By Mapping Disease Sequences Redefining Alzheimer's Development

University of California, Los Angeles researchers identified four distinct pathways leading to Alzheimer's disease.

Study

The researchers analyzed health data from 24,473 patients in the University of California Health Data Warehouse. They validated the findings in the nationally diverse All of Us Research Program, a diverse, nationally representative cohort.

After filtering out diagnoses that were not positively associated with subsequent AD, researchers identified 5,762 patients who contributed 6,794 unique disease trajectories of AD. Disease trajectory is defined as a sequence of health events over time occurring irregularly and encompassing diagnoses, medications, procedures, and laboratory tests. Each trajectory included at least three temporally ordered diagnoses, and many patients were found to follow more than one distinct disease path, with up to three trajectories per individual.

Researchers mapped the temporal relationships between diagnoses leading to AD using advanced computational methods, including dynamic time warping, a method for comparing time series with irregular timing, k-means clustering, and network analysis.

Results

The study identified four distinct disease trajectories leading to AD. These trajectories were: a mental health trajectory representing psychiatric conditions leading to cognitive decline; an encephalopathy trajectory representing brain dysfunctions that escalate over time; a mild cognitive impairment trajectory representing gradual progression of cognitive decline; and a vascular disease trajectory representing cardiovascular conditions contributing to dementia risk.

Each pathway had characteristic demographic features, comorbidity patterns, and progression rates, suggesting different progression trajectories for different populations.

The mental health trajectory focusing on depressive episode (F32) mainly affected women and Hispanic people and progressed to AD. The mild cognitive impairment trajectory showed the progression from mild cognitive impairment (G31.84) to AD, and the vascular disease trajectory exhibited the longest electronic health record histories and the highest comorbidity burden, which highlights the chronic nature of cerebrovascular disease.

The encephalopathy trajectory was associated with the most rapid progression to AD and subsequent death, highlighting a more aggressive disease course. The study further found that the encephalopathy cluster showed the shortest interval from the first disease indicator to AD diagnosis, and from AD diagnosis to death, suggesting a faster disease course in that subgroup.

The presence of shared vascular risk factors such as hypertension across multiple trajectories indicates that these distinct disease progression pathways may be associated with common pathophysiological mechanisms. These findings highlight the importance of considering and managing shared risk factors to prevent the progression of multiple disease pathways to AD.

The study found consistent directional ordering for approximately 26% of diagnostic progressions regarding directionality of relationships within these trajectories. For example, essential hypertension is frequently followed by depressive episodes, which then progress to AD, suggesting a potential causal sequence.

The validation of study findings in the All of Us Research Program highlighted the generalizability of these trajectories across diverse populations and healthcare settings. These progression trajectories were found to predict the risk of AD more accurately than individual risk factors.

As researchers suggest, healthcare professionals can use these trajectories to identify high-risk patients early, develop targeted interventions, and restrict harmful consequences.

The study used causal inference modeling (Greedy Equivalence Search) to identify likely directional links between diagnoses within each trajectory. The encephalopathy cluster showed more consistent directional relationships (42.9%), indicating a more substantial potential for causal interpretation in this group.

The researchers also constructed simplified "backbone" networks to highlight the most common disease sequences within each trajectory, using modularity-based pruning to reduce noise and emphasize dominant patterns.

Conclusion

The study provides a comprehensive framework for identifying distinct and interconnected disease progression routes that lead to AD. This approach can be applied in different clinical settings to improve risk assessment, timely diagnosis, and targeted interventions. Healthcare professionals should consider the cumulative impact of sequential disease progression while assessing AD risk.

The distinct trajectories identified in the study suggest that AD may develop through multiple pathways. The identification of specific risk factors such as depression, cerebrovascular disease, and other neurodegenerative conditions that often precede AD by several years provides opportunities for early intervention.

The dataset analyzed in the study excluded patients older than 90 years, which may restrict the generalizability of its findings to the population with a high prevalence of AD. Furthermore, health data was collected from six academic health systems in California, which may limit representativeness relative to population-based samples.

Potential misclassifications of AD patients in electronic health records may affect the study findings. Given this concern, researchers advise interpreting these trajectories as pathways leading to clinically diagnosed AD rather than biologically confirmed AD, which would require biomarkers for amyloid or tau pathology. Some diagnostic codes like "unspecified dementia" may reflect temporary or transitional clinical labels, highlighting the real-world complexity of disease classification in health records.

Source:

https://www.news-medical.net/news/20250709/Redefiningc2a0-Alzheimere28099s-development-by-mapping-disease-sequences.aspx