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Review

Pros and Cons of *APOE4* Homozygosity and Effects on Neuroplasticity, Malnutrition, and Infections in Early Life Adversity, Alzheimer's Disease, and Alzheimer's Prevention

Reinaldo B. Oriá[a,*], Carr J. Smith[b], J. Wesson Ashford[c,d,*], Michael P. Vitek[e] and Richard L. Guerrant[f]
[a]*Department of Morphology, Laboratory of Tissue Healing, Ontogeny, and Nutrition, School of Medicine, Institute of Biomedicine, Federal University of Ceara, Fortaleza, Brazil*
[b]*Society for Brain Mapping and Therapeutics, Pacific Palisades, CA, USA*
[c]*War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto, CA, USA*
[d]*Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA*
[e]*Department of Neurology, Duke University Medical Center, Durham, NC, USA*
[f]*Department of Medicine, Division of Infectious Diseases and International Health, School of Medicine, University of Virginia, Charlottesville, VA, USA*

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Abstract. Fortea et al.'s. (2024) recent data analysis elegantly calls attention to familial late-onset Alzheimer's disease (AD) with *APOE4* homozygosity. The article by Grant (2024) reviews the factors associated with AD, particularly the *APOE* genotype and lifestyle, and the broad implications for prevention, both for individuals with the lifestyles associated with living in resource-rich countries and for those enduring environmental adversity in poverty settings, including high exposure to enteric pathogens and precarious access to healthcare. Grant discusses the issue of *APOE* genotype and its implications for the benefits of lifestyle modifications. This review highlights that bearing *APOE4* could constitute an evolutionary benefit in coping with heavy enteric infections and malnutrition early in life in the critical formative first two years of brain development. However, the critical issue may be that this genotype could be a health concern under shifts in lifestyle and unhealthy diets during aging, leading to severe cognitive impairments and increased risk of AD. This commentary supports the discussions of Grant and the benefits of improving lifestyle for decreasing the risks for AD while providing further understanding and

*Correspondence to: Reinaldo B. Oriá, Department of Morphology, Laboratory of Tissue Healing, Ontogeny, and Nutrition, School of Medicine, Institute of Biomedicine, Federal University of Ceara, Fortaleza, Brazil. E-mail: oria@ufc.br and J. Wesson Ashford, Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, USA. E-mail: ashford@stanford.edu.

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modelling of the early life benefits of *APOE4* amidst adversity. This attention to the pathophysiology of AD should help further elucidate these critical, newly appreciated pathogenic pathways for developing approaches to the prevention and management in the context of the *APOE* genetic variations associated with AD.

Keywords: Alzheimer's disease, *APOE*, Apolipoprotein E, malnutrition, neuroplasticity, prevention

In a 1993 *Science* article, Corder et al.[1] published the observation that Alzheimer's disease (AD) risk increased with increasing gene dose of the ε4 allele of apolipoprotein E (*APOE4*). In the 30 years since Corder et al.'s initial report, researchers have supported this initial observation in a series of studies, although of significantly smaller numbers of AD cases than the recent publication by Fortea et al. (2024).[2] While the publication of Fortea et al. represents a significant contribution to the field, the contention that *APOE4/4*-associated AD differs in neuropathology or etiology is not supported by that paper, the literature or by clinical experience.

By contrast, the article by Grant (2024)[3] addresses the numerous lifestyle issues that are clearly related to AD risk. Grant addresses the nature/nurture debate that occurred in 2002[4] and has been at the center of understanding AD and developing measures to prevent AD. What is now clear is that it is likely that more effective strategies to prevent AD need to involve attention at least to *APOE* genotype for modifying lifestyles to reduce AD risk and possibly prevent it.

A critical question raised by the Fortea et al. paper is whether there are different types of AD, and this question has been addressed extensively.[5] True to the original description by Alzheimer (1907),[6] essentially identical pathology is found in Down syndrome,[7] the early onset familial cases,[8] numerous other rare mutations,[9] and the *APOE* genotype observations. These diverse causes of pathological AD suggest that the critical neuropathological issue centrally involves the amyloid-β protein precursor (AβPP)[8], though *APOE* clearly has an interaction with AβPP which appears related to its role in AD.[10] However, since AD is fundamentally a disorder of neuroplasticity[11,12] and memory processing,[13] to understand AD pathophysiology, it is necessary to appreciate the role AβPP plays in neuroplasticity and how *APOE* is involved. The actual AD pathological process more likely involves an imbalance of AβPP management by specific neural interactions,[10,14–16] which are related to the encoding of new memory. While extensive study of synaptic plasticity shows an interaction between the *APOE* protein and AβPP in the management of synapse formation and removal,[17–19] the actual pathological process is less likely related to a random turnover of synapses but more likely due to a failure of brainstem projections to orchestrate encoding-related interactions within complex cortical networks.[11,14,20]

Though AD is a complex process involving at least two major proteins, AβPP and ApoE, an important issue is aging,[21] which is a stress for all living systems. In the case of *APOE* genotype, a major point is the relation of age to dementia onset,[1,2,22] and in all variations of AD, the amyloid-β (Aβ) protein deposits develop decades before dementia onset in direct proportion to ε4/ε4, ε3/ε4, ε3/ε3 status.[23] However, Aβ deposition is not clearly related to dementia in any condition, while pathological microtubule-associated tau protein (tau) deposition, which develops much later, is closely related to dementia severity. But, it is loss of synapses which is most closely and directly related to the severity of dementia,[24] and the synapses are likely lost due to the development of neuropil threads of tau inside axons and dendrites,[25] leading to "synaptic slaughter.[26]" So, questions then arise as to how the ApoE proteins interacts with AβPP to subserve neuroplasticity over a long period of time, and how the interactions, particularly those related to long projecting axons from the brainstem, break down leading to AD pathology.

Before delving into the relative advantages and disadvantages of the AD *APOE* allelic combinations, it should be noted that until 300,000 years ago, ancestors of modern humans were ubiquitously ε4/ε4 and then the ε3 allele mutated from the ancestral ε4 allele.[27] The ε3 allele displayed a competitive survival advantage sufficiently robust to result in the current predominance of the ε3 allele, which occurs in about 95% of the US population and the ε3/ε3 genotype which is now found in over 60% of the US population.[28] The basis for this major genetic change could be related to a variety of factors, including protection from memory loss and dementia in progressively older age ranges. However, it is more likely that changing life styles associated with this period

of human history and developments of civilizations and agrarian societies led to the success of ε3.[29–32] Similarly, the ε2 allele mutated from the ε3 allele about 200,000 years ago, but this protective allele has remained relatively rare with the homozygous ε2/ε2 variant less than 1%, and the ε3/ε2 heterozygote in about 11% of the population.[33]

Increased attention to *APOE4* carriers, those with ε4/ε4, which represents 2% of the US population and approximately 15% of the AD patients and ε3/ε4, which represents 21% of the population and 41% of the AD patients,[4] sets the stage for population screening and precision medicine strategies, including early genetic interventions and targeting of biologically important genes. Individualized clinical follow-up and customized treatment approaches can be envisioned. With the aid of genetic counseling, individualized therapies might mitigate AD symptoms even before their onset in *APOE4/4* and *APOE3/4* patients. The complex multisystemic pathophysiology of AD includes numerous brain changes even decades before more severe memory loss develops, including amyloid build-up,[23] loss of brainstem neurons projecting to the cerebrum,[11,14,20] as well as chronic inflammation.[14,34] And signs of mild cognitive decline unfold well before severe memory loss, dementia diagnosis, and devastating erosion of the quality of life.[35] In a subset of the AD patient population, identifying genetic cause-and-effect markers of late-onset AD is a necessary step towards potentially reducing the burdensome medical care costs for patient and family members and improving longevity and daily-basis health measures.

Although *APOE4* homozygosity and heterozygosity are disadvantageous in developed societies, field studies have highlighted a potential neuroprotective effect of the *APOE4* allele in children afflicted by heavy diarrhea and malnutrition morbidities early in life (as occurred in most of the population over millennia up to the last 2–3 generations).[31,36–39] These findings have been supported by several studies, including data showing *APOE4*-related improvements in fertility rates (with increased number of offspring and reduced interbirth intervals), innate immunity, and cognition in remote Bolivian hunter-gatherer populations, distressed by ubiquitous parasitic infections throughout the lifespan.[40]

One consideration is that *APOE4* may be considered an antagonistic pleiotropic gene favoring survival in harsh and adverse environmental conditions early in life.[21,32] The protective effects could occur by *APOE4*-driven increases in blood cholesterol levels[41] that underlie support for synaptogenesis under adverse conditions, facilitating breastmilk intestinal absorption and defensive innate inflammation under early life stresses of malnutrition and frequent enteric infections.[42] In addition to enhancing protective inflammatory and potential host nutritional benefits, one presumed *APOE4* benefit would be shifting intestinal cholesterol from the cholesterol-feeding parasites to feeding the highly plastic growing brain, as many parasitic microorganisms rely on host cholesterol to thrive.[43] This trade-off of *APOE4*-mediated cholesterol rise may be key for innate immunity against infectious pathogens.[44] In advanced aging, these same pro-inflammatory genes might trigger early AD neurodegeneration. Such a "double-edged sword" effect was highlighted in an opinion article in the *New York Times* by Moises Velasquez-Manoff in June 2017, called "The upside of bad genes". This article raised awareness about the complexity of stereotyping genes as "bad or good . . . ", as genetic adaptations are selected to cope with different environmental conditions, stressors, and lifestyles.[15]

Previous suggestions have provided several examples of the "evolution of evolution" and how historically advantageous traits can change over time and living conditions into primarily disadvantageous traits that challenge healthy survival.[45] One might even postulate that, in addition to sickle cell hemoglobin and *APOE4*, such broader traits as aggressive behavior were once more advantageous to survival but are now becoming only dangerous risks to healthy survival.[45,46] With an improved understanding of the pathogenetic pathways now popularized by Fortea's group's work, there is hope for not only improved understanding and approaches for treating later-life cognitive decline but also for elucidating the potential mechanisms of benefit of *APOE4* in malnourished and chronically infected children whose early life is lived in poverty.

The unacceptably large contingent of children living in poor settings of the developing world who survive infant mortality only to face significant physical and cognitive impairments and be severely afflicted by environmental enteropathy and intestinal malabsorption of key nutrients should motivate the search for solutions. These children may gain an advantage with *APOE4*,[31,37] but later in life, under nutritional transitions to Western, cholesterol-

enriched diets, they may become more likely to develop overweight/obesity, hastening the early progression of AD well ahead of the expected timetable of AD pathophysiological events.[34] AD is specifically a condition of neuroplasticity, which leads to severe synapse loss[11,12,14] and ApoE-related cholesterol is considered an important factor for synaptogenesis.[18,19,46] Functional synaptogenesis is fundamental to brain development and maintenance throughout the lifespan,[17] and different *APOE* genotypes interact differently with AβPP in the context of synaptic plasticity.[47] However, it is critical to understand that the AD attack is on neuroplasticity, which involves the brain's complex machinery for managing information, which includes the neurons of both the brainstem and cortex involved in memory formation with their axons, and dendrites and the supporting glial cells, and all require substantial resources whose compromise leads to AD.[14]

The critical time window of first-year brain development is the same crucial period of potentially devastating high exposure to enteric pathogens (with or without overt diarrhea) in poor hygiene and sanitation settings. These exposures often coexist with early discontinuation of breastfeeding amidst inadequate nutrition and enhanced contact with contaminated water and food. The status of the intestinal microbiota, from a diverse and mature ecosystem to a more pathogenic and immature community of microorganisms, may play a critical role in the degree to which different exposures may undermine optimal brain development early in life and increase future susceptibility to early AD decrements in *APOE4* subjects.[48] The intestinal microbiota is recognized as strongly influenced by the *APOE* background both in humans and in experimental mice[49] and may also affect cholesterol absorption from the diet.

Another critical area for research is the potential crosstalk between *APOE4* and malnutrition/enteric infections, creating a vicious cycle in the first years of life with early gut and brain senescence drivers. Senescent cells are considered apoptotic-resistant and long-living cells that change their phenotype towards a more pro-inflammatory status, releasing many tissue-damaging cytokines and chemokines,[50] such as IFN-γ, IL-8, and IL-6. Of note, such inflammatory factors are important Th1 effector cytokines against *Cryptosporidium parvum* and other enteric parasites. *C. parvum* is a common protozoan associated with environmental enteropathy and poor growth and cognition in children. Indeed, *APOE* targeted replacement (TR) mice expressing the human *APOE4/4* gene are relatively protected against the gut pathology and intensity of infection with *C. parvum* infection. In addition, *APOE4/4*-TR mice have increased ileal CAT-1, arginase-1, and TLR9 transcripts relative to *APOE* knockout.[51] The exposome of pathogens early in life may drive chronic and low-grade brain neuroinflammatory conditions that may be sustained throughout the lifespan. Such senescent cells may be induced and persist even during childhood by early life stressors.[52] The breakthrough discovery of potential senolytic compounds that selectively target these cells could open new avenues of innovative nutritional and pharmacological therapies for the neuroprotection of *APOE4* carriers even before neurodegenerative processes start. Interestingly, there are beneficial effects of selected ApoE-mimetic peptides in different intestinal and brain injury models. Some ApoE-mimetic peptide effects are related to the SET-associated anti-inflammatory pathway, with augmented PP2A-mediated phosphatase activity.[53] It is important to determine whether such ApoE peptides possess senolytic activity in addition to the recently reported antimicrobial effects,[54] which may further improve the gut-brain axis. Furthermore, the pursuit of potential senolytic and anti-aging nutrients, with gut-brain trophic actions, such as alanyl-glutamine, taurine, curcumin, and flavanols could be used to ameliorate deleterious effects of senescent cells and their senescence-associated secretory phenotype mediators in children living in adverse environments. The discovery of novel senolytic compounds with antimicrobial effects could be particularly important in children with intestinal dysbiosis and enteric infections concomitant with unhealthy diets.

An important challenge remains to balance the strong inflammatory response needed to fight against infectious pathogens without damage-related over-inflammatory responses. Due to the recurrence of enteric infections in the first years of life of children living in contaminated environments, senescent cells may arise to enhance innate immunity. In contrast, these cells may be harmful once the infectious process has ceased and as the individual ages, with their persistence in the gut, brain, and immune system possibly accelerating AD-related events. Long-term malnutrition may be a critical factor in jeopardizing the immune system's ability to remove senescent cells.

Also it is important to highlight the breakthrough discoveries of the roles of meningeal and nasopharyngeal lymphatic vessels,[55] which play a crucial role in

brain-periphery immune-mediated interactions that may occur during enteric infections and malnutrition early in life. The trafficking of peripheral senescent T cells (or other immune cells) to brain meninges may adversely impact cognition, which *APOE4* may influence under such circumstances. We do not know whether such T cells may find lasting local residence in the meninges leading to disruptive behaviors and contributing to neuropsychiatric and neurodegenerative disorders later in life. Studying the brain microbiome under *APOE4/4* could also be instrumental in understanding how intestinal microbes translocate in an affected leaky intestinal barrier to the bloodstream and the brain. Accordingly, there is a need to understand and assess blood circulating exosomes from gut and brain-derived senescent cells as potential biomarkers for early neurodegenerative changes in *APOE4* carriers.

Intelligent-population-based screening approaches, predictive blood-based biomarkers of AD, and early senolytic interventions could be important tools in precision and preventive medicine to efficiently address health issues that *APOE4* carriers may cope with during their lifespan, especially for those individuals living under impoverished conditions. Poor accessibility to healthcare and low socioeconomic status are additional complications potentially associated with prolonged, costly treatments for AD. Hence, these strategies should address the causal effect of *APOE4* interactions with the intestinal microbiome, gut-brain senescence, and malnutrition-infectious disease pathogens under environmental-specific conditions. Hopefully, the results of these studies will predict and redirect the trajectory of developmental decrements, protect the gut-brain axis, and move forward to achieving full physical and cognitive potential across every individual's lifetime. Tracking complex environmental interactions early in life is key to defining optimal intervention strategies in long-term health assistance for *APOE4* carriers.

The paper by Grant[3] outlines the many lifestyle and environmental factors that are associated with AD risk. Of great importance outlined here is the need to determine the precise role of various genetic factors in the development of these risks. Once the specific interactions of the genes and lifestyle/environment (nature/nurture) are understood, the hope is that there can be substantial reduction in AD risk regardless of *APOE* or other genotype, if not a large degree of prevention. And a realistic issue is substantial delay of AD presentation, which would overall decrease the number of AD cases worldwide and provide more years of dementia-free life.

In summary, the validation and review of many earlier studies by the timely Fortea et al.[2] and Grant[3] papers should encourage new research opportunities in the AD field and raise new questions about how *APOE4* carriers are affected under adverse environments and how knowledge of *APOE* genotype can lead to effective AD prevention strategies. The relevance of these findings is not restricted to the elderly but is also critical in early life when developmental trajectories involve the vicious cycle of malnutrition and early childhood enteric infections in impoverished settings. Still, as outlined by Grant, there are also many variations in the Western lifestyle that are related to AD development which can potentially be modified, likely more successfully with attention to genetic factors.

AUTHOR CONTRIBUTIONS

Reinaldo B. Oria (Conceptualization; Funding acquisition; Writing – original draft); Carr J. Smith (Conceptualization; Writing – original draft); J. Wesson Ashford (Conceptualization; Writing – review & editing); Michael P. Vitek (Conceptualization; Supervision; Writing – original draft); Richard L. Guerrant (Conceptualization; Validation; Writing – original draft).

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CONFLICT OF INTEREST

The authors declare no competing interests. Dr. M. P. Vitek is a principal in Cognosci Inc., which has ownership rights to selected ApoE-mimetic peptides. Drs. Carr J. Smith and J. Wesson Ashford are Editorial Board Members of this journal but were not involved in the peer-review process of this article, nor did they have access to any information regarding its peer-review.

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