SPRINGER NATURE
Reference

Reinaldo Oriá
J. Wesson Ashford
Carr J. Smith
Editors

Apolipoprotein E

From Biochemistry and Biology to Translational Medicine

Springer

Reinaldo Oriá • J. Wesson Ashford •
Carr J. Smith
Editors

Apolipoprotein E

From Biochemistry and Biology to Translational Medicine

With 123 Figures and 43 Tables

Springer

Preface

We are delighted to introduce the first edition of our textbook entitled *Apolipoprotein E: From Biochemistry and Biology to Translational Medicine*, gathering worldwide experts in topics ranging from human evolution, molecular and cell biology, to translational medicine, highlighting key advances in apolipoprotein E (apoE) biomedical research and related breakthrough discoveries, including its intricate central role in the pathophysiology of Alzheimer's disease. The scope of this book is daring, with a broad, in-depth overview of this fascinating molecule, discovered in the early 1970s. Topics include evolving, cutting-edge discoveries and the unraveling of novel metabolic pathways in the homeostasis of different biological systems. In addition, the book aims to build intricate connections in life sciences, from the fascinating journey of cell biochemistry to its involvement in aging-related diseases. The textbook is structured into the following parts: Molecular Structure, Biochemistry, and Function; The Nervous System and Cognition; Digestive System; Cardiovascular System and Metabolism; Immune System and Inflammation; Biomarkers, Target Therapy, and Diagnostic Tools; Infectious Diseases and Host-Pathogen Interactions; and Environmental Toxicology.

The underlying concept of this book emerges from collaborative work, the editors' long-term research background, and their enthusiasm for apoE research and its involvement in human evolution, brain neuroplasticity, and cognition. The editors recognized the need to make this book's content available to the scientific community and the general public. The book is timely and urgently needed to gather recent findings in apoE research. The editors were eager to bring this book to academia and the general community, given recent outstanding findings on the roles of apoE in Alzheimer's disease, infectious diseases, and the gut-brain axis. The purpose of this book is to spark further discussion and encourage young scholars and researchers to examine the role of apoE across various disease conditions; advance biomarkers, drug discovery, and preventive measures for different pathological conditions; and ultimately improve human health to achieve full quality of life across the lifespan.

In a rapid PubMed search for apoE, we found more than 32,000 papers, and the field is evolving rapidly. We understand that rapid technological advances in biomarkers, diagnostic tools, omics sciences, and neuroimaging will bring unprecedented knowledge to the field. The editors acknowledge that modern science

requires continual updates, and we envision future editions of this book to better capture the top upcoming apoE research.

The editors hope that this long endeavor, from the initial stretch to this final compendium of 51 chapters, will encourage more apoE-related research collaborations and initiatives to better understand this molecule and its complex interactions in different biological systems, enabling compelling medical translation into products that benefit human health across the lifespan.

Fortaleza, CE, Brazil — Reinaldo Oriá
Palo Alto, CA, USA — J. Wesson Ashford
Pacific Palisades, CA, USA — Carr J. Smith
April 2026

Acknowledgments Since its discovery in the early 1970s, the research on apolipoprotein E (apoE) and related signaling pathways has inspired leading scientists and scholars worldwide to elucidate its complex molecular functions in lipid metabolism and its multisystem associations, profoundly immersed in the onset and pathophysiology of various disease outcomes. After 2 years of this journey and enterprise, from the book's conception, proposal acceptance, and conclusion, we would like to express our deepest gratitude to all those who supported this endeavor throughout the development of this book. We are deeply thankful and sincerely acknowledge the outstanding support of Dr. Gabriella Vieira Cunha Ciurleo from the Federal University of Ceará, Brazil, and Springer Nature representatives (special thanks to Thesneem Sulthana and Shobana Lenin) for their assistance with the authors' communications throughout the book planning stage and editorial production. Special thanks to colleagues and collaborators at the University of Virginia and Stanford University, whose insights and feedback have enriched this work in countless ways during our careers in apoE research. We also sincerely thank our institutions for providing a stimulating academic environment and essential resources. We give special thanks to the Brazilian National Institute of Brain Health (INCT-Saúde Cerebral) and the graduate programs in Medical Sciences, Morphofunctional Sciences, and Pharmacology from the Federal University of Ceará, Brazil, for key contributions and insights for our book. We extend heartfelt appreciation to our family and friends for their unwavering encouragement, patience, and love. Without their constant support, this book would not have been possible. Lastly, we are grateful to our post-doctoral and PhD students who continue to engage in this important topic. Your curiosity and dedication are the true inspiration behind this work.

Brain Neuroplasticity and Alzheimer's Disease Prevention: Health Considerations for Those with an ApoE-ε4 Gene

J. Wesson Ashford, Carr J. Smith, and Reinaldo Oriá

Contents

Preliminary Note:
For a more in-depth discussion of several of the issues discussed in this chapter, refer to: Handbook of Prevention and Alzheimer's Disease. Eds: Raji, C.A., Leng, Y., Ashford, J.W., Khalsa, D.S. Volume 10 of Advances in Alzheimer's Disease, Published by IOS Press. February 2024

J. W. Ashford (✉)
War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, USA

Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA
e-mail: ashford@stanford.edu

C. J. Smith
Society for Brain Mapping & Therapeutics, Pacific Palisades, CA, USA

R. Oriá
Department of Morphology and Institute of Biomedicine, Federal University of Ceará, Fortaleza, CE, Brazil
e-mail: oria@ufc.br

R. Oriá et al. (eds.), *Apolipoprotein E*,
https://doi.org/10.1007/978-3-031-96089-5_83

Abstract

Dementia, including the most common cause, Alzheimer's disease (AD), and related neurodegenerative disorders, is a rapidly increasing worldwide problem related to increased longevity and decreased fertility. The impact is not just due to the increasing number of cases but also to the increased proportion of affected individuals. Dementia will have an increasingly profound impact on many populations of Europe, Asia, and the Americas, as well as many developing nations, particularly those with limited health resources. Dementia is a condition that is personally devastating and creates a tremendous burden on caregivers and society. An important consideration is evidence that many AD contributing factors are modifiable and can be prevented. AD pathology starts long before its hallmark clinical symptoms appear. The earliest established brain alteration is the development of neurofibrillary changes composed of hyper-phosphorylated microtubule-associated protein tau (TAU) in the locus coeruleus, then in the midbrain raphe and the nucleus basalis of Meynert, followed by accumulation of the beta-amyloid protein (Abeta) in the neocortex, which accumulates over decades. With progression, there is synaptic loss, which becomes massive and corresponds most closely to the cognitive decline, particularly memory dysfunction, from mild cognitive impairment to profound dementia. ApoE-ϵ4 is the predominant risk factor, genetic or environmental, for this disease, and the AD process is substantially more prevalent and has a younger age-of-onset in ApoE-ϵ4 carriers relative to noncarriers. This chapter summarizes the current literature on the role of ApoE4 and its deleterious effects on brain synaptic function and provides recommendations for improving healthy aging practices to prevent or slow AD pathology, which may be important for several other causes of AD and dementia as well.

Keywords

Alzheimer's disease · Apolipoprotein E · ApoE-ϵ4 · Synapse · Modifiable factors · Neuroplasticity · Aging

Introduction

Brain neuroplasticity is the basic neural mechanism for building and modifying synaptic circuitry, establishing neuronal integrity and memory, and proper function throughout life, at all levels of system functions, i.e., biological, psychological, and social (Ashford et al. 1998a). Active and healthy brain neuroplasticity is a paramount feature of human development, enabling the achievement of full genetic potential, particularly in the development of cognitive domains and in encoding information into memory to cope with daily life situations and to support intellectual advancement, thereby contributing to improvements in societal and interpersonal relations. In humans, and presumably all mammals, synaptic circuitry is extensively developed throughout the brain before birth. Soon after birth, primary cortical regions undergo critical periods for synaptic adaptation to the environment, during which both arbitrary and irrelevant connections are pruned, and relevant connections are enhanced. Secondary cortical regions have later critical periods, while some associative cortical regions appear to maintain high levels of synaptic plasticity throughout life. Since the neurons and areas of the brain affected by Alzheimer's disease (AD) are all involved in memory mechanisms, the vulnerable factor in AD must be related to **neuroplasticity**, a central fact being that AD attacks mechanisms of neuroplasticity (Ashford 2023; Ashford and Jarvik 1985; Teter and Ashford 2002).

For a basic appreciation of the enormity of neuroplastic operations, consider that the brain has nearly 100 billion neurons, averaging 10,000 synapses each (a quadrillion in total). The half-life of synapses in the neocortex is about 100 days (Cotman and Nieto-Sampedro 1984), and in the hippocampus, it can be less than 15 min (Chang and Greenough 1984). So, the human brain, which has its largest number of synapses between 2 and 6 years of age and only decreases the total number by about half at 30 years of age, appears to destroy (synaptolysis) and create (synaptogenesis) about 10 trillion synapses every day.

Brain neuroplasticity is a dynamic process of remodeling synaptic circuitry throughout the lifespan. Such dynamic processes rely on synaptogenesis, physiological synaptic pruning (synaptolysis, to remove spurious synapses), proper myelination, and the neuronal-to-glial ratio and biological activity to support healthy synaptic unit function. The neuroplastic processes require large amounts of energy (vis-à-vis cerebral blood flow, ATP, and GTP), constructional resources (including cholesterol and other membrane lipids), and waste removal systems (glial-driven phagocytic activity and related homeostatic inflammatory mechanisms).

Apolipoprotein-E (ApoE), a 299 amino acid protein, which is primarily released from astrocytes, forms complexes with cholesterol from synapses being removed (synaptolysis), which is key for providing new cholesterol for synaptogenesis and synaptic integrity. The issue discussed in this chapter is how the ApoE gene relates to AD, with a focus on its effects on the brain's synaptic remodeling. While the ApoE protein is involved in numerous genetic processes (Theendakara et al. 2018), it must play a central role in a critical component of the neuroplastic process, which could best be explained by its role as a cholesterol chaperone (Oria et al. 2024). The more complex questions are what role does ApoE play in the pathophysiological

development of AD, and how can such information be used to slow the clinical development of AD, i.e., in prevention?

In pathological conditions, including AD, there can be an imbalance of neuroplasticity with increased synaptic pruning and decreased new synapse creation, leading to a devastating loss of synaptic mass and consequent brain atrophy (Teter and Ashford 2002). There is accumulating evidence of brain neuroplasticity disturbances in ApoE-ϵ4 gene carriers with age, fostering the increased risk and severity of AD. This chapter summarizes the current scientific literature on the roles of the ApoE-ϵ4 gene in the synaptic unit and its consequences for AD development. It also highlights the importance of modifiable lifestyle attitudes toward environmental enrichment and healthy habits in reducing and delaying deleterious AD outcomes with aging. Furthermore, it reviews recent neurophysiological findings that suggest several approaches to modulate the pathological mechanisms associated with the ApoE-ϵ4 allele and reduce AD risk. Further, some of these considerations could help to eliminate AD altogether. The main topics of this chapter are summarized in Fig. 1.

What We Know About the Pathophysiology of AD, Brain Neuroplasticity, and the Amyloid Precursor Protein (APP)

When Alois Alzheimer first described AD pathology in 1906 in a 51-year-old woman, he reported a consistently atrophic brain, arteriosclerosis, changes of neurofibrils (neuropil threads inside normal-looking cells and neurofibrillary tangles), loss of ganglion cells, deposits of a peculiar substance, and large fatty sacs in many glial cells (Alzheimer 1907; Jarvik 1990). Major advances in Alzheimer's disease (AD) have included determining that the neurofibrils are composed of the microtubular protein-tau (TAU), that the "peculiar substance" is beta amyloid (Abeta), and that there are critical genetic relationships. The first clear genetic link was with Down Syndrome, trisomy 21, with most cases developing AD pathology in their 20s and dementia in their 40s (Rumble et al. 1989; Salehi et al. 2016). Relevant to the understanding of AD, which is in part characterized by the presence of extracellular senile plaques filled with the Abeta, is that Abeta is derived from the amyloid precursor protein (APP) located on chromosome 21. Hence, Down Syndrome subjects produce a 50% excess of the APP protein. Other early onset cases have been found to have genetic mutations on the chromosome 21 region coding for APP and for other proteins (particularly presenilin-1 and -2) associated with the metabolism of APP, though all account for less than 5% of the AD cases.

In the first paper by Blessed et al. (1968), which recognized AD as a common condition in older humans, thereby initiating the modern era of attention to AD, the neurofibrillary tangles correlated with the cognitive impairments, although the Abeta plaques did not (Blessed et al. 1968). A major problem in the AD field is understanding this dichotomy (Ashford 2019a).

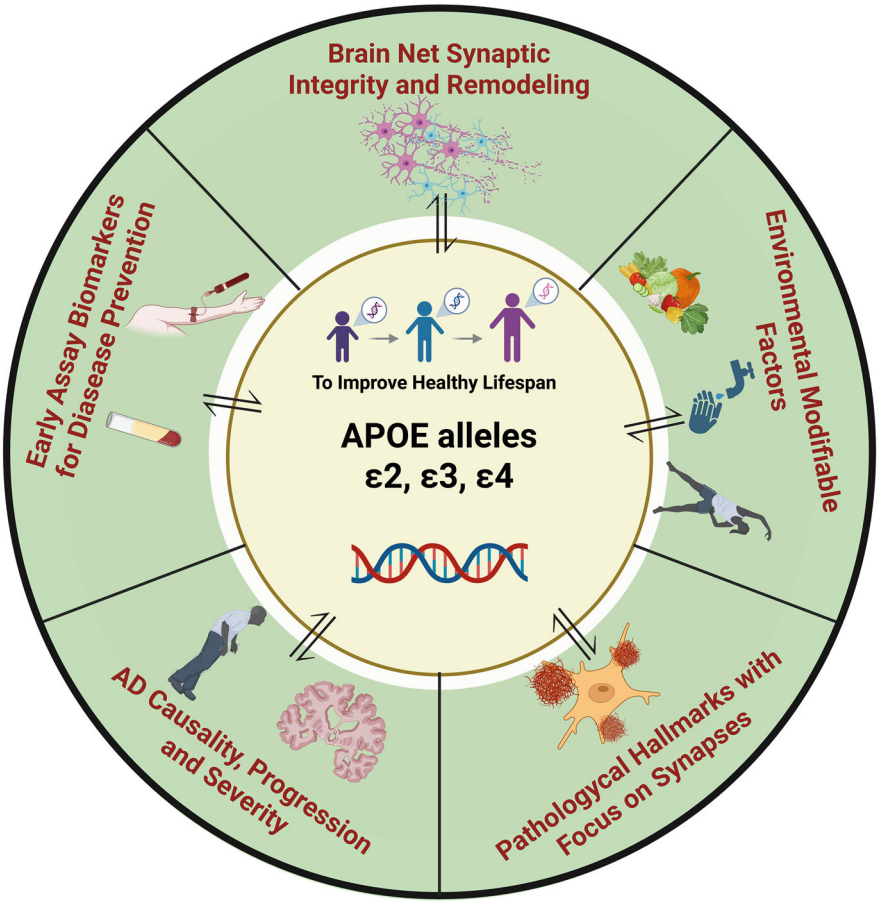

Fig. 1 Infographic of the topics reviewed by the current chapter. The interactions of the APOE alleles and other environmental factors can compound to influence the risk of Alzheimer's disease (AD) and its outcomes, mostly related to adaptations in neuroplasticity of the brain network of synaptic circuitry across the lifespan. (Created with Biorender.com)

The Chemistry of APP and Its Relationship to Neuroplasticity

APP appears to have a central role in neuroplasticity (Ashford 2002, 2023; Teter and Ashford 2002). APP is cleaved by either an alpha-secretase enzyme (ADAM-10), which leads to the production of new synapses, or a beta-secretase cleavage followed by a gamma-secretase cleavage, leading to the formation of the Abeta protein and an APP Intracellular Domain (AICD). Note, the alpha-product is not cleaved by the gamma secretase (Flammang et al. 2012). Abeta is toxic to synapses (Mark et al. 1995) and may be instrumental in removing synapses that are no longer needed or do not support the brain's perception of the external world. However, when excess APP

is produced, either by trisomy-21 (Down syndrome) or an APP-related mutation, this toxic beta-secretase/gamma-secretase product destroys an excess number of synapses, including ones not appropriate for removal, and then the excess of this protein is condensed into Abeta plaques rather than being properly removed, particularly during sleep. And when an excess of the destructive APP product occurs as in Down syndrome, the age of deposition of the Abeta protein is approximately 50 years earlier than in normal aging subjects (Rumble et al. 1989). And earlier onset (<60 years of age) also occurs in association with mutations in APP or related presenilin 1 or 2 genes (Cruchaga et al. 2012). The conundrum of considering Abeta the cause of AD is resolved by considering that the Abeta deposits are only a scar indicative of the underlying AD pathologic process.

The other APP beta-secretase/gamma-secretase product (AICD) (Sheng et al. 2012) stimulates normal phosphorylation of the TAU protein, involving the enzyme glycogen-synthase-kinase-3-beta (GSK-3b), and this normal process causes the withdrawal of the axonal terminals and dendritic spines supporting those synapses being appropriately destroyed by the Abeta mechanism. However, if too much of the AICD protein is produced, it may induce excess phosphorylation of the TAU protein (Sheng et al. 2012), leading to clogging of axons and dendrites, causing amputation (Ashford et al. 1998b) and synaptic slaughter (Coleman and Yao 2003). And when TAU is excessively phosphorylated, there is too much withdrawal of synaptic boutons. In this case, the hyperphosphorylated TAU forms paired helical filaments, which are retrogradely transported and form neuropil threads in the axons and dendrites, which amputate these critical connectors. However, many threads are pulled all the way back to the cell bodies to form neurofibrillary tangles (Ashford et al. 1998b), which eventually strangle the cell body, leading to the death of the neuron.

Thus, APP is a normal protein with a presumed central role in neuroplasticity. However, APP-related genetic factors associated with AD appear to be related to the overabundance of the beta products of APP, which includes a pathway to the formation of neurofibrillary changes, synapse loss, and dementia. In spite of the "amyloid cascade hypothesis," there is only an unclear relationship of AD cognitive impairment with Abeta deposits (Blessed et al. 1968).

The Role of ApoE in APP Chemistry, Neuroplasticity, and AD Causation

While there are many genetic factors that modify AD risk (Ashford and Mortimer 2002), the major genetic factor associated with AD is ApoE (Corder et al. 1993; Oria et al. 2024), with the ϵ4 allele likely accounting for over 50% of the cases (Raber et al. 2004). And the ApoE-ϵ4 allele affects learning in individuals at risk for AD, also impairing the "default mode network," which is associated with regions of the cortex involved in encoding information and later retrieval. If the dearth of cases associated with the protective ϵ2 allele is considered, this protein likely accounts for over 75% of the risk of AD and 90% of the cases with dementia onset before age

80 (Ashford 2008; Raber et al. 2004). The ApoE genotype is associated not only with the age of onset of AD, but also each specific ApoE genotype (ϵ3/ϵ3, ϵ3/ϵ4, ϵ4/ϵ4) is associated with the deposition of amyloid plaques 10–20 years before the onset of dementia for that genotype (Morris et al. 2010). So, there is a clear link between the ApoE gene and Abeta pathology, and similarly, the APP diathesis central to Down Syndrome and the APP-related mutations, but this link clearly indicates that the cause of AD involves APP but does not necessarily support a direct or major causative role of Abeta.

Since the ApoE-ϵ4 allele is the predominant cause of AD, the critical issue is how the various ApoE proteins influence the development of AD pathology, in the absence of an APP diathesis as seen in the rare genetic conditions, and consequently, how the management of the action of beta-secretase on APP can be controlled (Koutsodendris et al. 2022). The constant turnover of synapses associated with neuroplasticity and the role of the APP are central concerns (Huang 2024). The best explanation appears to be that the numerous brainstem neurons originating in the locus coeruleus (norepinephrine), the midbrain raphe (serotonin), and the nucleus basalis of Meynert (acetylcholine), all with long projections to the cortex (Ashford and Jarvik 1985; Garcia Rates et al. 2024; Trillo et al. 2013), are vulnerable not solely because of their length, but because of the constant turnover of synapses (Ashford and Jarvik 1985). These neurotransmitters are agents that stimulate cortical neuroplasticity and activate ADAM-10/alpha-secretase, balancing and controlling APP cleavage by beta-secretase. Loss of the norepinephrine neurons of the locus coeruleus is the first AD-related change in the brain (Bondareff et al. 1981; Braak et al. 2011; Falgas et al. 2024; Ishii 1966; Smegal et al. 2025), with serotonin losses occurring also in relationship to the developing pathology (Theofilas et al. 2018), and the acetylcholine projection losses corresponding closely to the dementia. While ApoE has an established role as a cholesterol chaperone, the ApoE-ϵ4 allele protein in longer-lived humans with large brains may be inadequate to manage the enormous volume of membrane cholesterol turnover resulting from the actions of the APP in stimulating new synapses and destroying old ones, particularly those connections associated with these long-projecting brainstem neurons, which have a central role in neuroplasticity.

Other Chemical Systems Associated with Neuroplasticity and AD

In vitro, human microglia and astrocytes are more active in phagocytosing synapses from AD patients than healthy controls via MGF-E8. Interestingly, in 3D-induced pluripotent stem cells-cerebral organoids derived from AD patients, ApoE-ϵ4 is associated with synaptic loss at week 12 following early neuronal differentiation. An earlier study showed that the ApoE/Aβ complex is found in AD cortical synaptosomes interacting with ApoE receptors in the synaptic terminals. Chung and colleagues report that ApoE isoforms differentially affect synaptic pruning by astrocytes; these authors suggest that the ApoE-ϵ4 allele reduces astrocytes' ability to remove senescent synapses tagged by C1q, a component of the complement

system (Chung et al. 2016). Such a defective effect could partly explain the synaptic dysfunction seen in the complement system-driven neurodegenerative processes that may lead to AD.

Given the high level of brain synaptic pruning that accompanies AD progression and severity, recent research initiatives to track neuron-derived extracellular vesicles (NDEVs) containing synaptic proteins in blood have been studied as potential biomarkers for developing a useful strategy for early screening for AD. Dendritic spine proteins may be a relevant choice for study, as dendritic spines are heavily affected in AD transgenic animal models. Specific dendritic spine proteins, including neurotransmitter receptors, scaffolding proteins, and signaling peptides, such as postsynaptic density protein-95 (PSD-95), may be relevant targets for monitoring. The use of these potential biomarkers of synaptic remodeling and synaptic disruption has yet to be tested in clinical studies. Still, these findings may guide customized, potential early therapeutic approaches to improved cognitive decline, even decades before AD pathological hallmarks occur, especially in ApoE-ϵ4 allele carriers.

ApoE-ϵ4 and Development of an Inflammatory Diathesis

In chapter ▶ "APOE and Proteomics in Chronic Inflammation" of this book, Artur Shvetcov and Caitlin A. Finney from the University of Sydney review the rapidly growing body of evidence on the role of ApoE genotypes in chronic inflammation. Studies conducted on large numbers of samples from plasma, cerebrospinal fluid (CSF), brain tissue, and liver demonstrate significant differences in immune signaling associated with the ApoE-ϵ2, -ϵ3, and -ϵ4 alleles. In asymptomatic ϵ4 carriers not expressing biomarkers of AD pathology, possession of one or more copies of the ϵ4 allele is associated with upregulation of cytokine signaling, interferon release, complement activation, and MHC class I-mediated antigen presentation. Further evidence for an interaction between other organ systems and the brain in the pathogenesis of AD has been provided by observations on the relationship between systemic and brain inflammation, i.e., neuroinflammation. Further, neuroinflammation and its management have been a long-studied issue in AD with substantial evidence that nonsteroidal anti-inflammatory agents may have some beneficial effect, though the actual mechanism of that effect may not be related to their anti-inflammatory mechanisms (Ashford 2020; McGeer et al. 2016).

The most common marker of systemic inflammation is C-reactive protein (CRP). For unknown reasons, carriers of the ε4 allele have lower baseline CRP levels than ε3 carriers. Two studies report that older ε4 carriers do not show symptoms of cognitive decline until their CRP levels rise acutely (Tao et al. 2018). As pneumonia is a common cause of CRP elevation in the elderly, this result raises the question of whether CRP levels should be monitored, and any infections treated as soon as possible, particularly in those at greater risk for AD. This finding argues for ApoE allele testing in older persons living in congregate settings to improve direct monitoring efforts for both systemic infections and cognitive changes.

Evolutionary pressures might further explain the robust proinflammatory responses sometimes seen in ϵ4 carriers. The ancestral ϵ4 allele has been highly preserved in isolated populations in tropical and Arctic regions with high pathogen burdens, e.g., helminths. Early humans experienced serious enteric infections that exerted evolutionary selection pressure, and factors that mitigate infant and childhood mortality from enteric infections also exert selection pressure. Pathogen-induced inflammation associated with infant and childhood diarrhea can damage the gut wall long after the invading organisms are no longer present. Inflammation not only resides in the mucosal wall but also induces systemic inflammation. ϵ4 carriers display a stronger host-inflammatory response that reduces pathogen burdens, increasing infant and early childhood survival. Evolutionary selection of the ϵ3 allele might have occurred after humans moved into temperate zones with lower pathogen burdens, unrelated to protection from Alzheimer's disease (Smith and Ashford 2023).

Elucidating Pathophysiological Mechanisms for Developing Preventive Measures for AD

Critical questions for preventing AD include how to maintain the vitality or augment the activity of brainstem neurons to stimulate the ADAM-10 enzyme appropriately to maintain a balance of the APP products, how to optimize the management of cholesterol, how to inhibit excess TAU hyperphosphorylation, and how to control neuroinflammation. A large part of this direction is efficiently removing the by-products of neuroplasticity. Also, neuro-inflammatory processes appear to be involved in the normal removal of obsolete synapses, but these processes may become excessive and need to be controlled as well. All of these issues are likely of great importance for individuals carrying an ApoE-ϵ4 gene (Koutsodendris et al. 2022).

Recommendations for Healthy Lifestyle Habits for Prevention of AD

While much discussion about the cause of AD and the pathophysiological pathway to dementia is still speculative, there is mounting evidence to support several ideas about how AD develops. Though there is not enough evidence to support any one scientific theory, there is enough evidence to discuss certain ideas with patients and to make practical recommendations (Rao et al. 2023). In the field of AD, there are several such issues that can now be brought to the clinic setting. Here are the initial ten recommendations derived from a 2002 LIAF article (Long-Island Alzheimer Foundation, www.medafile.com/TOP10-2002-LIAF.pdf), which were based on current experience treating Alzheimer patients at that time and on the associations between Alzheimer's disease and other dementing disorders. These recommendations were initially provided at the request of an individual with ApoE-ϵ4/ϵ4

genotype, and they are likely of at least equal importance for this group. Other suggestions have been added here based on scientific hypotheses and preliminary evidence. The recent, 2024, suggestions of the Lancet standing Commission mirror those of the 2002 LIAF article, with additional concerns about air pollution and hearing and vision loss, which could also be associated with impairment of activities of daily living, isolation, and loss of stimulation (Livingston et al. 2024).

1. **Take your blood pressure regularly and be sure that the systolic pressure is always less than 130.** This recommendation is based on the association between stroke and Alzheimer's disease (Snowdon et al. 1997). There are several articles relating high blood pressure to poor memory and a higher incidence of Alzheimer's disease, particularly in association with certain genes. There is also some evidence that patients taking diuretics for their elevated blood pressure develop less Alzheimer's disease. So, keep track of your blood pressure and, if necessary, make sure that it is well-treated.

   Note, 2025—this recommendation to keep blood pressure under control is still considered a primary issue but possibly related to cerebrovascular pathology.
2. **Watch your cholesterol; if your cholesterol is elevated, get treated with "statin" drugs.** Cholesterol levels are related to arteriosclerotic vascular disease, which is in turn related to heart disease and stroke. So, this is a good idea in any case. Pertaining to AD, there is evidence that brain cholesterol metabolism is controlled by the ApoE gene and is involved in the etiology of AD (Jones et al. 2010) and in this context plays an important role in memory (see chapter ► "ApoE and Brain Synaptic Dynamics" and discussion of the central relationship of cholesterol to neuroplasticity and AD). Further, two recent studies have suggested that individuals taking "statin" drugs are less likely to get Alzheimer's disease. While these findings would not warrant prescription of statin medication without cholesterol elevation, clearly these data give individuals with elevated cholesterol another reason to take their prescribed medications. A diet with reduced animal fat may also help lower cholesterol levels, and low animal fat diets may be associated with a lower Alzheimer's disease risk. However, there are also reasons to eat deep water fish (tuna, salmon, swordfish, etc.), which contain oils thought to be good for the brain.

   Note, 2025—there is some controversy about statins, and more research is needed, particularly as there is evidence that certain statins (Wolozin 2012), statins in certain individuals (Zissimopoulos et al. 2017), or related agents that help with cholesterol management may benefit those with an ApoE-ϵ4 genotype (Davidson et al. 2025). Specific dietary recommendations along these lines have become a major part of current Alzheimer's disease prevention recommendations (Grant 2024), similar to the Mediterranean and MIND diets. Also see the US-Pointer recommendations (Baker et al. 2025).
3. **Exercise your body and mind regularly.** Many studies extol the virtues of exercise, and while there are no specific links between exercise and Alzheimer's disease, there are links between exercise and health and cognition, which are

likely to benefit the synapse management of the brain. Data also suggest that people can get smarter by exercising. So, there is a logical recommendation to exercise to reduce the risk of Alzheimer's disease. But, beyond the clear benefits of exercise, there are recent theories linking insulin to Alzheimer's disease. The blood insulin level peaks about an hour after you eat. If you exercise for about 30 min after you eat, even just walking for about 15 min (for example, walking your dog), you might reduce your peak insulin level and leave the brain's insulin degrading enzyme to do its other task of breaking down the normal, toxic amyloid-beta protein after it has served its purpose.

There are some suggestions that keeping your mind active can also delay onset of cognitive impairment (Ashford et al. 2015). Further, education appears to play a significant role in delaying the age of AD onset (Butler et al. 1996). While this evidence can be challenged in various ways, it makes sense to continue seeking intellectual stimulation throughout your life.

Note, 2025—there are now numerous studies which demonstrate the benefit of exercise to reduce AD risk, potentially even frequent, short durations of exercise. And the second part of this recommendation, including socialization, has been supported with substantial evidence.

4. **Wear your seat belt; wear a helmet when riding a bicycle or participating in any activity where you might hit your head.** Many reports show a relationship between head injury and Alzheimer's disease, so playing it safe can help reduce this factor. For older individuals, reducing trip-hazards in the home and taking precautions against falling are relevant.

   Note, 2025—a related large issue has become contact sports or sports in which head injury is frequent, with specific concern about "CTE," chronic traumatic encephalopathy. Further, there is progressive concern about anyone, particularly juveniles, participating in any sports activity that can be associated with even occasional mild head trauma, particularly football and ice hockey. Also, the relationship with traumatic brain injury, especially those injuries associated with explosive blasts, particularly related to firing weapons and military combat, is being recognized as a potentially serious contributor to brain damage and cognitive impairment, and traumatic brain injury may produce worse AD-related outcomes in women (Sass et al. 2021).
5. **If you have diabetes, make sure that your blood sugar is optimally controlled.** Patients with diabetes tend to get vascular disease, and this disease itself may injure the brain. While there is no clear relationship between diabetes and Alzheimer's disease, patients who have uncontrolled blood sugars or develop insulin resistance may lose memory, and be at greater risk for suffering from dementia, either vascular or AD. And there are suggestions that medications for treating diabetes may have some role in AD prevention.

   Note, 2025—there are several indications that certain antidiabetic therapies may have long-term benefits for slowing cognitive decline in patients with AD (see below).
6. **Consult your doctor about treatment for your arthritis pain.** There have been several studies indicating that arthritis patients who take NSAIDs

(nonsteroidal anti-inflammatory drugs) have a reduced risk of Alzheimer's disease (Breitner 1996; in t' Veld et al. 2001; Rogers et al. 1996; Stewart et al. 1997). Because the risks of these drugs (especially internal bleeding) are significant, they cannot be recommended for routine prevention, though an early study suggested that an NSAID combined with a proton-pump inhibitor may be associated with decreased AD risk. However, if you have arthritis, you should seek the advice of your doctor for treatment. Other research suggests that only certain NSAIDs may prevent the development of a toxic protein from the beta-secretase by modifying the gamma secretase cleavage of APP in the brain, which can form amyloid-beta-1-42, that may be a specific contributor to the development of Alzheimer's disease (Ashford 2020). The specific NSAIDs identified with this benefit so far are flurbiprofen, ibuprofen (Motrin, Advil), sulindac (Clinoril), and indomethacin (Indocin). Indomethacin may be the most potent, and one study suggested that this drug does slow down the course of Alzheimer's disease (McGeer et al. 2016). Ibuprofen is most readily available, and sulindac is the most easily administered and has the fewest side effects.

Note, 2025—NSAID relationship to Alzheimer's disease has been supported by epidemiological research, but actual treatment of Alzheimer's disease has not been positive, possibly because treatment must begin many years before the onset of dementia, when the pathology associated with beta-amyloid is beginning, or other factors, including ApoE genotype.

7. **Take your vitamins.** There is little reason not to take supplemental vitamins after age 50, and they might even help if you have some transient deficiency in your diet, though best in consultation with a health-care professional, particularly for Vitamins folate and B12. There is general support to take extra supplements of Vitamin E (400 international units [IU]) and Vitamin C (500 milligrams [mg]) together (once per day for Alzheimer prevention, twice per day if memory problems are present, and three times per day if AD is diagnosed). These recommendations are based on the oxidation/free-radical theory of aging and Alzheimer's disease, and one large study which suggested that Vitamin E delayed specific end points for Alzheimer's disease patients by as much as 6 months. Though far from conclusive, this "neuro-protective regimen" has become a common treatment for Alzheimer's disease and is taken by many as a preventive.

   B12 and folate have also been advocated as brain-protective agents. B12 recommendations are complicated because its levels in the body are dependent on an individual's intestinal ability to absorb it. If an individual cannot absorb B12 taken orally, monthly injections can be given, though B12 is absorbed well when taken sublingually. However, these issues need to be discussed with your physician. The Recommended Daily Allowance (RDA) for folate is 400 micrograms (mcg) per day, but this dose can be increased to 1 mg per day if memory difficulty is a concern. Here again, because of the complicated relationship between B12 and folate, it is essential to discuss proper dosage with your health care professional. With recent findings showing a correlation between elevated homocysteine levels and Alzheimer's disease, B12 and folate have become even

more important because of their ability to keep homocysteine in check. Note too that alcohol and caffeine intake and tobacco use increase homocysteine levels. Your doctor may wish to check your homocysteine level.

Note, 2025—some recent studies have not fully supported this recommendation for Vitamin E. However, Vitamin D deficiency has become pervasive and is related to the development of Alzheimer's disease (Latimer et al. 2014), and this deficiency is easily treated. A causal association with Alzheimer's disease is not established and absorption and other factors could also explain the relationship. Care must be taken to measure serum vitamin D levels intermittently to ensure that enough is taken and toxicity does not occur.

8. **Discuss sex-hormone replacement therapy (HRT) with your physician (only women for now).** There are general recommendations to postmenopausal women to take HRT to reduce the risk of heart disease and improve life in a variety of ways. These hormones might reduce the risk of Alzheimer's disease. The issue is of interest because these chemicals seem to enhance the function of many brain cells. The reason to carefully consider this recommendation with a physician who specializes in this area is because there are considerations regarding risks such as breast cancer and stroke. The possible reduced risk of AD with HRT in women raises the question of whether female HRT could help elderly males as well. Certainly, men with prostate cancer should discuss this issue with their physicians.

   Note, 2025—the use of HRT for women is still of unclear benefit for preventing Alzheimer's disease, but there is still some supporting evidence, and many women feel that they have less "brain-fog" on HRT. Though the FDA has recently removed the "black-box warning" on HRT treatments, the decision for HRT should be carefully discussed with a gynecologist.

9. **If you have difficulty getting to sleep, consider trying up to 6 mg of melatonin at bedtime**. Despite little scientific evidence, melatonin, a natural substance produced in the brain, may help initiate and sustain sleep. With aging, the brain produces less melatonin, and older people sleep less. Although many people claim that melatonin helps sleep a great deal, it may be effective only in those individuals with a significant melatonin deficiency. However, melatonin is an excellent antioxidant, and there is evidence that suggests melatonin and/or sleep may prevent the formation of toxic amyloid fibrils in the brain.

   Note, 2025—sleep is good for the body and brain, and a considerable amount of recent evidence suggests that the brain's "glymphatic system" is most active at night, clears toxic chemicals from the brain, including beta-amyloid, which build up during the day, and may help to keep Alzheimer's disease pathology from developing (Galvani et al. 2024; Zhang et al. 2025a).

   Also, implementing melatonin use beneficially is somewhat difficult because the utility depends on melatonin's status in the brain, and melatonin may not be helpful if the level in the brain is adequate. Alternatively, benefit may require higher dosing or hybrid molecules to provide good sleep (Zhong et al. 2025).

   The antidepressant trazodone is currently the most widely used drug in the USA for insomnia, and there is some evidence that this medication, which is the

only sedative medication that improves deep sleep, may have an important role in preventing Alzheimer's disease (Ashford 2019b). Of particular interest, the brainstem neurons affected in AD are also related to several aspects of sleep, so sleep problems appear to be early symptomatic signs of AD (Oh et al. 2022).

10. **If you have significant difficulty with your memory, talk to your doctor about measuring your memory and a trial of a cholinesterase inhibitor.** Several drugs from this class, including donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl), have been approved by the FDA for treating Alzheimer's disease patients with mild dementia. While the primary evidence suggests that these drugs have only a modest benefit on cognition, there have been several studies that have suggested that these drugs may slow down the progression of Alzheimer's disease. These studies are only suggestive, not conclusive, but many physicians agree with this suggestion based on their own observations. Importantly, if these drugs can slow AD progression, then they may have their biggest advantage very early in the disease course. While doctors are not prescribing these drugs for preventing AD, many physicians are prescribing these drugs beneficially for patients with mild memory problems. It is possible that these drugs may become a central part of preventive therapy for Alzheimer's disease in the future.

    Note, 2025—while recent, expensive, antiamyloid therapies have been FDA approved and appear to slightly slow the progression of Alzheimer pathology, these drugs have not been tested against the significant disease slowing shown for the cholinesterase inhibitors (Daly et al. 2025), and there is a risk for brain vascular damage, particularly in those most at risk, those individuals with an ApoE-ϵ4 allele—even higher if ϵ4/ϵ4.

These recommendations are important to APOE4 carriers and should be compounded with early noninvasive biomarkers (neuroimaging, blood probes, etc.) of neurodegenerative processes for monitoring the risk and progression of AD. More studies are warranted to define more specific early nutritional and fitness interventions to improve the overall health status to APOE4 carriers versus APOE4 noncarriers. The recommendation of more long-term compliance and adherence to these measures is key for better preventive measures to these AD-prone individuals.

A summary of these recommendations is shown in Fig. 2.

More Options and Future Directions

There are several options in addition to those listed above that have been recommended for Alzheimer's disease as treatment or preventive agents. At this point, there is not enough data to make more explicit recommendations, but extensive multifactorial recommendations are being made (Grant 2024; Rao et al. 2023). For example, recommendations for turmeric and *Ginkgo biloba* remain ambiguous; coenzyme Q-10 has been recommended, but without wide support. And there is not enough evidence that aluminum is associated with Alzheimer's disease, but you

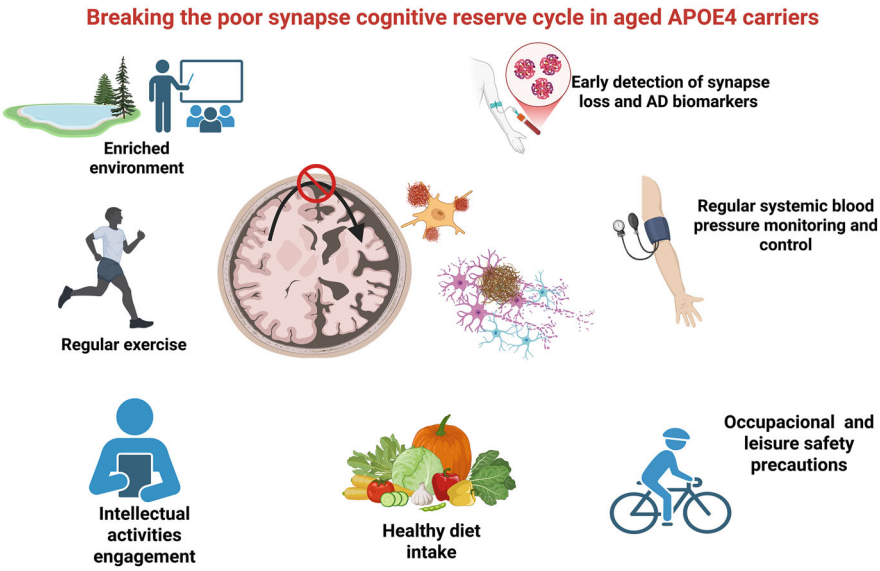

Fig. 2 Summary of recommendations for a healthy lifestyle to prevent neurodegenerative processes related to Alzheimer's disease (AD) (Angelopoulou et al. 2021; Miao et al. 2022; Vanitallie 2013). While these healthy lifestyle recommendations are of greatest importance for ApoE-ε4 carriers or other genetic risk factors, they are of potential relevance to AD prevention for all. The use of early blood biomarkers for AD (such as pTAU-217), other phosphorylated TAU markers, glial fibrillary acid protein (GFAP), etc. or combined with cognitive assessment, and/or brain imaging (Chen et al. 2025; Palmqvist et al. 2021; Tsoy et al. 2024). Synapse loss may help to identify risk or early changes suggesting the need for more aggressive prevention efforts. Environmental enrichment (especially early in postnatal life), schooling, engagement in intellectual activities, healthy diets enriched in E, D, and B complex vitamins and senolytics, regular exercise, safety precautions in occupational work and leisure activities, and systemic blood-pressure control are key protective factors that may break the cycle of lifelong degenerative processes that start even decades before AD manifests full symptoms. (Created by Biorender.com)

probably should not cook tomato sauce (or other acidic foods) in an aluminum pot. Alcohol in very low quantities may protect against heart disease and may protect against Alzheimer's disease as well, but any alcohol use has recently been linked to changes associated with AD (Durazzo et al. 2025), as well as an increased incidence of AD (and cancer).

There are many studies exploring potential new preventions and treatments for Alzheimer's disease, but the central issue is to fully understand the pathophysiology of AD. While many studies have been mired in the amyloid cascade hypothesis, it is critical to recognize that direct targeting of Abeta depositions may be helpful only for the rare APP mutations associated with early onset AD. Importantly, established pathways must be considered, particularly considering brainstem mechanisms (Garcia Rates et al. 2024). And addressing neuronal bioenergy has led to a suggestion for treatment of decreases of GTP to restore normal endocytosis and autophagy to remediate AD changes (Santana et al. 2025). Further, there are approximately

twice as many women who have AD as men, clearly related to the longer life-expectancy of women (Raber et al. 2004), but the male-female variations are also critical for determining additional modifiable risk factors (Rubin 2025).

Early Life Alzheimer Prevention Considerations

Postnatal environmental enrichment is key to brain neuroplasticity from birth and throughout the lifespan. Accumulating evidence suggests that the early exposome (the sum of biohazards one is exposed to in the environment, including pathogens, chemicals, and pollutants), especially in the first years of life, could jeopardize the gut-brain axis and increase the processes of systemic chronic inflammation and cause lasting impaired cognitive outcomes, even in a low-grade state (Oria et al. 2016; Tshala-Katumbay et al. 2015). The maturation of the intestinal microbiota is a key determinant of this process, as early life and chronic microbiota dysbiosis toward more pathogenic taxa could lead to long-term cognitive impairments and likely affect neurodegenerative diseases (Ginsberg and Blaser 2024). Interestingly, intestinal microbiota dysbiosis-influenced cerebral amyloid deposition is seen particularly in ApoE-ε4 carriers. Elevated brain Aβ burden was markedly correlated with the reduction of protective bacterial taxa and the abundance of proinflammatory bacterial populations (Wadop et al. 2025), suggesting that a gene-environmental cross talk is mediated by the intestinal microbiota with a disrupted gut-brain axis. And even air pollution has been suggested to be related to the modern epidemic of dementia (Finch and Burstein 2025). Such early protection related to ApoE-ϵ4 may later be reversed, leading to an increased risk of AD as lifestyles change and life expectancy rises with aging in countries with transitional economies facing health improvements with reduced childhood mortality, such as Brazil and other upper-middle-income countries (Lima et al. 2014; Oria et al. 2016).

Specific Considerations for AD Prevention Based on Theoretical Pathophysiology

Abeta Removal: Antibodies

Antiamyloid drugs have been approved by the FDA recently for slightly slowing the progression of Alzheimer's disease, though the degree of slowing has been unclear (Kurkinen et al. 2023), and these agents can be substantially harmful to the brain, particularly in individuals with an ApoE-ε4/ε4 genotype. Even the role of Abeta in AD treatment is controversial (Kurkinen et al. 2023). However, a recent study suggested that valiltramiprosate, a potent inhibitor of Abeta oligomer formation, decreased brain atrophy in ApoE-ϵ4/ε4 individuals (Abushakra et al. 2025).

Neurofibrillary Tangle Prevention

Clearly TAU is an important protein in the brain, involved in managing the microtubules of dendrites and axons. Hyperphosphorylation of TAU is a central problem in AD pathology and can even be detected in the blood (pTAU-217) before dementia develops. And TAU accumulation is related to Abeta burden, clearly indicating that there is an AD pathological process that needs to be understood.

There may be specific drugs now available that might slow the AD TAU neurofibrillary pathology. For example, lithium and valproic acid (Mark et al. 1995), two drugs used to treat manic-depression, may inhibit a brain enzyme (glycogen-synthase-kinase-3-beta: GSK-3b), which normally phosphorylates TAU. Some studies of manic-depressive patients taking lithium have suggested that this treatment may reduce AD risk. Reducing the activity of this enzyme could prevent the development of neurofibrillary tangles (which is the late Alzheimer pathology most correlated with dementia after synapse loss, and hyperphosphorylation of TAU leads to clogging of axons and dendrites, leading to their amputation and distal synaptic slaughter, see above). A recent study suggested that AD risk could be related to lithium deficiency (Aron et al. 2025). And another study suggested that an intranasal formulation of lithium could be beneficial for inhibiting GSK-3b (Buonerba et al. 2025). Of importance, the benefit of lithium may be best with very low doses at bedtime, for example, 150–300 mg, sustained action, which can also improve sleep (Ashford, observation managing patients in a nursing-care home). And lower but potentially helpful doses are even available over the counter. Many patients with AD, including those in very early phases, have problems with depression and paranoid ideas. These symptoms can and should be treated, but some may also benefit from a low dose of lithium. The lipid-related hormone, leptin, may have a similar effect on inhibiting GSK-3b (Greco et al. 2009). Further, lithium and stress reduction may reduce induction of TAU hyperphosphorylation (Lovell et al. 2004).

Supporting Neuroplasticity and Related Neurotransmitter Systems

Given the potential importance of management of neuroplasticity by brainstem systems, acetylcholine, norepinephrine, and serotonin, there are many suggestions and efforts to utilize therapeutic agents active in this area (Garcia Rates et al. 2024). The original question in AD treatment was based on the "cholinergic hypothesis," which led to the first attempt to treat AD (Ashford et al. 1981), and treatment of AD patients with cholinesterase inhibitors was long the only approved treatment for AD (Ashford 2015). While cholinesterase inhibitors have been referred to as "symptomatic" rather than "disease modifying," this dichotomy may be incorrect, as stimulation of cholinergic receptors may be beneficial for slowing the AD process, and these standard medications for AD patients should be directly compared with any new treatment (Daly et al. 2025), including examination of survival time (Kurkinen and Daly 2024). Further, since monoaminergic systems are also altered in AD,

consideration has been given to enhancing the activity of these systems for treating AD (Trillo et al. 2013). A related direction was the consideration of using agents to enhance norepinephrine function, such as formoterol (Dang et al. 2014). However, more importantly, the issue should be how to prevent the early damage to these systems in the first place.

Memantine (Namenda) was approved by the FDA in 2003 for the treatment of moderate dementia in AD and may significantly reduce mortality in Alzheimer's disease (Lazzeroni et al. 2013), though its specific effects on the brain have been difficult to demonstrate (Ashford et al. 2011). Memantine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist, and this receptor plays an important role in the initiation of neuroplasticity events. Memantine may stabilize cortical neurons and protect them from excess activity, particularly activities related to neuroplasticity.

Important Role of Neuroinflammatory Mechanisms

Neuroinflammation has been suspected of playing a role in dementia and AD. Clearly, inflammatory mechanisms, probably normal brain mechanisms for synapse pruning, could be overactive and remove an excess number of synapses. And anti-inflammatory drugs (NSAIDS) have been associated with less AD. And there are links between the inflammation seen in Alzheimer's disease and depression and obesity (Ly et al. 2023). However, another explanation for the benefit on NSAIDS is that some of them may modify the gamma-secretase and so prevent AD pathology (Ashford 2020; Grant 2024; Weggen et al. 2001).

Recent evidence has suggested that herpes vaccinations (to prevent "shingles") may reduce AD risk. Along these lines, CD8-T cells may play a role in AD prevention (Gate et al. 2020; Panwar et al. 2024).

Diabetes and Body-Energy Metabolism

There have been many suggestions that diabetes and insulin are related to AD (Craft 2007), and diabetic medications may reduce AD risk (Cholerton et al. 2016; Jiang et al. 2025). Further, recent studies of glucagon-like peptide 1 receptor agonists (GLP-1Ras) suggest that they may also have some effectiveness for reducing risk for neurocognitive disorders, including AD (Zhang et al. 2025b; Nance et al. 2025; Yassine et al. 2022; Xie et al. 2025). However, this issue is complicated by the relationships of body weight to vascular damage, including small strokes, as well as the dual role in the brain of the insulin-degrading enzyme for degrading Abeta. And eating a carbohydrate-restricted diet may reduce brain atrophy in patients with AD (Bramen et al. 2023).

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS, applied over premotor cortical regions, has been approved as a treatment for depression that has not responded to medications. However, there are now several

studies that have suggested that rTMS may slow or improve the dementia associated with AD (Cheng et al. 2022; Heath et al. 2025; Taylor et al. 2019). While the explanation for the benefit of rTMS for the brain is still not established, the first consideration has been that local activation would have positive effects on the frontal lobes, which is associated with depression. An additional consideration is that projections from the frontal lobes can activate brainstem mechanisms related to the benefits of the antidepressant medications that affect serotonin and norepinephrine pathways. Such stimulation could thus have a potential benefit on the brainstem neurons first affected by AD (Theofilas et al. 2015).

Direct ApoE-ϵ4 Modulation

A commonly used loop-diuretic agent, used to treat fluid retention, bumetanide (Bumex), is associated with a reduced risk of AD (Graber-Naidich et al. 2023) and may specifically modify the adverse effects of ApoE-ϵ4 and benefit carriers (Taubes et al. 2021) and be effective as an AD treatment (Boyarko et al. 2023).

There have been numerous studies of the role of cholesterol-reducing statin medications for reducing AD risk. The studies have been both positive and negative and may relate to variations in the statin molecules, sex, and race/ethnicity (Zissimopoulos et al. 2017). Given the role of ApoE in cholesterol management, this possible relationship needs to be better understood. There has been some suggestion that reducing cholesterol levels could be a key advantage of beneficial therapeutic diets, especially in ApoE-ϵ4 carriers. A recent study suggested that the benefit of statins may be stronger in ApoE-ϵ4 carriers (Rajan et al. 2024). Another study suggested that a cholesteryl ester transfer protein inhibitor, obicetrapib, may be beneficial in ApoE-ϵ4/ε4 carriers (Davidson et al. 2025).

There are other concepts which are still in research. For example, switching an ApoE-ϵ4 allele to an ApoE-ϵ2 allele is certainly an appealing idea but still in the mouse lab. There is a natural protective mechanism against AD known as the ApoE-ϵ3-Christchurch, which may induce astrocytes to promote TAU clearance, and understanding this mechanism may lead to AD-preventive therapies. Higher levels of the microglial transmembrane protein TREM2 (triggering receptor expressed on myeloid cells—2) may attenuate the adverse risk of the ApoE-ϵ4 allele and may provide another beneficial direction for treatment.

Conclusion

There are so many indications that AD might be prevented that there is hope mounting that we may be able to end or significantly delay the onset of this disease in the near future. However, the biggest factor associated with AD is aging, and ApoE-ϵ4 allele AD risk is synergistic with aging. So, the current recommendations to decrease AD risk are mostly about healthy living which should be primarily directed to those who carry an ApoE-ϵ4 allele. In addition, improving environmental

conditions (schooling, sanitation and hygiene, air pollution, balanced diets, parental care, etc.) and the exposome an individual is exposed to, especially early in life when the brain is undergoing profound neuroplasticity, are imperative for healthy brain development and for an adequate and functional cognitive and synaptic capacity to withstand the many stressors which are part of living a long life. While these recommendations all appear to be appropriate independently of ApoE genotype, new targeted approaches may turn out to be especially beneficial for those with the ApoE-ϵ4 gene. Numerous directions are developing that may specifically help to prevent Alzheimer's disease in all individuals, and there are even important developments to fully reach one's full genetic potential and cognitive abilities for long, healthy aging with good life quality.

Acknowledgments The authors would like to thank the Instituto Nacional de Saúde Cerebral (INSC) grant number 406020/2022-1 from the Brazilian National Council for Scientific and Technological Development (CNPq) and the Coordination for the Improvement of Higher Education Personnel (CAPES).

Competing Interest Declaration The author(s) has no competing interests to declare that are relevant to the content of this manuscript.

References

Abushakra S et al (2025) Clinical efficacy, safety and imaging effects of oral valiltramiprosate in APOEepsilon4/epsilon4 homozygotes with early Alzheimer's disease: results of the phase III, randomized, double-blind, placebo-controlled, 78-week APOLLOE4 trial. Drugs 85(11): 1455–1472

Alzheimer A (1907) Über eine eigenartige Erkrankung der Hirnrinde. Allg Z Psychiatr 64:146–148

Angelopoulou E et al (2021) APOE genotype and Alzheimer's disease: the influence of lifestyle and environmental factors. ACS Chem Neurosci 12(15):2749–2764

Aron L et al (2025) Lithium deficiency and the onset of Alzheimer's disease. Nature 645(8081): 712–721

Ashford JW (2002) ApoE4: is it the absence of good or the presence of bad? J Alzheimer's Dis 4(3): 141–143

Ashford JW (2008) Screening for memory disorders, dementia, and Alzheimer's disease. Aging Health 4(4):399–432

Ashford JW (2015) Treatment of Alzheimer's disease: the legacy of the cholinergic hypothesis, neuroplasticity, and future directions. J Alzheimer's Dis 47(1):149–156

Ashford JW (2019a) The dichotomy of Alzheimer's disease pathology: amyloid-beta and tau. J Alzheimer' Dis 68(1):77–83

Ashford JW (2019b) Treatment of Alzheimer's disease: trazodone, sleep, serotonin, norepinephrine, and future directions. J Alzheimer's Dis 67(3):923–930

Ashford JW (2020) Reader response: INTREPAD: a randomized trial of naproxen to slow progress of presymptomatic Alzheimer disease. Neurology 94(13):593–594

Ashford JW (2023) Neuroplasticity: the critical issue for Alzheimer's disease and links to obesity and depression. Am J Geriatr Psychiatry 31(10):867–875

Ashford JW, Jarvik L (1985) Alzheimer's disease: does neuron plasticity predispose to axonal neurofibrillary degeneration? N Engl J Med 313(6):388–389

Ashford JW, Mortimer JA (2002) Non-familial Alzheimer's disease is mainly due to genetic factors. J Alzheimer's Dis 4(3):169–177

Ashford JW et al (1981) Physostigmine and its effect on six patients with dementia. Am J Psychiatry 138(6):829–830
Ashford JW, Mattson M, Kumar V (1998a) Neurobiological systems disrupted by Alzheimer's disease and molecular biological theories of vulnerability. In: Kumar V, Eisdorfer C (eds) Advances in the diagnosis and treatment of Alzheimer's disease. Springer Publishing Company, New York
Ashford JW et al (1998b) Neuropil threads are collinear with MAP2 immunostaining in neuronal dendrites of Alzheimer brain. J Neuropathol Exp Neurol 57(10):972–978
Ashford JW et al (2011) MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia. J Alzheimers Dis 26 Suppl 3:331–336
Ashford JW, Mahoney L, Burkett T (2015) A role for complementary and integrative medicine in Alzheimer's disease prevention. J Alzheimer's Dis 48(1):13–14
Baker LD et al (2025) Structured vs self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. JAMA 334(8):681–691
Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 114(512):797–811
Bondareff W, Mountjoy CQ, Roth M (1981) Selective loss of neurones of origin of adrenergic projection to cerebral cortex (nucleus locus coeruleus) in senile dementia. Lancet 1(8223): 783–784
Boyarko B et al (2023) Evaluation of bumetanide as a potential therapeutic agent for Alzheimer's disease. Front Pharmacol 14:1190402
Braak H et al (2011) Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol 70(11):960–969
Bramen JE et al (2023) Impact of eating a carbohydrate-restricted diet on cortical atrophy in a cross-section of amyloid positive patients with Alzheimer's disease: a small sample study. J Alzheimer's Dis 96(1):329–342
Breitner JC (1996) The role of anti-inflammatory drugs in the prevention and treatment of Alzheimer's disease. Annu Rev Med 47:401–411
Buonerba A et al (2025) Lithium-charged gold nanoparticles: a new powerful tool for lithium delivery and modulation of glycogen synthase kinase 3 activity. Adv Mater 38:e13858
Butler SM, Ashford JW, Snowdon DA (1996) Age, education, and changes in the mini-mental state exam scores of older women: findings from the nun study. J Am Geriatr Soc 44(6):675–681
Chang FL, Greenough WT (1984) Transient and enduring morphological correlates of synaptic activity and efficacy change in the rat hippocampal slice. Brain Res 309(1):35–46
Chen W et al (2025) Predicting brain amyloid load with digital and blood-based biomarkers. Alzheimer's Res Ther 17(1):149
Cheng J et al (2022) Repetitive transcranial magnetic stimulation as a treatment for veterans with cognitive impairment and multiple comorbidities. J Alzheimer's Dis 85(4):1593–1600
Cholerton B et al (2016) Type 2 diabetes, cognition, and dementia in older adults: toward a precision health approach. Diabetes Spectr 29(4):210–219
Chung WS et al (2016) Novel allele-dependent role for APOE in controlling the rate of synapse pruning by astrocytes. Proc Natl Acad Sci USA 113(36):10186–10191
Coleman PD, Yao PJ (2003) Synaptic slaughter in Alzheimer's disease. Neurobiol Aging 24(8): 1023–1027
Corder EH et al (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261(5123):921–923
Cotman CW, Nieto-Sampedro M (1984) Cell biology of synaptic plasticity. Science 225(4668): 1287–1294
Craft S (2007) Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res 4(2):147–152
Cruchaga C et al (2012) Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. PLoS One 7(2):e31039

Daly T, Olluri A, Kurkinen M (2025) Treatments for Alzheimer's and the declaration of Helsinki. J Prev Alzheimers Dis 12(8):100260
Dang V et al (2014) Formoterol, a long-acting beta2 adrenergic agonist, improves cognitive function and promotes dendritic complexity in a mouse model of down syndrome. Biol Psychiatry 75(3):179–188
Davidson MH et al (2025) Effect of obicetrapib, a potent cholesteryl ester transfer protein inhibitor, on p-tau217 levels in patients with cardiovascular disease. J Prev Alzheimers Dis 13:100394
Durazzo TC, Joseff BDP, Meyerhoff DJ (2025) Low level alcohol consumption is associated with lower regional brain volume and thickness and lower choline-containing compounds and Myo-inositol levels in healthy adults. Alcohol 129:157
Falgas N et al (2024) Locus coeruleus integrity and neuropsychiatric symptoms in a cohort of early- and late-onset Alzheimer's disease. Alzheimers Dement 20(9):6351–6364
Finch CE, Burstein SM (2025) Dementia in ancient Greece and Rome. J Alzheimer's Dis 107(1): 55–56
Flammang B et al (2012) Evidence that the amyloid-beta protein precursor intracellular domain, AICD, derives from beta-secretase-generated C-terminal fragment. J Alzheimer's Dis 30(1): 145–153
Galvani F et al (2024) Protective activity of melatonin combinations and melatonin-based hybrid molecules in neurodegenerative diseases. J Pineal Res 76(8):e70008
Garcia Rates S et al (2024) Evidence for a novel neuronal mechanism driving Alzheimer's disease, upstream of amyloid. Alzheimers Dement 20(7):5027–5034
Gate D et al (2020) Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. Nature 577(7790):399–404
Ginsberg SD, Blaser MJ (2024) Alzheimer's disease has its origins in early life via a perturbed microbiome. J Infect Dis 230(Suppl_2):S141–S149
Graber-Naidich A et al (2023) Loop diuretics association with Alzheimer's disease risk. Front Aging 4:1211571. https://pmc.ncbi.nlm.nih.gov/articles/pmid/37822457/
Grant WB (2024) A brief history of the progress in our understanding of genetics and lifestyle, especially diet, in the risk of Alzheimer's disease. J Alzheimer's Dis 100(s1):S165–S178
Greco SJ et al (2009) Leptin inhibits glycogen synthase kinase-3beta to prevent tau phosphorylation in neuronal cells. Neurosci Lett 455(3):191–194
Heath AM et al (2025) Comparison of treatment schedules on cognitive effects of rTMS in the 3xTg-AD model of Alzheimer's disease. Exp Neurol 396:115551
Huang Z (2024) Evidence that Alzheimer's disease is a disease of competitive synaptic plasticity gone awry. J Alzheimer's Dis 99(2):447–470
in t' Veld BA et al (2001) Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 345(21):1515–1521
Ishii T (1966) Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. Acta Neuropathol 6(2):181–187
Jarvik L (1990) Alzheimer's original paper. Am J Psychiatry 147(1):127
Jiang C et al (2025) Impact of antidiabetic therapy on cognitive function in patients with type 2 diabetes and Alzheimer's disease: a comprehensive analysis. J Alzheimer's Dis 107(3): 1294–1303
Jones L et al (2010) Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. PLoS One 5(11):e13950
Koutsodendris N et al (2022) Apolipoprotein E and Alzheimer's disease: findings, hypotheses, and potential mechanisms. Annu Rev Pathol 17:73–99
Kurkinen M, Daly T (2024) Survival time in Alzheimer's disease: an overlooked measure of safety and efficacy of disease-modifying therapies. Adv Clin Exp Med 33(10):1039–1043
Kurkinen M et al (2023) The amyloid Cascade hypothesis in Alzheimer's disease: should we change our thinking? Biomolecules 13(3):453
Latimer CS et al (2014) Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats. Proc Natl Acad Sci USA 111(41):E4359–E4366

Lazzeroni LC et al (2013) Memantine is associated with longer survival than donepezil in a veterans affairs prescription database, 1997 to 2008. J Alzheimer's Dis 36(4):791–798
Lima AA et al (2014) Geography, population, demography, socioeconomic, anthropometry, and environmental status in the MAL-ED cohort and case-control study sites in Fortaleza, Ceara, Brazil. Clin Infect Dis 59(Suppl 4):S287–S294
Livingston G et al (2024) Dementia prevention, intervention, and care: 2024 report of the lancet standing commission. Lancet 404(10452):572–628
Lovell MA et al (2004) Induction of hyperphosphorylated tau in primary rat cortical neuron cultures mediated by oxidative stress and glycogen synthase kinase-3. J Alzheimer's Dis 6(6):659–671; discussion 673–681
Ly M et al (2023) Neuroinflammation: a modifiable pathway linking obesity, Alzheimer's disease, and depression. Am J Geriatr Psychiatry 31(10):853–866
Mark RJ et al (1995) Anticonvulsants attenuate amyloid beta-peptide neurotoxicity, Ca^{2+} deregulation, and cytoskeletal pathology. Neurobiol Aging 16(2):187–198
McGeer PL, Rogers J, McGeer EG (2016) Inflammation, Antiinflammatory agents, and Alzheimer's disease: the last 22 years. J Alzheimer's Dis 54(3):853–857
Miao Y et al (2022) Cognitive improvement after multi-domain lifestyle interventions in an APOE varepsilon4 homozygous carrier with mild cognitive impairment: a case report and literature review. J Alzheimer's Dis 89(4):1131–1142
Morris JC et al (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol 67(1):122–131
Nance N et al (2025) GLP-1RA comparative effectiveness against dementia onset relative to other antidiabetic medications in a large, multi-site cohort of patients with type 2 diabetes. Alzheimers Dement 21(9):e70621
Oh JY et al (2022) Subcortical neuronal correlates of sleep in neurodegenerative diseases. JAMA Neurol 79(5):498–508
Oria RB et al (2016) Early-life enteric infections: relation between chronic systemic inflammation and poor cognition in children. Nutr Rev 74(6):374–386
Oria RB et al (2024) Pros and cons of APOE4 homozygosity and effects on neuroplasticity, malnutrition, and infections in early life adversity, Alzheimer's disease, and Alzheimer's prevention. J Alzheimer's Dis 100(s1):S179–S185
Palmqvist S et al (2021) Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. Nat Med 27(6):1034–1042
Panwar A et al (2024) Antigen-specific age-related memory CD8 T cells induce and track Alzheimer's-like neurodegeneration. Proc Natl Acad Sci USA 121(29):e2401420121
Raber J, Huang Y, Ashford JW (2004) ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol Aging 25(5):641–650
Rajan KB et al (2024) Statin initiation and risk of incident Alzheimer disease and cognitive decline in genetically susceptible older adults. Neurology 102(7):e209168
Rao RV et al (2023) Rationale for a multi-factorial approach for the reversal of cognitive decline in Alzheimer's disease and MCI: a review. Int J Mol Sci 24(2):1659
Rogers J et al (1996) Inflammation and Alzheimer's disease pathogenesis. Neurobiol Aging 17(5): 681–686
Rubin R (2025) Trying to unravel why Alzheimer disease is more common in women. JAMA 334(16):1411–1413
Rumble B et al (1989) Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease. N Engl J Med 320(22):1446–1452
Salehi A, Ashford JW, Mufson EJ (2016) Editorial: the link between Alzheimer's disease and down syndrome. A historical perspective. Curr Alzheimer Res 13(1):2–6
Santana RA, McWhirt JM, Brewer GJ (2025) Treatment of age-related decreases in GTP levels restores endocytosis and autophagy. Geroscience
Sass D et al (2021) Sex differences in behavioral symptoms and the levels of circulating GFAP, tau, and NfL in patients with traumatic brain injury. Front Pharmacol 12:746491

Sheng, M., B.L. Sabatini, and T.C. Sudhof, Synapses and Alzheimer's disease. Cold Spring Harb Perspect Biol, 2012. 4(5):a005777
Smegal LF et al (2025) Lower locus coeruleus integrity is associated with diminished practice effects in clinically unimpaired older individuals. Neurobiol Aging 152:13–24
Smith CJ, Ashford JW (2023) Apolipoprotein varepsilon4-associated protection against pediatric enteric infections is a survival advantage in pre-industrial populations. J Alzheimer's Dis 93(3): 907–918
Snowdon DA et al (1997) Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 277(10):813–817
Stewart WF et al (1997) Risk of Alzheimer's disease and duration of NSAID use. Neurology 48(3): 626–632
Tao Q et al (2018) Association of Chronic low-grade Inflammation with Risk of Alzheimer disease in ApoE4 carriers. JAMA Netw Open 1(6):e183597
Taubes A et al (2021) Experimental and real-world evidence supporting the computational repurposing of bumetanide for APOE4-related Alzheimer's disease. Nat Aging 1(10):932–947
Taylor JL et al (2019) The effects of repetitive transcranial magnetic stimulation in older adults with mild cognitive impairment: a protocol for a randomized, controlled three-arm trial. BMC Neurol 19(1):326
Teter B, Ashford JW (2002) Neuroplasticity in Alzheimer's disease. J Neurosci Res 70(3):402–437
Theendakara V et al (2018) Transcriptional effects of ApoE4: relevance to Alzheimer's disease. Mol Neurobiol 55(6):5243–5254
Theofilas P et al (2015) Turning on the light within: subcortical nuclei of the isodentritic core and their role in Alzheimer's disease pathogenesis. J Alzheimer's Dis 46(1):17–34
Theofilas P et al (2018) Probing the correlation of neuronal loss, neurofibrillary tangles, and cell death markers across the Alzheimer's disease Braak stages: a quantitative study in humans. Neurobiol Aging 61:1–12
Trillo L et al (2013) Ascending monoaminergic systems alterations in Alzheimer's disease. Translating basic science into clinical care. Neurosci Biobehav Rev 37(8):1363–1379
Tshala-Katumbay D et al (2015) A global perspective on the influence of environmental exposures on the nervous system. Nature 527(7578):S187–S192
Tsoy E et al (2024) Scalable plasma and digital cognitive markers for diagnosis and prognosis of Alzheimer's disease and related dementias. Alzheimers Dement 20(3):2089–2101
Vanitallie TB (2013) Preclinical sporadic Alzheimer's disease: target for personalized diagnosis and preventive intervention. Metabolism 62(Suppl 1):S30–S33
Wadop YN et al (2025) Altered gut microbiota mediates the association between APOE genotype and amyloid-beta accumulation in middle-aged adults. J Neurol 272(10):670
Weggen S et al (2001) A subset of NSAIDs lower amyloidogenic Abeta42 independently of cyclooxygenase activity. Nature 414(6860):212–216
Wolozin B (2012) Statins and therapy of Alzheimer's disease: questions of efficacy versus trial design. Alzheimer's Res Ther 4(1):3
Xie Y, Choi T, Al-Aly Z (2025) Mapping the effectiveness and risks of GLP-1 receptor agonists. Nat Med 31(3):951–962
Yassine HN et al (2022) Brain energy failure in dementia syndromes: opportunities and challenges for glucagon-like peptide-1 receptor agonists. Alzheimers Dement 18(3):478–497
Zhang Y et al (2025a) DTI-ALPS index-assessed glymphatic dysfunction mediates Alzheimer's cognitive decline via amyloid-beta-dependent pathways: multimodal PET/MRI study. Eur J Nucl Med Mol Imaging 53(1):467–479
Zhang P et al (2025b) Real-world observations of GLP-1 receptor agonists and SGLT-2 inhibitors as potential treatments for Alzheimer's disease. Alzheimers Dement 21(9):e70639
Zhong YY et al (2025) Development of novel melatonin-isatin hybrids as multifunctional agents for Alzheimer's disease. Mol Divers 29:6363
Zissimopoulos JM et al (2017) Sex and race differences in the association between statin use and the incidence of Alzheimer disease. JAMA Neurol 74(2):225–232