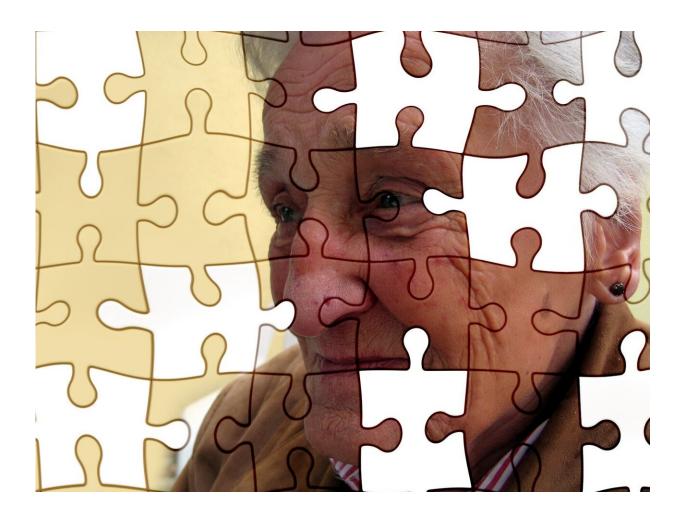# Identification of new risk factors or early signs of Alzheimer's disease

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What risk factors are associated with Alzheimer's up to 15 years before

the onset of the first symptoms? This is a vital question for specialists of this neurodegenerative disease—which develops over many years before becoming clinically visible—who aim to improve early prevention for at-risk patients. A multidisciplinary team of researchers from the Paris Brain Institute's (INSERM/CNRS/Sorbonne University) Aramis project led by Stanley Durrleman (Inria), from INSERM/University of Bordeaux, and from Cegedim Health Data, analyzed the anonymized health records of nearly 80,000 patients consulting general practitioners in France and the United Kingdom, taken from the THIN database.

The scientists identified 10 pathologies developed more frequently by patients reporting Alzheimer's dementia within 15 years than by other patients of the same age. Their results are published in the journal *The Lancet Digital Health*.

Despite the growing number of findings, our knowledge of the risk factors and early symptoms of Alzheimer's disease remains patchy and based on specific risk factor approaches. Until now, there has been no exhaustive, agnostic study conducted on a very large sample of patients that analyzes possible risk factors well ahead of the Alzheimer's diagnosis.

For the first time, a team of researchers has accessed the anonymized medical data of nearly 40,000 patients with Alzheimer's disease and of the same number of control subjects who did not develop neurodegenerative diseases over the period studied. The data was extracted from the THIN (The Health Improvement Network) database owned by Cegedim Group, an innovative technology and services company specializing in healthcare data.

The Aramis team's expertise in mathematical modeling made it possible to perform an analysis without predefined hypotheses, and test the possible link between the onset of Alzheimer's disease and 123 health

factors. Statistical explorations of historical medical records yielded a list of the 10 most common conditions experienced by patients who go on to develop Alzheimer's disease within 15 years. Depression topped the list, followed by anxiety, exposure to high stress, hearing loss, constipation, cervical spondyloarthritis, memory loss, fatigue (and discomfort), and finally falls and sudden weight loss.

"The connections made allowed us to confirm known associations, such as hearing problems or depression, and other less known factors or early symptoms, such as cervical spondylosis or constipation. However, we are only reporting statistical associations. These will have to be the subject of further studies to understand the underlying mechanisms," says researcher Thomas Nedelec from the Aramis team, "The question remains as to whether the health problems encountered are risk factors, symptoms, or warning signs of the disease."

Epidemiologist and INSERM research director Carole Dufouil and neurologist Stéphane Epelbaum helped validate the methodology and interpret the relevance of these statistical associations. Although these results still need to be refined, they are already valuable for health professionals and all those involved in prevention, who could try to address these risk factors as soon as they are detected in the hopes of preventing the disease.

This work opens up several prospects, the first of which will be to expand and diversify the corpus of data studied. A grant from the European program for the study of neurodegenerative diseases (Joint Program—Neurodegenerative Disease Research) will enable the Aramis researchers to add data from Sweden and Australia to the existing pool and extend their analyses to more than 26 million data from anonymized health records. This will also enable research to be extended to other degenerative diseases (Parkinson's, Charcot's disease, multiple sclerosis, etc.).

"We hope, through this approach, to identify the common basis of these diseases and the specificities associated with each one," concludes Stanley Durrleman.

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