Hyperlipidemia Causally Linked to Increased Risk of Alzheimer Disease

Key Takeaways

- Hyperlipidemia, particularly elevated cholesterol and triglycerides, is linked to increased Alzheimer disease risk, while higher HDL-C levels may offer protective effects.
- The study combined NHANES data and Mendelian randomization, revealing significant correlations between lipid levels and cognitive impairment in Alzheimer disease.
- Despite the need for further validation, targeting lipid abnormalities could be a promising strategy for Alzheimer disease prevention and management.
- Pharmacists can play a critical role in educating patients about cholesterol management and its potential impact on cognitive health.

Total cholesterol and triglyceride levels were linked to an increased risk of Alzheimer-related declines in cognitive function, while high-density lipoprotein cholesterol provided a protective effect.

Hyperlipidemia, especially elevated total cholesterol, triglycerides, and cholesteryl ester in small very low-density lipoprotein (VLDL), is causally linked to an increased risk of Alzheimer disease (AD), while higher high-density lipoprotein cholesterol (HDL-C) can offer a protective effect, according to new data published by investigators in Medicine.[1]

New Mechanisms Behind Alzheimer Disease

As science and technology advance, it has become possible to better investigate the underlying mechanisms of AD and begin to develop therapeutic measures for patients. Above all else, research has affirmed that the exact mechanisms behind AD development are complex and multifaceted. However, alterations to lipid metabolism could play a role in the course of the disease.[1,2]

In this vein, research establishing a potentially causative link has been inconclusive. Past studies have determined some associations, but they have been observational in nature, lowering its reliability. More recent work by Zhao et al has integrated National Health and Nutrition Examination Survey (NHANES) data with Mendelian randomization (MR) analyses to explore cognitive outcomes related to lipid metabolism. Gaps in this approach—including a lack of understanding regarding the directionality of these associations—necessitate more exhaustive efforts.[1,3]

The current investigators sought to fill these gaps by combining NHANES data and a multiple exposure MR examination. This approach considers both the observational link between hyperlipidemia and AD-related cognitive function and a thorough detailing of the possible causes and consequences of various lipid traits on the risk of developing AD.[1]

Individuals aged 60 and older were included from the NHANES dataset. Following the application of various exclusion criteria, 855 patients possessing available data on blood lipid levels and AD cognitive function were included. For cognitive assessment, the CERAD-WL assessment scale was utilized. Across the cohort, 620 individuals (72.5%) were classified as having normal cognition, while 235 participants (27.5%) were considered as having low cognition.[1]

Notable disparities in CERAD-Total scores were observed among the 2 groups. Multivariable logistic regression analysis indicated a statistically significant correlation between hyperlipidemia and AD cognitive impairment in the NHANES dataset. Compared with the non-hyperlipidemic population, individuals with hyperlipidemia had a significantly higher risk of being in the lowest quartile of CERAD-Total score, indicating the presence of severe cognitive dysfunction.[1]

What Are the Causal Associations Between Lipids and AD Risk?

The association remained statistically significant after controlling for a series of lifestyle factors and comorbidities, in addition to age, gender, ethnicity, marital status, and body mass index. The association appeared attenuated when stratified by sex, with the odds ratio (OR) in males being 1.218 (95% CI, 1.044—1.421; P < .05) compared with 1.387 (95% CI, 0.943—1.998; P = .097) in females. Despite this attenuation, the investigators discussed that the wide confidence interval and lack of statistical significance suggest a lack of sex-specific effects.[1]

In the MR analysis, there was strong evidence for causal correlations between the risk of AD and numerous cholesterol characteristics. There was a causal relationship between elevated levels of total cholesterol and AD risk, with estimates indicating an OR of 0.867 per standard deviation increase in total cholesterol (95% CI, 0.776—0.986; P = .011). Increased triglyceride levels have a similar association with AD risk (OR: 0.870 [95% CI, 0.767—0.985]; P = .028).[1]

Notably, a protective effect was observed between higher HDL-C levels and AD risk. A causal estimate demonstrated an OR of 1.045 per SD increase in HDL-C (95% CI, 1.000—1.092; P = .049), suggesting that genetically-determined HDL-C concentrations can confer a reduced risk of AD development. Contrastingly, there were no significant causal effects between low-density lipoprotein cholesterol on AD risk. The findings across each analysis were robust and consistent across a series of sensitivity analyses, which the authors wrote strengthens the causal inference.[1]

Pharmacists can play a critical role in counseling patients on the benefits of cholesterol monitoring and management, referring to the possibly causal association between cholesterol and cognitive impairment. Although this research requires further validation, it remains in line with emerging evidence and is gaining prominence throughout the medical field. Pharmacists, as first-line providers in the patient community, can advocate for cholesterol treatment in the form of statins or monoclonal antibodies.[1]

“These findings suggest that targeting lipid abnormalities may be a promising strategy for the prevention and management of this devastating neurodegenerative condition,” the study authors wrote in their conclusion.[1]

REFERENCES

1. Sun R, Liu Y. The causal association between hyperlipidemia and Alzheimer disease: a combined NHANES and Mendelian randomization study. Medicine. 2025;104(43):e45393. doi:10.1097/MD.0000000000045393
2. Pedrini S, Chatterjee P, Hone E, Martins RN. High-density lipoprotein-related cholesterol metabolism in Alzheimer's disease. Journ Neurochem. 2020;159(2):343-377. doi:10.1111/jnc.15170
3. Zhao H, Yang C, Xing F. Correlation of the serum fatty acids with cognitive function: An NHANES 2011-2014 and multivariate Mendelian randomization analysis. Journ Alzheimer. 2024;101(3). doi:10.3233/JAD-240715

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