

High LDL linked to early-onset Alzheimer's

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Dr. Thomas Wingo and Dr. Aliza Wingo (foreground) lead a lab at the Atlanta VA and Emory University dedicated to understanding the genetic basis of Alzheimer's disease and psychological well-being and resilience. Credit: Lisa Pessin

Researchers with the Atlanta Veterans Affairs Medical Center and

Emory University have found a link between high LDL cholesterol levels and early-onset Alzheimer's disease. The results could help doctors understand how the disease develops and what the possible causes are, including genetic variation.

According to Dr. Thomas Wingo, lead author of the study, the results show that LDL cholesterol levels may play a causal role in the development of Alzheimer's disease.

The results appear in the May 28, 2019, issue of *JAMA Neurology*.

"The big question is whether there is a [causal link](#) between cholesterol levels in the blood and Alzheimer's disease risk," says Wingo. "The existing data have been murky on this point. One interpretation of our current data is that LDL cholesterol does play a causal role. If that is the case, we might need to revise targets for LDC cholesterol to help reduce Alzheimer's risk. Our work now is focused on testing whether there is a causal link."

Wingo is a neurologist and researcher with the Atlanta VA and Emory University.

Elevated cholesterol levels have been linked to increased risk of Alzheimer's later in life. This risk may be due to [genetic factors](#) tied to cholesterol. Past research has shown that a major risk factor for Alzheimer's disease is a specific mutation in a gene referred to as APOE. It is the largest known single genetic risk factor for Alzheimer's disease. This APOE variant, called APOE E4, is known to raise levels of circulating cholesterol, particularly low-density lipoprotein (LDL). This type of cholesterol is sometimes referred to as "bad cholesterol" because high LDL levels can lead to a build-up of cholesterol in the arteries.

While late-onset Alzheimer's—the common form of the

disease—appears to be linked to cholesterol, little research has been done on a possible connection between cholesterol levels and early-onset Alzheimer's risk.

Early-onset Alzheimer's is a relatively rare form of the condition. The disease is considered "early-onset" when it appears before age 65. About 10% of all Alzheimer's cases are early-onset. Past research has shown that the condition is largely genetics-based, meaning it is likely to be inherited if a parent has it.

Three specific gene variants (dubbed APP, PSEN1, and PSEN2) are known to be related to early-onset Alzheimer's disease. APOE E4 is also a risk factor in this form of the disease, as well. These gene variants explain about 10% of early-onset Alzheimer's disease cases, meaning that 90% of cases are unexplained.

To test whether early-onset Alzheimer's disease is linked to cholesterol and identify the genetic variants that might underlie this possible association, the researchers sequenced specific genomic regions of 2,125 people, 654 of whom had early-onset Alzheimer's and 1,471 of whom were controls. They also tested [blood samples](#) of 267 participants to measure the amount of LDL cholesterol.

They found that APOE E4 explained about 10% of early-onset Alzheimer's, which is similar to estimates in late-onset Alzheimer's disease. The researchers also tested for APP, PSEN1, and PSEN2. About 3% of early-onset Alzheimer's cases had at least one of these known early-onset Alzheimer's risk factors.

After testing blood samples, the researchers found that participants with elevated LDL levels were more likely to have early-onset Alzheimer's disease, compared with patients with lower cholesterol levels. This was true even after the researchers controlled for cases with the APOE

mutation, meaning cholesterol could be an independent risk factor for the disease, regardless of whether the problematic APOE gene variant is present.

The researchers did not find a link between HDL (high-density lipoprotein) [cholesterol levels](#) and early-onset Alzheimer's, and only a very slight association between the disease and triglyceride levels.

The researchers also found a new possible genetic risk factor for early-onset Alzheimer's disease. Early-onset Alzheimer's cases were higher in participants with a rare variant of a gene called APOB. This gene encodes a protein that is involved in the metabolism of lipids, or fats, including cholesterol. The finding suggests a direct link between the rare APOB mutation and Alzheimer's disease risk, according to the researchers. However, the link between LDL-C level and early-onset Alzheimer's was not fully explained by APOE or APOB, suggestion that other genes and mechanisms also increase [disease risk](#).

While the study shines light on possible risk factors for early-onset Alzheimer's disease, the researchers say that more research is needed to fully explain the connection between the disease and [cholesterol](#). The relative rarity of early-onset Alzheimer's disease presents a challenge in finding enough samples to perform large genetic studies on the condition, they say.

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