# Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

## eTable 1. Demographic distribution by study cohort

| Study | N | Sex | | Age, mean (SD) | Clinical diagnosis | |
|---|---|---|---|---|---|---|
| | | Male (%) | Female (%) | | AD (%) | Control (%) |
| **ADNI** | 1197 | 668 (55.8) | 529 (44.2) | 73 (7.3) | 841 (70.3) | 356 (29.7) |
| **AIBL** | 164 | 80 (48.8) | 84 (51.2) | 73 (5.7) | 23 (14) | 141 (86) |
| **Barcelona1** | 59 | 26 (44.1) | 33 (55.9) | 70 (8.5) | 58 (98.3) | 1 (1.7) |
| **BIOCARD** | 20 | 7 (35) | 13 (65) | 58 (5.8) | 0 (0) | 20 (100) |
| **Blennow** | 56 | 15 (26.8) | 41 (73.2) | 83 (10.2) | 33 (58.9) | 23 (41.1) |
| **FACE** | 349 | 146 (41.8) | 203 (58.2) | 72 (8.1) | 226 (64.8) | 123 (35.2) |
| **Homburg** | 97 | 53 (54.6) | 44 (45.4) | 67 (9.2) | 97 (100) | 0 (0) |
| **Knight ADRC** | 589 | 275 (46.7) | 314 (53.3) | 71 (7.4) | 219 (37.2) | 370 (62.8) |
| **Lleo** | 115 | 43 (37.4) | 72 (62.6) | 64 (9.8) | 47 (40.9) | 68 (59.1) |
| **London** | 81 | 42 (51.9) | 39 (48.1) | 69 (9.4) | 60 (74.1) | 21 (25.9) |
| **MAYO** | 346 | 202 (58.4) | 144 (41.6) | 78 (5.4) | 0 (0) | 346 (100) |
| **Molineuvo** | 182 | 67 (36.8) | 115 (63.2) | 65 (8.3) | 132 (72.5) | 50 (27.5) |
| **NACC** | 286 | 125 (43.7) | 161 (56.3) | 72 (8.3) | 165 (57.7) | 121 (42.3) |
| **Sweden** | 283 | 104 (36.7) | 179 (63.3) | 76 (13.4) | 283 (100) | 0 (0) |
| **Upenn** | 12 | 3 (25) | 9 (75) | 69 (8.9) | 0 (0) | 12 (100) |
| **UW** | 218 | 98 (45) | 120 (55) | 57 (17.4) | 0 (0) | 218 (100) |
| **VMAP** | 74 | 52 (70.3) | 22 (29.7) | 72 (6.5) | 0 (0) | 74 (100) |
| **WiscADRC** | 199 | 66 (33.2) | 133 (66.8) | 62 (9) | 27 (13.6) | 172 (86.4) |
| **WRAP** | 222 | 75 (33.8) | 147 (66.2) | 62 (6.8) | 0 (0) | 222 (100) |
| **Zetter** | 43 | 20 (46.5) | 23 (53.5) | 74 (4.3) | 25 (58.1) | 18 (41.9) |
| **Total** | **4592** | **2167 (47.2)** | **2425 (52.8)** | **71 (10.2)** | **2236 (48.7)** | **2356 (51.3)** |

Abbreviations: SD, standard deviation. Means and standard deviations (SD) for age, was calculated based on samples by cohorts.

## eTable 2. Distribution of APOE genotypes across cohorts

| Study | APOE | | | | | | APOE ε4 count | | |
|---|---|---|---|---|---|---|---|---|---|
| | ε2/ε2 (%) | ε2/ε3 (%) | ε2/ε4 (%) | ε3/ε3 (%) | ε3/ε4 (%) | ε4/ε4 (%) | 0 ε4 Alleles (%) | 1 ε4 Alleles (%) | 2 ε4 Alleles (%) |
| **ADNI** | 2 (0.2) | 96 (8) | 13 (1.1) | 637 (53.2) | 348 (29.1) | 101 (8.4) | 735 (61.4) | 361 (30.2) | 101 (8.4) |
| **AIBL** | 0 (0) | 21 (12.8) | 4 (2.4) | 96 (58.5) | 41 (25) | 2 (1.2) | 117 (71.3) | 45 (27.4) | 2 (1.2) |
| **Barcelona1** | 0 (0) | 2 (3.4) | 2 (3.4) | 19 (32.2) | 35 (59.3) | 1 (1.7) | 21 (35.6) | 37 (62.7) | 1 (1.7) |
| **BIOCARD** | 0 (0) | 2 (10) | 0 (0) | 11 (55) | 6 (30) | 1 (5) | 13 (65) | 6 (30) | 1 (5) |
| **Blennow** | 0 (0) | 6 (10.7) | 2 (3.6) | 33 (58.9) | 15 (26.8) | 0 (0) | 39 (69.6) | 17 (30.4) | 0 (0) |
| **FACE** | 0 (0) | 27 (7.7) | 6 (1.7) | 186 (53.3) | 108 (30.9) | 22 (6.3) | 213 (61) | 114 (32.7) | 22 (6.3) |
| **Homburg** | 0 (0) | 11 (11.3) | 2 (2.1) | 34 (35.1) | 37 (38.1) | 13 (13.4) | 45 (46.4) | 39 (40.2) | 13 (13.4) |
| **Knight ADRC** | 4 (0.7) | 63 (10.7) | 13 (2.2) | 292 (49.6) | 187 (31.7) | 30 (5.1) | 359 (61) | 200 (34) | 30 (5.1) |
| **Lleo** | 0 (0) | 11 (9.6) | 1 (0.9) | 59 (51.3) | 37 (32.2) | 7 (6.1) | 70 (60.9) | 38 (33) | 7 (6.1) |
| **London** | 0 (0) | 3 (3.7) | 1 (1.2) | 39 (48.1) | 25 (30.9) | 13 (16) | 42 (51.9) | 26 (32.1) | 13 (16) |
| **MAYO** | 1 (0.3) | 39 (11.3) | 11 (3.2) | 221 (63.9) | 68 (19.7) | 6 (1.7) | 261 (75.4) | 79 (22.8) | 6 (1.7) |
| **Molineuvo** | 0 (0) | 5 (2.7) | 2 (1.1) | 104 (57.1) | 59 (32.4) | 12 (6.6) | 109 (59.9) | 61 (33.5) | 12 (6.6) |
| **NACC** | 1 (0.3) | 14 (4.9) | 3 (1) | 127 (44.4) | 112 (39.2) | 29 (10.1) | 142 (49.7) | 115 (40.2) | 29 (10.1) |
| **Sweden** | 0 (0) | 3 (1.1) | 8 (2.8) | 68 (24) | 141 (49.8) | 63 (22.3) | 71 (25.1) | 149 (52.7) | 63 (22.3) |
| **Upenn** | 0 (0) | 1 (8.3) | 0 (0) | 8 (66.7) | 3 (25) | 0 (0) | 9 (75) | 3 (25) | 0 (0) |
| **UW** | 1 (0.5) | 19 (8.7) | 5 (2.3) | 131 (60.1) | 55 (25.2) | 7 (3.2) | 151 (69.3) | 60 (27.5) | 7 (3.2) |
| **VMAP** | 1 (1.4) | 6 (8.1) | 1 (1.4) | 44 (59.5) | 19 (25.7) | 3 (4.1) | 51 (68.9) | 20 (27) | 3 (4.1) |
| **WiscADRC** | 0 (0) | 19 (9.5) | 7 (3.5) | 92 (46.2) | 61 (30.7) | 20 (10.1) | 111 (55.8) | 68 (34.2) | 20 (10.1) |
| **WRAP** | 0 (0) | 22 (9.9) | 5 (2.3) | 122 (55) | 66 (29.7) | 7 (3.2) | 144 (64.9) | 71 (32) | 7 (3.2) |
| **Zetter** | 0 (0) | 3 (7) | 1 (2.3) | 18 (41.9) | 13 (30.2) | 8 (18.6) | 21 (48.8) | 14 (32.6) | 8 (18.6) |
| **Total** | **10 (0.2)** | **373 (8.1)** | **87 (1.9)** | **2341 (51)** | **1436 (31.3)** | **345 (7.5)** | **2724 (59.3)** | **1523 (33.2)** | **345 (7.5)** |

Abbreviations: AD, Alzheimer's Disease; Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau; APOE, genotype. 0 ε4 alleles, no ε4 (e.g., ε2/ε2, ε2/ε3, ε3/ε3); 1 ε4 allele, one ε4 (e.g., ε2/ε4, ε3/ε4); 2 ε4 alleles, two ε4 (e.g., ε4/ε4).

## eTable 3. Distribution of CSF biomarkers by study cohort

| Study | Aβ42, pg/mL, median (IQR) | Phosphorylated tau, pg/mL, median (IQR) | Total tau, pg/mL, median (IQR) |
|---|---|---|---|
| **ADNI** | 158 (132-220) | 34 (22-49) | 75 (52-113) |
| **AIBL** | 794 (607-954) | 52 (42-68) | 247 (185-329) |
| **Barcelona1** | 633 (508-752) | 97 (72-120) | 705 (530-877) |
| **BIOCARD** | 441 (382-464) | 29 (24-43) | 64 (47-74) |
| **Blennow** | 502 (370-674) | 78 (46-94) | 595 (309-881) |
| **FACE** | 618 (504-930) | 70 (46-101) | 461 (250-683) |
| **Homburg** | 71 (63-86) | NA | 77 (59-109) |
| **Knight ADRC** | 618 (416-804) | 48 (34-76) | 264 (170-494) |
| **Lleo** | 337 (251-490) | 34 (26-45) | 108 (67-135) |
| **London** | 681 (485-952) | 40 (29-62) | 319 (224-491) |
| **MAYO** | 336 (253-408) | 18 (15-23) | 81 (60-112) |
| **Molineuvo** | 429 (341-580) | 79 (55-107) | 455 (266-732) |
| **NACC** | 287 (179-447) | 47 (29-88) | 115 (54-563) |
| **Sweden** | 265 (204-320) | 94 (77-125) | 724 (560-940) |
| **Upenn** | 230 (184-253) | 21 (15-28) | 45 (38-80) |
| **UW** | 162 (140-181) | 42 (36-52) | 41 (30-56) |
| **VMAP** | 796 (566-938) | 52 (43-67) | 328 (263-472) |
| **WiscADRC** | 684 (503-845) | 43 (32-57) | 297 (217-418) |
| **WRAP** | 866 (620-1192) | 17 (13-21) | 195 (157-242) |
| **Zetter** | 500 (409-965) | 82 (64-107) | 413 (334-636) |
| **Total** | **335 (182-638)** | **40 (25-64)** | **174 (75-397)** |

Abbreviations: AD, Alzheimer's Disease; Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau; SD, standard deviation; IQR, interquartile range. Median and interquartile range (IQR) for Aβ42, pTau, and Tau values, was calculated based on samples by cohorts.

## eTable 4. Sex effect within and across ancestry

| Trait | Model | European Ancestry | | African Ancestry | | Asian Ancestry | | Meta-analysis across ancestries | |
|---|---|---|---|---|---|---|---|---|---|
| | | β (SE) | P Value | β (SE) | P Value | β (SE) | P Value | β (SE) | P Value |
| Aβ42 | Sex | -0.00 (0.03) | $9.24x10^{-1}$ | 0.27 (0.19) | $1.44x10^{-1}$ | -0.28 (0.32) | $3.93x10^{-3}$ | -0.58 (0.02) | $3.5x10^{-162}$ |
| pTau | Sex | 0.08 (0.03) | $7.25x10^{-3}$ | 0.45 (0.17) | $1.01x10^{-2}$ | 0.60 (0.32) | $4.31x10^{-1}$ | 0.35 (0.02) | $1.70x10^{51}$ |
| Tau | Sex | 0.12 (0.03) | $1.43x10^{-4}$ | 0.55 (0.21) | $9.28x10^{-3}$ | 0.60 (0.35) | $3.60x10^{-1}$ | 0.32 (0.02) | $3.10x10^{46}$ |

Abbreviations: Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau. Sex, evaluates the main effect of the sex on CSF biomarkers from model 1.

## eTable 5. Meta-analysis across ancestry

| CSF | Variable | Fixed | | | Random | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|
| | | β | SE | P Value | β | SE | P Value | I^2 (%) | P Value |
| Aβ42 | Sex | 0 | 0.03 | $9.40x10^{-01}$ | 0.03 | 0.1 | $7.50x10^{-01}$ | 47.3 | $1.50x10^{-01}$ |
| Aβ42 | APOE_ε4 | -0.58 | 0.02 | $3.50x10^{-162}$ | -0.61 | 0.06 | $1.10x10^{-22}$ | 0 | $3.68x10^{-01}$ |
| Aβ42 | Sex × APOE_ε4 | 0.11 | 0.04 | $1.40x10^{-02}$ | 0.11 | 0.04 | $1.40x10^{-02}$ | 58.7 | $8.87x10^{-02}$ |
| Aβ42 | APOE_ε4 in males | -0.63 | 0.03 | $7.00x10^{-90}$ | -0.63 | 0.03 | $8.20x10^{-90}$ | 36.5 | $2.07x10^{-01}$ |
| Aβ42 | APOE_ε4 in females | -0.53 | 0.03 | $2.10x10^{-75}$ | -0.6 | 0.09 | $3.80x10^{-11}$ | 35.3 | $2.13x10^{-01}$ |
| PTAU | Sex | 0.1 | 0.03 | $7.10x10^{-04}$ | 0.25 | 0.14 | $7.50x10^{-02}$ | 67.1 | $4.81x10^{-02}$ |
| PTAU | APOE_ε4 | 0.35 | 0.02 | $1.70x10^{-51}$ | 0.35 | 0.02 | $1.70x10^{-51}$ | 0 | $5.90x10^{-01}$ |
| PTAU | Sex × APOE_ε4 | 0.06 | 0.05 | $2.30x10^{-01}$ | 0.34 | 0.26 | $1.90x10^{-01}$ | 68.4 | $4.23x10^{-02}$ |
| PTAU | APOE_ε4 in males | 0.32 | 0.03 | $1.10x10^{-21}$ | 0.14 | 0.18 | $4.60x10^{-01}$ | 65.6 | $5.47x10^{-02}$ |
| PTAU | APOE_ε4 in females | 0.38 | 0.03 | $3.30x10^{-31}$ | 0.43 | 0.1 | $9.20x10^{-06}$ | 27.5 | $2.52x10^{-01}$ |
| TAU | Sex | 0.12 | 0.03 | $1.80x10^{-05}$ | 0.28 | 0.16 | $8.00x10^{-02}$ | 63.4 | $6.51x10^{-02}$ |
| TAU | APOE_ε4 | 0.32 | 0.02 | $3.10x10^{-46}$ | 0.32 | 0.02 | $3.10x10^{-46}$ | 0 | $6.67x10^{-01}$ |
| TAU | Sex × APOE_ε4 | 0.1 | 0.05 | $2.60x10^{-02}$ | 0.3 | 0.23 | $1.90x10^{-01}$ | 51 | $1.30x10^{-01}$ |
| TAU | APOE_ε4 in males | 0.27 | 0.03 | $2.30x10^{-16}$ | 0.27 | 0.03 | $2.40x10^{-16}$ | 54.4 | $1.11x10^{-01}$ |
| TAU | APOE_ε4 in females | 0.37 | 0.03 | $4.30x10^{-32}$ | 0.41 | 0.09 | $2.20x10^{-06}$ | 0 | $4.00x10^{-01}$ |

Abbreviations: Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau; $I^2$, Inconsistency Index. Sex, evaluates the main effect of the sex on CSF biomarkers from model 1; APOE_ε4, evaluates the main effect of the APOE-ε4 allele on CSF biomarkers from model 1; Males, focuses on the effect of APOE-ε4 in males from model 2; Females, focuses on the effect of APOE-ε4 in females from model 3; Interaction, evaluates the interaction between sex and APOE-ε4 on CSF biomarkers from model 4. Fixed, fixed effect; random, random effect.

Random-effects model prioritized when significant heterogeneity across ancestries was observed ($P < 0.05$); otherwise, fixed-effect meta-analysis models were used.

## eTable 6. Sensitivity analysis with ε3/ε3 as reference

| | | European Ancestry | | | African Ancestry | | | Asian Ancestry | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Trait** | **Model** | **β** | **SE** | **P Value** | **β** | **SE** | **P Value** | **β** | **SE** | **P Value** |
| Aβ42 | Sex | 0 | 0.03 | 9.24E-01 | 0.27 | 0.19 | 1.44E-01 | -0.28 | 0.32 | 3.93E-01 |
| Aβ42 | APOE_ε4 | -0.55 | 0.02 | 2.64E-127 | -0.76 | 0.14 | 8.93E-07 | -0.67 | 0.24 | 7.55E-03 |
| Aβ42 | Males | -0.61 | 0.03 | 4.79E-72 | -0.81 | 0.24 | 2.05E-03 | 0.43 | 0.63 | 5.07E-01 |
| Aβ42 | Females | -0.50 | 0.03 | 7.09E-58 | -0.65 | 0.18 | 6.87E-04 | -0.85 | 0.23 | 1.44E-03 |
| Aβ42 | Interaction | 0.11 | 0.04 | 1.31E-02 | 0.18 | 0.30 | 5.61E-01 | -1.33 | 0.63 | 4.19E-02 |
| pTau | Sex | 0.08 | 0.03 | 7.25E-03 | 0.45 | 0.17 | 1.01E-02 | 0.6 | 0.32 | 6.80E-02 |
| pTau | APOE_ε4 | 0.33 | 0.02 | 1.17E-40 | 0.45 | 0.13 | 9.92E-04 | 0.19 | 0.24 | 4.30E-01 |
| pTau | Males | 0.31 | 0.04 | 1.78E-18 | 0.10 | 0.19 | 5.96E-01 | -0.56 | 0.46 | 2.36E-01 |
| pTau | Females | 0.35 | 0.03 | 5.50E-24 | 0.66 | 0.18 | 5.45E-04 | 0.32 | 0.31 | 3.29E-01 |
| pTau | Interaction | 0.03 | 0.05 | 4.83E-01 | 0.55 | 0.27 | 4.68E-02 | 0.89 | 0.64 | 1.72E-01 |
| Tau | Sex | 0.12 | 0.03 | 1.43E-04 | 0.55 | 0.21 | 9.28E-03 | 0.6 | 0.35 | 9.17E-02 |
| Tau | APOE_ε4 | 0.31 | 0.02 | 1.67E-37 | 0.47 | 0.16 | 4.38E-03 | 0.23 | 0.26 | 3.77E-01 |
| Tau | Males | 0.26 | 0.03 | 6.36E-14 | 0.21 | 0.24 | 3.87E-01 | -0.71 | 0.44 | 1.25E-01 |
| Tau | Females | 0.35 | 0.03 | 9.46E-26 | 0.66 | 0.22 | 4.73E-03 | 0.42 | 0.35 | 2.52E-01 |
| Tau | Interaction | 0.09 | 0.05 | 5.97E-02 | 0.45 | 0.34 | 1.84E-01 | 1.08 | 0.69 | 1.26E-01 |

Abbreviations: Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau. Sex, evaluates the main effect of the sex on CSF biomarkers from model 1; APOE_ε4, evaluates the main effect of the APOE-ε4 allele on CSF biomarkers from model 1; Males, focuses on the effect of APOE-ε4 in males from model 2; Females, focuses on the effect of APOE-ε4 in females from model 3; Interaction, evaluates the interaction between sex and APOE-ε4 on CSF biomarkers from model 4.

First sensitivity analyses were conducted by comparing APOE-ε4 carriers to APOE-ε3/ε3 homozygotes. In this analysis, APOE-ε4 was coded as follows: 0 for 3/ε3 , 1 for ε3/ε4 and ε2/ε4 , and 2 for ε4/ε4.

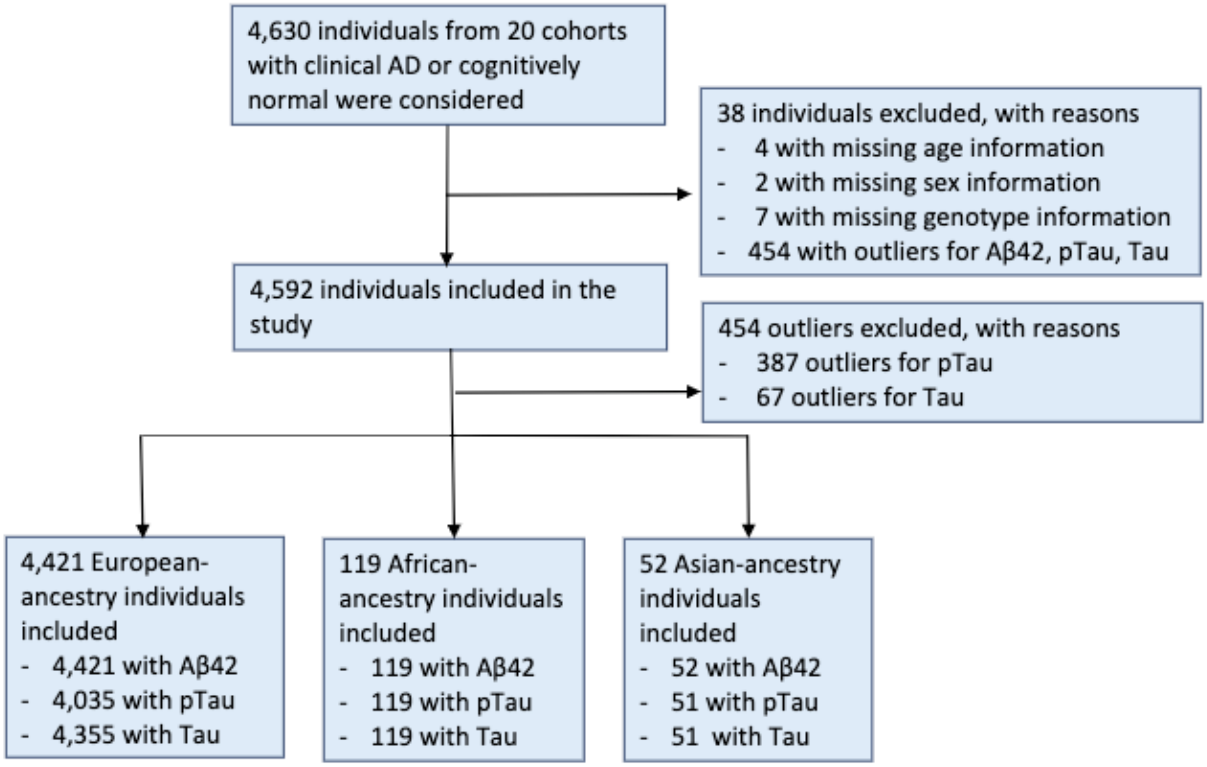
## eTable 7. Sensitivity analysis without any APOE-ε2 carriers

| | | European Ancestry | | | African Ancestry | | | Asian Ancestry | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Trait** | **Model** | **β** | **SE** | **P Value** | **β** | **SE** | **P Value** | **β** | **SE** | **P Value** |
| Aβ42 | Sex | 0 | 0.03 | 9.75E-01 | 0.29 | 0.19 | 1.29E-01 | -0.28 | 0.32 | 3.93E-01 |
| Aβ42 | APOE_ε4 | -0.55 | 0.02 | 4.32E-127 | -0.74 | 0.15 | 1.88E-06 | -0.67 | 0.24 | 7.55E-03 |
| Aβ42 | Males | -0.61 | 0.03 | 1.17E-71 | -0.81 | 0.24 | 2.05E-03 | 0.43 | 0.63 | 5.07E-01 |
| Aβ42 | Females | -0.50 | 0.03 | 5.18E-58 | -0.63 | 0.19 | 1.27E-03 | -0.85 | 0.23 | 1.44E-03 |
| Aβ42 | Interaction | 0.11 | 0.04 | 1.49E-02 | 0.20 | 0.30 | 5.17E-01 | -1.33 | 0.63 | 4.19E-02 |
| pTau | Sex | 0.08 | 0.03 | 7.50E-03 | 0.44 | 0.17 | 1.32E-02 | 0.6 | 0.32 | 6.80E-02 |
| pTau | APOE_ε4 | 0.34 | 0.02 | 6.71E-42 | 0.44 | 0.14 | 1.53E-03 | 0.19 | 0.24 | 4.30E-01 |
| pTau | Males | 0.32 | 0.04 | 5.50E-19 | 0.10 | 0.19 | 5.96E-01 | -0.56 | 0.46 | 2.36E-01 |
| pTau | Females | 0.36 | 0.03 | 9.37E-25 | 0.64 | 0.18 | 9.05E-04 | 0.32 | 0.31 | 3.29E-01 |
| pTau | Interaction | 0.04 | 0.05 | 4.72E-01 | 0.54 | 0.28 | 5.49E-02 | 0.89 | 0.64 | 1.72E-01 |
| Tau | Sex | 0.12 | 0.03 | 1.54E-04 | 0.57 | 0.21 | 7.58E-03 | 0.6 | 0.35 | 9.17E-02 |
| Tau | APOE_ε4 | 0.31 | 0.02 | 8.14E-39 | 0.49 | 0.16 | 3.44E-03 | 0.23 | 0.26 | 3.77E-01 |
| Tau | Males | 0.26 | 0.03 | 2.16E-14 | 0.21 | 0.24 | 3.87E-01 | -0.71 | 0.44 | 1.25E-01 |
| Tau | Females | 0.36 | 0.03 | 1.21E-26 | 0.68 | 0.22 | 3.48E-03 | 0.42 | 0.35 | 2.52E-01 |
| Tau | Interaction | 0.09 | 0.05 | 5.75E-02 | 0.47 | 0.33 | 1.60E-01 | 1.08 | 0.69 | 1.26E-01 |

Abbreviations: Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau. Sex, evaluates the main effect of the sex on CSF biomarkers from model 1; APOE_ε4, evaluates the main effect of the APOE-ε4 allele on CSF biomarkers from model 1; Males, focuses on the effect of APOE-ε4 in males from model 2; Females, focuses on the effect of APOE-ε4 in females from model 3; Interaction, evaluates the interaction between sex and APOE-ε4 on CSF biomarkers from model 4.

Second sensitivity analyses were conducted by comparing APOE-ε4 carriers to APOE-ε3/ε3 homozygotes and removing APOE-*ε*2/4 heterozygotes. Specifically, in this analysis, APOE-ε4 was coded as follows: 0 for ε3/ε3; 1 for ε3/ε4; and 2 for ε4/ε4.

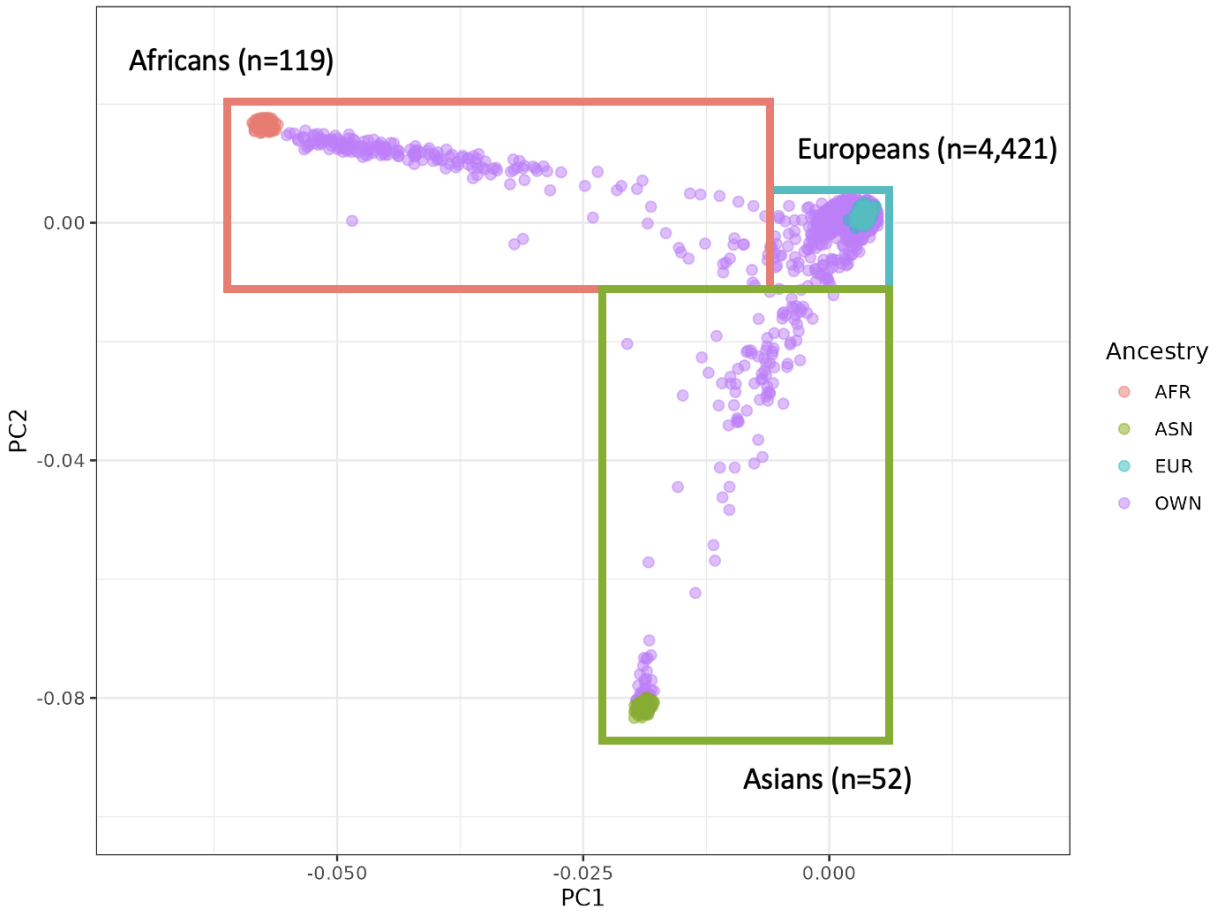
## eFigure 1. Flow chart




Abbreviations: Aβ42, Amyloid β1–42; pTau, phosphorylated tau; Tau, total tau.

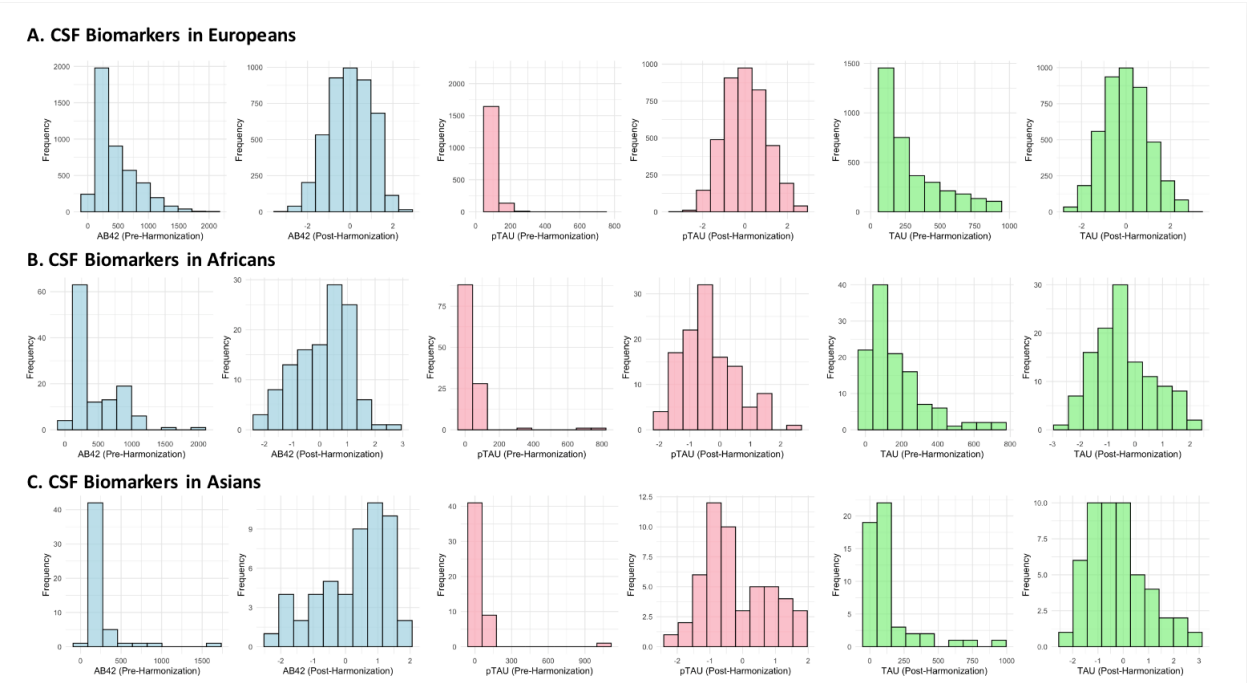
This flowchart illustrates the inclusion process for participants from 20 cohorts. Out of 4,630 individuals, our analysis included 4,421 individuals of European ancestry, 119 individuals of African ancestry, and 52 individuals of Asian ancestry. This classification ensures the robust analysis of CSF biomarkers across groups.

## eFigure 2. Genetically derived ancestry information



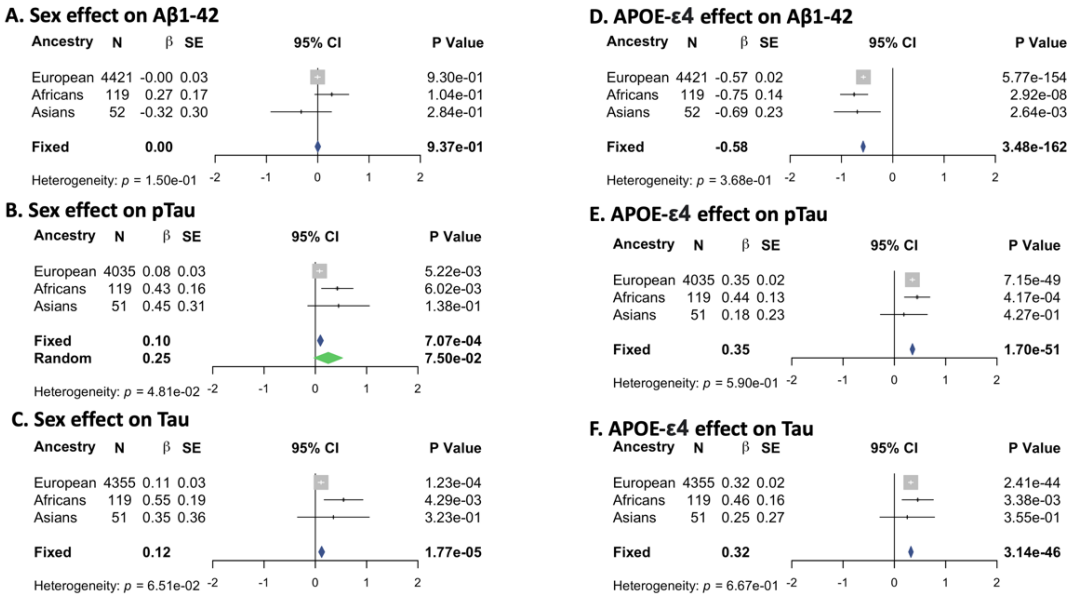

This figure presents the genetically derived information by ancestry. To determine ancestry, we used the first two principal components (PC) from the principal component analysis (PCA). By anchoring HapMap data with European (EUR; in cyan), African (AFR, in orange) and Asian (ASN, in green), samples across 20 cohorts (OWN, in purple) were grouped to European (n=4,421, in cyan box). African (n=119, in orange box) and Asian (n=52, in green box).

# eFigure 3. Histogram of CSF biomarkers before and after harmonization



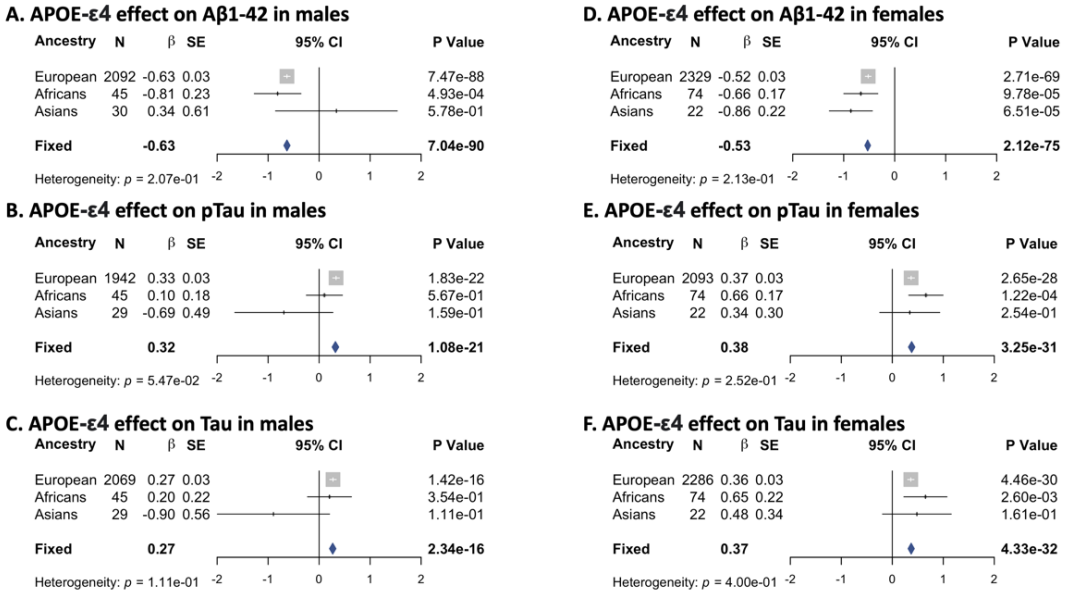

This figure presents the distribution of cerebrospinal fluid (CSF) biomarkers (Aβ42, pTau, and Tau) before and after harmonization, stratified by ancestry groups: Europeans (Panel A), Africans (Panel B), and Asians (Panel C). Pre-harmonization data displays a skewed distribution. Post-harmonization, applying log10 transformation and Z-score normalization, improves distributions. This highlights ancestry-specific variations and the effect of harmonization.

# eFigure 4. Sex and APOE-ε4 effect across both sexes




For CSF biomarkers Aβ1-42, pTau, and Tau, the main effect of sex (Panel A, B, C) and APOE-ε4 (Panel D, E, F) were analyzed using the model $Y = \alpha + \beta_1 \times APOE\_\varepsilon 4 + \beta_2 \times Sex + \beta_3 \times Age + \varepsilon$ were presented. The results are stratified by ancestry, including European, African, and Asian populations, and are displayed in order of effect size. Each effect is represented by a square proportional to the sample size, along with its 95% confidence interval indicated by horizontal lines. Fixed-effect meta-analyses were performed for all three biomarkers, as heterogeneity tests across ancestries were not significant (P > .05).
However, for pTau, heterogeneity was significant ($P = 4.81 \times 10^{-2}$), necessitating both fixed-effect (blue diamond) and random-effect (green diamond) meta-analyses.

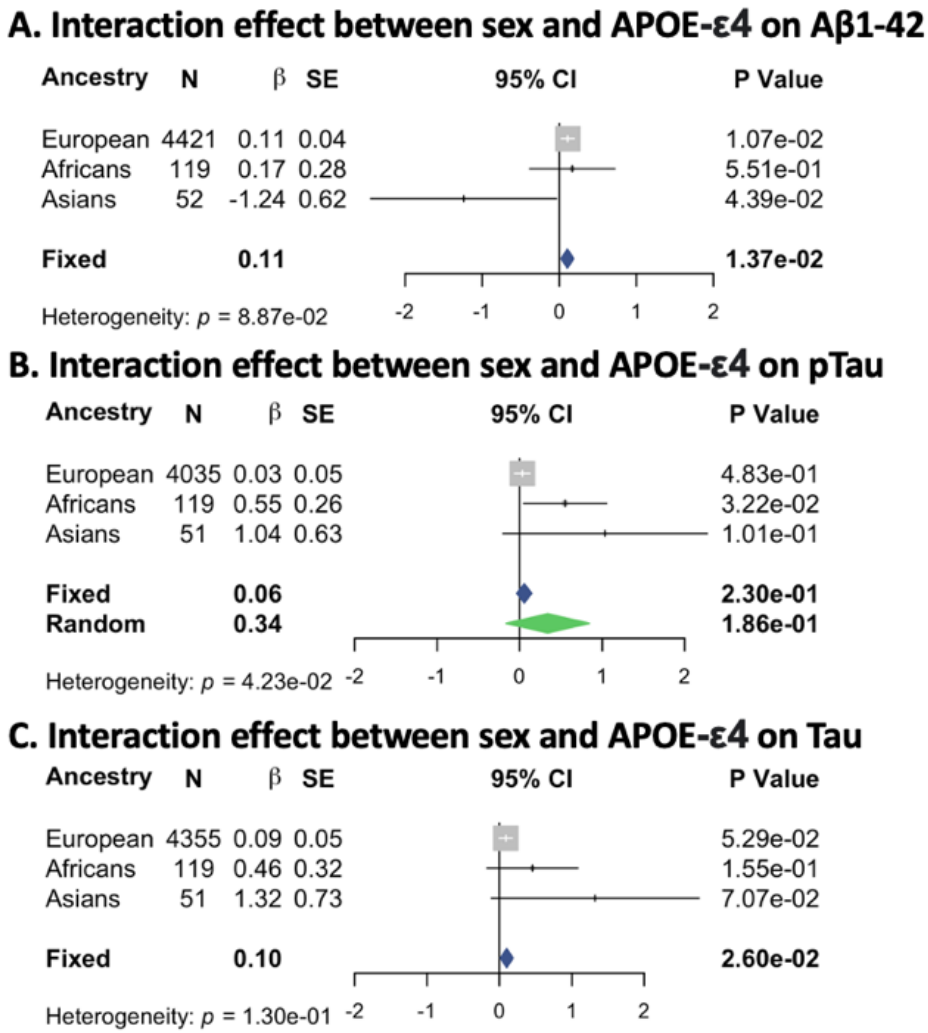
# eFigure 5. Sex-stratified APOE-ε4 effects




For CSF biomarkers Aβ1-42, pTau, and Tau, the effect of APOE-ε4 was analyzed separately in males using the stratified models $Y = a + \beta_1 \times APOE\_\varepsilon 4 + \beta_2 \times Age + \varepsilon$. The results, stratified by ancestry (European, African, and Asian), are presented in Panels A-F, with effects displayed in order of effect size. Each effect is represented by a square proportional to the sample size, with horizontal lines indicating the 95% confidence intervals.

Fixed-effect meta-analyses (blue diamond) were conducted across ancestries. This stratified analysis highlights potential differences in APOE-ε4 effects on CSF biomarkers between sexes across different ancestry groups.

## eFigure 6. Interaction effect between sex and APOE-ε4

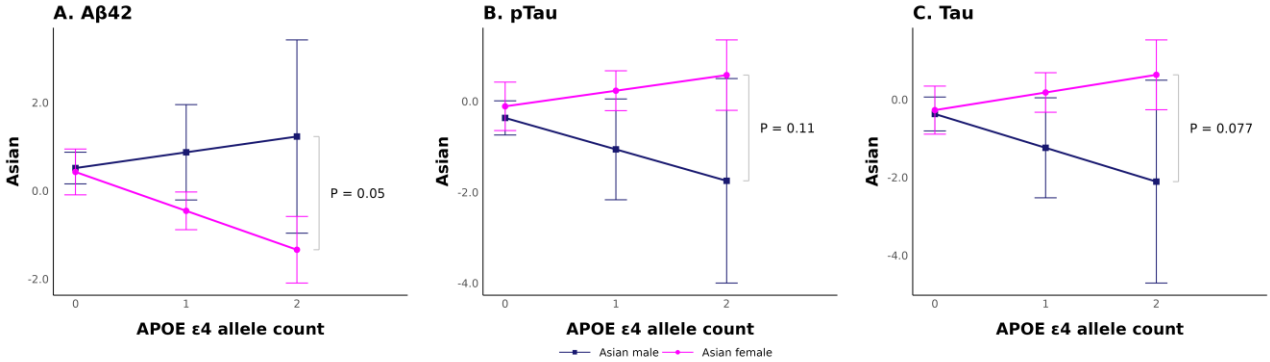



For the CSF biomarkers Aβ1-42, pTau, and Tau, the interaction effects between sex and APOE-ε4 across ancestries were accessed using the model $Y = a + \beta_1 \times APOE\_\varepsilon4 + \beta_2 \times Sex + \beta_3 \times Age + \beta_4 \times APOE\_\varepsilon4 \times Sex + \varepsilon$. The results, stratified by ancestry (European, African, and Asian), are presented in Panels A-C, with interaction effects displayed in order of effect size. Each interaction effect is represented by a square proportional to the sample size, with horizontal lines indicating the 95% confidence intervals.

For Aβ1-42 (Panel A) and Tau (Panel C) , fixed-effect meta-analyses were performed due to the absence of significant heterogeneity across ancestries (P>.05), as indicated by the blue diamond.

For pTau (Panel B), heterogeneity across ancestries was significant (P=4.23×10−2), necessitating both fixed-effect (blue diamond) and random-effect (green diamond) meta-analyses.

## eFigure 7. Sex-stratified APOE-ε4 effect in Asian ancestry




For CSF biomarkers Aβ42, pTau, and Tau, the interaction effect of sex and APOE-ε4 (Panels A, B, and C, respectively) in individuals of Asian ancestry was analyzed using stratified models. Specifically, Model 2 ($Y = a + \beta_1 \times \mathrm{APOE}_{\varepsilon 4} + \beta_2 \times Age + \varepsilon$ (stratified analysis with males only)) was applied to males, and Model 3 ($Y = a + \beta_1 \times \mathrm{APOE}_{\varepsilon 4} + \beta_2 \times Age + \varepsilon$ (stratified analysis with females only)) was applied to females. The predicted biomarker levels, stratified by sex, are shown as separate lines for males (black) and females (pink), with error bars representing 95% confidence intervals.

The x-axis represents the APOE-ε4 allele count (0, 1, or 2), while the y-axis shows the predicted normalized biomarker levels. The plots display separate trajectories for males (black) and females (pink), with error bars representing 95% confidence intervals.

## eMethods 1. Cohort description

**Alzheimer's Disease Neuroimaging Initiative (ADNI)**

Data used in the analyses performed in this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

**Australian Imaging, Biomarkers and Lifestyle (AIBL)**

Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL) study was initiated in November 2006 with a prospective longitudinal study design, intending to assess all participants at 18-month intervals. Over 1100 participants, comprising of healthy controls (HC), individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD) were evaluated over 4.5 years. Data collection was done in two centers with 40% of subjects from Perth in Western Australia and 60% from Melbourne, Victoria. Neuroimaging was planned for 25% of each of these groups. However, the actual enrollment in the neuroimaging arm included 177 HC, 57 MCI, and 53 individuals with mild AD, constituting 26% of the entire cohort[1]. All individuals in the study were aged 60 or older, and they were in generally good health, with no prior history of stroke or any other neurological conditions. Those diagnosed with AD met the criteria outlined by the National Institute of Neurological and Communicative Disorders–Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) for probable AD, as defined by McKhann et al in 19844. Additionally, these AD patients exhibited a Clinical Dementia Rating (CDR) of 1 or higher. For additional information see https://aibl.csiro.au/.

**Barcelona-1**

Barcelona -1 is a longitudinal observational study consisting of ~300 subjects at baseline carried out in the Memory and Disorder unit at the University Hospital Mutua de Terrassa, Terrassa, Barcelona, Spain. Cases include subjects diagnosed with AD dementia (ADD), non-AD dementias (non-ADD), mild cognitive impairment (MCI), or subjective memory complaints (SMC). Clinical information was collected at baseline as well as longitudinally and lumbar puncture (LP) and amyloid PET were performed if subjects had diagnosis of MCI, early-onset dementia (<65 years), or dementia with atypical clinical features[3].

**Biomarkers for Older Controls at Risk for Dementia (BIOCARD)**

The Biomarkers for Older Controls at Risk for Dementia (BIOCARD) study is a longitudinal study that was initiated in 1995 in the National Institute of Mental Health (NIMH) Intramural Research Program. The study encompassed clinical, neuropsychological, and neuropsychiatric evaluations, neuroimaging, and fluid biomarkers assessment to understand and predict progression from normal cognition to mild cognitive impairment (MCI) and dementia, particularly Alzheimer's disease (AD). The average age at enrollment was 55 years. The study was stopped in 2005, however, in 2009 it was re-started at Johns Hopkins University (JHU). Between 1995 and 2005, clinical and cognitive assessments were performed annually, and CSF, blood sampling, and magnetic resonance imaging (MRI) were done every 2 years[2]. From 2009 until

2015, participants were annually evaluated for clinical, and cognitive assessments and blood sample collection with bi-annual MRI and CSF being restarted since 2015[2].

**Ace Alzheimer Center Barcelona (FACE)**

We obtained cerebrospinal biomarker data from Ace Alzheimer Center Barcelona also known as Fundació ACE (FACE) which is a leading non-profit research and clinical center specializing in Alzheimer's disease and other neurodegenerative disorders. Founded in 1995 and headquartered in Barcelona, this center combines both research activities and clinical care services. To date, the center has diagnosed over 30,000 patients, collected 20,000 blood and 1,831 cerebrospinal fluid samples, analyzed almost 13,000 genetic samples, and participated in almost 150 clinical trials during its existence[4]. For more details, visit http://www.fundacioace.com/en.

**Saarland University in Homburg/Saar, Germany (Homburg)**

CSF biomarker data from 107 subjects were collected at Saarland University in Germany. These included demented outpatients who referred to a hospital memory clinic between 1995 and 2001 for diagnostic evaluation [5]. For clinical diagnosis of probable AD, the National Institute of Neurological and Communication Disorders and Stroke/AD and Related Disorders Association criteria were applied [5]. Additional evaluation performed included CSF and blood sample collection, assessment of cognitive impairment, APOE genotyping among others. Age at onset was defined by the appearance of the first clinical symptoms [5].

**Knight ADRC**

Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC), housed at Washington University in St. Louis, is one of 30 ADRCs funded by NIH. The goal of this collaborative research effort is to advance AD research with the goal of treatment or prevention of AD. The subjects included in this study are from the Memory and Aging Project (MAP) supported by Knight ADRC. As part of the project, subjects undergo annual psychometric testing and interviews along with biennial or triennial PET, MRI, and CSF collection. Further details on Knight ADRC and MAP can be found at https://knightadrc.wustl.edu/.

**Hospital Sant Pau (Lleo)**

The memory unit of Hospital Sant Pau located in Barcelona, Spain, attends more than 2000 patients annually. Routine assessment includes neuropsychological evaluation, CSF blood sample collection and MRI tests. Additionally, PET examination is conducted in a select group of subjects. The subjects included in this study were recruited from the year 2009 to 2016[6]. Additional information on the study can be found at https://santpaumemoryunit.com/.

**London**

The CSF biomarker data under the London cohort were from EDAR and DESCRIPA studies. EDAR is a prospective, longitudinal study aimed at examining and evaluating biomarkers of early AD[8,9]. In particular, the study is focused on Aβ oligomers and the effect of genetic variants on these oligomers. More information on the cohort can be found at http://www.edarstudy.eu. DESCRIPA study is also a prospective, multicenter study. Led by the European AD Consortium, the focus of the study is on collecting data from non-demented subjects to develop screening

and diagnostic criteria for AD[9]. Further details of this study can be found in Visser et. al, (2008)[10].

**MAYO**

The CSF biomarker data under the Mayo cohort were collected by biospecimen accessioning and processing core at Mayo Clinic in Rochester, Minnesota. The research core at Mayo Clinic usually serves study groups affiliated with the clinic, however, some facilities are available to investigators worldwide. The Proteomics Core in particular offers routine services to identify and quantify proteins. Longitudinal CSF samples were available from 443 individuals comprising close to 100% control group.

**Clinic de Barcelona (Molineuvo)**.

CSF samples in this cohort were collected from individuals recruited at the Alzheimer's disease and other cognitive disorder unit, from the Hospital Clinic de Barcelona (Barcelona, Spain)[12]. CSF samples were collected from 256 individuals with 36.8% being male. In addition to CSF profiling, an assessment of cognitive impairment was also performed as part of data collection. Samples were provided by Dr. Molineuvo.

**National Alzheimer's Coordinating Center (NACC)**

The National Alzheimer's Coordinating Center (NACC) is the central data repository for all NIA's Alzheimer's Disease and Research Centers (ADRC) Programs, including Mayo ADRC and Knight ADRC. The CSF biomarker data utilized from NACC in this paper were selected after proper IBD to make sure no duplicates or close relatives of samples from other ADRC cohorts were included in GWAS. Currently, NACC houses data from 47000 participants from across 33 ADRCs and 4 exploratory centers. The data is collected using a prospective, standardized, and longitudinal clinical evaluation of subjects. NACC protocol requires annual follow-up for as long as the participant can be involved and is thus longitudinal. CSF as well as Imaging data are available as a part of the data repository. However, the data collection schedule and subject enrollment protocol vary by center. For additional information please check this link https://naccdata.org/.

**Skåne University Hospital, Sweden (SWEDEN)**

The samples included in this cohort were evaluated at the memory disorder unit at Skåne University Hospital. Of the total 315 subjects included in this study, 100% of them were diagnosed as having AD. Details of sample collection in this cohort have been described previously[13]. Briefly, at the thorough physical, neurological, and psychiatric examination, as well as a clinical interview focusing on cognitive symptoms are performed as baseline visit. Furthermore, cognitive tests, analysis of APOE genotype, and imaging of the brain were also done. Additional information on the center can be found at https://vard.skane.se/en/skane-university-hospital/.

**University of Pennsylvania (UPENN)**

The CSF biomarker data used in this study were received from the University of Pennsylvania's Alzheimer's Disease Research Center. Participants should be of age 55 years or older to be enrolled in the cohort. Annual visit includes cognitive testing, neurological exam, blood samples and interviews. MRI and PET scan data are available for a subset of the samples. The

longitudinal biomarker data used in this study were from 182 unique participants and were measured using the Luminex platform.

**University of Washington (UW)**

The UW Alzheimer's Disease Research Center, located in Seattle, is part of one of the NIH-funded ADRCs focused on Alzheimer's disease and related dementia. The center conducts yearly visits during which participants are required to complete tests of their memory and thinking and have a brief physical and neurological examination. Blood draw is usually part of the annual visits, but CSF collection is voluntary. For additional information on the center please visit https://depts.washington.edu/mbwc/adrc.

**Vanderbilt Memory and Aging Project (VMAP)**

Founded in 2012, the Vanderbilt Memory and Aging Project (VMAP) is a longitudinal study focused on the study of brain aging. As part of the project, physical and frailty examination, fasting blood draw, neuropsychological assessment, echocardiogram, cardiac MRI, CSF collection and brain MRI are usually obtained at baseline visits. Follow-up visits are then scheduled at 18 months, 3 years, 5 years, and so on. To be a part of the study, individuals must be 50+ years old and show no signs of cognitive decline. More details on the project can be found at https://www.vumc.org/vmac/home.

**Wisconsin Alzheimer's Disease Research Center (WiscADRC)**

The Wisconsin Alzheimer's Disease Research Center housed at the University of Wisconsin-Madison is one of the several NIH-funded ADRC centers in the USA. Established in 2009, the primary focus of the center is to improve early detection of Alzheimer's disease and find ways to delay onset and progression. As of 2023, the center has collected data from 1075 core participants of which 601 have undergone CSF collection and 572 have PET scans available. Cognitive assessment is done either annually or at every other year visit. Further details can be found at https://www.adrc.wisc.edu/.

**Wisconsin Registry for Alzheimer's Prevention (WRAP)**

The Wisconsin Registry for Alzheimer's Prevention is a longitudinal observational cohort study enriched with persons with a parental history (PH) of probable Alzheimer's disease (AD) dementia. Since late 2001, the Wisconsin Registry for Alzheimer's Prevention has enrolled 1561 people at a mean baseline age of 54 years. Participants return for a second visit 4 years after baseline, and subsequent visits occur every 2 years.

**Note:** Samples included in Blennow and Zetter cohorts were provided by Dr. Blennow and Dr. Zetterberg respectively. DNA samples along with CSF biomarker measurement, disease status, gender and age at sample collection information were provided. Additional information about these cohorts is not available current.

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