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Effects of apolipoprotein E on nutritional metabolism in dementia

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Abstract

Purpose of review—Various groups have explored the effect of apolipoprotein E (*APOE*) on neurodegeneration through nutritional and metabolic alterations. In this review, we hope to summarize recent findings in humans as well as preclinical *APOE* models.

Recent findings—Metabolic pathways including lipid metabolism appear to play a large role in the pathophysiology of Alzheimer's disease. Carrier status of the E4 variant of the *APOE* gene is the strongest genetic risk factor for Alzheimer's disease, and increasing evidence suggests that E4 carriers may respond differently to a host of dietary and metabolic-related treatments. A new appreciation is forming for the role of *APOE* in cerebral metabolism, and how nutritional factors may impact this role.

Summary—Considering the role dietary factors play in APOE-associated cognitive decline will help us to understand how nutritional interventions may facilitate or mitigate disease progression.

Keywords

Alzheimer's disease; apolipoprotein E; dietary interventions; high-fat diet; insulin resistance

INTRODUCTION

Apolipoprotein E (*APOE*) is the major apolipoprotein in the central nervous system, responsible for lipid transport and cholesterol homeostasis. This gene has three human isoforms – E2, E3, and E4 – with population frequencies of 8.4, 77.9, 13.7%, respectively. The *APOE* gene has attracted much attention as the strongest genetic risk factor for the development of late onset Alzheimer's disease. Carriage of the E4 allele substantially raises

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Conflicts of interest

There are no conflicts of interest.

one's risk of developing late onset Alzheimer's disease, whereas the E2 allele is protective [1]. A new appreciation is forming for the role of *APOE* in cerebral metabolism of both glucose and lipid substrates. In the current review, we will summarize recent findings in both humans and experimental *APOE* mouse models.

Alzheimer's disease is characterized by several neuropathological hallmarks, including accumulation of extracellular amyloid plaques, intracellular tau tangles, and metabolic abnormalities including disruption of glucose metabolism and mitochondrial dysfunction [2■■]. The mechanisms by which E4 carrier status influences or causes these pathologies are still unclear, but there are likely both amyloid dependent and independent effects. Although it only differs from E3 and E2 by one or two amino acids, the structure of apoE4 protein is more compact and unstable which alters its ability to bind lipid, and in turn bind and clear amyloid breakdown products from the brain. The E4 isoform also appears to alter mitochondrial function, interfere with insulin signaling, and increase lipid oxidation [2■■]. E4 carriers also demonstrate more pronounced and earlier defects in cerebral glucose metabolism [3,4]. The effects of E4 are numerous, and many of the pathologies appear to involve cerebral energy metabolism, suggesting nutritional interventions could delay or prevent cognitive decline in these individuals [4].

APOLIPOPROTEIN E INFLUENCES THE CONNECTION BETWEEN DIET AND BRAIN HEALTH

Abundant epidemiologic evidence shows high-fat diets (HFDs) and resultant metabolic abnormalities such as obesity and insulin resistance are risk factors for Alzheimer's disease [5,6]. Importantly, these findings are often modulated by *APOE* genotype. The association between HFD and Alzheimer's disease in human epidemiological work is limited to E4 noncarriers in some [7,8] but not all studies [9]. For example, we showed that acute high-fat feeding improved cognition and plasma Alzheimer's disease biomarkers in E4 carriers, but worsened these biomarkers in E4 noncarriers [10]. Reasons for this paradoxical response to HFD in E4 carriers is unknown, and could involve differences in transport of macronutrients, differences in lipidation status of the apoE protein, or differences in insulin and glucose metabolism [2■■,11■■,12■■].

One major consequence of HFD is peripheral insulin resistance, which decreases brain insulin transport and subsequent function [13]. Both E4 carriers and noncarriers with Alzheimer's disease have reduced CSF insulin and demonstrate signs of brain insulin resistance. However, the relationship between peripheral and brain insulin, and the connection between insulin resistance and brain aging, is less established in E4 carriers [14–16]. Similarly, E4 status influences the correlation between Aβ and insulin resistance. Only E4 noncarriers showed a correlation between CSF Aβ and CSF : plasma glucose ratio [15], and showed reduced plasma amyloid and memory improvement after an insulin infusion; E4 carriers had no changes in memory and their plasma amyloid increased in response to insulin [17]. In addition, in an acute meal study, E4 noncarriers showed an increase in plasma Aβ42 after a high-fat meal compared with a high carbohydrate meal. Conversely, E4 carriers demonstrated higher plasma Aβ after the high carbohydrate meal accompanied by

larger changes in insulin [10]. Given the brain insulin dysfunction in Alzheimer's disease patients, insulin sensitizers and intranasal insulin are being investigated as treatments, and although the data are mixed, and the majority of these treatments improve cognition only in E4 noncarriers [12■■].

Promisingly, healthy diets and certain nutritional factors improve cognition and reduce Alzheimer's disease risk, but these findings are also influenced by *APOE* genotype. Perhaps the best studied diet for Alzheimer's disease prevention is the Mediterranean (MeDi) [18]. Most studies which have demonstrated cognitive or Alzheimer's disease biomarker benefits of MeDi included *APOE* geno-type as a control factor [19–21]. However, few if any have done prespecified subgroup analyses by *APOE* status. A multicomponent interventional study involving a diet similar to MeDi showed that 2 years of a healthy Nordic diet (abundant fish, fruits, and vegetables), exercise and brain training can prevent cognitive decline [22]. A subgroup analysis revealed that E4 carriers benefited more on tests of cognition from this intervention [23].

Seafood intake is another dietary pattern associated with slower cognitive decline, but in one study this finding was only noted in E4 carriers [24]. Seafood contains high levels of polyunsaturated fatty acids (FAs), or PUFAs, including DHA and EPA, and high intake of these nutrients is protective against Alzheimer's disease. Despite the stronger protective effect of seafood in E4 carriers, studies specifically examining PUFAs show more benefit in noncarriers. In an intervention study in older adults, E4 noncarriers who received DHA for 18 months declined significantly less on a cognitive test compared with placebo, whereas DHA had no effect on E4 carriers [25]. In another study, there was a stronger association between fish consumption and increased plasma DHA levels in E4 noncarriers, whereas in E4 carriers there was a positive association between meat and DHA [26]. Follow-up studies have suggested several potential mechanisms, including decreased lipoprotein lipase activity and differential FA processing, increased VLDL turnover, or higher levels of lipid peroxidation and beta-oxidation in E4 carriers [26,27]. How these peripheral differences affect brain transport and utilization of PUFAs and other FFA remains unknown [26,27].

As patients with Alzheimer's disease have decreased cerebral glucose metabolism, diets and pharmacologic agents which induce ketosis and supply the brain with ketone bodies are being investigated as treatments [28]. Although E4 carriers have more pronounced and earlier cerebral glucose dysregulation, only E4 noncarriers with Alzheimer's disease responded to a ketosis-inducing medium-chain triglyceride supplement. The authors speculated that the mitochondrial dysfunction in E4 carriers, renders this group less able to use ketone bodies in lieu of glucose for brain fuel; alternatively there could be differences in ketone body brain transport [29].

The evidence continues to accumulate around the idea that *APOE* genotype influences cognitive and neurological responses to diet and dietary supplements. To understand the pathophysiology of diet and dementia risk, in-vitro and in-vivo mouse models serve as ways to examine these mechanisms more carefully. However, most human cell lines are studied without respect to *APOE* status, and the most utilized rodent models of Alzheimer's disease which have provided much of the data for the experimental link between dietary factors and

Alzheimer's disease pathology are analogous to E4 non-carriers [30]. However, new models of human induced pluripotent stem cells (iPSC) edited to include *APOE3* and *APOE4* hold promise, and recent studies have demonstrated important differences in function with respect to lipid and cholesterol metabolism in neuronal-derived and glial-derived iPSCs [31]. In the next sections, we will discuss how humanized *APOE* mice can help us better understand the differences we are seeing *in vivo*, in particular the response to HFDs and lipid-based therapies in E4 carriers.

BASIC STUDIES: WHAT KNOWLEDGE AND TOOLS ARE AVAILABLE TO STUDY APOLIPOPROTEIN E EFFECTS ON NUTRITIONAL METABOLISM IN DEMENTIA?

Research into the effect of *APOE* on nutritional metabolism has often relied on mouse models as a correlate for human disease. Although several mouse models of human *APOE* exist (Table 1), the most widely used are the targeted replacement mice developed by Sullivan *et al.* in the laboratory of Dr Nobuyo Maeda. These mice were created by mating C57BL/6J mice with chimeras whose embryos had been injected with embryonic stem cells electroporated with human *APOE2, APOE3, or APOE4* constructs [32]. The vector was inserted at the normal murine *APOE* locus to maintain physiologic expression of the human variant. The metabolic profiles of these mice have been explored by many groups, specifically with respect to how they differ from wild type mice and humans.

Although 5 –10% of human E2 homozygotes develop type II hyperlipoproteinemia, all E2-targeted replacement mice display features of it, including spontaneous atherosclerosis, xanthomas, and decreased VLDL clearance [37]. Although the abnormal lipid profile confounds studies of E2's lipid-associated role in mitigating Alzheimer's disease risk, the model is still useful for probing alternative roles of E2. For example, some have posited that E2 provides a metabolic advantage and thereby decreases Alzheimer's disease risk. Venzi *et al.* found E2 mice to exhibit a significant increase in cerebral glucose metabolism beyond 3 months of age. Compared with E3 mice at 6 months, E2 mice showed increased glucose uptake by [^{18}F]FDG imaging in whole brain, cingulate cortex, cortex, and hippocampus and then a global increase at 9 months of age [38■■]. However, the first comprehensive human study to examine E2 carriers with [^{18}F]FDG imaging showed that age-related decreases in glucose uptake did not significantly differ from E3 individuals [39]. Thus, the cerebral metabolic effects of E2 remain an important, but unsettled issue.

The E3 and E4-targeted replacement mice also express their human isoforms at physiologic levels [32,37,40]. They are normolipidemic but become hyperlipidemic in response to a westernized diet [37,41]. Although E4 confers a higher risk of dementia in humans, it is controversial what cognitive effects are present in targeted replacement E4 mice (in the absence of amyloid or tau over expressing mutations). Rodriguez *et al.* [42] observed impairments in spatial learning and memory in young E4-targeted replacement mice in the Barnes maze test, but no difference in a hidden platform water maze experiment. In contrast to mixed effects of E4 on behavioral outcomes and age-related cognitive decline, the association of E4 with cerebral metabolic changes is more clear. Several groups have

demonstrated reductions in cerebral glucose uptake in E4 mice compared with mice expressing E3 [43 – 45] – similar to the well established findings via FDG PET in human E4 carriers.

In humans, E4 carrier status is associated with a higher brain amyloid burden, but it has been more difficult to demonstrate this in E4 mice unless other Alzheimer's disease-related genes are present [11■■]. When Alzheimer's disease mice are crossed with *APOE* knockout mice, the resultant phenotype is less amyloid depositions, suggesting that the apoE protein is necessary for amyloid breakdown products to cause plaques. Alzheimer's disease mice that express human *APOE* alleles do recapitulate what is seen in humans with more amyloid in E4 compared with E3, and less still in E2 [46]. One important difference that may affect amyloid burden studies is that humanized E4 is less stable in mouse brain and is degraded, whereas this does not appear to be the case in humans [11■■,47].

As glucose uptake and utilization is impaired in E4 carriers and Alzheimer's disease individuals, many groups have studied the insulin-signaling pathway as a potential target of *APOE* modulation. Hippocampal RNA from middle-aged female E2, E3, and E4-targeted replacement mice was arrayed for genes involved in insulin signaling. This revealed that E2 mice have higher levels of Igf1, insulin receptor substrates, and the glucose transporter GLUT4 than E3 and E4 [48]. Furthermore, E4 mice showed a significant decrease in PPAR-gamma and insulin-degrading enzyme, pointing to a further compromise of insulin signaling and glucose utility. These findings were confirmed by another group who used an array for glucose and ketone body metabolism and identified glucose transporters and hexokinases were robustly altered by *APOE* genotype [49■]. The Bu group discovered that E4 restricts insulin receptors to endosomes and thereby impairs trafficking and signaling, an effect exacerbated by HFD [50■■]. To test the effect of *APOE* on peripheral insulin receptor sensitization, To *et al.* fed E3 and E4 mice a diabetogenic diet then treated the mice with a thiazolidinedione. They found a reduction in tau phosphorylation, but only in E3 mice [51]. These studies support the idea that E4 renders the brain insulin resistant, likely through regulation of insulin receptors and glucose transporters.

Despite growing evidence for a role of diet in Alzheimer's disease and the potential of personalized medicine and gene–diet interactions, very few studies have attempted to tackle the interaction between *APOE* and diet in the context of Alzheimer's disease or cognitive function. Our group explored the potential interactive effects of diet and E4 on cognition by using a mouse model of chronic high-fat feeding. We found that disruption of glucose homeostasis following 6 months of HFD led to more pronounced cognitive impairments in E4 compared with E3 mice. These cognitive deficits were specific to hippocampal-dependent spatial learning and memory outcomes, and were accompanied by wide-ranging isoform-specific alterations in the epigenetic landscape and changes in cerebral metabolism [52]. It is hypothesized that its effects on cerebrovascular function could be the driving force of the cognitive impairing effects of HFD. We found that E4 mice fed a HFD exhibit reduced glucose uptake compared with both E4 mice on a control diet and E3 mice on both control and HFD [52]. Further, E4 carriage and HFD acted synergistically to lower cerebral blood flow [44]. Significantly, when challenged with an acute glucose bolus, E4 but not E3 mice responded beneficially in terms of both increased blood flow and enhanced performance in a

memory task; hinting at a potential role for *APOE* in modulating neurovascular coupling and cognitive function [44].

In the APP mouse model of distorted amyloid processing, expression of E4 along with a HFD significantly increases amyloid deposition compared with E3 [53]. E4 was also found to increase amyloid and glial activation in the EFAD model of Alzheimer's disease when fed a westernized diet [54]. E3 mice gain more weight on a HFD, whereas E4 mice seem to upregulate genes involved in FA mobilization and utilization in the periphery [55]. This could parallel a central E4 promoted HFD-induced bioenergetic shift toward FAs and away from glucose as the primary cerebral energy source. Together, these studies show that E4 seems to exacerbate the negative effects of a HFD on cognition.

CONCLUSION

As we continue to uncover the role of the *APOE* gene as a contributor to cognitive decline, we must take into account the additive effects that the westernized HFD and insulin resistance seem to have on disease progression. Human epidemiologic and experimental evidence suggests that *APOE* genotype changes the relationship between several lipid-related macronutrients and markers of brain health and cognition. Whether it is diet-induced insulin resistance, PUFAs from fatty fish, or ketone bodies from medium chain triglycerides, *APOE* status appears to modulate important responses to lipid-related therapies. Mouse models have been vital in confirming that E4 exacerbates the negative cognitive effects of diabetogenic and HFD, and also suggest reasons by which E2 carriers are less susceptible to developing Alzheimer's disease. Future studies should utilize these and other experimental models of *APOE* to implicate specific cells and tissues in the E4 response to nutritional interventions, and include *APOE* genotype as an important subgroup for analysis of human interventions.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 2013; 9:106–118. [PubMed: 23296339]

2■■. Mahley RW, Huang Y, Weisgraber KH. Detrimental effects of apolipoprotein E4: potential therapeutic targets in Alzheimer's disease. Curr Alzheimer Res 2007; 4:537–540. [PubMed:

18220516] The article summarizes some of the known brain metabolic effects of the apolipoprotein E (apoE)4 protein isoform.

3. Reiman EM, Chen K, Alexander GE, et al. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. Proc Natl Acad Sci U S A 2004; 101:284–289. [PubMed: 14688411]
4. Brandon JA, Farmer BC, Williams HC, Johnson LA. APOE and Alzheimer's disease: neuroimaging of metabolic and cerebrovascular dysfunction. Front Aging Neurosci 2018; 10:180. [PubMed: 29962946]
5. Gustaw-Rothenberg K. Dietary patterns associated with Alzheimer's disease: population based study. Int J Environ Res Public Health 2009; 6:1335–1340. [PubMed: 19440521]
6. Solfrizzi V, Panza F, Frisardi V, et al. Diet and Alzheimer's disease risk factors or prevention: the current evidence. Expert Rev Neurother 2011; 11:677–708. [PubMed: 21539488]
7. Huang TL, Zandi PP, Tucker KL, et al. Benefi of fatty fi h on dementia risk are stronger for those without APOE epsilon4. Neurology 2005; 65:1409–1414. [PubMed: 16275829]
8. Barberger-Gateau P, Samieri C, Feart C, Plourde M. Dietary omega 3 polyunsaturated fatty acids and Alzheimer's disease: interaction with apolipoprotein E genotype. Curr Alzheimer Res 2011; 8:479–491. [PubMed: 21605054]
9. Kivipelto M, Rovio S, Ngandu T, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med 2008; 12:2762–2771. [PubMed: 18318693]
10. Hanson AJ, Bayer JL, Baker LD, et al. Differential effects of meal challenges on cognition, metabolism, and biomarkers for apolipoprotein E varepsilon4 carriers and adults with mild cognitive impairment. J Alzheimers Dis 2015; 48:205–218. [PubMed: 26401941]
11■■. Fan J, Donkin J, Wellington C. Greasing the wheels of Abeta clearance in Alzheimer's disease: the role of lipids and apolipoprotein E. Biofactors 2009; 35:239–248. [PubMed: 19472365] The article summarizes the different lipid binding patterns of the apoE isoforms, including the decreased ability of apoE4 to bind lipid and bind and clear amyloid breakdown products.
12■■. Hanson AJ, Craft S, Banks WA. The APOE genotype: modification of therapeutic responses in Alzheimer's disease. Curr Pharm Des 2015; 21:114–120. [PubMed: 25330331] The article is a review of how APOE genotype influences responses to several different treatments for Alzheimer' s disease, focusing on metabolic-related therapeutics.
13. Cholerton B, Baker LD, Craft S. Insulin resistance and pathological brain ageing. Diabet Med 2011; 28:1463–1475. [PubMed: 21974744]
14. Craft S, Peskind E, Schwartz MW, et al. Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype. Neurology 1998; 50:164–168. [PubMed: 9443474]
15. Dumurgier J, Paquet C, Peoc'h K, et al. CSF Ab1–42 levels and glucose metabolism in Alzheimer's disease J Alzheimers Dis 2011; 27:845–851. [PubMed: 21897007]
16. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest 2012; 122:1316–1338. [PubMed: 22476197]
17. Craft S, Asthana S, Schellenberg G, et al. Insulin effects on glucose metabolism, memory, and plasma amyloid precursor protein in Alzheimer's disease differ according to apolipoprotein-E genotype. Ann N Y Acad Sci 2000; 903:222–228. [PubMed: 10818510]
18. Tsivgoulis G, Judd S, Letter AJ, et al. Adherence to a Mediterranean diet and risk of incident cognitive impairment. Neurology 2013; 80:1684–1692. [PubMed: 23628929]
19. Pelletier A, Barul C, Feart C, et al. Mediterranean diet and preserved brain structural connectivity in older subjects. Alzheimers Dement 2015; 11:1023–1031. [PubMed: 26190494]
20. Vassilaki M, Aakre JA, Syrjanen JA, et al. Mediterranean diet, its components, and amyloid imaging biomarkers. J Alzheimers Dis 2018; 64:281–290. [PubMed: 29889074]
21. Scarmeas N, Stern Y, Mayeux R, et al. Mediterranean diet and mild cognitive impairment. Arch Neurol 2009; 66:216–225. [PubMed: 19204158]
22. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-

risk elderly people (FINGER): a randomised controlled trial. Lancet 2015; 385:2255–2263. [PubMed: 25771249]

23. Solomon A, Turunen H, Ngandu T, et al. Effect of the apolipoprotein E genotype on cognitive change during a multidomain lifestyle intervention: a subgroup analysis of a randomized clinical trial. JAMA Neurol 2018; 75:462–470. [PubMed: 29356827]
24. van de Rest O, Wang Y, Barnes LL, et al. APOE epsilon4 and the associations of seafood and long-chain omega-3 fatty acids with cognitive decline. Neurology 2016; 86:2063–2070. [PubMed: 27164694]
25. Quinn JF, Raman R, Thomas RG, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. JAMA 2010; 304:1903–1911. [PubMed: 21045096]
26. Samieri C, Lorrain S, Buaud B, et al. Relationship between diet and plasma long-chain n-3 PUFAs in older people: impact of apolipoprotein E genotype. J Lipid Res 2013; 54:2559–2567. [PubMed: 23801662]
27. Chouinard-Watkins R, Rioux-Perreault C, Fortier M, et al. Disturbance in uniformly 13C-labelled DHA metabolism in elderly human subjects carrying the apoE epsilon4 allele. Br J Nutr 2013; 110:1751–1759. [PubMed: 23631810]
28. Cunnane S, Nugent S, Roy M, et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition 2011; 27:3–20. [PubMed: 21035308]
29. Henderson ST, Vogel JL, Barr LJ, et al. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab 2009; 6:31.
30. Pendse AA, Arbones-Mainar JM, Johnson LA, et al. Apolipoprotein E knock-out and knock-in mice: atherosclerosis, metabolic syndrome, and beyond. J Lipid Res 2009; 50(Suppl):S178–S182. [PubMed: 19060252]
31. Lin YT, Seo J, Gao F, et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. Neuron 2018; 98:1141–1154.e7. [PubMed: 29861287]
32. Sullivan PM, Mezdour H, Aratani Y, et al. Targeted replacement of the mouse apolipoprotein E gene with the common human APOE3 allele enhances diet-induced hypercholesterolemia and atherosclerosis. J Biol Chem 1997; 272:17972–17980. [PubMed: 9218423]
33. Raber J, Wong D, Buttini M, et al. Isoform-specific effects of human apolipoprotein E on brain function revealed in ApoE knockout mice: increased susceptibility of females. Proc Natl Acad Sci U S A 1998; 95:10914–10919. [PubMed: 9724804]
34. Sun Y, Wu S, Bu G, et al. Glial fibrillary acidic protein-apolipoprotein E (apoE) transgenic mice: astrocyte-specific expression and differing biological effects of astrocyte-secreted apoE3 and apoE4 lipoproteins. J Neurosci 1998; 18:3261–3272. [PubMed: 9547235]
35. Liu CC, Zhao N, Fu Y, et al. ApoE4 accelerates early seeding of amyloid pathology. Neuron 2017; 96:1024–1032.e3. [PubMed: 29216449]
36. Haddadi M, Nongthomba U, Jahromi SR, Ramesh SR. Transgenic Drosophila model to study apolipoprotein E4-induced neurodegeneration. Behav Brain Res 2016; 301:10–18. [PubMed: 26706888]
37. Knouff C, Hinsdale ME, Mezdour H, et al. Apo E structure determines VLDL clearance and atherosclerosis risk in mice. J Clin Invest 1999; 103: 1579–1586. [PubMed: 10359567]
38■■. Venzi M, Tóth M, Häggkvist J, et al. Differential effect of APOE alleles on brain glucose metabolism in targeted replacement mice: an [18F]FDG-mPET study. J Alzheimers Dis Rep 2017; 1:169–180. [PubMed: 30480236] The study details novel amyloid-independent metabolic effects of the APOE isoforms in targeted replacement mice by PET imaging.
39. Grothe MJ, Villeneuve S, Dyrba M, et al. Multimodal characterization of older APOE2 carriers reveals selective reduction of amyloid load. Neurology 2017; 88:569–576. [PubMed: 28062720]
40. Sullivan PM, Han B, Liu F, et al. Reduced levels of human apoE4 protein in an animal model of cognitive impairment. Neurobiol Aging 2011; 32:791–801. [PubMed: 19577821]

41. Arbones-Mainar JM, Johnson LA, Altenburg MK, et al. Impaired adipogenic response to thiazolidinediones in mice expressing human apolipoproteinE4. FASEB J 2010; 24:3809–3818. [PubMed: 20501792]

42. Rodriguez GA, Burns MP, Weeber EJ, Rebeck GW. Young APOE4 targeted replacement mice exhibit poor spatial learning and memory, with reduced dendritic spine density in the medial entorhinal cortex. Learn Mem 2013; 20:256–266. [PubMed: 23592036]

43. Lin AL, Jahrling JB, Zhang W, et al. Rapamycin rescues vascular, metabolic and learning deficits in apolipoprotein E4 transgenic mice with presymptomatic Alzheimer's disease. J Cereb Blood Flow Metab 2017; 37:217–226. [PubMed: 26721390]

44. Johnson LA, Torres ER, Weber Boutros S, et al. Apolipoprotein E4 mediates insulin resistance-associated cerebrovascular dysfunction and the postprandial response J Cereb Blood Flow Metab 2017 [Epub ahead of print]

45. Alata W, Ye Y, St-Amour I, et al. Human apolipoprotein E varepsilon4 expression impairs cerebral vascularization and blood-brain barrier function in mice. J Cereb Blood Flow Metab 2015; 35:86–94. [PubMed: 25335802]

46. Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. Sci Transl Med 2011; 3:89ra57.

47. Hanson AJ, Bayer-Carter JL, Green PS, et al. Effect of apolipoprotein E genotype and diet on apolipoprotein E lipidation and amyloid peptides: randomized clinical trial. JAMA Neurol 2013; 70:972–980. [PubMed: 23779114]

48. Keeney JT, Ibrahimi S, Zhao L. Human ApoE isoforms differentially modulate glucose and amyloid metabolic pathways in female brain: evidence of the mechanism of neuroprotection by ApoE2 and implications for Alzheimer's disease prevention and early intervention. J Alzheimers Dis 2015; 48:411–424. [PubMed: 26402005]

49■. Wu L, Zhang X, Zhao L. Human ApoE isoforms differentially modulate brain glucose and ketone body metabolism: implications for Alzheimer's disease risk reduction and early intervention. J Neurosci 2018; 38:6665–6681. [PubMed: 29967007] In this study, Wu et al. study the impact of human APOE isoforms on glucose and ketone metabolism in ex-vivo mice brains and in-vitro neurons.

50■■. Zhao N, Liu CC, Van Ingelgom AJ, et al. Apolipoprotein E4 impairs neuronal insulin signaling by trapping insulin receptor in the endosomes. Neuron 2017; 96:115–129.e5. [PubMed: 28957663] The article lays the groundwork for further studies investigating insulin signalling from an ApoE/Alzheimer's disease perspective and offers rich follow-up opportunities for other cell types in the brain that utilize insulin and are modulated by ApoE.

51. To AW, Ribe EM, Chuang TT, et al. The epsilon3 and epsilon4 alleles of human APOE differentially affect tau phosphorylation in hyperinsulinemic and pioglitazone treated mice. PLoS One 2011; 6:e16991. [PubMed: 21347323]

52. Johnson LA, Torres ERS, Impey S, et al. Apolipoprotein E4 and insulin resistance interact to impair cognition and alter the epigenome and metabolome. Sci Rep 2017; 7:43701. [PubMed: 28272510]

53. Nam KN, Wolfe CM, Fitz NF, et al. Integrated approach reveals diet, APOE genotype and sex affect immune response in APP mice. Biochim Biophys Acta Mol Basis Dis 2018; 1864:152–161. [PubMed: 29038051]

54. Moser VA, Pike CJ. Obesity accelerates Alzheimer-related pathology in APOE4 but not APOE3 mice eNeuro 2017; 4:.

55. Huebbe P, Dose J, Schloesser A, et al. Apolipoprotein E (APOE) genotype regulates body weight and fatty acid utilization – studies in gene-targeted replacement mice. Mol Nutr Food Res 2015; 59:334–343. [PubMed: 25381750]

KEY POINTS

- Many attempted nutritional therapies for cognitive decline have not shown promise in E4 carriers.
- Epidemiological dietary studies should include APOE genotype in subgroup analysis to better inform the field of APOE's nutritional role in disease progression.
- E4 seems to exacerbate the cognitively deleterious effects of a high-fat diet.
- Other models of APOE should be studied to detail cell and tissue-specific effects of APOE in metabolism.

Table 1.

Summary of apolipoprotein E models by expression and original report or source

Model	APOE expression	Original study
Targeted replacement mice	Global E2, E3, E4	Sullivan et al. [32]
NSE promoter	Neuron	Raber et al. [33]
GFAP promoter	Astrocyte	Sun *et al.* [34]
Dox inducible	Cell specific	Liu et al. [35]
APOE$_*$ KI mice	Global E2, E3, E4	Jackson Laboratory
hApoE4 knock-in rat	Global E4	Horizon Discovery
hApoE knock-in fly	Global E3, E4	Haddadi et al. [36]

APOE, apolipoprotein E.