Received: 20 November 2024 | Revised: 19 December 2024 | Accepted: 28 December 2024

DOI: 10.1002/alz.14564

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Unraveling temporal patterns of diagnostic markers and comorbidities in Alzheimer's disease: Insights from large-scale data

Bayard Rogers

University College London, London, UK

Correspondence
Bayard Rogers, University College London, London, United Kingdom.
Email: bayard.rogers.23@alumni.ucl.ac.uk,

Abstract

INTRODUCTION: Comorbid conditions associated with Alzheimer's disease (AD) are poorly understood regarding timing and potential impact on disease onset and progression.

METHODS: Medical Information Mart for Intensive Care-IV electronic health records from 2008 to 2019 were examined. The study identified 2527 AD patients (34.9% male, mean age 80.27 years) among 299,712 patients. We examined the timing of 12 cardiovascular and metabolic diseases relative to AD diagnosis. Data from the National Alzheimer's Coordinating Center validated the findings.

RESULTS: Hypertension was the most common comorbidity, diagnosed 1.09 years before AD. Depression was the only comorbidity diagnosed after AD start, 0.16 years on average. AD patients had greater rates of hypertension, hypercholesterolemia, and depression compared to the general population.

DISCUSSION: The findings emphasize early detection and therapy of AD-related comorbidities, notably cardiovascular and metabolic diseases. The temporal link between these diseases and AD suggests opportunities for preventive strategies and improved care pathways.

KEYWORDS
Alzheimer's disease (AD), comorbidities, disease progression, electronic health record (EHR), hypertension

Highlights

- **Temporal analysis of comorbidities**: The study reveals hypertension and hyperlipidemia as leading precursors to AD, typically diagnosed 1 to 1.3 years prior to AD onset, while depression emerges predominantly after diagnosis.
- **Unique data integration**: Large-scale datasets from MIMIC-IV (n = 299,712) and NACC (n = 51,836) were leveraged to identify chronological patterns in 12 key comorbid conditions relative to AD diagnosis.

- **Sex- and age-specific insights**: AD prevalence peaks at 80 to 86 years, with females exhibiting higher rates of LOAD compared to males.
- **Depression as a post-diagnostic marker**: Unlike other comorbidities, depression's post-diagnostic mean onset (0.16 years after AD diagnosis) highlights the need for targeted mental health interventions in AD patients.
- **Implications for early detection**: Findings suggest that managing hypertension, hyperlipidemia, and other modifiable conditions in midlife may delay or reduce the risk of AD development.
- **Comorbidity variability across cohorts**: Hypertension and hypercholesterolemia showed significantly higher prevalence in the NACC cohort compared to MIMIC-IV, reflecting potential dataset-specific biases or regional healthcare differences.
- **Future research directions**: Advocates for longitudinal, multiethnic, and global studies to refine early diagnostic criteria and explore preventive strategies tailored to comorbid conditions.

1 | BACKGROUND

Alzheimer's disease (AD) is a degenerative neurological disorder that progressively damages the brain and is the leading cause of dementia, especially in older individuals.[1–3] It is characterized by a decline in cognitive functions, including memory, problem-solving skills, language, and perceptual abilities.[4–7] The hallmark pathological features of AD include the accumulation of amyloid beta (Aβ) plaques and tau protein tangles in the brain.[5–7] The tau protein builds up in the long, slender projections of neurons and in the main body of these cells, where it creates solid, insoluble clumps or structures called intracellular aggregates or inclusion bodies, specifically known as neurofibrillary tangles (NFTs).[8,9] The accumulation of proteins, particularly in astrocytes, disrupts cell function and eventually leads to cell atrophy and death.[10–16] This study aims to offer a unique perspective on the factors that contribute to AD, transcending the confines of tau and amyloid plaque investigations.

The etiology of AD is not entirely understood; however, it is hypothesized to occur from a combination of biological, environmental, and behavioral determinants, the most prominent of which is age.[17–20] It is a chronic condition that includes extended periods of preclinical and prodromal (also referred to as mild cognitive impairment [MCI]) stages lasting up to 20 years, followed by a typical clinical duration of 8 to 10 years.[21] Early-onset AD (EOAD) typically presents in individuals under the age of 65 and has distinct patterns of progression in comparison to late-onset AD (LOAD), which is more common in older adults.[17,22] The illness is estimated to affect approximately 10% to 30% of individuals who are at least 65 years old, with an average occurrence rate of 1% to 3% annually.[23] The majority of individuals diagnosed with AD (>95%) exhibit a sporadic variant, which is distinguished by late onset (80 to 90 years old) and is caused by the inability to effectively remove the Aβ peptide from the brain's space.[24] A family history of AD also increases the risk.[25,26] Additionally, genetic factors have been identified as risk contributors.[27–29] To date, genetic research has identified almost 100 risk loci for this disease, contributing to an increased risk of AD onset, with variable effect sizes.[30,31]

It is estimated that over 55 million people worldwide are living with dementia, with AD accounting for 60% to 70% of these cases.[32,33] This number is expected to increase rapidly as the global population ages, potentially reaching 82 million by 2030 and 152 million by 2050.[34] The disease not only affects those who are diagnosed but also places a heavy burden on caregivers and healthcare systems. This leads to significant healthcare costs and social implications, as people with AD require increasing levels of care and support as the disease progresses. While the therapeutic research pipeline for AD is progressing with the development of medicines that target several mechanisms, there is presently no cure for AD.[35–37] Treatment generally focuses on managing symptoms and improving the quality of life for patients and their caregivers including medications to address memory decline and other cognitive symptoms, as well as therapies to assist with mood and behavior management.[38–40] Research is ongoing to better understand AD and find effective treatments.

The analysis of this study is grounded in hypotheses pertaining to the mechanisms of neurodegeneration and the process of aging, examining AD through biological components such as health and molecular changes, and centering on fundamental inquiries, such as the following: What are the key diagnostic events related to AD? When do they transpire over the patient's medical history? What actionable insights may be obtained from large-scale patient trajectories for the benefit of healthcare professionals and patients? Gaining a complete understanding of these distinctions is crucial to create effective treatments and intervention strategies that are specifically designed to meet the unique requirements of each patient. Thus, a comprehensive approach to studying patients' complete medical history in relation to AD enables a more in-depth understanding of disease progression.

2 | METHODS

The main data used in this project were acquired via the Medical Information Mart for Intensive Care (MIMIC)-IV database version 2.2.[41,42] This database contains anonymized electronic health records (EHRs) of patients who were admitted to the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts. The MIMIC-IV dataset consists of patient data from 2008 to 2019, containing information on (N = 299,712) individuals, (n = 431,231) admissions, and (n = 73,181) intensive care unit (ICU) stays. The patient table contains time-related information for each patient, indicated by the anchor year and anchor year group columns. "Anchoring" is the method used by the MIMIC-IV to protect patient data, maintain patient privacy, and enable researchers to estimate the year in which the patient received medical care without giving the exact year. Anchor age refers to the age of the patient in their anchor year, which is a predetermined future time used for patient deidentification. If the patient's age exceeded 89 years in the anchor year, that patient's anchor age was adjusted to 91. This means that all patients older than 89 years were categorized into a single group with an anchor age of 91 years, regardless of their actual age.

The MIMIC-IV comprises data acquired from two separate clinical information systems: CareVue and MetaVision.[42] The MIMIC-IV is divided into two modules: the hospital and ICU. The purpose of these modules is to capture the data's origin or source. This study focused primarily on the hospital module, utilizing patient demographics, hospitalization admission, prescription medicine, and online medical record data. The statistical programs/languages employed were R version 2024.04.2 + 764 for conducting comorbidity analyses, general data handling, and producing graphs. Jamovi Desktop 2.4.12 was used to evaluate patient demographics. The extraction of symptomatic data, medication, and diagnostic events relevant to AD diagnosis was performed utilizing structured code and search term encoding for diagnostic code descriptors, specifically utilizing disease descriptor titles. Researchers have conducted online training to carry out research involving patient EHRs, with the data or samples managed exclusively via PhysioNet[43] Credentialed Health, Data Use Agreement 1.5.0 for MIMIC-IV version 2.2. The entirety of deidentified patient data was securely stored and handled on the University College London (UCL) OneDrive platform. All methods were carried out in accordance with relevant guidelines and regulations in full compliance with UCL's Code of Conduct for Research throughout the research lifecycle and in accordance with the Declaration of Helsinki.

To capture diagnostic occurrences across the medical history of AD patients in the MIMIC-IV, we identified and assessed all concurrent patient diseases, disease events, and diagnoses categorized under International Classification of Disease (ICD) versions 9 and 10. The AD patient data were further evaluated to find the most prevalent comorbidity by the ICD code, frequency, percentage of prevalence, and ICD version in descending order. A decision was made to refrain from mapping ICD-9 codes to ICD-10 codes to maintain medical record consistency and diagnostic accuracy. The ICD-10 provides more detailed descriptors for AD than the ICD-9 does. Codes for other types of dementia were excluded from the comorbidity analysis, as this study focused specifically on non-multifactorial dementia. After assessing all the concurrent medical disorders, we concluded that studying disorders with the highest frequency of incidence would be appropriate for assessment. Patient hospital admittance calendar days and times were utilized to develop disease timelines. We subsequently determined the most prescribed drugs for these patients by merging the MIMIC-IV prescription data frame with individuals diagnosed with AD. We then documented the quantity of prescriptions for each drug. This analysis was performed to ascertain the congruity between the patients' prescribed medications and their diagnosed comorbidities. In this study, medication records were not used to analyze individual treatment regimens. The research did not differentiate

RESEARCH IN CONTEXT

1. **Systematic review**: This study builds upon prior research examining the multifactorial etiology of AD, including its hallmark neuropathological features (Aβ plaques and tau tangles) and its association with various comorbidities. While previous studies established correlations between cardiovascular, metabolic, and neuropsychiatric conditions and AD, they often lacked temporal granularity in defining the onset of comorbidities relative to AD diagnosis. The current research leverages comprehensive data from MIMIC-IV and the NACC to evaluate the chronological relationships between these conditions and AD, enabling the identification of potential early diagnostic markers and intervention windows.
2. **Interpretation**: Our findings underscore hypertension, hyperlipidemia, and depression as significant comorbidities with AD, with unique temporal trends that highlight hypertension and hyperlipidemia often preceding AD diagnosis. Depression, conversely, emerges predominantly after diagnosis. These results suggest distinct pathological interactions between cardiovascular health, metabolic disturbances, and cognitive decline. Importantly, the onset patterns provide actionable insights into disease monitoring and preventive strategies, emphasizing the critical need for early detection and management of these comorbid conditions to potentially delay or mitigate AD progression.
3. **Future directions**: The study advocates for a paradigm shift in AD research, focusing on longitudinal, timeline-based assessments of comorbid conditions. Expanding this work to include diverse, multinational datasets and refining phenotyping techniques will enhance generalizability and applicability. Additionally, integrating biomarkers with temporal comorbidity data may unveil novel intervention targets and therapeutic opportunities for slowing AD onset and progression.

between treated and untreated individuals or assess controlled versus uncontrolled conditions. Comorbidity presence was deduced by the existence of a corresponding medical diagnosis and the presumed standard of care, which assumes medication prescription at the time of diagnosis. This assumption avoids biases introduced by incomplete or unavailable medication data and enables a uniform approach to analyzing comorbidities. Most importantly, although AD is not synonymous with dementia and current knowledge emphasizes the heterogeneity of dementia syndromes, this study uses "AD" as recorded in the patient medical records. These diagnoses were based on clinical criteria available at the time of documentation and may not fully account for the underlying mixed or non-AD pathologies contributing to dementia in these patients. We acknowledge this limitation and emphasize that our findings pertain to individuals diagnosed with "AD" as defined in the clinical context of the dataset.

The selection criteria for the examination of the 12 histograms were established by considering both the frequency of occurrence and the factors identified in earlier research as potential contributors to AD, as mentioned in our literature review. Disease phenotyping was used to more efficiently search for comorbidities within individualized patient records. This step was accomplished by searching for patterns in character vectors to identify comorbidity matches within the patient data items. Each patient was evaluated for the presence of any comorbidity ICD codes according to ICD-9 and 10. For each comorbid condition, the first occurrence was recorded based on the earliest documented ICD code in the MIMIC-IV dataset examining a constant time window prior to an AD diagnosis. Histograms differentiate between longstanding conditions (more than 5 years before AD diagnosis) and those diagnosed proximally (within 5 years before AD designation). The first occurrence of medication relative to comorbidity use was not factored into the analysis. The process of disease phenotyping led to the detailed refinement of 435 ICD codes representing 12 comorbidities (Appendix A). For example, when examining hypertension, there are a total of 19 distinct ICD codes coding for this comorbidity, with seven falling under the ICD-9 category and 12 falling within the ICD-10 category.

To validate or challenge comorbidity findings from the MIMIC-IV, an additional database was examined with individualized patient data. The National Alzheimer's Coordinating Center (NACC) serves as the centralized data repository and hub for collaboration and communication for the National Institute on Aging's (NIA's) Alzheimer's Disease Research Centers (ADRCs) program. The current composition of this program includes a total of 42 research centers and four exploratory centers, which are distributed across 26 states in the United States. From 2005 to the present, ADRCs have been providing data to the uniform dataset (UDS) through a systematic, standardized, and long-term clinical examination of participants in the NIA's ADRC program.[44,45] It comprises individuals with varying cognitive statuses, ranging from no cognitive impairment to dementia. Although this is a larger sample of AD patients than available in MIMIC-IV, this dataset could not be used as the primary source, as it did not contain onset dates for all AD comorbidities. This investigation utilized data from 46 ADRCs for UDS visits conducted between January 2005 and June 2024.

TABLE 1 Demographic description of the MIMIC-IV study sample comparing the total population with AD patients.

	All patients	AD patients
	N (%)	*N* (%)
Total	299,712 (100%)	2527 (0.84%)
Gender		
Female	158,553 (52.9%)	1644 (65.1%)
Male	141,159 (47.1%)	883 (34.9%)
Age groups		
18–40	122,632 (40.92%)	0 (0%)
41–64	100,653 (33.58%)	111 (4.4%)
65–75	38,025 (12.69%)	419 (16.6%)
>76	38,402 (12.81%)	1997 (79%)
Ethnicity		
American Indian/Alaska Native	377 (0.13%)	5 (0.2%)
Asian	7522 (2.51%)	59 (2.3%)
Black/African	1143 (0.38%)	8 (0.3%)
Black/African American	19,304 (6.44%)	255 (10.1%)
Black/Cape Verdean	1886 (0.63%)	25 (1%)
Black/Caribbean Island	1076 (0.36%)	13 (0.5%)
Hispanic or Latino	9765 (3.26%)	84 (3.3%)
Multiple race/Ethnicity	264 (0.09%)	4 (0.2%)
Native Hawaiian or other Pacific Islander	213 (0.07%)	1 (0%)
Other	7475 (2.49%)	62 (2.5%)
Patient declined to answer	971 (0.32%)	10 (0.4%)
Portuguese	511 (0.17%)	2 (0.1%)
South American	240 (0.08%)	4 (0.2%)
Unable to Obtain	1077 (0.36%)	14 (0.6%)
Unknown	8056 (2.69%)	92 (3.6%)
White	115,010 (38.37%)	1789 (70.8%)
White - Brazilian	534 (0.18%)	1 (0%)
White - Eastern European	3670 (1.22%)	49 (1.9%)
White - Russian	1639 (0.55%)	50 (2%)
Missing	118,979 (39.7%)	0 (0%)

Abbreviation: AD, Alzheimer's disease.

3 | RESULTS

By analyzing the medical records of AD patients in the MIMIC-IV, we documented and evaluated a total of 5749 simultaneous occurrences of patient diseases, disease episodes, and diagnoses classified according to ICD-9 and 10. After evaluating all the coexisting medical conditions, we determined that the top 50 most common comorbidities would be an appropriate criterion for inclusion to assess the most prevalent disorders for the study (Appendix B). We subsequently determined the top 50 drugs that were most frequently prescribed to AD patients (n = 15,416,708) (Appendix C). Examination of the drug

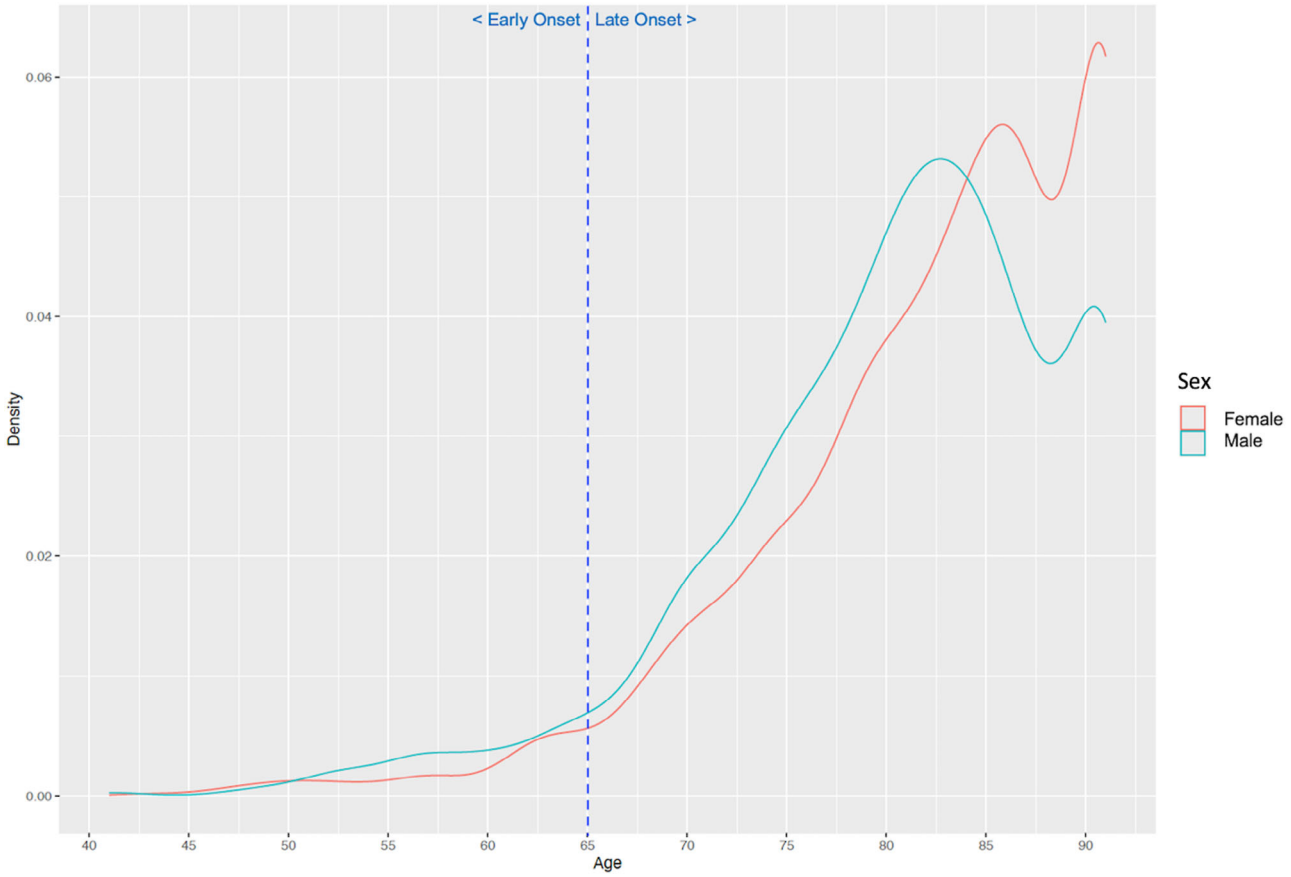

FIGURE 1 A density plot of 2527 Alzheimer's disease (AD) patients presenting a graphical representation of age and sex distributions during their time at Beth Israel Deaconess Medical Center.

data revealed that the outcomes of the prescribed medication were mostly in line with the patients' comorbidities; however, the evaluation revealed no drugs that could indicate novel comorbidity associations with AD.

Within the total sample population (N = 299,712), a subset of individuals (n = 2527) was identified as AD patients. These were determined by searching ICD-9 and 10 for any of the five AD-relevant diagnosis codes (ICD-9 code 3310: AD, n = 1615; ICD-10 G300: AD with early onset, n = 43; ICD-10 G301: AD with late onset, n = 27; ICD-10 G308: other AD, n = 51; and ICD-10 G309: AD unspecified, n = 922). Across all unique AD patients, 2400 patients had one of the above listed codes, 123 patients were diagnosed with two different codes, and four patients had three different codes. Among the AD patients, 65.1% were female (n = 1644), and 34.9% were male (n = 883), as shown in Table 1. The mean age of the AD patients was 81.50 years (SD = 8.37). Among the AD demographics of 2527 individuals, Whites were the most prevalent ethnicity, accounting for 70.8% of the cohort. Next were Black African Americans, accounting for 10.1% of the sample.

Figure 1 shows the density distribution of patients by age at their first AD diagnosis, stratified by sex. The red (female) density curve displays small oscillations compared with the green curve between the ages of 60 and 85, indicating that the density distribution of females slightly varies within this age range. The most significant concentration of AD was found in individuals aged 80 to 86 years, regardless of sex. The density curve for males decreases at the age of 83, whereas the curve for females decreases at the age of 86. The chart shows that females exhibit a somewhat greater prevalence of AD cases than males from 80 to 86 years of age, indicating a greater likelihood or frequency of the disease among women in this age bracket. The marginal rise found at 89 years for both sexes can be attributed to the patient's age being above 89 years and being standardized to 91 years as per the MIMIC-IV deidentification procedure. The dashed blue line designates the age of 65 years as the demarcation point between EOAD and LOAD. Very few observations of EOAD were found in this dataset.

Figure 2 histograms depict the frequency of the 12 most common and prevalent comorbidities found in the AD patient group, which were established after the initial thresholds of the 50 conditions were examined. In the MIMIC-IV dataset, hypertension was the most prevalent comorbidity (n = 1628, 64.42%), followed by general infectious disease (n = 1167, 46.18%) and kidney disease (n = 1103, 43.64%). The histograms illustrate the onset of comorbid disorders, ranging from hyperlipidemia, with a mean onset of −1.27 years, to depression, with a mean onset of 0.16 years. Table 2 displays the histogram data in a comparable manner, including a calculation of the relative frequency in

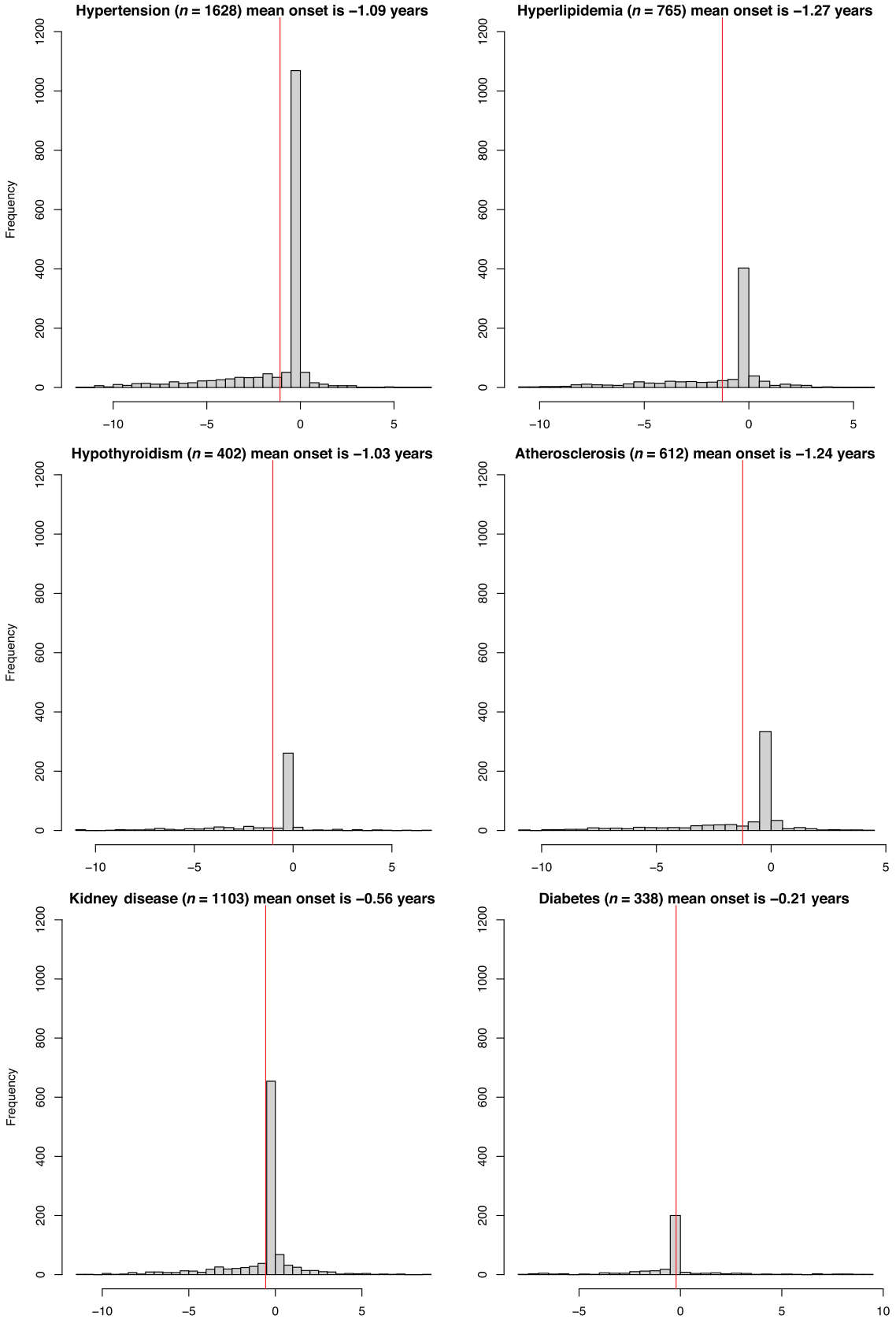

FIGURE 2 Histograms depicting the time of comorbidity initiation in years for a group of 2527 patients with Alzheimer's disease (AD) relative to their AD diagnosis. The *y*-axis depicts the frequency of comorbid diseases, whereas the *x*-axis represents the timing of comorbidity in relation to the patient's diagnosis of AD. A numerical value of zero signifies the first AD diagnosis. Negative values represent the duration in years prior to the initial clinical diagnosis of AD, whereas positive values indicate the duration in years after the clinical diagnosis. The red line represents the average period when comorbidity first appears across all patients with that comorbidity.

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

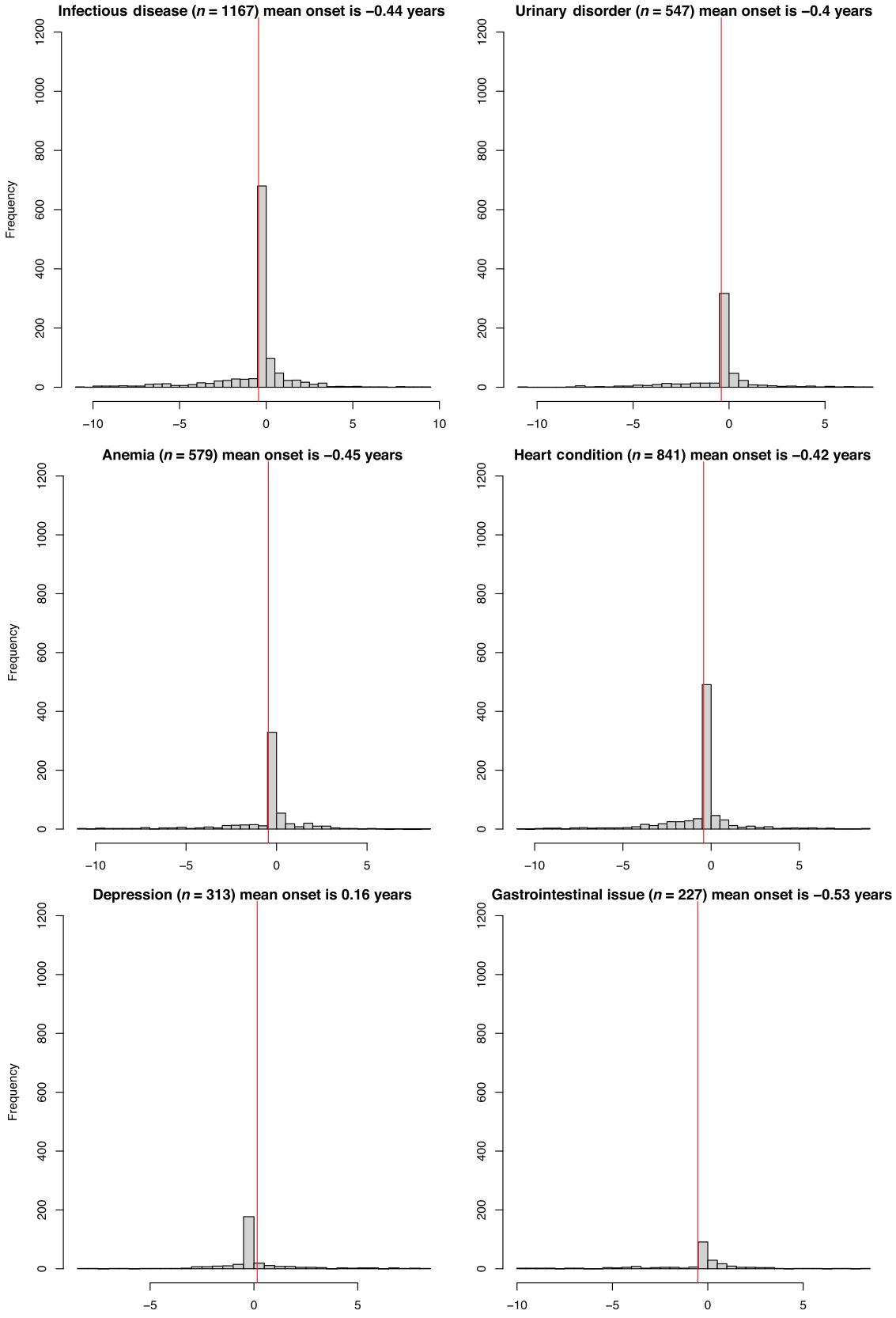

FIGURE 2 Continued

TABLE 2 A table of the top 12 most common comorbidities sorted by *N* and relative frequency (percent) of all patients with AD.

Comorbidity	*N*	Relative frequency (%)	Mean onset (+ – years)	Min onset (+ – years)	Max onset (+ – years)
Hypertension	1628	64.42	−1.09	−11.58	6.58
Infectious disease	1167	46.18	−0.44	−10.81	9.37
Kidney disease	1103	43.64	−0.56	−11.23	8.54
Heart condition	841	33.28	−0.42	−10.89	8.69
Hyperlipidemia	765	30.27	−1.27	−10.95	5.57
Atherosclerosis	612	24.21	−1.24	−10.9	4.16
Anemia	579	22.91	−0.45	−10.83	8.03
Urinary disorder	547	21.64	−0.4	−10.83	7.15
Hypothyroidism	402	15.9	−1.03	−10.95	6.58
Diabetes	338	13.37	−0.21	−7.68	9.37
Depression	313	12.38	0.16	−8.13	8.01
Gastrointestinal issue	227	8.98	−0.53	−9.79	8.01

percentage and the range between the minimum and maximum onset in years.

Hyperlipidemia, characterized by elevated levels of lipids or lipoproteins in the blood, was linked to the longest average time before the diagnosis of AD, with a mean onset of −1.27 years, and in certain instances it was up to −10.95 years. Similarly, arteriosclerosis has a relatively substantial period between diagnosis and the onset of AD, with a mean onset of −1.24 years. A greater number of comorbidities are associated with cardiovascular disease. Moreover, research suggests a significant correlation between anemia, occurring with a relative frequency of 22.91%, and chronic heart disease, kidney disease, and diabetes.[46–53] Similarly, urinary disorders, with a relative frequency of 21.64%, have been linked to AD and MCI.[54–56] Every comorbidity has its own distinct clinical manifestation; however, a shared characteristic across all of them, including depression, is that each one involves an imbalance in the control of the immune system that could lead to a subsequent condition of systemic inflammation.[57–62] Depression is the sole comorbidity with a mean onset time after AD diagnosis. Depression disorder was included in the analysis, as it ranked 14th among the top 50 comorbidities, with a prevalence of 18.36% in the AD sample. Additionally, the literature has established a correlation between depression and cognitive impairment. With respect to the gut–brain axis, gastrointestinal comorbidities had the lowest occurrence rate, at 8.98%, in the MIMIC-IV sample. The variability in these histograms pertains to the dispersion of the onset times around the mean. Narrower histogram indicate that bars that are closer to the mean have lower variability. Conversely, a wider histogram suggests greater variability. As such, diabetes, depression, and gastrointestinal issues have a relatively low level of variability, with most occurrences happening near the mean onset time. Compared with these three comorbidities, all other comorbidities have a somewhat broader range of occurrence, indicating that their onset periods are substantially more varied.

TABLE 3 NACC data sample demographics comparing entire patient population with patients diagnosed with AD.

	All patients *N* (%)	AD patients *N* (%)
Total	51,836 (100%)	24,602 (47.46%)
Gender		
Female	29,689 (57.3%)	13,453 (54.7%)
Male	22,147 (42.7%)	11,149 (45.3%)
Ethnicity		
White	21,021 (40.55%)	19,982 (81.2%)
Black or African American	4432 (8.55%)	3189 (13.0%)
American Indian or Alaska Native	280 (0.54%)	187 (0.8%)
Native Hawaiian or other Pacific Islander	33 (0.06%)	25 (0.1%)
Asian	841 (1.62%)	591 (2.4%)
Other (specify)	418 (0.81%)	471 (1.9%)
Unknown	209 (0.4%)	157 (0.6%)

Abbreviation: AD, Alzheimer's disease.

The NACC data, which were used for replication of findings, included (n = 51,836) unique patients, of whom n = 24,602 had a formal diagnosis of AD; a demographic overview of this sample is shown in Table 3. Among the AD patients, 54.7% were female (n = 13,453), and 45.3% were male (n = 11,149). Among the AD demographics, White ethnicity was again the most prevalent ethnicity, accounting for 81.2% of the cohort. Next were Black African Americans, with a representation of 13.0%. The demographic outcomes and proportions of White to Black African Americans in the MIMIC cohort exhibited considerable similarity. Among the 12 comorbidities from the MIMIC-IV dataset, only five were classified as unique categories in the NACC investigator dataset, potentially suggesting a specific focus or research interest

TABLE 4 NACC data overview of comorbidities comparing frequencies in whole patient population with only patients diagnosed with AD.

Comorbidity	All patients in NACC with comorbidity *N* (%)	AD patient in NACC with comorbidity *N* (%)	AD patient in MIMIC-IV with comorbidity *N* (%)
Diabetes	7359 (14.2%)	3556 (14.5%)	338 (13.37%)
Hypertension	26,469 (51.1%)	13,249 (53.9%)	1628 (64.42%)
Hypercholesterolaemia	27,037 (52.2%)	13,531 (55.0%)	765 (30.27%)
Thyroid Disease	9041 (17.4%)	4426 (18.0%)	402 (15.90%)
Depression[a]	18,354 (35.4%)	10,457 (42.5%)	313 (12.38%)

Note: The MIMIC-IV AD patient comorbidity data have been included in the adjacent column, allowing for comparison.
Abbreviations: AD, Alzheimer's disease; MIMIC-IV, Medical Information Mart for Intensive Care-IV; NACC, National Alzheimer's Coordinating Center.
[a]The NACC depression code used for this study was defined as having depression within the last 2 years.

in these conditions. We examined these five datasets for comparison with the MIMIC-IV dataset, as shown in Table 4.

The results of the NACC and MIMIC-IV datasets are largely similar, with the exceptions of hypertension, hypercholesterolemia, and depression. In the NACC sample, Alzheimer's patients with comorbidities had a greater prevalence of hypertension, hypercholesterolaemia, thyroid illness, and depression than did all non-Alzheimer's patients with comorbidities. The frequency of diabetes is approximately equal in both categories. These findings indicate that individuals with AD may have a slightly elevated likelihood of experiencing specific comorbidities, such as hypertension, hypercholesterolaemia, and depression. Like the MIMIC-IV cohort, the NACC AD group exhibited cardiovascular disease as the predominant medical condition. Notably, hypercholesterolemia had a relative frequency of 55.0% in NACC AD patients compared with 30.27% in the MIMIC-IV AD patients. Compared with the MIMIC-IV cohort, the NACC AD group presented similar prevalence rates (within a 5% range) of diabetes and thyroid disease. Depression showed the greatest significant difference in comorbidities, with a prevalence of 42.5% in the NACC AD sample. The odds ratio (OR), together with its standard error and 95% confidence range, is computed in Table 5 for NACC hypertension, hypercholesterolaemia, thyroid disease, and diabetes patients with an AD diagnosis via the methodology described by Altman in 1990.[63] Depression was excluded from testing since it typically occurs after AD diagnosis in the MIMIC-IV analysis. In addition, the data on depression in the NACC database rely partially on self-reports, which may introduce some degree of unreliability.

In summary, the evidence suggests a statistically significant impact, with a moderate although substantial rise in the likelihood of an AD diagnosis for patients with hypertension or hypercholesterolemia. The results also indicate that the presence of a thyroid condition or diabetes does not have a significant effect on the capacity to accurately predict a diagnosis of AD in this assessment.

4 | DISCUSSION

The objective of this study was to explore the current gap in AD research by employing a timeline-focused, data-driven approach to assess the frequency and onset of other medical disorders that might contribute to the complex etiology of AD. The aim of this approach was not only to detect patterns of disease comorbidity across time but also to determine the specific time when individuals were diagnosed with comorbidities in relation to their Alzheimer's diagnosis.

The examination of the histograms for 11 out of 12 coexisting medical conditions reveals a noteworthy trend concerning the chronological connection between the initiation of these ailments and the identification of AD. Histograms show that most of the comorbidities analyzed typically start occurring prior to AD diagnosis. This discovery implies that there could be an opportunity for early management and surveillance, as these coexisting medical conditions may act as early signs of the potential onset of AD. The identification of hypothyroidism, which typically initiates approximately 1.09 years before the manifestation of symptoms and, in certain cases, 10.95 years earlier, was unexpected, as initial investigations did not uncover any notable associations between hypothyroidism and AD. Hypothyroidism is a condition characterized by insufficient production of thyroid hormone by the thyroid gland. The initial phases of hypothyroidism may not exhibit any symptoms. Untreated hypothyroidism can lead to several health issues, such as increased levels of cholesterol, cardiovascular problems, and impaired cognitive function.[64,65] Thyroid disease was diagnosed in 18.0% of the NACC AD population.

While kidney illness and infectious disease were frequently observed in the MIMIC-IV AD group, it is crucial to exercise caution when declaring them to be primary causes of AD. The effects of the normal aging process are relevant to all comorbidities. Specifically, diabetes, kidney disorders, urological ailments, and infectious diseases serve as examples of this phenomenon.[66–69] Phenotyping identified a total of 72 distinct ICD-9 and ICD-10 codes for infectious diseases, comprising internal, external, bacterial, and viral infections. In addition, a total of 77 distinct renal disorders were identified, potentially contributing to the elevated prevalence of these diseases. Conversely, while only 19 different ICD-9 and 10 codes were identified for hypertension and only three codes were identified for defining hyperlipidemia, the incidence rates of both diseases were high. Importantly, some studies suggest that individuals in their forties, who are younger adults, are more vulnerable to cardiovascular disease than older individuals.[70–72] Curiously, depression is the only exception

TABLE 5 NACC OR calculation for comorbidities in AD patients.

NACC AD odds ratio for comorbidity	Hypertension *N*	Hypercholesterolemia *N*	Thyroid disease *N*	Diabetes *N*
Subjects with AD				
Exposed group	13,249	13,531	4426	3556
Nonexposed group	11,353	11,071	20,176	21,046
Subjects without AD				
Exposed group	26,469	27,037	9041	7359
Nonexposed group	25,367	24,799	42,795	44,477
Odds ratio	1.1184	1.121	1.0384	1.0212
95% CI	1.0849 to 1.1530	1.0874 to 1.1557	0.9980 to 1.0804	0.9780 to 1.0663
z statistic	7.213	7.351	1.861	0.95
Significance level	$p < 0.0001$	$p < 0.0001$	$p = 0.0628$	$p = 0.3419$

Note: Exposure reflects a comorbidity diagnosis. An OR of 1.1184 indicates that the odds of receiving an AD diagnosis are 1.1184 times greater in patients with hypertension, indicating an 11.84% increase in the odds of receiving an AD diagnosis if a patient has hypertension. A hypercholesterolemia diagnosis is associated with a 12.10% increase in the odds of receiving an AD diagnosis. Thyroid disease and diabetes do not significantly increase the risk of a patient developing AD.
Abbreviations: AD, Alzheimer's disease; NACC, National Alzheimer's Coordinating Center.

among the comorbidities studied, with the mean onset observed in this study after the diagnosis of AD. The unique temporal pattern shown in depression, appearing on average 0.16 years after the diagnosis of AD, with the possibility of onset ranging up to 8.01 years after, highlights the importance of targeted mental health treatments after clinical diagnosis. Upon evaluation, 42.5% of the NACC AD group reported experiencing depression over the preceding 2 years. These findings emphasize the necessity of therapies that specifically target the intricate connection between AD and the emergence of subsequent depressive symptoms.

The MIMIC-IV dataset shows that the top 50 diseases and conditions that occur alongside AD include a diverse spectrum of afflictions, mostly chronic, cardiovascular, metabolic, and neurological issues. The list provides an overview of the main health issues linked to the process of aging, including AD, various cardiovascular conditions (such as atrial fibrillation and congestive heart failure), diabetes mellitus, and hypertension. Moreover, it includes lifestyle-related illnesses such as hyperlipidemia. Notably, modest variations in disease categorization were detected between the two databases. Hypercholesterolemia is a type of hyperlipidemia. Hyperlipidemia is a comprehensive term that includes both genetic and acquired conditions that cause high levels of lipids in the bloodstream. Nevertheless, it is crucial to emphasize that hypercholesterolemia does not encompass the quantification of triglycerides. Furthermore, the NACC employs the framework of thyroid illness as opposed to the more specific hypothyroidism. Hashimoto's disease is the most common type of autoimmune disorder that causes an underactive thyroid. Importantly, most of the medical disorders associated with the evaluation of the 12 comorbidities examined in this study can be effectively controlled and regulated to different extents. The results presented here emphasize the possibility of using an intervention strategy to possibly delay the advancement of AD.

The differing definitions of EOAD (eg, occurring before 65 years of age) and LOAD (eg, occurring after 65 years of age), based on clinical observations and epidemiological analysis, suggest a level of AD onset that cannot be adequately represented by a single age. The inherent variation in the manifestation of AD among individuals, with some showing symptoms earlier or later than the expected age of onset, underscores the limitations of relying solely on a fixed age criterion to categorize distinct patient groups. The existence of this variance emphasizes the need for an individualized approach to the diagnosis and treatment of AD, rather than just depending on a generic age criterion, especially for disease classification.

Concerns about the timing of comorbidity onset relative to AD diagnosis neglect numerous important factors that underscore the significance of these findings. First, AD is characterized by a prolonged preclinical phase, where pathological changes such as Aβ accumulation occur decades before clinical symptoms emerge, making late-stage comorbidities potentially integral to disease progression. Additionally, many comorbidities, including hypertension and hyperlipidemia, share risk factors with AD, such as aging and vascular health, and may influence AD onset even when detected closer to diagnosis. Systemic mechanisms like chronic inflammation or vascular compromise may further accelerate AD progression, creating a tipping point coinciding with clinical diagnosis. Detection bias must also be considered, as individuals experiencing cognitive decline often undergo more rigorous medical evaluations, increasing the likelihood of identifying comorbidities. Furthermore, fragmented or incomplete medical records may underestimate the true timing of comorbidity onset, inadvertently skewing the observed temporal relationship. The identification and management of comorbidities, even shortly before AD diagnosis, remain crucial for secondary prevention, as they may delay progression or mitigate symptom severity. Lastly, a reclassification of current ICD Alzheimer's codes into AD pathology-positive and AD pathology-

negative categories could improve clinical accuracy by distinguishing individuals based on biomarker-confirmed pathology rather than clinical symptoms alone. This distinction is particularly significant given the frequent coexistence of additional dementia-causing pathological features, such as vascular pathology, Lewy bodies (LB), or TAR DNA-binding protein (TDP) pathology, alongside AD pathology. Recognizing and categorizing these coexistent pathologies would enable more precise targeting of comorbidities and interventions, ultimately enhancing the scope and impact of Alzheimer's research and care strategies.

The MIMIC-IV dataset was selected as the primary dataset due to the inclusion of diagnostic information with exact dates derived from EHR data for all comorbidities. The NACC dataset does not provide information on the time interval between the diagnosis of AD and the occurrence of comorbidities in all patients. The MIMIC-IV dataset consists of data obtained from a single hospital's comprehensive EHR system. In contrast, NACC exploratory centers have unique research goals and recruitment strategies that are integrated into the UDS. The UDS data are collected through in-person UDS-related appointments, visits to individuals' homes, and discussions conducted via video or phone. The dataset consists of a combination of patient record data and patient self-reported information obtained through questionnaires. Therefore, the precision of EHR, which is a chargeable medical occurrence present in the MIMIC-IV database, is lacking. NACC was included as a secondary analysis to compare demographics and comorbidities in the secondary sample and to explore the robustness of findings in independent samples.

A noteworthy limitation of the primary study is that the sample of participants in the MIMIC-IV was exclusively derived from a single institution and a single database. The use of the NACC as a secondary sample helped explore some of the findings from MIMIC on a larger nationwide scale. Another limitation is that it is conceivable that certain individuals may have received a diagnosis of AD or another medical ailment from an alternate healthcare facility or a different primary care physician. Frequently, individuals' personal medical information fails to accompany them throughout their lifetime, or physical records are not converted into digital formats. Unobserved progress also imposes a constraint. Individuals may exhibit signs of a condition, but they are only officially diagnosed when they seek medical attention at a hospital. This introduces uncertainty when analyzing the occurrence of multiple conditions simultaneously. Therefore, the evaluations conducted in this study are likely to underestimate the total number of diagnoses.

The MIMIC-IV dataset comprises patient data collected between 2008 and 2019; this study used both ICD-9 and ICD-10 codes for disease classification. The switch to the ICD-10 occurred on October 1, 2015. Compared with the ICD-9 codes, the ICD-10 codes have a significantly greater level of specificity. Within the scope of this research, the ICD-10 encompasses four distinct codes for AD, with a particular emphasis on differentiating between early- and late-onset AD diagnoses. In contrast, the ICD-9 has only one code for AD that does not distinguish AD based on onset. Among the 2527 unique AD patients, $n = 1615$ (63.9%) had the ICD-9 code. The variability of the definitions across the five AD diagnostic codes used in the MIMIC-IV dataset made it difficult to accurately differentiate and assess the distinctions between EOAD and LOAD. While ICD codes provide a reliable marker for clinical diagnosis, it is essential to recognize that pathophysiological changes in AD begin decades prior to clinical designation. Furthermore, most patients with an AD designation exhibit additional coexisting pathologies, such as vascular, LB, or TDP-43-related pathologies. These factors were considered when interpreting comorbidity timelines, as they may influence the onset and progression of clinical symptoms. Results should, therefore, be viewed as reflective of broader dementia pathology and not solely of AD. The observed prevalence of 0.8% in the MIMIC-IV dataset likely reflects selection biases, including underdiagnosis, late diagnosis, and the fact that this dataset captures hospitalized patients. Comorbid conditions may disproportionately bring patients to healthcare settings, potentially confounding the relationship between these conditions and AD diagnosis. This highlights the need for cautious interpretation of causal inferences, as comorbidities may serve as proxies for healthcare engagement rather than direct contributors to AD pathology.

While it was essential to utilize NACC data to validate the results of the MIMIC-IV study, it is crucial to acknowledge that the individuals participating in the NACC study do not constitute a statistically representative sample of the whole US population, regardless of their dementia status. Alternatively, a more accurate perspective would be to consider them as a sequence of medical cases obtained via referrals or volunteers. Hence, the data obtained from NACC are inadequate for ascertaining the prevalence or incidence of certain types of dementia in the entire population of the U.S. Leveraging the longitudinal nature of the NACC dataset to analyze comorbidities in cognitively normal individuals and tracking their progression to MCI or AD designation could provide valuable insights into the temporal sequence of disease events. Such an analysis would complement the MIMIC-IV findings by offering a broader perspective on disease progression and the interplay between comorbidities and cognitive decline. Future studies should prioritize longitudinal designs to elucidate causal pathways.

Finally, although the diversity of Boston's population (from which the MIMIC-IV data originate) has increased, 70.8% of the 2575 individuals diagnosed with AD and 38.37% of the 299,712 cohort in this sample self-identified as White. According to the 2010 US Census Bureau, the city and its surrounding region had a white population of 47.0% and a Black/African American population of 22.4%. In 2020, the US Census Bureau reported a marginal shift in these numbers to 44.6% and 19.1%, respectively, indicating little change.[73] These data may have had an impact on the ethnic composition of patient admissions.[74,75] Future studies on AD will benefit from the use of hospitals or databases that contain a broader range of demographic variables within significant multinational datasets. Analyzing data from this type of cohort could reveal whether there are variations in comorbidity patterns among different ethnic groups.

This study highlights comprehensive methodologies for achieving a deeper understanding of AD and aims to enhance knowledge of AD through several investigative perspectives. The findings provide evidence indicating that several diseases may play a role, to varying degrees, in the development of AD. This revelation is significant since it

has the potential to fundamentally change the approach to conducting AD research, with the aim of expediting the development of remedies for the illness. Understanding AD comorbidities is crucial, as they might influence the onset and progression of AD or, alternatively, share common risk factors that contribute to the development of the disease. By documenting crucial diagnostic events throughout a patient's medical history, this analysis serves as an example of how researchers can illustrate the variations in symptoms and disease signs at different times of an AD patient's life. This approach affords a more complete understanding of the evolution of AD and its long-term effects. By analyzing medical records across large datasets, it is feasible to extract significant data that have the potential to reveal patterns or attributes that can improve the precision of diagnosis, treatment approaches, and general well-being of those affected by AD.

ACKNOWLEDGMENTS

The NACC database is funded by the NIA/National Institutes of Health Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI John Morris, MD), P30 AG066518 (PI Jeffrey Kaye, MD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI David Bennett, MD), P30 AG072978 (PI Neil Kowall, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Eric Reiman, MD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Todd Golde, MD, PhD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Justin Miller, PhD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), and P30 AG072959 (PI James Leverenz, MD).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

The Institutional Review Board at the Beth Israel Deaconess Medical Center approved the data sharing initiative and waived informed consent for collecting MIMIC-IV patient information and creation of the research resource. The NIA's ADRCs collect written informed consent from all participants and coparticipants.

REFERENCES

1. Tay LX, Ong SC, Tay LJ, Ng T, Parumasivam T. Economic burden of Alzheimer's disease: a systematic review. *Value Health Reg Issues*. 2024;40:1-12.
2. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25:5789.
3. McGirr S, Venegas C, Swaminathan A. Alzheimers disease: a brief review. *J Exp Neurol*. 2020;1:89-98.
4. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol*. 2020;19:271-278.
5. Guo T, Noble W, Hanger DP. Roles of tau protein in health and disease. *Acta Neuropathol*. 2017;133:665-704.
6. Mietelska-Porowska A, Wasik U, Goras M, Filipek A, Niewiadomska G. Tau protein modifications and interactions: their role in function and dysfunction. *Int J Mol Sci*. 2014;15:4671-4713.
7. Wang Y, Mandelkow E. Tau in physiology and pathology. *Nat Rev Neurosci*. 2016;17:22-35.
8. Zhang H, Cao Y, Ma L, Wei Y, Li H. Possible mechanisms of tau spread and toxicity in Alzheimer's disease. *Front Cell Dev Biol*. 2021;9:707268.
9. Moloney CM, Lowe VJ, Murray ME. Visualization of neurofibrillary tangle maturity in Alzheimer's disease: a clinicopathologic perspective for biomarker research. *Alzheimers Dement*. 2021;17:1554-1574.
10. Franzmeier N, Neitzel J, Rubinski A, et al. Functional brain architecture is associated with the rate of tau accumulation in Alzheimer's disease. *Nat Commun*. 2020;11:347.
11. Richetin K, Steullet P, Pachoud M, et al. Tau accumulation in astrocytes of the dentate gyrus induces neuronal dysfunction and memory deficits in Alzheimer's disease. *Nat Neurosci*. 2020;23:1567-1579.
12. Reid MJ, Beltran-Lobo P, Johnson L, Perez-Nievas BG, Noble W. Astrocytes in tauopathies. *Front Neurol*. 2020;11:572850.
13. Sengoku R. Aging and Alzheimer's disease pathology. *Neuropathology*. 2020;40:22-29.
14. Sehar U, Rawat P, Reddy AP, Kopel J, Reddy PH. Amyloid beta in aging and Alzheimer's disease. *Int J Mol Sci*. 2022;23:12924.
15. Pini L, Pievani M, Bocchetta M, et al. Brain atrophy in Alzheimer's disease and aging. *Ageing Res Rev*. 2016;30:25-48.
16. Henstridge CM, Hyman BT, Spires-Jones TL. Beyond the neuron–cellular interactions early in Alzheimer disease pathogenesis. *Nat Rev Neurosci*. 2019;20:94-108.
17. Ayodele T, Rogaeva E, Kurup JT, Beecham G, Reitz C. Early-onset Alzheimer's disease: what is missing in research? *Curr Neurol Neurosci Rep*. 2021;21:1-10.
18. Yadav M, Pandey P, Sharma P. Understanding the genetic, molecular, and cellular basis of ageing as the biggest risk factor of Alzheimer's disease. *Eur J Biol Res*. 2022;12:62-76.
19. Zhu D, Montagne A, Zhao Z. Alzheimer's pathogenic mechanisms and underlying sex difference. *Cell Mol Life Sci*. 2021;78:4907-4920.
20. Sharma P, Sharma A, Fayaz F, Wakode S, Pottoo FH. Biological signatures of Alzheimer's disease. *Curr Top Med Chem*. 2020;20:770-781.
21. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimers Dement*. 2019;15:888-898.
22. Duara R, Barker W. Heterogeneity in Alzheimer's disease diagnosis and progression rates: implications for therapeutic trials. *Neurotherapeutics*. 2023;19:8-25.
23. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. *Nat Rev Dis Primers*. 2015;1:1-18.
24. Ochalek A, Mihalik B, Avci HX, et al. Neurons derived from sporadic Alzheimer's disease iPSCs reveal elevated TAU hyperphosphorylation, increased amyloid levels, and GSK3B activation. *Alzheimer's Res Ther*. 2017;9:1-19.
25. Andrews SJ, Fulton-Howard B, Goate A. Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. *Lancet Neurol*. 2020;19:326-335.

26. Zhang Q, Sidorenko J, Couvy-Duchesne B, et al. Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture. *Nat Commun*. 2020;11:4799.
27. Franzmeier N, Suárez-Calvet M, Frontzkowski L, et al. Higher CSF sTREM2 attenuates ApoE4-related risk for cognitive decline and neurodegeneration. *Mol Neurodegeneration*. 2020;15:1-10.
28. Pasqualetti G, Thayanandan T, Edison P. Influence of genetic and cardiometabolic risk factors in Alzheimer's disease. *Ageing Res Rev*. 2022:101723.
29. Serrano-Pozo A, Das S, Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *Lancet Neurol*. 2021;20:68-80.
30. Kong F, Wu T, Dai J, et al. Knowledge domains and emerging trends of Genome-wide association studies in Alzheimer's disease: a bibliometric analysis and visualization study from 2002 to 2022. *PLoS One*. 2024;19:e0295008.
31. Li J, Chen D, Liu H, et al. Identifying potential genetic epistasis implicated in Alzheimer's disease via detection of SNP-SNP interaction on quantitative trait CSF Aβ42. *Neurobiol Aging*. 2024;134:84-93.
32. Sârbu F, Lungu M, Oprea VD, Romila A. Early depressive manifestations in patients with dementia caused by Alzheimer's disease. *Exp Ther Med*. 2024;27:1-15.
33. Kamble SM, Patil KR, Upaganlawar AB. Etiology, pathogenesis of Alzheimer's disease and amyloid beta hypothesis. *Alzheimer's Disease and Advanced Drug Delivery Strategies*. Elsevier; 2024:1-11.
34. Jain M, Hogervorst E. The impact of the dementia epidemic. *Design for Dementia*. Routledge; 2024:5-17.
35. Golde TE. Disease-modifying therapies for Alzheimer's disease: more questions than answers. *Neurotherapeutics*. 2023;19:209-227.
36. Kurkinen M, Fułek M, Fułek K, Beszłej JA, Kurpas D, Leszek J. The amyloid cascade hypothesis in Alzheimer's disease: should we change our thinking? *Biomolecules*. 2023;13:453.
37. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement (N Y)*. 2023;9:e12385.
38. Buccellato FR, D'anca M, Tartaglia GM, Del Fabbro M, Scarpini E, Galimberti D. Treatment of Alzheimer's disease: beyond symptomatic therapies. *Int J Mol Sci*. 2023;24:13900.
39. Pless A, Ware D, Saggu S, Rehman H, Morgan J, Wang Q. Understanding neuropsychiatric symptoms in Alzheimer's disease: challenges and advances in diagnosis and treatment. *Front Neurosci*. 2023;17:1263771.
40. Heilman KM, Nadeau SE. Emotional and neuropsychiatric disorders associated with Alzheimer's disease. *Neurotherapeutics*. 2023;19:99-116.
41. Johnson A, Bulgarelli L, Pollard T, et al. MIMIC-IV (version 3.1). *PhysioNet*. 2024. doi:10.13026/kpb9-mt58
42. Johnson AEW, Bulgarelli L, Shen Lu, et al. MIMIC-IV, a freely accessible electronic health record dataset. *Sci Data*. 2023;10.
43. Goldberger AL, Amaral LAN, Glass L, et al. PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals. *Circulation*. 2000;101:e215-e220.
44. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: the uniform data set. *Alzheimer Dis Assoc Disord*. 2007;21:249-258.
45. Beekly DL, Ramos EM, van Belle G, et al. The national Alzheimer's coordinating center (NACC) database: an Alzheimer disease database. *Alzheimer Dis Assoc Disord*. 2004;18:270-277.
46. Lanser L, Fuchs D, Scharnagl H, et al. Anemia of chronic disease in patients with cardiovascular disease. *Front Cardiovasc Med*. 2021;8:666638.
47. Kurz K, Lanser L, Seifert M, Kocher F, Pölzl G, Weiss G. Anaemia, iron status, and gender predict the outcome in patients with chronic heart failure. *ESC Heart Fail*. 2020;7:1880-1890.
48. Graham FJ, Masini G, Pellicori P, et al. Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure. *Eur J Heart Fail*. 2022;24:807-817.
49. Portolés J, Martín L, Broseta JJ, Cases A. Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. *Front Med*. 2021;8:642296.
50. van Haalen H, Jackson J, Spinowitz B, Milligan G, Moon R. Impact of chronic kidney disease and anemia on health-related quality of life and work productivity: analysis of multinational real-world data. *BMC Nephrol*. 2020;21:1-15.
51. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. *Lancet*. 2021;398:786-802.
52. Mokgalaboni K, Phoswa W. Cross-link between type 2 diabetes mellitus and iron deficiency anemia. A mini-review. *Clin Nutr Open Sci*. 2022;45:57-71.
53. Paolillo S, Scardovi AB, Campodonico J. Role of comorbidities in heart failure prognosis Part I: anaemia, iron deficiency, diabetes, atrial fibrillation. *Eur J Prev Cardiol*. 2020;27:27-34.
54. Wang Y, Wang Y, Zhu J, et al. Systematic evaluation of urinary formic acid as a new potential biomarker for Alzheimer's disease. *Front Aging Neurosci*. 2022;14:1046066.
55. Yilmaz A, Ugur Z, Bisgin H, et al. Targeted metabolic profiling of urine highlights a potential biomarker panel for the diagnosis of Alzheimer's disease and mild cognitive impairment: a pilot study. *Metabolites*. 2020;10:357.
56. Seol W, Kim H, Son I. Urinary biomarkers for neurodegenerative diseases. *Exp Neurobiol*. 2020;29:325.
57. Foo K, Roofeh D. Inflammatory diseases. *Pediatric Rotations: A Quick Guide for Medical Students*. Springer; 2024:335-348.
58. Petreski T, Piko N, Ekart R, Hojs R, Bevc S. Review on inflammation markers in chronic kidney disease. *Biomedicines*. 2021;9:182.
59. Canny SP, Orozco SL, Thulin NK, Hamerman JA. Immune mechanisms in inflammatory anemia. *Annu Rev Immunol*. 2023;41:405-429.
60. Kumar S, Pollok R, Goldsmith D. Renal and urological disorders associated with inflammatory bowel disease. *Inflamm Bowel Dis*. 2023;29:1306-1316.
61. Majd M, Saunders EF, Engeland CG. Inflammation and the dimensions of depression: a review. *Front Neuroendocrinol*. 2020;56:100800.
62. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. *Neuron*. 2020;107:234-256.
63. Altman DG. *Practical Statistics for Medical Research*. Chapman and Hall/CRC; 1990.
64. Feldt-Rasmussen U, Effraimidis G, Bliddal S, Klose M. Consequences of undertreatment of hypothyroidism. *Endocrine*. 2024;84:301-308.
65. Rose SR, Wassner AJ, Wintergerst KA, et al. Congenital hypothyroidism: screening and management. *Pediatrics*. 2023;151:e2022060420.
66. Prasad N, Patel MR. Infection-induced kidney diseases. *Front Med*. 2018;5:327.
67. Pavkov ME, Collins AJ, Coresh J, Nelson RG. *Kidney Disease in Diabetes, (National Institute of Diabetes and Digestive and Kidney Diseases (US), Bethesda (MD), 2018)*. 3rd edn. National Institute of Diabetes and Digestive and Kidney Diseases (US): Bethesda (MD). 2018.
68. Scherberich JE, Fünfstück R, Naber KG. Urinary tract infections in patients with renal insufficiency and dialysis–epidemiology, pathogenesis, clinical symptoms, diagnosis and treatment. 2021.
69. Chávez-Reyes J, Escárcega-González CE, Chavira-Suárez E, et al. Susceptibility for some infectious diseases in patients with diabetes: the key role of glycemia. *Front Public Health*. 2021;9:559595.
70. Tsai M-C, Lee C-C, Liu S-C, Tseng P-J, Chien K-L. Combined healthy lifestyle factors are more beneficial in reducing cardiovascular disease in younger adults: a meta-analysis of prospective cohort studies. *Sci Rep*. 2020;10:18165.

71. Hasebe T, Hasebe N. Impact of risk factors related to metabolic syndrome on acute myocardial infarction in younger patients. *Hypertens Res*. 2022;45:1447-1458.
72. Gooding HC, Gidding SS, Moran AE, et al. Challenges and opportunities for the prevention and treatment of cardiovascular disease among young adults: report from a National Heart, Lung, and Blood Institute Working Group. *J Am Heart Assoc*. 2020;9:e016115.
73. Boston Planning & Development Agency, Research Division. Race and Ethnicity in the 2020 Census: Self-Identification or classification? 5 (BPDA Research Division, Boston, MA, 2020).
74. U.S. Census Bureau. American Community Survey (ACS). Vol. 2024. Accessed February 12, 2024.
75. Muñoz AP, Kim M, Chang M, Jackson R, Hamilton D, Darity WA. The color of wealth in Boston. March 26, 2015. doi:10.2139/ssrn.2630261

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rogers B. Unraveling temporal patterns of diagnostic markers and comorbidities in Alzheimer's disease: Insights from large-scale data. *Alzheimer's Dement*. 2025;21:e14564. https://doi.org/10.1002/alz.14564