Data-driven discovery of probable Alzheimer's disease and related dementia subphenotypes using electronic health records

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Abstract

Introduction: We sought to assess longitudinal electronic health records (EHRs) using machine learning (ML) methods to computationally derive probable Alzheimer's Disease (AD) and related dementia subphenotypes.

Methods: A retrospective analysis of EHR data from a cohort of 7587 patients seen at a large, multi-specialty urban academic medical center in New York was conducted. Subphenotypes were derived using hierarchical clustering from 792 probable AD patients (cases) who had received at least one diagnosis of AD using their clinical data. The other 6795 patients, labeled as controls, were matched on age and gender with the cases and randomly selected in the ratio of 9:1. Prediction models with multiple ML algorithms were trained on this cohort using 5-fold cross-validation. XGBoost was used to rank the variable importance.

Results: Four subphenotypes were computationally derived. Subphenotype A (n = 273; 28.2%) had more patients with cardiovascular diseases; subphenotype B (n = 221; 27.9%) had more patients with mental health illnesses, such as depression and anxiety; patients in subphenotype C (n = 183; 23.1%) were overall older (mean (SD) age, 79.5 (5.4) years) and had the most comorbidities including diabetes, cardiovascular diseases, and mental health disorders; and subphenotype D (n = 115; 14.5%) included patients who took anti-dementia drugs and had sensory problems, such as deafness and hearing impairment. The 0-year prediction model for AD risk achieved an area under the receiver operating curve (AUC) of 0.764 (SD: 0.02); the 6-month model, 0.751 (SD: 0.02); the 1-year...
1 | INTRODUCTION

Alzheimer’s Disease (AD), a progressive and irreversible neurodegenerative disease with insidious onset, causes problems with memory, cognition, and behavior, and affects more than 5 million people in the United States \( ^1 \); Lazarov and Tesco \( ^2 \). AD is a complex disease and the cause of 60% to 70% of cases of dementia. The biggest known risk factor for AD is age, but AD is not a normal part of aging. Depression, diabetes, head injuries, hearing loss, high cholesterol, inflammation, diabetes, and insulin resistance syndrome, oxidative damage, stress, and many other factors may lead to dementia \( ^3,4 \); Lazarov and Tesco \( ^2,5 \). In the clinical diagnosis and treatment of AD, all of these risk factors need to be considered \( ^5,6 \); Lazarov and Tesco \( ^2 \); Light and Lebowitz \( ^7 \).

Most existing data-driven research for AD progression, risk factors, and endophenotypes utilizes cohort study data, where rigorous and stricter inclusion-exclusion criteria are applied for participant enrollment. This leads to poor generalizability of the results in the real-world \( ^3,8,9 \). In addition, extensive follow-up to study the risk factors for AD is needed, because of the long prodrome before the suspicion of diagnosis and reverse causality. Certain symptoms or diseases may be a consequence of AD, rather than a risk factor. Moreover, it is likely that different factors influence the development of AD at different stages of life. \( ^4 \) Prospective studies, in general, are resource- and time-intensive \( ^10,11 \) and retrospective studies using existing data might offer complementary insights, improving our understanding for better diagnosis and treatment of AD. Electronic health records (EHRs), which capture a wide variety of important health events and include patients with the most severe manifestations of AD or disability, might be useful resources to identify new targets for intervention and help improve AD care \( ^8,12-14 \).

In this retrospective study, our goal was to identify distinct subphenotypes from routinely collected structured EHR data. Instead of targeting the precise biomarker-confirmed AD phenotype, we aimed to identify subgroups of patients given a clinical diagnosis of AD by their treating physician (which we categorize as “probable AD and related dementia”) using broader and more readily available EHR data to characterize their clinical features. The identification of subphenotypes might uncover “clusters” of patients with specific characteristics, allowing more precise treatment and improved care. Since it is currently uncertain whether EHRs are sufficient and complete to capture AD, we first assessed the effectiveness of variables extracted from longitudinal EHRs by training 0-year, 6-month, 1-year, and 2-year AD risk prediction models using multiple machine learning (ML) algorithms. Then, we applied the validated variables to computationally derive probable AD and related dementia subphenotypes.

2 | METHODS

2.1 | Data sources

This study used de-identified EHR data from Weill Cornell Medicine (WCM)/NewYork-Presbyterian Hospital (NYP)—a large, urban academic medical center located in the Upper East Side of Manhattan, New York. The study dataset was standardized using the Observational Medical Outcomes Partnership common data model (OMOP CDM). The current OMOP database at WCM/NYP has over 2.7 million patients mapped from both outpatient (EpicCare) and inpatient (Allscript Sunrise Clinical Manager) clinical care systems. The mapping process normalizes conditions to standardized medical vocabularies, including SNOMED-CT for conditions (diagnoses), RxNorm for medications, and LOINC for laboratory results. The OMOP vocabulary provides mappings to other classification systems, such as Anatomical Therapeutic Chemical (ATC) and VA Classes for medications. The study was approved by the WCM Institutional Review Board (protocol# 1408015423).

2.2 | Study cohort

An incidence-based, matched case-control design was used in this study. We identified a cohort of study patients older than 65 years who had a diagnosis of AD after January 2012 based on the presence of one or more AD related SNOMED-CT codes in our OMOP database (see Table 1). These patients were labeled as “Probable AD” (cases). We use the term “probable” since a definite diagnosis of AD would require pathologic confirmation of disease biomarkers at autopsy or the use of an amyloid positron emission tomography (PET)
scan and/or cerebrospinal fluid (CSF) markers as part of the clinical diagnostic process. These information were not routinely available via the OMOP database. The inclusion-exclusion criteria used in the study are shown in Figure 1.

We randomly selected nine controls for each probable AD patient with age and gender matching from control candidate sample as shown in Figure 1, where control candidate samples were specified by excluding the patients without a diagnosis of AD or mild cognitive impairment (MCI) and those who had less than 5 years EHR data. This ratio was determined based on an estimated prevalence of 10% of AD in the general population of 65 years and older 1.

### 2.3 Cohort characteristics

The probable AD cohort included 792 patients (487 female [61.5%]; mean [SD] age, 78.4 (5.4) years) who were matched at a ratio of 1:9 with 6795 control patients (4175 female [61.4%]; mean [SD] age, 78.5 [5.4] years). The characteristics of the study cohort are shown in Table 2.

### 2.4 Data preparation

For probable AD patients, we extracted EHR data for over 8 years prior to their AD diagnosis. For the controls, we extracted the latest 8 years or more worth of EHR data. The extracted data included demographics, comorbidities, and medications, where comorbidities were derived based on the Chronic Condition Data Warehouse (CCW) algorithms (Medicare & Medicaid Services, Centers. 2017). Medications were mapped to drug classes derived from the ATC 3rd level. The CCW and ATC mappings to SNOMED are maintained at the latest version. Uniform 10-Bins Discretizer and one-hot encoding were chosen to encode age and gender variables. By determining whether a patient has received diagnosis or medication in those categories, the final study CCW and ATC categories included 32 different diagnoses and 171 medication classes, respectively. Therefore, data

| TABLE 1 | Concept code description |
|---|---|
| SNOmed | Concept Name |
| 378419 | Alzheimer's disease |
| 4218017 | Primary degenerative dementia of the Alzheimer type, presenile onset |
| 4220313 | Primary degenerative dementia of the Alzheimer type, senile onset |
| 4297400 | Mild cognitive disorder |
| 439795 | Minimal cognitive impairment (MCI) |

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**FIGURE 1** Cascade flow identifying Probable AD patients from EHR data
To derive the subphenotypes, we first assessed the effectiveness of variables extracted from the EHRs by training 0-year, 6-month, 1-year, and 2-year AD risk prediction models on 7587 patients using five times 5-fold cross-validation. Figure 3 shows the prediction window setting in these experiments, where we randomly chose a subset of controls to minimize class imbalance between the probable AD patients and the controls. We compared the prediction performance of four traditional ML algorithms including logistic regression (LR), LASSO, random forest (RF), and XGBoost. In addition, a decision-tree-based ensemble ML algorithm XGBoost was used to rank the variable importance in distinguishing probable AD patients and controls.

After validating the effectiveness of the extracted variables using the prediction task, we arbitrarily chose 5 years of EHR data for identifying probable AD patients before their first AD diagnosis to derive subphenotypes. After representing the patient data as binary codes as previously described, Ward’s hierarchical agglomerative clustering method was performed to derive probable AD and related dementia subphenotypes by minimizing within-group dispersion at each binary fusion. Dice distance matrices, calculated from these binary codes, were chosen as input dissimilarities.

### Measurements

To assess the ML algorithm’s prediction performance, we chose the area under the receiver operating characteristic curve (AUC) as our primary evaluation metric. In addition to AUC, we also calculated sensitivity, specificity, and F1 score for 0-year, 6-month, 1-year, 2-year, and 3-year prediction models. We assessed the variable importance using F-score, which reflects how much the variables contribute to the prediction task. After deriving the subphenotypes, we reported the frequency of each variable in each subphenotype. We used the Chi-square test to compare the subphenotypes. A significance level of 5% was used for deriving the main inferences.
3 | RESULTS

3.1 | Variable assessing results

Table 3 shows the results for various prediction models studied. The 0-year prediction model for probable AD achieved an AUC (SD) of 0.764 (0.02); the 6-month model, 0.751 (0.02); the 1-year model, 0.752 (0.02); the 2-year model, 0.749 (0.03); and the 3-year model, 0.735 (0.03). Patient records from the 0-year prediction window before AD diagnosis showed the best results, suggesting that the closer the AD diagnosis, the more pronounced the AD symptoms were.

Table 4 shows the top features and their importance (F score) associated with different times of various prediction windows. There are some differences between the top important features among the different prediction windows. Compared to the controls, depression became more distinguishable in probable AD patients closer to AD diagnosis. Hypertension as a common chronic disease played a more important role several years before the patients received an AD diagnosis. The top-ranked comorbidities verified by XGBoost included depression, stroke/transient ischemic attack, hypertension, anxiety, mobility impairments, and atrial fibrillation. The top-ranked medications included anti-dementia drugs, antipsychotics, antiepileptics, angiotensin II antagonists, adrenergics, and antidepressants.


3.2 Subphenotypes

After assessing the effectiveness of variables extracted from longitudinal EHRs, we then leveraged these variables to identify distinct subphenotypes from the 792 probable AD patients. Four subphenotypes were computationally derived. We plotted chord diagrams in Figure 4 to show the major differences across the subphenotypes. (Table 5 shows the characteristics of each subphenotype). To further compare subphenotypes, we conducted Chi-square tests to identify variables whose P value was larger than .05 between two subphenotypes, as shown in Table 6.

Among the four derived subphenotypes, Subphenotype A (n = 273; 28.2%) was mainly characterized by cardiovascular diseases. 70.7% of the patients in subphenotype A had hypertension, and 75.1% of the patients took lipid-modifying agents. Subphenotype B (n = 221; 27.9%) was mainly characterized by mental health illnesses where 31.7% of the patients had depression and 45.7% of the patients took antidepressants. 21.7% of the patients had anxiety and 24% of the patients took anxiolytics. Patients in Subphenotype C (n = 183; 23.1%) were overall older (mean [SD] age, 79.5 (5.4) years) and had the highest number of comorbidities, including diabetes, cardiovascular diseases, and mental health diseases. 86.3% of the patients had hypertension, 62.3% had diabetes, and 60.1% had depression. Accordingly, 74.9% of the patients took lipid-modifying agents, 79.2% of the patients took antidepressants, and 60.3% of the patients took anxiolytics. Subphenotype D (n = 115; 14.5%) included patients who took anti-dementia drugs and had sensory problems, such as deafness and hearing impairment. 75.7% of the patients took anti-dementia drugs and 45.2% of the patients had sensory problems.

We observed significant gender differences across the four subphenotypes (P < .001). While, in general, there were more females across the study population, 73.8% of patients were females in

| Feature Name                          | Conditions                        | Prediction window (y) | 0  | 0.5 | 1  | 2  | 3  |
|---------------------------------------|-----------------------------------|-----------------------|----|-----|----|----|----|
| Depression                            | 33                                | 33                    | 31 | 20  | 16 |
| Stroke/Transient Ischemic Attack      | 22                                | 22                    | 20 | 15  | 15 |
| Hypertension                          | 19                                | 19                    | 23 | 33  | 42 |
| Anxiety                               | 17                                | 17                    | 18 | 20  | 10 |
| Mobility Impairments                 | 17                                | 17                    | 15 | 12  | 6  |
| Acquired Hypothyroidism               | 14                                | 14                    | 9  | 6   | 4  |
| Epilepsy                              | 12                                | 12                    | 12 | 15  | 9  |
| Asthma                                | 10                                | 10                    | 12 | 12  | 10 |
| Heart Failure                         | 8                                 | 8                     | 7  | 15  | 16 |
| Anemia                                | 7                                 | 7                     | 1  | 4   | 1  |
| Migraine and Chronic Headache        | 6                                 | 6                     | 7  | 6   | 6  |
| Atrial Fibrillation                   | 6                                 | 6                     | 16 | 18  | 15 |
| Hip/Pelvic Fracture                   | 5                                 | 5                     | 1  | 1   | 2  |
| Bipolar Disorder                      | 3                                 | 3                     | 7  | 7   | 7  |
| Sensory—Deafness and Hearing Impairment | 3                            | 3                     | 8  | 5   | 8  |

| Medications                           |                                    |                       |    |     |    |    |    |
|---------------------------------------|-----------------------------------|-----------------------|----|-----|----|----|----|
| Anti-dementia Drugs                   | 40                                | 40                    | 40 | 41  | 40 |
| Antipsychotics                        | 21                                | 21                    | 25 | 24  | 29 |
| Antiepileptics                        | 17                                | 17                    | 16 | 15  | 11 |
| Angiotensin II Antagonists, Plain     | 16                                | 16                    | 15 | 15  | 18 |
| Adrenergics, Inhalants                | 16                                | 16                    | 25 | 20  | 20 |
| Dopaminergic Agents                   | 16                                | 16                    | 13 | 13  | 14 |
| Vasodilators used in Cardiac Diseases | 13                                | 13                    | 8  | 6   | 7  |
| Anti-inflammatory Agents              | 13                                | 13                    | 13 | 10  | 11 |
| Other Mineral Supplements             | 11                                | 11                    | 10 | 7   | 6  |
| Direct Acting Antivirals              | 11                                | 11                    | 16 | 13  | 10 |
| Vitamin B12 and folic acid            | 10                                | 10                    | 14 | 10  | 5  |
| Beta Blocking Agents                  | 8                                 | 8                     | 12 | 11  | 13 |
| Antidepressants                       | 6                                 | 6                     | 9  | 15  | 19 |
Subphenotype B. After adjusting significance in terms of age, no significant differences were observed for race. This could be potentially attributed to missing race information on >30% of the patients in our study cohort. Significant differences between the resulting four subphenotypes were found for diabetes ($P \leq 0.001$), chronic kidney disease ($P \leq 0.05$), lipid-modifying agents ($P \leq 0.001$), antidepressants ($P \leq 0.05$), anxiolytics ($P \leq 0.05$), beta-blocking agents ($P \leq 0.05$), and antiepileptics ($P \leq 0.05$).
TABLE 5 Characteristics of the four subphenotypes

| Characteristic               | Total | Subphenotypes | Adjust age | χ² | P value |
|------------------------------|-------|---------------|------------|----|---------|
| No. of patients (%)         | 792   | 273 (34.5) 221 (27.9) 183 (23.1) 115 (14.5) |
| Age, Mean (SD), y            | 78.4 (5.4) 77.6 (5.5) 79.5 (5.4) 77.7 (5.4) |
| Sex, No. (%)                 |       | Female 487 (61.5) 145 (53.1) 163 (73.8) 116 (63.4) 63 (54.8) |
|                             |       | Male 305 (38.5) 128 (46.9) 58 (26.2) 67 (36.6) 52 (45.2) |
| Race, No. (%)                |       | White 434 (54.8) 146 (53.5) 121 (54.8) 102 (55.7) 65 (56.5) |
|                             |       | Black 70 (8.8) 33 (12.1) 12 (5.4) 18 (9.8) 7 (6.1) |
|                             |       | Asian 15 (1.9) 9 (3.3) 3 (1.4) 3 (1.6) 0 (0) |
|                             |       | Others and Unknown 273 (34.5) 85 (31.1) 85 (38.5) 60 (32.8) 43 (37.4) |
| Hypertension, No. (%)        | 433 (54.7) 193 (70.7) 64 (29) 158 (86.3) 18 (15.7) ≤ .001 0.289 |
| Diabetes, No. (%)            | 249 (31.4) 102 (37.4) 19 (8.6) 114 (62.3) 14 (12.2) ≤ .001 ≤ 0.001 |
| Depression, No. (%)          | 224 (28.3) 35 (12.8) 70 (31.7) 110 (60.1) 9 (7.8) ≤ .001 0.289 |
| Hip/Pelvic Fracture, No. (%) | 196 (24.7) 48 (17.6) 57 (25.8) 80 (43.7) 11 (9.6) ≤ .001 0.368 |
| Anemia, No. (%)              | 182 (23) 65 (23.8) 26 (11.8) 90 (49.2) 1 (0.9) ≤ .001 0.985 |
| Sensory—Deafness and Hearing Impairment, No. (%) | 181 (22.9) 48 (17.6) 25 (11.3) 56 (30.6) 52 (45.2) ≤ .001 0.335 |
| Stroke/Transient Ischemic Attack, No. (%) | 173 (21.8) 70 (25.6) 28 (12.7) 72 (39.3) 3 (2.6) ≤ .001 0.326 |
| Anxiety, No. (%)             | 154 (19.4) 32 (11.7) 48 (21.7) 66 (36.1) 8 (7) ≤ .001 0.129 |
| Chronic Kidney Disease, No. (%) | 153 (19.3) 60 (22) 5 (2.3) 84 (45.9) 4 (3.5) ≤ .001 0.003 |
| Bipolar Disorder, No. (%)    | 135 (17) 21 (7.7) 38 (17.2) 73 (39.9) 3 (2.6) ≤ .001 0.685 |
| Atrial Fibrillation, No. (%) | 128 (16.2) 48 (17.6) 11 (5) 66 (36.1) 3 (2.6) ≤ .001 0.166 |
| Acquired Hypothyroidism, No. (%) | 127 (16) 47 (17.2) 16 (7.2) 57 (31.1) 7 (6.1) ≤ .001 0.956 |
| Migraine and Chronic Headache, No. (%) | 120 (15.2) 43 (15.8) 24 (10.9) 53 (29) 0 (0) ≤ .001 0.327 |
| Heart Failure, No. (%)       | 106 (13.4) 44 (16.1) 1 (0.5) 61 (33.3) 0 (0) ≤ .001 0.733 |
| Lipid Modifying Agents, Plain, No. (%) | 484 (61.1) 205 (75.1) 68 (30.8) 137 (74.9) 74 (64.3) ≤ .001 ≤ 0.001 |
| Anti-Dementia Drugs, No. (%) | 389 (49.1) 117 (42.9) 95 (43) 90 (49.2) 87 (75.7) ≤ .001 0.135 |
| Antidepressants, No. (%)     | 366 (46.2) 79 (28.9) 101 (45.7) 145 (79.2) 41 (35.7) ≤ .001 0.003 |
| Beta Blockers, No. (%)       | 310 (39.1) 142 (52) 23 (10.4) 130 (71) 15 (13) ≤ .001 0.013 |
| Antiepileptics, No. (%)      | 196 (24.7) 42 (15.4) 42 (19) 99 (54.1) 13 (11.3) ≤ .001 0.027 |
| Anxiolytics, No. (%)         | 191 (24.1) 41 (15) 53 (24) 92 (50.3) 5 (4.3) ≤ .001 0.001 |
| Antipsychotics, No. (%)      | 140 (17.7) 37 (13.6) 28 (12.7) 67 (36.6) 8 (7) ≤ .001 0.899 |
| Angiotensin II Antagonists, Plain, No. (%) | 134 (16.9) 61 (22.3) 20 (9) 51 (27.9) 2 (1.7) ≤ .001 0.899 |
| Vitamin B12 and folic acid, No. (%) | 172 (21.7) 63 (23.1) 36 (16.3) 66 (36.1) 7 (6.1) ≤ .001 0.068 |
| Other Mineral Supplements, No. (%) | 171 (21.6) 56 (20.5) 8 (3.6) 105 (57.4) 2 (1.7) ≤ .001 0.164 |
| Adrenergics, Inhalants, No. (%) | 107 (13.5) 39 (14.3) 7 (3.2) 58 (31.7) 3 (2.6) ≤ .001 0.265 |

4 | DISCUSSION

The purpose of this study was to computationally derive probable AD and related dementia subphenotypes using routinely collected data from EHRs to potentially enhance our understanding of AD, and help develop better diagnosis and treatment pathways. In particular, by applying multiple “off-the-shelf” ML algorithms on EHR data, including patient demographics, comorbidities, and medication history, we assessed the effectiveness of variables extracted from longitudinal EHRs. Recent work also used ML to predict AD with large-scale administrative claims data. While our study only used EHR data, we observed comparable performance at the 0-year prediction task, and significantly improved performance at 1-year, 2-year, and 3-year prediction tasks.
Four subphenotypes were computationally derived. Subphenotype A included more patients with cardiovascular diseases; Subphenotype B included more patients with mental health illnesses like depression and anxiety; Subphenotype C was relatively older (mean [SD] age, 79.5 [5.4] years) and had the most comorbidities including diabetes, cardiovascular diseases, and mental health disorders; and Subphenotype included patients who took anti-dementia drugs and had sensory problems, such as deafness and hearing impairment. Patients in Subphenotypes, B and D, were younger overall and had fewer comorbidities.

After adjusting for significance in terms of age, we observed statistically significant differences across the subphenotypes for comorbidities, including history of diabetes and chronic kidney disease, and treatment, including the use of lipid-modifying agents, antidepressants, anxiolytics, beta-blocking agents, and antiepileptics. Prior studies indicate that the prevalence of diabetes and AD is increasing in our aging population.18,19 Clinical studies also demonstrated that patients with chronic kidney disease are more prone to cognitive impairment and AD.20 There is some evidence from experimental studies that lowering cholesterol may slow the expression of AD.21 Depression is very common among people with AD.22 Studies have also reported that anxiety may be an early sign of increased risk for AD.23 In addition, while prior studies have reported on environmental risk factors for AD, including the role of aluminum in drinking water and occupational exposure to solvents and pesticides,24 studying the associations between built environment (eg, local air pollution, proximity to open space, access to public transportation) and risk of AD is beyond the scope of the current work.

This study has several limitations. First, the findings from this study have not been replicated using external EHR data sets. Given that this study was conducted using EHR data from patients at a single large, urban academic medical center in New York, the study population may not be representative of the general AD population. Conducting a replication study will be a critical next step. Moreover, to our knowledge, there is a dearth of existing work in data-driven identification of probable AD and related dementia subphenotypes using EHR data to compare our results. In addition, due to the insufficient number of patients who have longitudinal EHR data, we arbitrarily chose 5 years of EHR data for identifying probable AD patients before their first AD diagnosis to derive subphenotypes. This assumption might not completely reflect the characteristics of AD patients since patients might have early signs and symptoms of the disease prior to the 5-year time window. There exists a substantial level of overdiagnosis and underdiagnosis of AD (Sodenaga25). Moreover, several presenting symptoms of vascular dementia are similar to symptoms of AD—and become more similar as dementia progresses. It is sometimes difficult to tell whether a person has AD or vascular dementia26 and it is not unusual to have a mixed form of dementia, meaning the person has both vascular dementia and AD together.27 A definite diagnosis of AD would require pathologic confirmation of disease biomarkers at autopsy, or the use of an amyloid imaging scan and/or CSF markers as part of the clinical diagnostic process. Due to the high cost of amyloid imaging and lack of reimbursement by insurance companies, and the cost and invasive nature of CSF samples, most healthcare providers do not incorporate these measures in their routine clinical practice. This is an important limitation of an EHR-based approach. This study also did not analyze

| Variables                     | A vs B | A vs C | A vs D | B vs C | B vs D | C vs D |
|-------------------------------|--------|--------|--------|--------|--------|--------|
| Diabetes                      |        |        | 0.296  |        |        |        |
| Depression                    |        |        | 0.157  |        |        |        |
| Anxiety                       |        |        | 0.159  |        |        |        |
| Chronic Kidney Disease        |        |        |        | 0.513  |        |        |
| Atrial Fibrillation           |        |        |        | 0.303  |        |        |
| Acquired Hypothyroidism       |        |        |        | 0.691  |        |        |
| Migraine and Chronic Headache| 0.114  |        |        |        |        |        |
| Lipid Modifying Agents, Plain| -      | 0.956  |        |        |        | 0.052  |
| Anti-Dementia Drugs           | 0.977  | 0.184  | 0.214  |        |        |        |
| Antidepressants               |        | 0.191  |        | 0.077  |        |        |
| Beta Blocking Agents          |        |        |        | 0.469  |        |        |
| Antiepileptics                | 0.287  |        | 0.293  |        | 0.070  |        |
| Antipsychotics                | 0.773  | 0.064  |        | 0.108  |        |        |
| Angiotensin II Antagonists, Plain| -    | 0.179  |        |        |        |        |
| Vitamin B12 and folic acid    | 0.061  |        |        |        |        |        |
| Other Mineral Supplements     |        |        |        |        |        | 0.336  |
| Adrenergics, Inhalants        |        |        |        |        |        | 0.775  |

*P value ≤ 0.05.
unstructured clinical text from EHRs, including clinician encounter notes, which may contain additional information about an individual's comorbidities and treatment. In the future, we will apply our extensive work in natural language processing to analyze such data.28,29

## 5 CONCLUSION

Using routinely collected longitudinal EHR data and ML algorithms, we computationally derived probable AD and related dementia subphenotypes that can potentially guide improved diagnosis and treatment of AD patients. The derived subphenotypes had statistically significant differences with respect to patient demographics, comorbidities, and treatment, suggesting that despite converging to a final common clinico-pathological endpoint, AD is a heterogeneous disorder with multiple phenotypes.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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