Alzheimer's disease risk factors

- A Comprehensive Systematic Review and Meta-Analysis to Unravel the Noise-Dementia Nexus
- Value of muscle strength in improving the predictive capability for cognitive decline in older women by established risk factors: A prospective cohort study in the Otassha Study
- Infections with Chlamydia pneumoniae and SARS-CoV-2 and Alzheimer's disease pathogenesis
- Physical activity as a resistance or resilience mechanism in Down syndrome Alzheimer's disease
- Functional connectivity alterations in women with subjective cognitive decline
- Genetics of PLCG2 expression and splicing relative to Alzheimer's disease risk
- Estimating a change-point of baseline age in the longitudinal trajectories of biomarkers: application to an imaging study of preclinical Alzheimer disease
- Cerebral Blood Flow Alterations in the Precuneus of Alzheimer's Disease Using Arterial Spin Labeling: A Systematic Review and Meta-Analysis

Alzheimer's disease (AD) is a complex neurodegenerative disorder influenced by a combination of genetic, environmental, and lifestyle factors. While the exact cause of AD is not fully understood, several risk factors have been identified that may increase the likelihood of developing the disease. These risk factors include:

Age: Increasing age is the most significant risk factor for Alzheimer's disease. The risk of AD rises with advancing age, particularly after the age of 65. The prevalence of AD doubles approximately every five years after age 65.

Family history: Having a first-degree relative, such as a parent or sibling, with Alzheimer's disease increases an individual's risk of developing the condition. This suggests a genetic component to the disease, although environmental factors shared within families may also contribute.

Down syndrome: Individuals with Down syndrome have an increased risk of developing Alzheimer's disease, with symptoms often appearing at an earlier age than in the general population. This may be related to the presence of an extra copy of chromosome 21, which contains the gene encoding amyloid precursor protein (APP).

Cardiovascular risk factors: Several cardiovascular risk factors have been linked to an increased risk of Alzheimer's disease, including hypertension, high cholesterol, diabetes, obesity, and smoking. These factors may contribute to the development of vascular changes in the brain, which can increase the risk of dementia.

Traumatic brain injury (TBI): A history of moderate to severe traumatic brain injury, particularly repeated head injuries, has been associated with an increased risk of developing Alzheimer's disease later in life. This has been observed in athletes, military personnel, and others with a history of head trauma.

Lifestyle factors: Certain lifestyle factors may influence the risk of developing Alzheimer's disease. These include physical inactivity, poor diet, lack of mental stimulation, social isolation, and limited engagement in cognitively stimulating activities. Conversely, regular physical exercise, a healthy diet rich in fruits, vegetables, and omega-3 fatty acids, social engagement, and intellectually stimulating

activities may help reduce the risk of AD.

While these risk factors may increase the likelihood of developing Alzheimer's disease, it's important to note that not everyone with these risk factors will develop the condition. Additionally, other factors, such as inflammation, oxidative stress, and environmental toxins, may also play a role in the development of AD. Ongoing research is needed to further understand the complex interplay of factors contributing to Alzheimer's disease.

Lipid metabolism for Alzheimer's disease risk factor

- The Role of APOA-I in Alzheimer's Disease: Bridging Peripheral Tissues and the Central Nervous System
- Serum Npas-4 and Nptx-2 Levels in Alzheimer's Disease: Potential Biomarkers of Synaptic Dysfunction in a Cross-Sectional Study
- Astrocytic lipidopathy and bioenergetic failure in ApoE4-associated late-onset Alzheimer's disease: A unifying hypothesis
- Signs of Premature Kidney Aging in Mice With Error-Prone Protein Synthesis
- Lipid profiling of Parkinson's disease brain highlights disruption in Lysophosphatidylcholines, and triacylglycerol metabolism
- Association of Blood Lipoprotein Levels With Incident Alzheimer Disease in Community-Dwelling Individuals: The Framingham Heart Study
- Causal relationships between plasma proteins and Alzheimer's disease using bidirectional Mendelian randomization
- High-Fat Diet-Induced Excessive Accumulation of Cerebral Cholesterol Esters and Microglial Dysfunction Exacerbate Alzheimer's Disease Pathology in APP(NL-G-F) mice

---

Lipid metabolism plays a significant role in Alzheimer's disease (AD) risk and progression. Here's how:

High levels of cholesterol, particularly low-density lipoprotein (LDL) cholesterol, have been linked to an increased risk of AD. Cholesterol is involved in the formation of amyloid plaques, which are one of the hallmark pathological features of AD. Additionally, cholesterol is essential for the structure and function of neuronal membranes, and alterations in cholesterol metabolism can affect synaptic function and neuronal health. Apolipoprotein E (APOE): APOE is a protein involved in lipid transport and metabolism, and it exists in three isoforms: APOE2, APOE3, and APOE4. The APOE4 allele is a major genetic risk factor for late-onset AD. APOE4 has been shown to influence cholesterol metabolism, amyloid-beta clearance, and neuroinflammation, contributing to the pathogenesis of AD.

Omega-3 Fatty Acids: Omega-3 fatty acids, found in fatty fish and certain plant sources, have been associated with a reduced risk of AD. These fatty acids have anti-inflammatory and neuroprotective properties and may help maintain neuronal membrane integrity and function.

Lipid Peroxidation: Oxidative stress-induced lipid peroxidation, which leads to the production of

reactive oxygen species (ROS), can damage neuronal membranes and contribute to neurodegeneration in AD. Lipid peroxidation products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), are elevated in the brains of AD patients.

Insulin Resistance: Dyslipidemia, characterized by elevated levels of triglycerides and LDL cholesterol, often accompanies insulin resistance, a condition associated with type 2 diabetes. Insulin resistance and dyslipidemia can impair brain insulin signaling, promote neuroinflammation, and contribute to AD pathogenesis.

Lipoprotein Metabolism: Alterations in lipoprotein metabolism, including abnormalities in the clearance of lipoproteins from the brain, have been implicated in AD. Dysfunction of lipoprotein receptors, such as the LDL receptor-related protein 1 (LRP1), may impair the clearance of amyloid-beta from the brain, leading to its accumulation and the formation of amyloid plaques.

Understanding the intricate interplay between lipid metabolism and AD pathogenesis is crucial for developing targeted therapeutic interventions aimed at modulating lipid metabolism to reduce AD risk and slow disease progression. Additionally, lifestyle interventions promoting a healthy lipid profile, such as a balanced diet rich in omega-3 fatty acids and regular physical activity, may help mitigate AD risk factors associated with dyslipidemia.

Recent research suggests that microglia carrying the APOE4 genotype display abnormal lipid metabolism and accumulate lipid droplets, which may exacerbate the pathology of AD. Microglia play a critical role in immune surveillance within the central nervous system and are responsible for removing harmful particles and preserving neuronal function. The APOE4 genotype causes abnormal lipid metabolism in microglia, resulting in excessive accumulation of lipid droplets. This accumulation not only impairs the phagocytic and clearance capabilities of microglia but also disrupts their interactions with neurons, resulting in disorganization and neurodegenerative alterations at the neuronal network level. In addition, the presence of APOE4 modifies the metabolic landscape of microglia, particularly affecting purinergic signaling and lipid metabolism, thereby exacerbating the pathological processes of AD. In conclusion, the accumulation of lipid droplets and abnormal lipid metabolism may be critical mechanisms in the progression of AD in microglia carrying the APOE4 genotype [1)]

Alzheimer's disease genetic risk factors

Genetic factors play a role in the development of Alzheimer's disease. Mutations in certain genes, such as the APOE gene (specifically the ε4 allele), are associated with an increased risk of developing late-onset AD. Other genes implicated in familial forms of AD include APP (amyloid precursor protein) and PSEN1/PSEN2 (presenilin 1 and presenilin 2).

APOE4 is widely recognized as a genetic risk factor for Alzheimer's disease (AD), implicated in 60-80% of all AD cases. Recent research suggests that microglia carrying the APOE4 genotype display abnormal lipid metabolism and accumulate lipid droplets, which may exacerbate the pathology of AD.

Microglia play a critical role in immune surveillance within the central nervous system and are responsible for removing harmful particles and preserving neuronal function. The APOE4 genotype causes abnormal lipid metabolism in microglia, resulting in excessive accumulation of lipid droplets. This accumulation not only impairs the phagocytic and clearance capabilities of microglia but also disrupts their interactions with neurons, resulting in disorganization and neurodegenerative alterations at the neuronal network level. In addition, the presence of APOE4 modifies the metabolic landscape of microglia, particularly affecting purinergic signaling and lipid metabolism, thereby exacerbating the pathological processes of AD. In conclusion, the accumulation of lipid droplets and abnormal lipid metabolism may be critical mechanisms in the progression of AD in microglia carrying the APOE4 genotype [2)]

A history of preeclampsia was associated with an increased risk of all-cause dementia and Alzheimer's Disease [3)].

Research with neuropathologic or biomarker evidence of Alzheimer's disease (AD) casts doubt on traumatic brain injury (TBI) as a risk factor for AD. We leveraged the National Alzheimer's Coordinating Center to examine the association between self-reported TBI with loss of consciousness and AD neuropathologic changes, and with baseline and longitudinal clinical status.

The sample included 4761 autopsy participants (453 with remote TBI with loss of consciousness; 2822 with AD neuropathologic changes) from National Alzheimer's Coordinating Center.

Self-reported TBI did not predict AD neuropathologic changes ($P > .10$). Reported TBI was not associated with baseline or change in dementia severity or cognitive function in participants with or without autopsy-confirmed AD.

Self-reported TBI with loss of consciousness may not be an independent risk factor for clinical or pathological AD. Research that evaluates number and severity of TBIs is needed to clarify the neuropathological links between TBI and dementia documented in other large clinical databases [4)].

1) , 2)
Hu X, Ma YN, Xia Y. Association between abnormal lipid metabolism and Alzheimer's disease: New research has revealed significant findings on the APOE4 genotype in microglia. Biosci Trends. 2024 Apr 17. doi: 10.5582/bst.2024.01092. Epub ahead of print. PMID: 38631884.
3)
Wang K, Guo K, Ji Z, Liu Y, Chen F, Wu S, Zhang Q, Yao Y, Zhou Q. Association of Preeclampsia with Incident Dementia and Alzheimer's Disease among Women in the Framingham Offspring Study. J Prev Alzheimers Dis. 2022;9(4):725-730. doi: 10.14283/jpad.2022.62. PMID: 36281677.
4)
Sugarman MA, McKee AC, Stein TD, Tripodis Y, Besser LM, Martin B, Palmisano JN, Steinberg EG, O'Connor MK, Au R, McClean M, Killiany R, Mez J, Weiner MW, Kowall NW, Stern RA, Alosco ML. Failure to detect an association between self-reported traumatic brain injury and Alzheimer's disease neuropathology and dementia. Alzheimers Dement. 2019 Mar 6. pii: S1552-5260(19)30009-3. doi: 10.1016/j.jalz.2018.12.015. [Epub ahead of print] PubMed PMID: 30852157.