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REVIEW ARTICLE

How *APOE4* Interacts with Biological Sex and Cognitive Differences to Shape Cognitive Decline in Alzheimer's Disease

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ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disorder that is the cause of around 70% of cases of dementia, affecting memory, thinking, and behavior. One of the most widely recognised genetic risk factors is the presence of the Apolipoprotein E epsilon 4 (*APOE4*) gene variant, which significantly impacts brain structure, cognitive decline, and inflammation within the brain. Growing literature proposes that sex differences - including different cognitive patterns, hormonal changes, and sex genes influence how the *APOE4* gene affects the brain. This review explores how the *APOE4* gene variant increases the risk of AD and how cognitive differences and biological sex influence this relationship. Previous studies have utilised functional Magnetic Resonance Imaging (fMRI) to focus on key brain regions and explore how *APOE4* affects the hippocampus and prefrontal cortex, which are essential for memory and cognitive functions. Moreover, further research has considered how menopause and estrogen contribute to negative progression in women. This paper argues that sex based genetic and cognitive factors change how the *APOE4* gene variant expresses itself in the brain, leading to differences in AD progression and symptoms. These findings can shape future research and guide upcoming clinical approaches and treatment strategies towards sex specific AD diagnosis.

KEYWORDS: Genetics, Neurogenetics, Alzheimer's Disease, Cognitive Decline, Cognitive Functions, Sex Differences, Inflammation.

Introduction

Alzheimer's disease (AD) is one of the most common causes of dementia globally and among the most severe and complex neurodegenerative brain disorders, with factors such as genetics and biological sex that contribute to the development of the disease.[1] Nonetheless, one of the strongest known genetic risk factors for late-onset Alzheimer's disease is the Apolipoprotein E epsilon 4 (*APOE4*) allele, which contributes to earlier cognitive decline. Similarly, homozygous carriers of the *APOE4* gene variant have a significant likelihood of developing AD.[2] Researchers estimate that people who carry two *APOE4* copies have up to 60% chance of developing dementia by age 85.[3] However, the latest research has underlined the influence of biological sex and cognitive abilities of individuals with AD. Several studies suggest that biological sex has a significant impact on the expression of *APOE4*.[4] Furthermore, women with *APOE4* experience greater brain shrinkage, increased amyloid buildup, and faster memory decline compared to men with the same genes. Researchers suggest that hormonal influences, such as estrogen and menopause, relate to *APOE4* and contribute to heightened risks. In addition to that, neuroimaging methods such as fMRI have displayed patterns in hippocampal and prefrontal cortex activity in cognitive function and brain structure due to the influence of *APOE4* and biological sex. Although thorough research has been conducted on *APOE4* as a genetic risk factor, there is limited understanding of how sex-specific factors interact with *APOE4* to impact the development of AD. This reveals a significant gap in awareness that this paper aims to address.

Ultimately, the *APOE4* gene increases the risk of developing Alzheimer's and significantly increases the symptoms due to its influence on cognitive function, brain structure, and brain inflammation. Moreover, these effects can differ due to gender because of hormonal differences, which can worsen symptoms, vary cognitive patterns, and lead to differences in diagnosis between males and females. This analysis examines how the *APOE4* gene variant increases the risk of Alzheimer's disease (AD) and the risks contributed by cognitive differences and biological sex. The interaction between *APOE4* and the influence of sex-specific factors will be investigated, such as hormonal changes, brain structure, and function. Moreover, it is vital to investigate how the interactions between *APOE4*, cognitive function, and biological sex could contribute to specialised diagnosis and treatment approaches, which could lead to significant progress in medicine for Alzheimer's care.

This paper reviews existing literature on *APOE4* and its role in Alzheimer's disease, focusing on key biological factors influenced by *APOE4*, including amyloid-beta and tau pathology, as well as neuroinflammation and brain structure. It will then examine how these processes interact with sex-specific variables such as hormonal changes, like estrogen decline, and cognitive differences. Therefore, this paper will investigate the knowledge gap regarding how sex differences influence the relationship between *APOE4* and Alzheimer's disease risk.

Biological effects of the *APOE4* gene

The effect of the *APOE4* gene variant on the brain, such as neuroinflammation, amyloid-beta accumulation, tau protein, and structural brain changes, has been extensively evaluated. Evidence suggests that the *APOE4* gene variant contributes to these factors, which increase the risk of Alzheimer's disease (AD). [5]

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The APOE gene codes for the making of a protein called apolipoprotein E. A particular allele known as *APOE4* poses the most significant genetic risk for Alzheimer's disease. APOE is a specialised protein that aids in the transportation of lipids in the brain. Compared to alternative alleles - APOE2 and APOE3, the *APOE4* allele is associated with greater risk factors and severe outcomes. Studies have revealed that the *APOE4* gene has correlations with amyloid-beta accumulation, increased levels of tau protein, neuroinflammation, synaptic impairment, and damage to memory regions such as the hippocampus.[5]

Research suggests that the *APOE4* gene variant is found in more than 40% of the population with AD, although this gene occurs in around 15% of the global population.[5] Research underlines that the gene variant and being biologically female are often linked to a higher risk of developing AD.[5] However, even though APOE is a major contributing gene to Alzheimer's, several genes are linked to cholesterol metabolism and cellular transport. These include Clusterin (CLU), Bridging integrator 1 (BIN1), and the ATP-binding cassette transporter A7 (ABCA7) genes, which have all been identified in genome-wide association studies (GWAS).[6–10] Moreover, APOE plays a significant role in the central nervous system (CNS) by transporting cholesterol and beta amyloid between brain cells. Because of this, the ε4 allele is the most notable genetic risk factor for late-onset Alzheimer's disease (LOAD).[11]

APOE4, Amyloid-Beta, and Tau pathology:

One of the most validated and studied biological effects of the *APOE4* gene variant is its contribution to facilitating amyloid-beta accumulation in the brain and the influence of tau protein in the progression of AD. The interaction between APOE and amyloid β (Aβ) plays a key role in AD pathogenesis. *APOE4* increases the aggregation and clearance of Aβ. This contributes to the development of amyloid plaques and tau-related pathology. This Aβ deposition worsens neurodegeneration and disrupts brain cell communication. Aβ deposition refers to amyloid-beta proteins accumulating in the brain, assembling plaques that can damage cells. This, therefore, contributes to memory loss and other symptoms of AD. Research shows that people with the *APOE4* allele have higher Aβ buildup and more amyloid plaques in their brains compared to others with different gene variants of APOE.[12] Similarly, studies show that there is a negative correlation between APOE and Aβ levels, meaning lower APOE levels are related to higher Aβ levels in various regions of the brain in individuals without dementia. Furthermore, animal-based studies utilised mice that express the human *APOE4* and APOE3 gene. Findings show that *APOE4* impacts key stages in the amyloid process, such as increasing Aβ accumulation, where the effects are observed to be stronger for *APOE4* compared to APOE3 and APOE2. Ultimately, these findings suggest that *APOE4* contributes significantly to controlling Aβ buildup and is therefore important in AD development.[12]

While *APOE4* is known for increasing Aβ accumulation, it also has a notable effect on tau protein, which is another vital feature of Alzheimer's disease. Tau facilitates the stabilization of structures inside the brain. However, in AD, *APOE4* worsens tau pathology by promoting hyperphosphorylation, which forms tangles, leading to cell death and cognitive decline. Animal studies have demonstrated that tau hyperphosphorylation can result in neurodegeneration, indicating that tau is harmful to neurons and plays a major role in Alzheimer 's-related brain damage. This impact has been seen in various mouse models, where mice are engineered to express human *APOE4* mainly in astrocytes and neurons.[12] In addition, research has shown that *APOE4* escalates the spread of tau tangles, which can cause impairment in areas related to memory, like the hippocampus. In addition to this, while amyloid-beta and tau proteins are significant factors in Alzheimer's disease pathology, another key feature influenced by *APOE4* is neuroinflammation.

APOE4 and neuroinflammation:

APOE4 also leads to increased neuroinflammation, which can potentially stimulate neurodegeneration within individuals dealing with AD. Neuroinflammation is the brain's immune response and helps the brain protect itself from pathogens and pathological states such as AD. *APOE4* is known to increase inflammation in the brain by affecting how immune cells like microglia and astrocytes behave and interact with each other. A study found that the relationship between activated microglia and complement proteins with AD-related brain damage, as well as data obtained from people with rheumatoid arthritis who take anti-inflammatory medication regularly, is less likely to develop Alzheimer's, highlighting that neuroinflammation plays a role in the disease's development.[3] Moreover, previous studies show that APOE co-localises with microglia in the brain, illustrating the gene's role in the brain's immune response. *APOE4* triggers microglia to become overactive, causing them to release toxic chemicals that damage neurons, which can potentially lead to rapid cognitive decline.[3] Further studies provide evidence that female *APOE4* carriers display distinct gene expressions within excitatory neurons and astrocytes, which influence cognitive decline. These findings signify that females may be more vulnerable to *APOE4*-related neuroinflammation and degeneration within the brain. One possible explanation for this is hormonal changes, specifically a decline in estrogen levels during menopause in women. This can increase AD risk in women due to an increase in amyloid-beta buildup, disrupted glucose metabolism, and chronic inflammation.[2] Lastly, several studies have found a strong association between physical activity and an improvement in cognitive function and ability.[1] This is because movement can lower the risk of dementia by promoting oxygen supply to the brain and increasing the growth of neurons, which ultimately decreases inflammation and lowers the risk of AD development.[1] Although inflammation can severely impact the brain, *APOE4* also interferes with the structure and function of neurons and neuronal pathways in the brain that are vital for cognition and memory.

APOE4 and brain structure:

APOE4 can lead to structural deformations in the brain, especially in memory-related regions such as the hippocampus,

which can disrupt function. The *APOE4* allele is associated with early and progressive structural changes in the brain, particularly in regions that control memory and cognition. In addition, the hippocampus is essential for memory, learning, and emotion. Several studies suggest that *APOE4* carriers have smaller hippocampus volumes, leading to memory decline. Moreover, the prefrontal cortex (PFC) is involved in executive functions such as attention regulation, memory processing, and response inhibition. Individuals with *APOE4* regularly display reduced grey matter in the PFC. Overall, *APOE4* reduces synaptic plasticity, making neurons in these brain areas more vulnerable to damage and susceptible to cognitive decline. [11]

Brain structure and function can significantly vary due to biological sex, as it is generally influenced by chromosomes and hormones, as well as social and cultural differences. Prior research supports the idea that behavior differs between men and women.[11] Previous studies have used MRI to show these differences, and the results suggest that men tend to have larger amygdala and thalamus, whereas women generally have larger hippocampus. These sex based differences in brain structure and cognitive function are more evident in older adults and can be the reason for an increase in the risk and development of AD.[11] In a current study, Ingalhalikar *et al.* established a prominent difference in cognition and connections between the two sexes. Diffusion-based MRI was used to study a population of 949 young people ages 8-22. The data collected suggested that male brains are wired for intra-hemispheric communication, meaning connections within each hemisphere. On the other hand, female brains are optimised for inter-hemispheric communication (connection between hemispheres). These wiring patterns within the brain emerge early in development and continue to develop throughout adulthood. This proposes that male brains are more suited for perception and collaborative processes, while female brains are adapted for stronger communication between logical and intuitive thinking.[11] Understanding these biological impacts defines the role of *APOE4* in Alzheimer's disease, particularly with the contribution of biological sex differences and hormonal changes, which will be covered in the following section.

Ultimately, *APOE4* significantly increases the risk of developing Alzheimer's disease through factors such as amyloid-beta accumulation, structural degeneration of brain regions, and chronic inflammation. Nonetheless, future research should consider how biological sex can alter these effects regarding hormonal changes, estrogen levels, and menopause.

■ Sex-Based Differences in Alzheimer's Progression

Biological sex considerably influences the risk and progression of Alzheimer's disease, particularly in individuals carrying the *APOE4* allele. Female *APOE4* carriers experience more extreme side effects than men with the same allele. Evidence shows that women face greater cognitive decline and more severe symptoms, resulting from hormonal differences and brain structure and function.

Even though Alzheimer's disease can severely affect both males and females, studies suggest that women are more greatly impacted, especially those who carry the *APOE4* gene variant.[2] This can potentially be linked to female hormones such as estrogen, post-menopause hormonal changes, and sex-specific reasons for brain ageing. Alzheimer's disease (AD) is the most common cause of dementia globally,[2] where females make up approximately two-thirds of AD cases worldwide.[11] Over the following years, the number of cases is projected to increase. At age 65, the risk of developing AD is 21.2% for women compared to 11.6% for men, meaning women are on average 2 times more likely to develop Alzheimer's.[1] Biological sex differences - the XX and XY chromosomes play a key role in shaping the brain, which leads to differences in how males and females experience cognition.[11] Moreover, the key findings of a study highlight that the progression of early onset (EOAD) and late onset (LOAD) AD are severely modified due to sex and *APOE4* status.[5] Figure 1 illustrates how sex-related factors and *APOE4* interact to facilitate differences in brain resilience and cognitive decline.

Female *APOE4* carriers experience faster cognitive decline and more severe neurodegenerative changes.[5] Females deteriorate faster than males in language, delayed memory, and cognitive function, implying how sex influences the speed at which cognitive decline can progress.[5] It is also important to highlight that the correlation between *APOE4* and AD is stronger in females than in males who carry the same gene. This accentuates that the presence or absence of sex specific hormones may influence how *APOE4* contributes to the disease progression.[3] Another cross-sectional study involving 1246 cognitively normal participants aged 30-95 assessed memory function by focusing on sex and *APOE4* status. Results showed that even though memory was shown to decline and hippocampal volume shrank with age, it was highlighted that women *APOE4* carriers face a greater vulnerability to AD-related changes within brain structure and function and are therefore more prone to cognitive decline.[11] In addition, there is a clear diversity between ethnic groups; however, female ε4 carriers almost always show a higher risk of developing AD compared to male carriers. On a biological level, numerous studies have reported that the ε4 allele appears to be more harmful and pronounced in females. Compared to the opposite sex, women with ε4 have reduced cortical thickness, decreased hippocampal volume and functional brain connectivity, and higher levels of tau protein in the cerebrospinal fluid.[11] Moreover, research shows that women with the ε4 allele generally experience worse memory and show faster cognitive decline than men. Another study suggested that this could be due to hormonal changes related to menopause.[4] In general, the connection between *APOE4* and rapid cognitive decline, based on assessed cognitive performance, is stronger in women compared to in men.[13] Though these findings highlight greater cognitive deficits in women, hormonal differences can further explain why women are more vulnerable than men.

Sex Differences in Cognitive Decline and Neuropathology:

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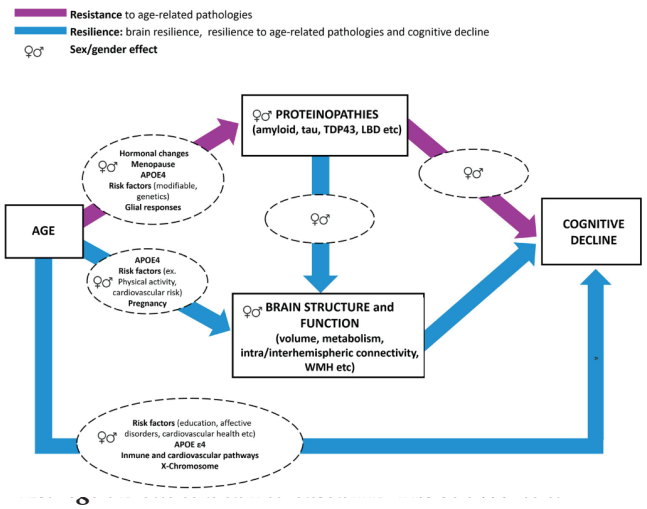

Figure 1: This illustrates how resilience and resistance processes integrate with sex and gender influences to determine cognitive outcomes. Sex and gender specific factors affect Alzheimer's-related pathology, therefore increasing resistance and resilience, ultimately impacting brain structure and function, further progressing cognitive decline. Major components include APOE, apolipoprotein; TDP43, Tar DNA-binding protein; WMH, white matter hyperintensities. As well as this, biological and hormonal differences and lifestyle-related risks can contribute to the vulnerability or protection against neurodegenerative changes.[4]

Hormonal changes due to ageing, such as post menopause estrogen loss, can interact with *APOE4* to worsen Alzheimer's pathology. Estrogen stimulates the growth and survival of cholinergic neurons and reduces cerebral amyloid deposition, which both slow progression or prevent AD.[14] This study investigated how the use of estrogen during the postmenopausal period impacts the risk of AD. The researchers studied 1124 women without Alzheimer's, Parkinson's, or stroke initially. Clinical assessments and Cox models were used to estimate risk and age of onset over 1-5 years. Findings showed that women who used estrogen post menopause had a substantially later onset of AD and a reduced risk of developing the disease compared to those who did not use estrogen. Data showed that only 5.8% of women who used estrogen developed Alzheimer's, while 16.3% of women who did not use estrogen developed Alzheimer's.[14] Moreover, estrogen use not only reduces the risk of AD but also offers several health benefits for women. A previous study found that estrogen reduced the risk of death due to AD.[14] Estrogen stimulates the growth of cholinergic neurons, promotes the processing of the amyloid precursor protein, and interacts with apolipoprotein E. The findings from this study indicate that using estrogen postmenopause can significantly delay the onset of AD and reduce its risks. Taking estrogen for a longer duration offers the greatest protection, as women with prolonged use showed the lowest risk.[14] In addition, during menopause, women experience a sharp decline in estrogen levels - over 90%, which increases AD risk. [4] These findings illustrate that biological, sex-based, and hormonal factors impact neuropathology and escalate the risks for *APOE4* carriers. This underscores the necessity for distinct therapies, diagnoses, and technology.

In summary, biological sex plays a key role in the risk and progression of Alzheimer's disease. Women tend to face greater risks and more severe symptoms in comparison to male *APOE4* carriers. Future research should focus on hormone-based therapies to reduce the risks associated with hormonal differences for women.

Cognitive differences and brain resilience

Cognitive differences and brain resilience influence the risk and advancement of AD and the effect that the *APOE4* gene variant has on the brain's ability to cope with damage and pathology.

Cognitive differences are variations in thinking abilities, whereas brain resilience refers to the brain's potential to resist damage. Moreover, components such as education level, lifestyle, and mental and physical activity can improve brain resilience and possibly reduce the effects of *APOE4*. Moreover, female brains decline faster compared to those of males in language, memory, and cognitive ability.[5] This underscores that female *APOE4* carriers experience an increased risk of earlier decline due to AD.[11] Moreover, lifestyle factors such as physical activity and mental stimulation can help decrease age-related cognitive decline, which can delay the onset of dementia and increase cognitive reserve.[15]

Cognitive Differences and Influencing Factors:

Cognitive testing regularly reveals that *APOE4* carriers and biological sex influence memory differences and cognitive function, while lifestyle, environmental factors, and education strongly affect brain resilience and cognitive function. Research shows that female *APOE4* carriers decline faster in memory, more specifically in recall and verbal tasks, compared to males.[5] It was found that the ε4 gene carriers declined faster in memory, executive functioning, and processing speeds.[5] After several tests, it was concluded that adult men perform better in tasks containing spatial memory, whereas women excel at verbal skills and object location.[5] However, these cognitive differences are also determined by environmental factors. A large study was conducted across 14 European countries with 38,000 participants over the age of 50, and it found that better living conditions and equal educational opportunities tend to increase sex differences, where women potentially benefit in factors such as episodic memory and reducing differences in other cognitive abilities.[11] Furthermore, the results of a previous study[5] presents evidence that the ε4 allele is linked to faster cognitive decline, specifically in memory and language tasks in both EOAD and LOAD. In EOAD, *APOE4* carriers displayed a more rapid decline in immediate and delayed memory recall and decision-making abilities in comparison to non-carriers of the gene variant. In addition, in both LOAD and EOAD, females showed a faster decline than males on several cognitive tasks, including memory and language.[5] Moreover, factors related to gender identity and social roles influence AD risk and progression through factors such as education, occupation, diet, exercise, smoking, and drinking habits. Similarly, poor education and low occupational history are associated with higher AD risks. Historically, women have lower cognitive engagement than men due to limited access to education and jobs, therefore increasing the risk of AD in the long run.[11] It is widely

recognised that physical activity offers multiple benefits to the brain by preserving brain integrity through neuronal growth, synaptic plasticity, and dendritic spine growth, which has been investigated through animal-based studies. Additionally, in a previous study, physical activity was associated with better processing speed, suggesting that exercise promotes brain health and therefore preserves brain volume and improves cognitive performance.[15] This aligns with other findings that state that aerobic exercise strengthens executive functions and processing speeds, such as episodic memory.[15] The same study also reported that women gain more cognitive benefits from exercise than men. However, men strongly surpass women in several cognitive abilities, including language, semantic, and visuospatial abilities, and episodic memory. Likewise, women generally have improved verbal abilities, whereas men exhibit better visuospatial skills.[16] Moreover, there are complex interactions between sex and *APOE4* on cognitive decline and disease progression. Female *APOE4* carriers show higher rates of dementia than male carriers between the ages of 65 and 75. This is highlighted as women with *APOE4* also experience worse memory and decline more rapidly in comparison to men.[16] Furthermore, research not only reveals that AD is more prevalent in females, but women also experience faster and worse mild cognitive impairment (MCI) to AD dementia. Eventually, as Alzheimer's progresses, females lose their verbal memory much more quickly.[2] Alternatively, greater formal education, more physical activity, and social engagement throughout life can decrease the risk of late-life dementia. Conventionally, women have had limited access to education, which has made them more vulnerable to this socioeconomic factor.[1] Moreover, the number of years of education received is a common measure of cognitive reserve in AD research. Higher education is often linked to higher levels of cognition and delayed initiation of symptoms.[16] However, research has suggested that once older women receive education, they display better cognitive function than men and show greater cognitive and mood benefits from education despite having fewer years of it compared to men.[16] While brain reserves can lead to protection against harmful pathologies, lifestyle and environment enhance brain resilience. It is critical to understand the protective role of cognitive reserve against AD pathology.

Brain Resilience and Cognitive Reserve as Protective Factors:

Cognitive reserve and brain resilience help protect individuals against Alzheimer 's-related impairment, delaying the onset and severity of symptoms despite certain genetic risk factors such as the *APOE4* gene variant. Cognitive reserve refers to the brain's ability to resist and cope with damage, whereas brain resilience is the brain's response to injury and disease.[4] Studies demonstrate that improving cognitive reserve despite the impacts of brain pathology can significantly prevent dementia.[15] Prevention can further be enhanced with improvements in physical activity and cognitive stimulation in order to lower the risk of dementia. Additionally, in this study,[15] it was investigated how sex and *APOE4* influence the correlation between lifestyle activities and cognitive reserve, which is critical for developing clinical trials and prevention strategies. This study concluded that physical activity was associated with higher speed reserve in only women, not men. Similarly, cognitive activity was linked to enhanced speed reserve in both sexes, but greater memory reserve only in women.[15] Furthermore, resilience explains how some individuals maintain strong cognitive function despite experiencing brain damage, illustrating the brain's ability to conserve thinking skills during ageing and disease. Previous research using AD biomarkers reveals that some individuals, even during disease and high risk, have reduced brain pathologies.[4] These findings suggest that factors such as physical and cognitive activities can decrease and slow down the accumulation of Alzheimer's pathologies.[4] However, resilience can vary due to sex based differences, based on sex chromosomes (XY vs XX), and social and environmental factors may also affect this risk. Furthermore, AD resilience refers to an affected individual's ability to reduce the dangerous impacts of risk factors such as *APOE4*, ageing, and brain pathologies such as amyloid beta and tau proteins on their cognitive abilities and functions. Researchers investigate brain resilience by observing how risk factors influence the link between pathology and cognitive decline.[4] Recent imaging studies using beta amyloid tracers have demonstrated that individuals with higher education and work involvement have greater pathological changes compared to subjects with lower education at the same level of cognitive reserve.[11] It was found that these lifestyle factors account for over 10% of the differences in cognitive performance and abilities within individuals. This underscores that greater education, qualified jobs, and frequent cognitive tasks and engagement build significantly greater cognitive reserve, which can therefore protect individuals against AD and decrease the levels and speed of cognitive decline and ageing.[11] Overall, developing awareness of cognitive and biological differences and the corresponding effects of *APOE4* is crucial for establishing targeted treatments in AD.

Ultimately, brain resilience determines how individuals with the *APOE4* experience Alzheimer's disease and its dangerous pathologies. Cognitive differences can help avoid more severe symptoms and risks for a longer period of time despite the genetic risk factors for the disease. Future studies should research how cognitive differences and brain reserve interact with *APOE4* and how these elements can either worsen or improve the progression, which may lead to more advanced prevention strategies and treatments.

■ Future treatments, directions, and clinical implications

As AD progresses, it is vital to consider future approaches for AD treatments that are more targeted for individual needs based on sex and cognitive differences. As the number of affected individuals dealing with Alzheimer's disease increases and our understanding of this disease deepens, future interventions should become more specialized rather than applied uniformly. Moreover, studying cognitive reserves and differences within biological sex can help develop treatments leading to valuable clinical trials focused on early-onset Alzheimer's.

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Targeting Pathology and Cognitive Health:

Future treatments for AD should focus on the cause of brain damage and rapid cognitive decline, like Aβ accumulation, tau, and neuroinflammation. A study implies that there is a major lack of efficiency in nonsteroidal anti-inflammatory drug (NSAID) treatments.[3] Since the presence of *APOE4* in AD can lead to increased neuroinflammation, it is suggested that inflammation-related treatments should be developed to help *APOE4* carriers decrease the progression of the disease.[3] Moreover, other studies reveal that although prevention for this disease is critical, disease-modifying treatments remain inadequate for AD. It is recommended to improve cognitive reserve to strengthen cognitive health and brain pathology to aid in dementia prevention.[15] In addition, race-specific studies are required to explain how sex and race influence AD outcomes. To achieve this, it is suggested that upcoming research should focus on underrepresented populations such as black, Hispanic, and Asian populations. This should be done to increase the diversity and better understand how genetic, environmental, social, and sex related factors interact in AD with different individuals. However, current studies largely focus on non-Hispanic white populations, which limits the generalizability of findings.[2] Alternatively, it is essential for both sexes that effective care should address multiple factors such as vascular risk factors, sleep and mood disorders, and other comorbid conditions rather than just focusing on AD-specific medications.[1]

Personalized Therapies and Advanced Monitoring:

One possible future treatment for AD could target amyloid-beta and tau protein buildup using gene therapies or targeted drugs specific to each patient.[3] Another approach is developing an anti-inflammatory drug to reduce inflammation within the brain that is often caused by *APOE4*.[5] This can slow down the progression of the disease and protect the brain from further damage, and therefore reduce cognitive decline. Moreover, to test these potential treatment ideas, brain imaging methods can be used. fMRI, also known as functional magnetic resonance imaging, measures activity within the brain by detecting changes in blood flow, allowing researchers to see the impact of these drugs on the brain.[13] More specifically, fMRI enables the detection of abnormalities in the brain as well as the detailed function of the brain. Because of this, this method can be used by researchers to see whether memory-related brain regions like the hippocampus or prefrontal cortex change activity levels during and after treatments.[2] In general, advanced brain imaging techniques and specific drug therapies and treatments are a beneficial approach to not only observe changes in brain activity and function over a period of time but also to slow disease progression and reduce the overall risks. Finally, it is vital to begin working on individually tailored treatments and interventions to reduce the risks of AD, especially for those who are *APOE4* carriers.[15] Similarly, it is necessary to consider all the factors, such as sex, lifestyle, and differences in thinking abilities, to create effective medical procedures and reduce cognitive decline over time.[14]

■ Conclusion

This paper reviewed how the *APOE4* gene increases the risk of developing Alzheimer's disease and accelerates the progression of AD pathology. Additionally, how cognitive differences and biological sex influence the relationship with *APOE4* was examined to show their impact on the development of the disease. It demonstrated that *APOE4* disrupts brain structure and function through amyloid-beta buildup and neuroinflammation, whereas sex and hormonal differences and cognitive reserve vary the genetic risks associated with AD.

The *APOE4* gene significantly impacts brain structure and function, with a focus on key memory regions such as the hippocampus. The paper focuses on biological sex-based differences in Alzheimer's risk and progression, and more specifically focuses on hormonal factors. In addition to that, the reviewed cognitive differences and brain resilience mirror how education and cognitive abilities can protect the brain against severe symptoms. Lastly, future treatments should focus on individual-specific therapies and clinical implications, therefore emphasising the importance of targeting *APOE4* processes and considering cognitive and sex factors before the pathology progresses.

One major question that remains unanswered is the development of crucial therapies to overcome the disease or slow down the progression before it worsens. The best methods for early interventions in *APOE4* carriers are unclear; therefore, future research should use advanced medical procedures such as neuroimaging to examine the brain and track brain patterns.

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