**Supplementary Materials**

**Supplementary Table S1. Phecodes for the three most common comorbidities of Alzheimer's disease (AD).**

|  |  |  |  |
| --- | --- | --- | --- |
| Disease Category | Neurological72–74 | Cardiovascular75,76 | Diabetes-related77,78 |
| Phecodes | Phe\_Memory loss,  Phe\_Altered mental status,  Phe\_Transient alteration of awareness,  Phe\_Hallucinations,  Phe\_Schizophrenia and other psychotic disorders,  Phe\_Schizophrenia,  Phe\_Paranoid disorders,  Phe\_Mood disorders,  Phe\_Bipolar,  Phe\_Depression,  Phe\_Major depressive disorder,  Phe\_Suicidal ideation,  Phe\_Anxiety disorders,  Phe\_Anxiety disorder,  Phe\_Phobia,  Phe\_Personality disorders,  Phe\_Eating disorder,  Phe\_Anorexia nervosa,  Phe\_Sleep disorders,  Phe\_Insomnia. | Phe\_Essential hypertension,  Phe\_Hypertension,  Phe\_Hypertensive heart and/or renal disease,  Phe\_Other forms of chronic heart disease,  Phe\_Ill-defined descriptions and complications of heart disease,  Phe\_Hypertensive heart disease,  Phe\_Congestive heart failure, nonhypertensive, Phe\_Other chronic ischemic heart disease, unspecified,  Phe\_Heart failure with reduced EF [Systolic or combined heart failure],  Phe\_Acute rheumatic heart disease | Phe\_Type 2 diabetes,  Phe\_Diabetes mellitus,  Phe\_Type 2 diabetes with renal manifestations,  Phe\_Type 2 diabetes with neurological manifestations,  Phe\_Polyneuropathy in diabetes,  Phe\_Type 1 diabetes,  Phe\_Type 2 diabetes with ophthalmic manifestations,  Phe\_Diabetes type 2 with peripheral circulatory disorders,  Phe\_Type 1 diabetes with neurological manifestations,  Phe\_Diabetes type 1 with peripheral circulatory disorders,  Phe\_Type 1 diabetes with ophthalmic manifestations,  Phe\_Type 2 diabetes with ketoacidosis |

**Supplementary Table S2. Descriptive statistics on the characteristics of the study cohort**

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| --- | --- | --- | --- |
|  | **Total AD Patients**  **(N = 1,665)** | **Female AD Patients**  **(N = 961)** | **Male AD Patients**  **(N = 704)** |
| **Demographics and Vital Signs** | | | |
| Age at AD diagnosis, mean (std) | 76.7 (9.2) | 77.1 (9.5) | 76.1 (8.8) |
| Female, N (%) | 961 (57.7%) | 961 (100.0%) | 0 (0.0%) |
| Male, N (%) | 704 (42.3%) | 0 (0.0%) | 704 (100.0%) |
| **Disease development, mean (std)** | | | |
| Duration days | 2**,**958.1 (620.2) | 2**,**998.0 (613.7) | 2**,**903.2 (627) |
| Days before diagnosis | 2**,**043.0 (627.5) | 2**,**041.4 (632.4) | 2**,**045.0 (620) |
| Days after diagnosis | 915.8 (565.7) | 957.7 (579.2) | 859.6 (541.0) |
| Days MCI to AD | 827.0 (622.1) | 825.2 (627.0) | 829.1 (618.7) |
| Convert rate | 266 (16.0%) | 150 (15.6%) | 116 (16.5%) |
| Days AD to death | 833.0 (531.1) | 874.6 (541.7) | 787.5 (518.2) |
| Age at death | 81.7 (8.9) | 82.1 (9.4) | 81.2 (8.4) |
| Mortality rate, N (%) | 209 (12.55%) | 109 (11.34%) | 100 (14.20%) |
| **Hispanic, N (%)** | | | |
| Hispanic | 426 (25.6%) | 248 (25.8%) | 178 (18.5%) |
| Not Hispanic | 1**,**230 (73.9%) | 707 (73.6%) | 523 (54.4%) |
| No Hispanic information | 9 (0.5%) | 6 (0.6%) | 3 (0.3%) |
| **Race, N (%)** | | | |
| American Indian or Alaska Native | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Asian | 10 (0.6%) | 5 (0.5%) | 5 (0.7%) |
| Black or African American | 259 (15.6%) | 157 (16.3%) | 102 (14.5%) |
| White | 1**,**298 (77.96%) | 741 (77.11%) | 557 (79.12%) |
| Multiple race | 15 (0.90%) | 6 (0.62%) | 9 (1.28%) |
| Unknown | 83 (5.0%) | 52 (5.4%) | 31 (4.40%) |
| Body Mass Index (BMI) | 26.5 (5.11) | 26.8 (4.21) | 26.3 (5.71) |
| Smoking status**, N (%)** | | | |
| Non-smoker | 125 (7.5%) | 81 (8.4%) | 44 (4.6%) |
| Current smoker | 15 (0.9%) | 10 (1.0%) | 5 (0.5%) |
| Ex-smoker | 87 (5.2%) | 37 (3.9%) | 50 (5.2%) |
| Unknown | 1**,**438 (86.4%) | 833 (86.7%) | 605 (63.0%) |
| Comorbidity**, N (%)** | | | |
| Neurological | 1**,**483 (89.1%) | 876 (91.2%) | 607 (86.2%) |
| Cardiovascular disease | 696 (41.8%) | 370 (38.5%) | 326 (46.3%) |
| Diabetes-related | 779 (46.8%) | 439 (45.7%) | 340 (48.3%) |

**Supplementary Table S3. Descriptive statistics of sex-specific AD progression subsequence clusters**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **C1**  **(N =** 4,726, 17.3%**)** | **C2**  **(N=** 983, 3.6%**)** | **C3**  **(N=** 2,498, 9.1%**)** | **C4**  **(N=** 9,537, 34.9%**)** | **C5**  **(N=** 1,258, 4.6%**)** | **C6**  **(N=** 3,743, 13.7%**)** | **C7**  **(N=** 4,583, 16.8%**)** |
| **Demographics and Vital Signs** | | | | | | | |
| Age at AD diagnosis, mean (std) | 77.1 (9.27) | 78.1 (9.85) | 77.6 (9.54) | 77.2 (9.43) | 75.5 (9.27) | 76.1 (8.73) | 77.2 (8.35) |
| Female, N (%) | 921 (95.8%) | 554 (57.7%) | 866 (90.1%) | 846 (88.0%) | 52 (5.4%) | 3 (0.3%) | 1 (0.1%) |
| Male, N (%) | 704 (100.0%) | 18 (2.6%) | 4 (0.6%) | 0 (0.0%) | 514 (73.0%) | 681 (96.7%) | 531 (75.4%) |
| **Disease course, mean (std)** | | | | | | | |
| **Duration days** | 2,958.3 (620.1) | 2,981.1 (607.3) | 3,007.3 (610.0) | 3,036.6 (601.0) | 2,913.8 (617.2) | 2,916.2 (621.7) | 2,985.3 (586.2) |
| **Days before AD diagnosis** | 2,042.4 (626.0) | 2,026.7 (628.5) | 2,043.1 (637.0) | 2,064.0 (637.2) | 2,029.0 (599.0) | 2,050.3 (620.3) | 2,091.8 (625.1) |
| **Days after AD diagnosis** | 915.2 (565.0) | 955.1 (583.5) | 963.3 (579.2) | 971.5 (575.3) | 883.2 (548.0) | 866.7 (542.5) | 894.4 (543.8) |
| **Days MCI to AD** | 827.0 (622.1) | 780.5 (592.0) | 825.7 (615.7) | 837.5 (613.4) | 819.9 (605.2) | 826.6 (636.5) | 835.5 (653.4) |
| Days AD to death | 833.0 (531.1) | 854.5 (536.0) | 853.7 (526.0) | 876.1 (548.4) | 863.5 (554.5) | 790.4 (522.6) | 797.0 (539.9) |
| Age at death | 81.7 (8.9) | 82.2 (9.1) | 82.1 (9.7) | 82.4 (9.3) | 80.3 (8.9) | 81.2 (8.4) | 81.5 (8.3) |
| **Convert rate** | 45 (2.7%) | 36 (2.2%) | 85 (5.1%) | 136 (8.2%) | 36 (2.2%) | 85 (5.1%) | 93 (5.6%) |
| **Hispanic, N (%)** | | | | | | | |
| Hispanic | 426 (25.6%) | 142 (8.5%) | 225 (13.5%) | 223 (13.4%) | 141 (8.5%) | 173 (10.4%) | 132 (7.9%) |
| Not Hispanic | 1230 (73.9%) | 426 (25.6%) | 639 (38.4%) | 619 (37.2%) | 423 (25.4%) | 508 (30.5%) | 398 (23.9%) |
| No Hispanic information | 9 (0.5%) | 4 (0.2%) | 6 (0.4%) | 4 (0.2%) | 2 (0.1%) | 3 (0.2%) | 2 (0.1%) |
| **Race, N (%)** | | | | | | | |
| American Indian or Alaska Native | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Asian | 10 (0.6%) | 3 (0.2%) | 4 (0.2%) | 5 (0.3%) | 5 (0.3%) | 5 (0.3%) | 4 (0.2%) |
| Black or African American | 259 (15.6%) | 83 (5.0%) | 139 (8.3%) | 143 (8.6%) | 83 (5.0%) | 102 (6.1%) | 86 (5.2%) |
| White | 1,298 (77.96%) | 448 (26.9%) | 669 (40.2%) | 645 (38.7%) | 448 (26.9%) | 539 (32.4%) | 418 (25.1%) |
| Multiple race | 15 (0.90%) | 4 (0.2%) | 6 (0.4%) | 6 (0.4%) | 9 (0.5%) | 8 (0.5%) | 5 (0.3%) |
| Unknown | 83 (5.0%) | 34 (2.0%) | 52 (3.1%) | 47 (2.8%) | 21 (1.3%) | 30 (1.8%) | 19 (1.1%) |
| Body Mass Index (BMI) | 26.5 (5.1) | 27.0 (4.3) | 26.7 (4.1) | 26.7 (4.1) | 26.3 (5.7) | 26.4 (5.9) | 26.4 (5.9) |
| Smoking status**, N (%)** | | | | | | | |
| Non-smoker | 125 (7.5%) | 58 (6.0%) | 76 (7.9%) | 65 (6.8%) | 36 (3.7%) | 42 (4.4%) | 36 (3.7%) |
| Current smoker | 15 (0.9%) | 7 (0.7%) | 9 (0.9%) | 7 (0.7%) | 5 (0.5%) | 5 (0.5%) | 3 (0.3%) |
| Ex-smoker | 87 (5.2%) | 24 (2.5%) | 36 (3.7%) | 33 (3.4%) | 45 (4.7%) | 46 (4.8%) | 34 (3.5%) |
| Unknown | 1,438 (86.4%) | 483 (50.3%) | 749 (77.9%) | 741 (77.1%) | 480 (49.9%) | 591 (61.5%) | 459 (47.8%) |
| Comorbidity**, N (%)** | | | | | | | |
| Neurological | 1,483 (89.1%) | 226 (39.5%) | 521 (59.9%) | 780 (92.2%) | 219 (38.7%) | 439 (64.2%) | 470 (88.3%) |
| Cardiovascular disease | 696 (41.8%) | 64 (11.2%) | 191 (22.0%) | 343 (40.5%) | 105 (18.6%) | 235 (34.4%) | 276 (51.9%) |
| Diabetes | 779 (46.8%) | 133 (23.3%) | 295 (33.9%) | 403 (47.6%) | 174 (30.7%) | 273 (39.9%) | 268 (50.4%) |

**Supplementary Table S4. Descriptive statistics of sex-specific AD progression subtypes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **S1**  **[C1, C2, C3, C4]**  **(N =** 413, 24.8%**)** | **S2**  **[C1, C3, C4]**  **(N=** 329, 19.8%**)** | **S3**  **[C1, C5, C6, C7]**  **(N=** 346, 20.8%**)** | **S4**  **[C1, C6, C7]**  **(N=** 178, 10.7%**)** | **S5**  **[C1, C5, C6]**  **(N=** 137, 8.2%**)** |
| Age at AD diagnosis, mean (std) | 77.2 (9.8) | 76.9 (9.2) | 76.2 (8.7) | 77.1 (8.3) | 74.8 (9.5) |
| Female, N (%) | 406 (98.3%) | 326 (99.1%) | 1 (0.3%) | 6 (3.4%) | 2 (1.5%) |
| Male, N (%) | 7 (1.7%) | 3 (0.9%) | 345 (99.7%) | 172 (96.6%) | 135 (98.5%) |
| **Duration days** | 3033.4 (586.8) | 3027.3 (619.8) | 3009.1 (573.9) | 2937.8 (608.4) | 2697.4 (656.1) |
| **Days before AD diagnosis** | 2070.5 (632.9) | 2077.4 (643.4) | 2102.7 (606.3) | 2073.9 (656.8) | 1915.5 (555.7) |
| **Days after AD diagnosis** | 962.9 (568.3) | 949.9 (562.6) | 906.4 (532.7) | 863.9 (555.7) | 781.9 (519.4) |
| **Days MCI to AD** | 601.2 (786.9) | 655.3 (886.7) | 655.7 (838.2) | 658.2 (841.2) | 613.8 (813.4) |
| Days AD to death | 828.2 (534.7) | 843.7 (483.7) | 825.0 (541.9) | 704.3 (549.8) | 865.2 (445.2) |
| Age at death | 82.9 (9.0) | 82.1 (10.1) | 80.7 (8.8) | 82.7 (7.1) | 79.6 (8.7) |
| **MCI to AD Conversion rate** | 398 (96.4%) | 322 (97.9%) | 342 (98.8%) | 172 (96.6%) | 136 (99.3%) |
| Hispanic | 111 (26.9%) | 84 (25.5%) | 85 (24.6%) | 43 (24.2%) | 38 (27.7%) |
| Not Hispanic | 293 (70.9%) | 240 (72.9%) | 260 (75.1%) | 128 (71.9%) | 97 (70.8%) |
| No Hispanic information | 2 (0.5%) | 2 (0.6%) | 1 (0.3%) | 1 (0.6%) | 1 (0.7%) |
| American Indian or Alaska Native | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Asian | 3 (0.7%) | 0 (0.0%) | 3 (0.9%) | 1 (0.6%) | 1 (0.7%) |
| Black or African American | 56 (13.6%) | 60 (18.2%) | 55 (15.9%) | 26 (14.6%) | 12 (8.8%) |
| White | 321 (77.7%) | 245 (74.5%) | 279 (80.6%) | 133 (74.7%) | 109 (79.6%) |
| Multiple race | 2 (0.5%) | 2 (0.6%) | 3 (0.9%) | 2 (1.1%) | 3 (2.2%) |
| Unknown | 124 (30.0%) | 89 (27.1%) | 122 (35.3%) | 56 (31.5%) | 37 (27.0%) |
| Height, inch | 62.7 (4.8) | 67.1 (57.9) | 69.0 (3.1) | 69.0 (2.9) | 70.8 (17.6) |
| Weight, lbs. | 152.8 (32.6) | 154.3 (34.4) | 193.0 (40.6) | 189.1 (33.8) | 182.2 (36.4) |
| Diastolic Blood Pressure, mmHg | 72.6 (11.3) | 73.3 (12.2) | 76.2 (11.6) | 75.7 (12.3) | 74.8 (10.5) |
| Systolic Blood Pressure, mmHg | 135.8 (21.6) | 135.4 (21.4) | 134.6 (20.4) | 133.2 (17.6) | 133.6 (22.3) |
| Body Mass Index (BMI) | 26.9 (5.1) | 27.0 (5.8) | 27.9 (4.3) | 27.7 (4.6) | 27.9 (4.3) |
| Non-smoker | 26 (6.3%) | 11 (3.3%) | 14 (4.0%) | 5 (2.8%) | 2 (1.5%) |
| Current smoker | 0 (0.0%) | 0 (0.0%) | 3 (0.9%) | 1 (0.6%) | 0 (0.0%) |
| Ex-smoker | 6 (1.5%) | 6 (1.8%) | 17 (4.9%) | 7 (3.9%) | 5 (3.6%) |
| Unknown | 144 (34.9%) | 109 (33.1%) | 152 (43.9%) | 66 (37.1%) | 37 (27.0%) |
| Neurological | 149 (36.1%) | 113 (34.3%) | 143 (41.3%) | 70 (39.3%) | 37 (27.0%) |
| Cardiovascular disease | 68 (16.5%) | 65 (19.8%) | 78 (22.5%) | 34 (19.1%) | 21 (15.3%) |
| Diabetes | 77.2 (9.8) | 76.9 (9.2) | 76.2 (8.7) | 77.1 (8.3) | 74.8 (9.5) |