**Supplementary table e-1. Difference of the TRS between CN (N=243) and AD (N=223) according to various criteria for selecting AD-associated SNPs in AddNeuroMed**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Criteria for selecting SNPs | TRS using all candidate genes, mean (SD) | | OR of TRS  (95% CI, *P* value) | TRS using target genes from coloc, mean (SD) | | OR of TRS  (95% CI, *P* value) | TRS using target genes from SMR, mean (SD) | | OR of TRS  (95% CI, *P* value) |
| CN | AD | CN | AD | CN | AD |
| *P* < 5×10-8a | -0.943  (3.54) | 0.962  (3.79) | 1.15 (1.09–1.22, 2.64×10-7) | -0.459  (2.74) | 0.590  (2.96) | 1.14 (1.07–1.22, 1.60×10-7) | -0.228  (1.89) | 0.349  (2.01) | 1.16 (1.05–1.28, 4.06×10-3) |
| *P* < 1×10-7 | -0.654  (4.19) | 0.928  (4.60) | 1.09 (1.04–1.14, 1.41×10-4) | -0.554  (2.52) | 0.622  (2.64) | 1.20 (1.12–1.30, 1.94×10-6) | -0.511  (2.12) | 0.478  (2.29) | 1.23 (1.13–1.35, 5.49×10-6) |
| *P* < 1×10-6 | -0.652  (4.49) | 1.04  (4.97) | 1.08 (1.04–1.13, 1.49×10-4) | -0.554  (2.52) | 0.622  (2.64) | 1.20 (1.12–1.30, 1.94×10-6) | -0.511  (2.12) | 0.478  (2.29) | 1.23 (1.13–1.35, 5.49×10-6) |
| *P* < 1×10-5 | -0.894  (5.24) | 1.29  (5.78) | 1.07 (1.04–1.12, 3.75×10-5) | -0.633  (2.92) | 0.775  (3.01) | 1.18 (1.10–1.26, 1.33×10-6) | -0.589  (2.57) | 0.631  (2.69) | 1.19 (1.11–1.29, 4.16×10-6) |
| *P* < 1×10-4 | -0.969  (4.96) | 0.857  (5.23) | 1.07 (1.03–1.12, 1.88×10-4) | -0.644  (2.84) | 0.833  (2.86) | 1.21 (1.13–1.30, 1.13×10-7) | -0.589  (2.57) | 0.631  (2.69) | 1.19 (1.11–1.29, 4.16×10-6) |
| *P* < 1×10-3 | -2.58  (9.38) | 1.85  (9.69) | 1.05 (1.03–1.07, 1.27×10-6) | -0.907  (3.57) | 1.05  (3.72) | 1.17 (1.10–1.23, 6.39×10-8) | -0.665  (3.05) | 0.746  (3.17) | 1.15 (1.09–1.23, 7.10×10-6) |
| *P* < 1×10-2 | -0.298  (15.2) | 1.33  (14.8) | 1.01 (0.999–1.02, 8.11×10-2) | -0.982  (4.09) | 1.20  (4.33) | 1.13 (1.08–1.19, 1.97×10-7) | -0.562  (3.30) | 0.813  (3.46) | 1.13 (1.06–1.19, 6.70×10-5) |

ORs and 95% CIs of TRS were derived from the logistic regression analysis with adjustment of age and sex.

aSNPs in strong linkage disequilibrium (r2 > 0.8) with the SNPs which had genome-wide-significant associations (*P* < 5×10-8) were also included for analysis.

Abbreviation: AD: Alzheimer's disease; CI: confidence interval; CN: cognitively normal older adults; OR: odds ratio; SD: standard deviation; SNP: single nucleotide polymorphism; TRS: transcriptional risk score.

**Supplementary table e-2. Association between TRS and hippocampal volume in ADNI**

|  |  |  |  |
| --- | --- | --- | --- |
| Criteria for selecting SNPs | *β* coefficient of TRS using all candidate genes (95% CI, *P* value) | *β* coefficient of TRS using target genes from coloc (95% CI, *P* value) | *β* coefficient of TRS using target genes from SMR (95% CI, *P* value) |
| *P* < 5×10-8a | -1.17×10-2 (-2.09×10-2–-2.54×10-3, 1.24×10-2) | -1.43×10-2 (-2.41×10-2–-4.54×10-3, 4.17×10-3) | -1.45×10-2 (-2.83×10-2–-7.74×10-3, 3.84×10-2) |
| *P* < 1×10-7 | -1.13×10-2 (-2.10×10-2–-1.62×10-3, 2.23×10-2) | -2.48×10-2 (-4.08×10-2–-8.84×10-3, 2.38×10-3) | -2.12×10-2 (-3.89×10-2–-3.55×10-3, 1.87×10-2) |
| *P* < 1×10-6 | -1.10×10-2 (-1.93×10-2–-2.62×10-3, 1.01×10-2) | -2.19×10-2 (-3.82×10-2–-5.49×10-3, 8.94×10-3) | -2.12×10-2 (-3.89×10-2–-3.55×10-3, 1.87×10-2) |
| *P* < 1×10-5 | -1.13×10-2 (-1.86×10-2–-3.96×10-3, 2.62×10-3) | -2.43×10-2 (-3.83×10-2–-1.04×10-2, 6.63×10-4) | -2.12×10-2 (-3.61×10-2–-6.20×10-3, 5.66×10-3) |
| *P* < 1×10-4 | -5.79×10-3 (-1.18×10-2–1.67×10-4, 5.68×10-2) | -2.27×10-2 (-3.71×10-2–-8.31×10-3, 2.04×10-3) | -1.68×10-2 (-3.32×10-2–-4.71×10-4, 4.38×10-2) |
| *P* < 1×10-3 | -2.36×10-3 (-5.73×10-3–1.01×10-3, 8.92×10-2) | -2.36×10-2 (-3.50×10-2–-1.21×10-2, 6.37×10-5) | -2.04×10-2 (-3.45×10-2–-6.40×10-3, 4.39×10-3) |
| *P* < 1×10-2 | -2.93×10-4 (-2.01×10-3–1.42×10-3, 7.38×10-1) | -1.49×10-2 (-2.32×10-2–-6.63×10-3, 4.35×10-4) | -1.84×10-2 (-3.02×10-2–-6.69×10-3, 2.15×10-3) |

*β* coefficients and 95% CIs of TRS were derived from the linear regression analysis with adjustment of age, sex, intracranial volume and MRI field strength.

Among 661 ADNI participants, hippocampal volume data for 2 participants were not available.

aSNPs in strong linkage disequilibrium (r2 > 0.8) with the SNPs which had genome-wide-significant associations (*P* < 5×10-8) were also included for analysis.

Abbreviation: ADNI: Alzheimer's Disease Neuroimaging Initiative; CI: confidence interval; TRS: transcriptional risk score.

**Supplementary table e-3. Association between TRS and entorhinal cortical thickness in ADNI**

|  |  |  |  |
| --- | --- | --- | --- |
| Criteria for selecting SNPs | *β* coefficient of TRS using all candidate genes (95% CI, *P* value) | *β* coefficient of TRS using target genes from coloc (95% CI, *P* value) | *β* coefficient of TRS using target genes from SMR (95% CI, *P* value) |
| *P* < 5×10-8a | -6.92×10-3 (-1.54×10-2–1.58×10-3, 1.10×10-2) | -1.02×10-2 (-1.92×10-2–-1.12×10-3, 2.77×10-2) | -9.59×10-3 (-2.23×10-2–3.13×10-2, 1.39×10-1) |
| *P* < 1×10-7 | -7.18×10-3 (-1.62×10-2–1.80×10-3, 1.17×10-1) | -2.04×10-2 (-3.52×10-2–-5.62×10-3, 6.90×10-3) | -1.74×10-3 (-3.37×10-2–-1.01×10-3, 3.75×10-2) |
| *P* < 1×10-6 | -6.44×10-3 (-1.42×10-2–1.31×10-3, 1.03×10-1) | -1.53×10-2 (-3.05×10-2–-1.76×10-4, 4.74×10-2) | -1.74×10-3 (-3.37×10-2–-1.01×10-3, 3.75×10-2) |
| *P* < 1×10-5 | -6.13×10-3 (-1.29×10-2–6.88×10-4, 7.79×10-2) | -2.07×10-2 (-3.36×10-2–-7.76×10-3, 1.76×10-3) | -1.90×10-2 (-3.29×10-2–-5.20×10-3, 7.07×10-3) |
| *P* < 1×10-4 | -5.51×10-3 (-1.10×10-2–-8.13×10-6, 4.97×10-2) | -1.76×10-2 (-3.09×10-2–-4.22×10-3, 9.97×10-3) | -1.90×10-2 (-3.41×10-2–-3.94×10-3, 1.35×10-2) |
| *P* < 1×10-3 | -2.69×10-3 (-5.80×10-3–-4.14×10-4, 8.92×10-2) | -1.92×10-2 (-2.98×10-2–-8.55×10-3, 4.29×10-4) | -2.06×10-2 (-3.36×10-2–-7.66×10-3, 1.86×10-3) |
| *P* < 1×10-2 | 4.04×10-5 (-1.54×10-3–1.63×10-3, 9.60×10-1) | -1.03×10-2 (-1.80×10-2–-2.59×10-3, 8.87×10-3) | -1.49×10-2 (-2.58×10-2–-4.04×10-3, 7.28×10-3) |

*β* coefficients and 95% CIs of TRS were derived from the linear regression analysis with adjustment of age, sex, intracranial volume and MRI field strength.

Among 661 ADNI participants, entorhinal thickness data for 2 participants were not available.

aSNPs in strong linkage disequilibrium (r2 > 0.8) with the SNPs which had genome-wide-significant associations (*P* < 5×10-8) were also included for analysis.

Abbreviation: ADNI: Alzheimer's Disease Neuroimaging Initiative; CI: confidence interval; TRS: transcriptional risk score.

**Supplementary table e-4. Association between TRS and global cortical amyloid accumulation in ADNI**

|  |  |  |  |
| --- | --- | --- | --- |
| Criteria for selecting SNPs | *β* coefficient of TRS using all candidate genes (95% CI, *P* value) | *β* coefficient of TRS using target genes from coloc (95% CI, *P* value) | *β* coefficient of TRS using target genes from SMR (95% CI, *P* value) |
| *P* < 5×10-8a | 3.76×10-3 (-2.88×10-4–7.81×10-3, 6.86×10-2) | 4.97×10-3 (6.59×10-4–9.28×10-3, 1.00×10-2) | 4.89×10-3 (-1.14×10-2–1.09×10-2, 1.12×10-1) |
| *P* < 1×10-7 | 6.50×10-3 (2.25×10-3–1.08×10-2, 2.77×10-3) | 6.97×10-3 (-1.09×10-4–1.41×10-2, 5.36×10-2) | 8.68×10-3 (9.21×10-4–1.64×10-2, 2.84×10-2) |
| *P* < 1×10-6 | 5.93×10-3 (2.27×10-3–9.60×10-3, 1.56×10-3) | 5.80×10-3 (-1.49×10-3–1.31×10-2, 1.19×10-1) | 8.68×10-3 (9.21×10-4–1.64×10-2, 2.84×10-2) |
| *P* < 1×10-5 | 4.94×10-3 (1.72×10-3–8.16×10-3, 2.71×10-3) | 4.87×10-3 (-1.36×10-3–1.11×10-2, 1.25×10-1) | 7.00×10-3 (3.94×10-4–1.36×10-2, 3.79×10-2) |
| *P* < 1×10-4 | 4.49×10-3 (1.86×10-3–7.13×10-3, 8.48×10-4) | 3.48×10-3 (-2.92×10-3–9.89×10-3, 2.86×10-1) | 7.42×10-3 (1.56×10-4–1.47×10-2, 4.53×10-2) |
| *P* < 1×10-3 | 2.26×10-3 (7.77×10-4–3.74×10-3, 2.85×10-3) | 4.30×10-3 (-8.43×10-4–9.45×10-3, 1.01×10-1) | 6.13×10-3 (-1.37×10-4–1.24×10-2, 5.52×10-2) |
| *P* < 1×10-2 | 5.22×10-4 (-2.39×10-4–1.28×10-3, 1.79×10-1) | 3.17×10-3 (-5.17×10-4–6.86×10-3, 9.18×10-2) | 4.92×10-3 (-2.84×10-4–1.01×10-2, 6.28×10-2) |

*β* coefficients and 95% CIs of TRS were derived from the linear regression analysis with adjustment of age and sex.

Among 661 ADNI participants, [18F] florbetapir PET scans for 99 participants were not available.

aSNPs in strong linkage disequilibrium (r2 > 0.8) with the SNPs which had genome-wide-significant associations (*P* < 5×10-8) were also included for analysis.

Abbreviation: ADNI: Alzheimer's Disease Neuroimaging Initiative; CI: confidence interval; TRS: transcriptional risk score.

**Supplementary table e-5. Association between TRS and ADAS-cog13 in ADNI**

|  |  |  |  |
| --- | --- | --- | --- |
| Criteria for selecting SNPs | *β* coefficient of TRS using all candidate genes (95% CI, *P* value) | *β* coefficient of TRS using target genes from coloc (95% CI, *P* value) | *β* coefficient of TRS using target genes from SMR (95% CI, *P* value) |
| *P* < 5×10-8a | 1.38×10-1 (-3.59×10-2–3.12×10-1, 1.17×10-1) | 2.08×10-1 (2.23×10-2–3.93×10-1, 3.24×10-2) | 2.28×10-1 (-3.15×10-2–4.88×10-1, 9.55×10-2) |
| *P* < 1×10-7 | 1.70×10-1 (-1.48×10-2–3.54×10-1, 7.67×10-2) | 3.19×10-1 (1.32×10-2–6.25×10-1, 3.54×10-2) | 3.59×10-1 (2.37×10-2–6.94×10-1, 3.02×10-2) |
| *P* < 1×10-6 | 1.79×10-1 (1.87×10-2–3.38×10-1, 3.39×10-2) | 2.61×10-1 (-5.42×10-2–5.75×10-1, 9.94×10-2) | 3.59×10-1 (2.37×10-2–6.94×10-1, 3.02×10-2) |
| *P* < 1×10-5 | 1.48×10-1 (8.18×10-3–2.88×10-1, 4.46×10-2) | 3.07×10-1 (4.00×10-2–5.75×10-1, 2.69×10-2) | 3.69×10-1 (8.41×10-2–6.54×10-1, 1.24×10-2) |
| *P* < 1×10-4 | 1.40×10-1 (2.57×10-2–2.54×10-1, 2.40×10-2) | 2.88×10-1 (1.38×10-2–5.62×10-1, 4.29×10-2) | 3.55×10-1 (4.32×10-2–6.67×10-1, 3.15×10-2) |
| *P* < 1×10-3 | 2.16×10-2 (-4.26×10-2–8.59×10-2, 5.66×10-1) | 3.22×10-1 (1.01×10-1–5.42×10-1, 5.90×10-3) | 3.71×10-1 (1.03×10-1–6.38×10-1, 9.12×10-3) |
| *P* < 1×10-2 | 4.11×10-3 (-2.88×10-2–3.70×10-2, 7.96×10-1) | 1.79×10-1 (2.05×10-2–3.37×10-1, 2.99×10-2) | 2.70×10-1 (4.63×10-2–4.93×10-1, 2.03×10-2) |

*β* coefficients and 95% CIs of TRS were derived from the linear regression analysis with adjustment of age, sex and educational level.

Among 661 ADNI participants, ADAS-cog13 data for 5 participants were not available.

aSNPs in strong linkage disequilibrium (r2 > 0.8) with the SNPs which had genome-wide-significant associations (*P* < 5×10-8) were also included for analysis.

Abbreviation: ADAS-cog13: Alzheimer's Disease Assessment Scale Cognitive Subscale 13; ADNI: Alzheimer's Disease Neuroimaging Initiative; CI: confidence interval; TRS: transcriptional risk score.

**Supplementary table e-6. Association between TRS and entorhinal cortical thickness in AddNeuroMed**

|  |  |  |  |
| --- | --- | --- | --- |
| Criteria for selecting SNPs | *β* coefficient of TRS using all candidate genes (95% CI, *P* value) | *β* coefficient of TRS using target genes from coloc (95% CI, *P* value) | *β* coefficient of TRS using target genes from SMR (95% CI, *P* value) |
| *P* < 5×10-8a | -2.53×10-2 (-4.12×10-2–-9.43×10-3, 1.89×10-3) | -1.78×10-2 (-3.89×10-2–3.25×10-3, 9.72×10-2) | -2.10×10-2 (-5.38×10-2–1.17×10-2, 2.07×10-1) |
| *P* < 1×10-7 | -1.31×10-2 (-2.72×10-2–9.56×10-4, 6.76×10-2) | -2.83×10-2 (-5.12×10-2–-5.31×10-3, 1.60×10-2) | -3.35×10-2 (-6.23×10-2–-4.64×10-3, 2.30×10-2) |
| *P* < 1×10-6 | -9.63×10-3 (-2.28×10-2–3.53×10-3, 1.51×10-1) | -2.83×10-2 (-5.12×10-2–-5.31×10-3, 1.60×10-2) | -3.35×10-2 (-6.23×10-2–-4.64×10-3, 2.30×10-2) |
| *P* < 1×10-5 | -9.99×10-3 (-2.13×10-2–1.30×10-3, 8.28×10-2) | -2.53×10-2 (-4.54×10-2–-5.23×10-3, 1.37×10-2) | -2.89×10-2 (-5.32×10-2–-4.72×10-3, 1.94×10-2) |
| *P* < 1×10-4 | -1.10×10-2 (-2.34×10-2–1.30×10-3, 7.93×10-2) | -2.81×10-2 (-4.81×10-2–-8.06×10-3, 6.14×10-3) | -2.89×10-2 (-5.32×10-2–-4.72×10-3, 1.94×10-2) |
| *P* < 1×10-3 | -7.40×10-3 (-1.36×10-2–-1.18×10-3, 1.98×10-2) | -2.12×10-2 (-3.72×10-2–-5.27×10-3, 9.30×10-3) | -2.20×10-2 (-4.20×10-2–-2.05×10-3, 3.08×10-2) |
| *P* < 1×10-2 | -1.65×10-3 (-5.56×10-3–2.26×10-3, 4.06×10-1) | -1.62×10-2 (-3.03×10-2–-2.18×10-3, 2.37×10-2) | -1.55×10-2 (-3.44×10-2–3.38×10-3, 1.07×10-1) |

*β* coefficients and 95% CIs of TRS were derived from the linear regression analysis with adjustment of age, sex, intracranial volume and MRI field strength.

Among 674 AddNeuroMed participants, entorhinal thickness data for 381 participants were not available.

aSNPs in strong linkage disequilibrium (r2 > 0.5) with the SNPs which had genome-wide-significant associations (*P* < 5×10-8) were also included for analysis.

Abbreviation: CI: confidence interval; TRS: transcriptional risk score.

**Supplementary table e-7. Relationship between the AD-associated SNPs at *P* value less than 1×10-7 and target genes that were identified from coloc and SMR**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CHR | SNP | AD risk allele | *P* value of the SNP in GWAS meta-analysis | Gene | Predicted expression at AD risk allele in public database of blood eQTLa | *H4* | *PSMR* | Position of the SNP with regard to the gene  (Distance between the SNP and gene) | Real expression identified from ADNI and AddNeuroMed database |
| 1 | rs4575098 | A | 2.05×10-10 | *B4GALT3* | Low | 94.7% | 2.05×10-5 | Downstream variant (7634 bp) | Significantly low in AD (AddNeuroMed) |
| 7 | rs1859788 | G | 2.22×10-15 | *PILRA* | High | 99.8 | 1.68×10-6 | Missense variant | Significantly high in AD  (ADNI and AddNeuroMed) |
| 19 | rs3865444 | C | 6.34×10-9 | *CD33* | High | 85.9% | 4.65×10-6 | 5 prime UTR variant (372 bp) | Significantly high in AD (ADNI and AddNeuroMed) |
| 19 | rs123187 | G | 3.70×10-8 | *KLC3* | Low | < 1% | 6.42×10-6 | Upstream variant (13050 bp) | N/S |
| 19 | rs10421247 | T | 6.57×10-9 | *TRAPPC6A* | Low | 99.2% | 4.27×10-8 | Downstream variant (8699 bp) | Significantly low in AD (ADNI and AddNeuroMed) |

aThe concept of "high expression" and "low expression" was used to denote whether the AD risk allele was associated with increased (high expression) or decreased (low expression) gene expression from the integration of GWAS summary statistics and eQTL data.

Abbreviation: AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; CHR: chromosome; eQTL: expression quantitative trait locus; GWAS: genome-wide association study; *H4*: posterior probability of the hypothesis of one causal variant common to both traits in coloc; N/A: not available; N/S: not significantly increased or decreased in AD; SNP: single nucleotide polymorphism.

**Supplementary figure e-1. Relationship between TRS and entorhinal cortical thickness**

The relationship between the TRS and entorhinal cortical thickness in ADNI (A) and AddNeuroMed (B) was represented in a scatter plot. Target genes identified from SMR were used to calculate the TRS with *P* value for selecting AD-associated SNPs less than 1×10-7. The blue line was obtained from a linear regression analysis, and the gray zone around the blue line indicates 95% confidence interval.

Abbreviation: AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; SMR: summary-data-based Mendelian randomization; TRS: transcriptional risk score.



**Supplementary figure e-2. Line plots of *β* coefficients and 95% CIs of TRS for AD biomarkers across various criteria for selecting AD-associated SNPs**

Various criteria for selecting AD-associated SNPs (*P* < 5×10-8, 1×10-7, 1×10-6, 1×10-5, 1×10-4, 1×10-3 and 1×10-2) were displayed along the *X*-axis, with the *β* coefficient and 95% CI for each AD biomarker displayed on the *Y*-axis. Target genes identified from SMR were used to calculate the TRS.

Abbreviation: AD: Alzheimer's disease; ADNI: Alzheimer's Disease Neuroimaging Initiative; AV45\_ADNI: mean standardized uptake value of [18F] florbetapir PET in ADNI; ET\_ADNI: entorhinal thickness in ADNI; ET\_ANM: entorhinal thickness in AddNeuroMed; HV\_ADNI: hippocampal volume in ADNI; CI: confidence interval; SMR: summary-data-based Mendelian randomization; SNP: single nucleotide polymorphism; TRS: transcriptional risk score.



**Supplementary figure e-3. Violin plots for gene expression level between CN, MCI and AD**

Genes (*CD33* (A), *PILRA* (B), *TRAPPC6A* (C), *KLC3* (D), *B4GALT3* (E) in ADNI and *CD33* (F), *PILRA* (G), *TRAPPC6A* (H), *B4GALT3* (I) in AddNeuroMed) were identified by COLOC and SMR from AD-associated SNPs with *P* < 1×10-7 and used to calculate the transcriptional risk score. The violin plots show the probability density of gene expression level as well as median and interquartile ranges between diagnosis groups (CN, MCI and AD).

Abbreviation: AD: Alzheimer's disease; CN: cognitively normal older adults; MCI: mild cognitive impairment; SMR: summary-data-based Mendelian randomization.

