentary individuals who were ε4 carriers had significantly higher levels of brain Aβ and lower levels of CSF Aβ42 compared to sedentary non-carriers, findings associated with AD pathology (12). Another study showed that the least physically active ε4 carriers had significantly higher levels of brain Aβ than the least physically active non-carriers, whereas the most physically active individuals had similar levels of brain Aβ regardless of ε4 carrier status (22). These findings have important implications for physical activity recommendations and suggest that increasing physical activity, while important for all AD prevention patients, may have more pronounced effects in ε4 carriers compared to non-carriers. The findings also suggest that physical activity may prevent Aβ accumulation that occurs in the brains of ε4 carriers before clinical symptoms of AD even become apparent.

Physical activity may not only prevent cognitive decline, but may also improve cognitive function. For example, one neuroimaging study showed that physical activity improved semantic memory processing for ε4 carriers as measured by fMRI brain imaging (23). While another RCT found that non-carriers had greater improvement in cognitive function in response to physical activity, this study was performed in patients already experiencing

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subjective cognitive complaints at baseline (24). This further suggests that physical activity may be most effective for ε4 carriers during a critical window of AD prevention before clinical symptoms begin to develop. Overall, the current evidence demonstrates that exercise is a critical intervention, especially for non-impaired ε4 carriers. Specialized, more effective prevention strategies for ε4 carriers may be possible in the future but will require additional investigation into the type and intensity of physical activity necessary to optimize AD risk reduction for this population.

Tobacco Use

A meta-analysis indicated that there was conflicting evidence about the association between tobacco use and risk of AD (25). When accounting for APOE ε4 carrier status several studies have found that ε4 carriers have a greater risk of AD associated with tobacco use than non-carriers (20, 26), although some have found no association (27). In one study, smokers who were ε4 carriers had lower auditory-verbal learning and memory scores compared to smokers who were non-carriers and compared to non-smokers regardless of ε4 carrier status (26). The study further showed that ε4 carriers who were smokers had more brain Aβ deposition compared to carriers who were non-smokers as well as non-carriers regardless of smoking history. Overall, these findings demonstrate that ε4 carrier status may exacerbate the effects of smoking on the development of AD pathology and cognitive impairment. While smoking cessation is an important preventative health strategy for numerous health reasons, it may be especially important for ε4 carriers for AD prevention as well.

Alcohol Use

Light-to-moderate alcohol consumption has been associated with a decreased risk of AD (28), whereas heavy alcohol consumption has been associated with an increased risk (29). However, this relationship may not apply to ε4 carriers. Up to three servings of wine per day has been associated with a lower risk of AD for ε4 non-carriers (30), while consumption of any amount of alcohol may increase the risk of AD for ε4 carriers (20, 31, 32). In one study, both light (1-6 drinks per week) and moderate (7-14 drinks per week) alcohol consumption was associated with improvement in learning and memory for ε4 non-carriers, but with a decline in learning and memory for ε4 carriers (31). Similarly, in other studies ε4 carriers who consumed alcohol one or more times per month had a higher risk of AD than those who never consumed alcohol (20) and the risk of AD for ε4 carriers increased with increasing amounts of alcohol consumption (32). While another study showed that alcohol consumption was associated with a decreased risk of AD for ε4 carrier women, this study was conducted retrospectively through interviews with relatives and only had ε4 carrier status for 64% of cases and for none of the controls (27). Overall, the majority of evidence suggests that alcohol consumption for AD prevention may need to be tailored to ε4 carrier status. Whereas light-to-moderate alcohol consumption may be beneficial for non-carriers for AD prevention, decreasing alcohol intake or abstaining from alcohol may be beneficial for carriers.

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Cognitive Engagement

Participating in cognitively engaging activities such as games, crafts, music, computer usage, and social activities has been associated with a decreased risk of incident Mild Cognitive Impairment (MCI) (33) and AD (34, 35). Some studies suggest that this protective effect may be particularly significant for ε4 carriers (36, 37). Among others, one study showed that engaging in recreational activities or hobbies was associated with a significantly reduced risk of cognitive decline, and this effect was more pronounced for ε4 carriers (36). Consistent with these findings, a neuroimaging study showed Aβ deposition was decreased in ε4 carriers who had greater lifetime cognitive activity (38). However, other studies suggest that non-carriers benefit more from cognitive engagement (33, 39). For example, in one study ε4 non-carriers who engaged in cognitively stimulating activities had the lowest risk of MCI (hazard ratio [HR] of 0.73), while ε4 carriers who did not engage in these activities had the highest risk (HR of 1.74) (33). Another study showed that engaging in cognitively stimulating activities was not associated with a reduced risk of cognitive decline in ε4 carriers, although this study had a smaller sample size and follow-up was only up to 18 months (39). Overall, the evidence suggests that increasing amounts of cognitive engagement may decrease the risk of AD, although it is unclear whether these activities have greater benefits for ε4 carriers or non-carriers. It is possible that carriers and non-carriers may respond differently to specific types of cognitive engagement. It is also possible that individuals with greater cognitive reserve elect to participate in more cognitively stimulating activities. Therefore, further research is required to explore the impact of cognitive engagement on AD risk in both carriers and non-carriers, as well as to explore the specific types of cognitive activities that may offer the greatest impact based on carrier status.

Nutrigenomic Considerations

Diet

The Mediterranean diet (MeDi), which generally emphasizes vegetables, legumes, monounsaturated and polyunsaturated fats, moderate amounts of fish, poultry and alcohol and limited amounts of dairy and red meat (40), has been associated with a decreased risk of AD (40, 41). For example, one study showed that MeDi adherence reduced the risk of cognitive impairment by 33% (41). Neuroimaging findings have also supported the benefits of MeDi adherence for AD prevention. One study demonstrated that non-impaired subjects with higher MeDi adherence exhibited greater cortical thickness in AD-affected brain regions compared to those with lower adherence (40). Studies also suggest that MeDi adherence has more importance for ε4 non-carriers compared to carriers for the purposes of AD prevention (40, 42). Among those with high MeDi adherence, ε4 non-carriers had greater cortical thickness in AD-affected brain regions than carriers, whereas there was no difference between carriers and non-carriers among those with low MeDi adherence (40). Another study demonstrated that MeDi adherence was associated with better performance on the clock drawing test, a measure of executive functioning and spatial reasoning, for ε4 non-carriers but not for ε4 carriers (42). These findings present both anatomical and clinical evidence that MeDi adherence may have greater AD preventative effects for ε4 non-carriers. However, a recent study demonstrated that there was no association between MeDi adherence and Aβ deposition in healthy individuals regardless of ε4 carrier status (43). This

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raises the question of whether the association between MeDi adherence and cognitive function and cortical thickness seen in prior studies is due to another mechanism unrelated to decreasing Aβ deposition. Therefore, additional research is warranted to confirm this finding and further explore the benefits of MeDi adherence for ε4 non-carriers.

In addition to MeDi adherence, dietary saturated fatty acid (SFA) content has also been examined for AD risk and prevention. Diets high in SFAs have been associated with lower cognitive function and increased risk of incident MCI (44). Some studies also suggest that high SFA diets are associated with a greater risk of AD for ε4 carriers compared to non-carriers (20, 45). For example, one study showed that ε4 carriers who consumed a diet high in SFAs had a 7-fold increased risk for AD compared to non-carriers (20). However, another recent study demonstrated conflicting results regarding the effect of a low SFA diet for ε4 carriers. In this study, non-impaired ε4 carriers who consumed a diet high in SFAs (50% total fat, 25% SFA) with a high glycemic index (GI > 70) as opposed to a diet low in SFA (25% total fat, 7% SFA) with a low glycemic index (GI < 70) exhibited greater improvement in cognitive function, whereas non-carriers exhibited decreased cognitive function on the high SFA and high GI diet (46). A RCT is underway that aims to further explore the impact of a high SFA and high GI diet on cognitive function for ε4 carriers and non-carriers (47). The results of this trial, which is scheduled to be completed in 2020, will potentially offer more clarity on whether a high or low SFA diet may offer the most benefit for AD prevention. It should be noted, however, that this study investigates the impact of both high SFA and high GI together so it may not be possible to discern the impact of either dietary intervention alone on cognitive function. Future studies should assess the impact of high SFA and high GI diets separately to explore their individual impacts on cognitive function and AD risk reduction.

n-3 Polyunsaturated Fatty Acids

Optimizing levels of the n-3 polyunsaturated fatty acids (n-3 PUFAs) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) is another important consideration for AD prevention (48, 49). Three recent RCTs support the use of high-dose DHA supplementation in non-impaired ε4 carriers for AD prevention (49). One RCT showed that male ε4 carriers who received 1.16g/day of DHA exhibited greater improvement in memory reaction time compared to non-carriers (50). Another RCT showed that ε4 carriers who received 800 mg of DHA for 3 years exhibited improvement in composite scores (49, 51). A third RCT showed that ε4 carriers receiving either low-dose (0.4g/day) or high dose (1.8g/day) EPA and DHA supplementation for 26 weeks improved in attentional measures of cognition (52). While other studies have found that non-carriers have greater improvement in response to fish consumption or DHA supplementation, these subjects already had mild to moderate AD or subjective memory complaints and therefore these ε4 carriers may already be outside a possible critical window for prevention (53–55).

Overall, these results suggest that n-3 PUFAs may have the greatest AD preventive effect for non-impaired ε4 carriers and may have less of a therapeutic effect after clinical symptoms of AD begin to appear. However, another important consideration is the impact of n-3 PUFA supplementation on serum LDL cholesterol. One review showed that n-3 PUFA

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supplementation resulted in higher serum LDL and the effects were greater in ε4 carriers compared to non-carriers (56). Another RCT showed that DHA supplementation (3.7g/day) resulted in a non-significant 10% increase in LDL for ε4 carriers compared to a non-significant 4% reduction in LDL for non-carriers (57). While not statistically significant, this trend towards elevated LDL in ε4 carriers following DHA supplementation requires more investigation as elevated LDL is another risk factor for AD. Therefore, further research is necessary to define the precise relationship between APOE ε4 and n-3 PUFA supplementation, as well as to determine the most effective dose or formulation to maximize AD risk reduction.

Vitamin D

A recent systematic review and meta-analysis showed that the risk of cognitive impairment was more than doubled in those with low vitamin D levels, ranging from less than 25-50 nmol/1 depending on the study (58). However, analysis of the 1958 British birth cohort of over 18,000 individuals demonstrated that both low (<25 nmol/1) and high (≥ 75 nmol/1) vitamin D levels were associated with lower cognitive functioning (59). This non-linear association was further described in a recent study investigating the impact of vitamin D concentrations and APOE ε4 carrier status on cognitive function. In this study, researchers demonstrated that ε4 homozygotes with high vitamin D concentrations had higher cognitive functioning and those with low vitamin D concentrations had lower cognitive functioning (60). However, ε4 heterozygotes and non-carriers with high vitamin D concentrations had lower cognitive functioning. Along with the previous study, these findings suggest that there might be an ideal range of vitamin D that could vary based on individual characteristics, such as ε4 carrier status, and that vitamin D supplementation may be preferential for APOE ε4 homozygotes. However, additional research is required to define the precise range of vitamin D for optimal cognitive functioning in ε4 carriers and non-carriers, as well as to determine whether vitamin D supplementation improves cognitive function in those with deficiency.

Pharmacogenomic Considerations

Few pharmacologic AD prevention studies to date have factored in APOE ε4 carrier status into their trials. One such study showed that individuals taking antihypertensive medication at baseline had a lower risk of AD, and that the risk was decreased to a greater extent in ε4 carriers compared to non-carriers (61). NSAIDs have also been associated with a decreased risk of AD in ε4 carriers (62, 63). However, the ADAPT trial, which randomized non-impaired subjects to receive naproxen, celecoxib, or placebo, paradoxically showed worse cognitive scores in the naproxen and celecoxib groups compared to placebo at two years and was stopped prematurely due to an increased risk of negative outcomes (64). In addition, the TOMORROW Phase III AD prevention trial was recently terminated as the diabetes drug pioglitazone was not found to prevent transition from normal cognition to MCI due to AD compared to placebo regardless of APOE ε4 carrier status (65).

New clinical trials, such as the Alzheimer's Prevention Initiative Generation Study, will hopefully clarify the importance of APOE ε4 carrier status on new potential drug targets

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(66). The Generation Study consists of two ongoing longitudinal trials of APOE ε4 carriers with the goal of determining the effectiveness of new medications on preventing the development of AD in preclinical AD patients. The results of these trials will help to characterize the importance of targeting pharmaceutical-based interventions to at risk populations and can ultimately advance the field of clinical precision medicine for AD prevention.

AD Comorbidity Considerations

Risk factors for cardiovascular disease, including hypertension, diabetes mellitus, and hyperlipidemia, have also been shown to be risk factors for AD and cognitive decline (67). The association between these risk factors and APOE ε4 carrier status is discussed below.

Hypertension

While the literature is inconsistent about the risk of AD associated with hypertension in individuals over age 60 (68–71), studies indicate that elevated systolic blood pressure (SBP) (≥ 160 mm Hg) in midlife is associated with an increased risk of eventual AD (68, 72, 73). Hypertension has also been associated with an increased risk of AD and cognitive decline in APOE ε4 carriers compared to non-carriers (74, 75). One study investigated the longitudinal impact of high SBP and APOE ε4 carrier status on cognitive function in non-impaired individuals age 45-68 over a 26-year time frame (74). Compared to non-carriers with normal SBP (<160 mm Hg), the relative risk (RR) for poor cognitive function for ε4 carriers with normal SBP was 1.3, for non-carriers with high SBP was 2.6, and for carriers with high SBP was 13.0 (74). The authors further showed that treatment of hypertension reduced the risk for carriers with high SBP from 13.0 to 1.9. In addition, another study showed that elevated SBP (≥ 140 mm Hg) or diastolic blood pressure (DBP) (≥ 90 mm Hg) exacerbated Aβ deposition in cognitively healthy individuals who were APOE ε4 carriers aged 47 to 89 years old (75). Therefore, adequate management of blood pressure may be particularly important for AD prevention for ε4 carriers, although additional research is necessary to determine optimal blood pressure ranges for AD prevention for ε4 carriers in younger and older cohorts.

Diabetes Mellitus

Management of Type 2 Diabetes Mellitus (T2DM) is also an important AD prevention strategy (76). A meta-analysis reported that four out of five studies evaluating the association between T2DM and APOE ε4 carrier status on AD risk had positive associations and three were statistically significant, with odds ratios that ranged from 2.4-5.0 (77). Two of these studies demonstrated a synergistic effect with a two-fold increased risk of AD in individuals with T2DM who were ε4 carriers compared to non-carriers (78, 79). While one study demonstrated a negative association between T2DM and APOE ε4, carrier status was only provided for 59% of its subjects (80). Overall, these findings demonstrate that ε4 carriers with T2DM may have an even greater risk of AD and adequate management of T2DM may have particular importance for this population for the purposes of AD prevention.

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Hyperlipidemia

Hyperlipidemia has been associated with an increased risk of AD (72, 81). For example, one study evaluated the impact of midlife hyperlipidemia on the development of AD three decades later and showed that the hazard ratio for AD was 1.23 for borderline high cholesterol (200-239 mg/dl) and 1.57 for high cholesterol (≥ 240 mg/dl) (81). APOE ε4 carrier status is associated with higher levels of total cholesterol and LDL cholesterol (82–84) and lower levels of HDL cholesterol compared to non-carriers (82). However, the risk of hyperlipidemia on incident AD may not be the same for ε4 carriers and non-carriers. In one study, hyperlipidemia doubled the risk of dementia in ε4 non-carriers but was not associated with an increased risk in ε4 carriers (85). Other studies have similarly shown that increasing levels of total cholesterol (86, 87) and LDL (87) increased the risk of AD in non-carriers but not in carriers. This suggests that managing hyperlipidemia, while important for improving cardiovascular risk for all patients, may be particularly important for ε4 non-carriers for AD prevention.

Other APOE-Related Considerations

Sex

There are established differences in the effects of APOE ε4 carrier status depending on male or female sex (88). One study showed that non-impaired women who were ε4 carriers had almost double the risk of converting to MCI or AD compared to non-carriers, while men who were carriers had only slightly higher rates of conversion (89). A neuroimaging study using FDG-PET showed that women who were ε4 carriers had significantly more brain hypometabolism and cortical thinning compared to non-carriers, while the difference between ε4 carriers and non-carriers in men was much less substantial (90). However, recent evidence suggests that ε4 carrier status may confer the greatest risk for women between the ages of 65-75, and may not confer additional risk compared to men outside of that age bracket (91). Therefore, it is important to consider sex differences when evaluating for AD risk, and additional research may help to elucidate the multi-factorial relationship seen among sex, ε4 carrier status, age, and other factors such as menopause.

Genotype Disclosure

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) trial was the first RCT to evaluate the impact that disclosure of APOE ε4 carrier status had on behavioral change in cognitively normal individuals (92). The researchers found that individuals who learned they were ε4 carriers reported more behavioral changes related to diet, exercise, medications, and vitamins compared to those who learned they were non-carriers. In addition, the Food4Me trial demonstrated that ε4 non-carriers informed about their carrier status reduced SFA intake less than non-carriers who were not informed (83). These studies demonstrate that the act of disclosing ε4 carrier status, as well as non-carrier status, may affect behavior and play a role in commitment to interventions, which is critical for AD prevention success. While APOE ε4 carrier status is a sensitive topic that requires a collaborative discussion between patient and treating clinician, in cases deemed clinically appropriate by both parties, disclosing this information may be a beneficial way to encourage behavioral change.

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Conclusion and Future Directions

This review indicates that prevention strategies targeted to APOE carrier status may hold a great deal of promise. Various findings demonstrate that optimizing physical activity, cognitive engagement, alcohol consumption and tobacco use are critical steps toward AD prevention, especially in ε4 carriers. Dietary changes also hold substantial importance for AD prevention, with specific emphasis on different aspects of diet in carriers versus non-carriers. Evidence suggests that supplementation with n-3 PUFAs is especially important for ε4 carriers, whereas there is a non-linear relationship between vitamin D and cognitive functioning, and more evidence is required to determine the optimal range for AD prevention. Further research into pharmaceutical targets for AD prevention is also critical, and new clinical trials such as the Generation Studies may help to clarify the role of ε4 carrier status on pharmaceutical-based prevention interventions.

In addition, the management of hypertension and T2DM may warrant special attention in ε4 carriers for the purposes of AD prevention, while the management of hyperlipidemia may warrant special attention in non-carriers. Defining specific treatment goals for these comorbidities, as well as investigation into other comorbidities should also be explored in the future. While sex is a non-modifiable risk factor, it is important to be aware of the different risks associated with ε4 carrier status for men and women in order to optimize AD prevention strategies. Finally, the use of genotype disclosure for consenting patients may promote behavioral change and compliance with prevention recommendations although further study is warranted to determine whether this leads to better outcomes.

As genotyping for APOE ε4 and other genetic risk factors becomes more widely available, both commercially and in the healthcare setting, its role in clinical care will become more important (93). New technological innovations and tracking devices that facilitate monitoring responses to interventions for both patients and clinicians will further aid in developing effective AD prevention approaches (93). In light of these advances and potential benefits of targeted interventions for ε4 carriers, inclusion of APOE ε4 carrier status in AD prevention strategies is likely to be of greater importance in the future.

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