# Study seeks to explain why Sephardi Jews more likely to get early-onset Alzheimer's

NIH grants $13 million for genetic research after 2018 research showed Jews with roots in Spain, Middle East and North Africa see far more cases of early cognitive decline

By RENEE GHERT-ZAND FOLLOW
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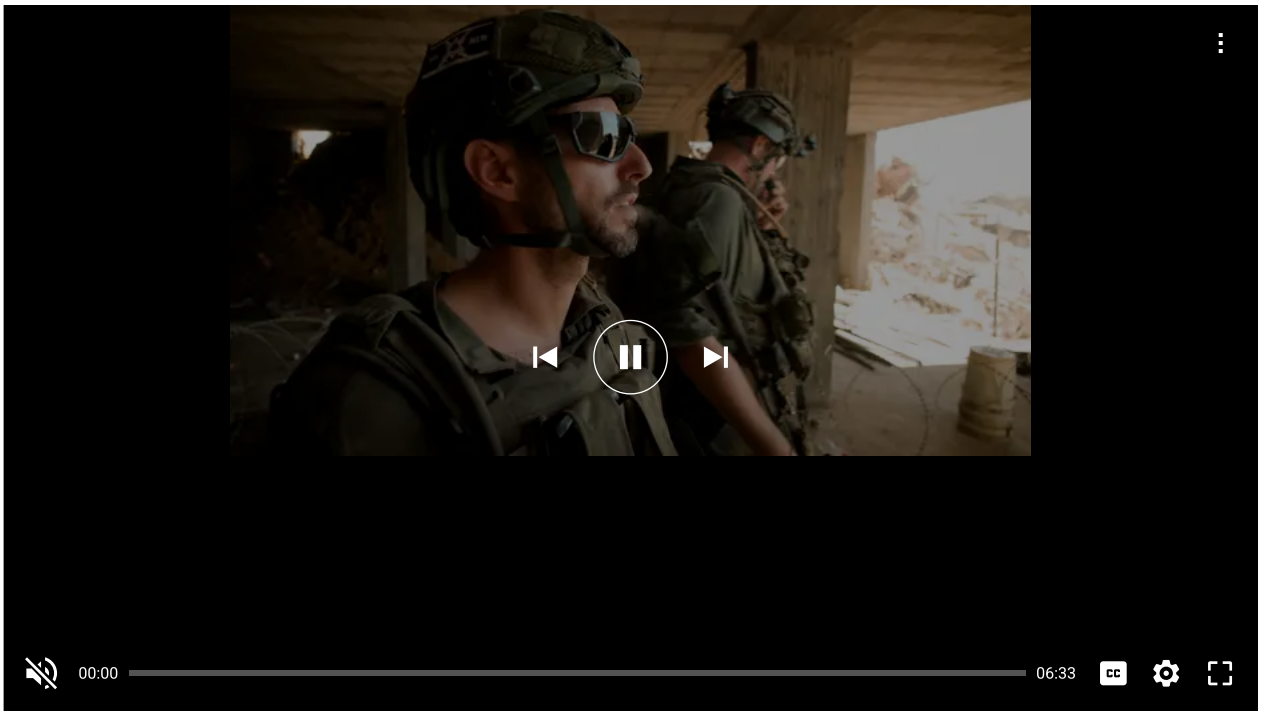
Illustrative image of a doctor comforting a patient with Alzheimer's Disease. (Chinnapong, iStock by Getty Images)

A new study funded by a grant of more than $13 million from the US National Institutes of Health will look into possible genetic reasons why Sephardic Jews are diagnosed with Alzheimer's disease at younger ages than other people.

The project officially launched on May 5 as representatives of partner institutions met at Beilinson Hospital in Petah Tikva. Aside from Beilinson, the research consortium includes Rambam Medical Center in Haifa, Barzilai Medical Center in Ashkelon, Laniado Hospital in Netanya, and Prof. Lindsay A. Farrer from Boston University School of Medicine.

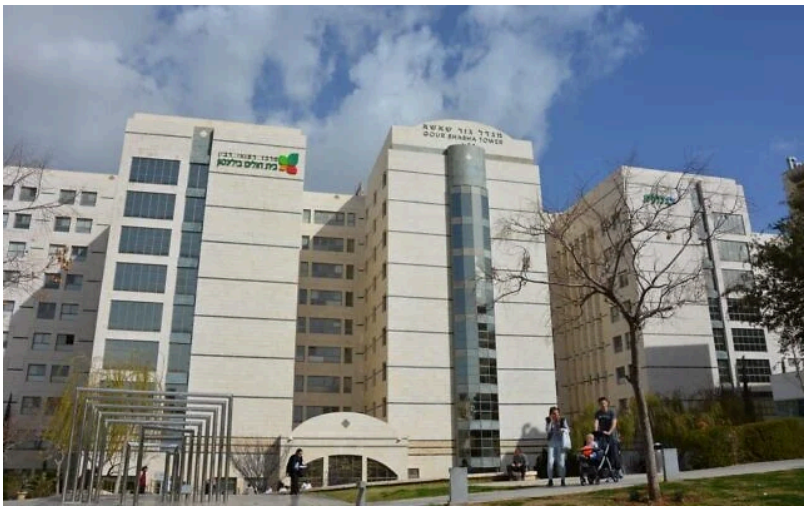
This new research builds on a peer-reviewed study conducted at Beilinson and published in 2018 in the Journal of Alzheimer's Disease. It showed a disparity between the prevalence of early-onset Alzheimer's disease (EOAD) in Sephardi versus Ashkenazi Jews.




Sephardi Jews have roots in the diasporas of the Iberian Peninsula, the Middle East and North Africa, while Ashkenazi Jews' ancestors are from the diasporas of Central and Eastern Europe.

According to the research, significantly more Sephardi Jews than Ashkenazi Jews have EOAD, meaning diagnosis before the age of 65 with the neurodegenerative disease that leads to dementia.

Of the 55 million people around the world who have Alzheimer's (including 6.5 million Americans and 150,000 Israelis) about five percent receive EAOD diagnoses.



Beilinson Hospital in Petah Tikva (Courtesy)

"The original study was born of the fact that my colleagues and I noticed that as we examined patients who complained of cognitive deterioration and impairment, the Sephardi ones were coming in at younger ages than their Ashkenazi counterparts," said Dr. Amir Glik, director of Beilinson's cognitive neurology department.

"Usually with Alzheimer's we see people coming in at ages 70 to 75, but here we saw people coming in at 62 or 63," he said.

Glik and his team decided to see if the phenomenon they observed in the clinic would bear the application of scientific tools.

"We were pretty confident that what we were seeing was real and that we could prove it. The cognitive neurology service here is very large with hundreds of thousands of patients in our database. We see many patients every year. The study's results show that our gut feeling was correct," Glik said.

After receiving Institutional Review Board approval, the researchers reviewed the records of Alzheimer's-diagnosed patients in the hospital's database. They found that 64% of EOAD diagnoses were of individuals of Sephardi backgrounds while 36% were of individuals from Ashkenazi backgrounds.

Dr. Amir Glick, Director of Cognitive Neurology at Beilinson Hospital (Shlomi Yosef)

Statistical methods revealed that the EOAD rate among the Sephardi patients varied greatly from their representation in the general Sephardic population in Beilinson's catchment area in central Israel. For example, if the Sephardi population makes up 40% of the area's general population, one would expect that 40% of the hospital's EOAD cases would be Sephardi individuals.

"This was not what we found. Instead of the representative 45%, we found that the percentage of EOAD cases that were Sephardi were 57-60%," Glik said.

"This significant difference was especially seen among Yemeni Jews," he added.

By contrast, this disparity was not seen among Ashkenazi Jews. In their case, their portion of the EOAD diagnoses was very similar to their representation in the area's population.

The next step was for the researchers to try to determine the cause for the observed — and now statistically proven — phenomenon. The first thing they did was rule out the possibility that the Sephardi Jews coming in with EOAD had Familial Alzheimer's Disease (FAD), which is caused by an autosomal genetic mutation that is passed down hereditarily.

A Habbani Yemeni family celebrates Passover in their new home, April 1, 1946. (Zoltan Kluger/GPO via Wikimedia Commons)

"We were not dealing with this because people with FAD usually are diagnosed in their 30s to 50s and they have siblings with it as well," Glik said.

"What were were seeing were people only several years younger than most people when they initially come in, so we concluded that this was actually late-onset Alzheimer's disease (LOAD) that appears to be affecting these Sephardi individuals at younger ages than the Ashkenazi individuals," Glick said.

The team posited three possible explanations for this. First, there could be an environmental cause. Second, it may have to do with vascular pathologies associated with hypertension, hyperlipidemia, and diabetes, all of which are risk factors for Alzheimer's. Finally, it could be genetic risk factors, with Sephardi Jews having genetic mutations that could make them more vulnerable to EOAD.

"There could be a synergism among all three of these, but our feeling is that the genetic risk factors are much more important in this story. That is why we approached the NIH with a grant application to take the research forward in

this direction," Glik said.

A kick-off meeting on May 5, 2024 for a five-hospital collaboration for an NIH-funded Alzheimer's study is attended by: Beilinson Hospital Director of Cognitive Neurology Dr. Amir Glik; Prof. Lindsay Farrer, Director, Boston University Molecular Genetics Core Facility, Boston University School of Medicine; Rambam Health Care Campus Director of Cognitive Neurology Dr. Rachel Ben Hayun; Barzilai Medical Center Director of Cognitive Neurology Dr. Zeev Nitsan; and Prof. Bowirrat Abdalla, Senior Neurologist at Laniado hospital. (Courtesy of Beilinson Hospital)

The study to be done by the consortium is getting underway now, after a delay due to the war, and will involve recruiting 2,000 Israelis with LOAD and 2,000 healthy controls. The study will involve a cohort of Arab Israelis, as well as Sephardi Jews.

Glik explained that this genetic research on homogenous populations is critical because genetic mutations and risk factors are far more pronounced and frequent in these groups than in heterogenous populations.

"If you study a heterogenous population, you have to involve tens of thousands of subjects to discover genetic risk factors. But if you go to a homogenous population from the same ancestry, you can identify the genetic factors in a smaller sample," Glik said.

"Then you can go and test for the same genetic mutation among a more heterogenous population, like in the US," he said.

There are currently only two FDA-approved drugs available to treat Alzheimer's (lecanemab and aducanumab), both of which have only recently come on the market. Eli Lilly's donanemab is expected to be available in June.

Glik said he hopes that the consortium's NIH-funded research will reveal critical genetic findings that will allow scientists to better understand the impaired mechanisms that cause Alzheimer's, perhaps leading to new drugs to repair them.

"I'm a neurologist. The thing that interests me is whether I can help my patients. I am not doing these studies only for academic purposes," Glik said.