

Validation of newly-derived polygenic risk scores for dementia in a prospective study of older individuals

Supplementary Information

This file includes 4 tables and 1 figure.

Table S1: Information of 83 variants used in the PRS-83SNP.

| Variant ID | CHR | Position ^a | Gene ^b | Minor/Major allele ^c | MAF ^d in ASPREE | Source in ASPREE |
|-------------|-----|-----------------------|-------------------|---------------------------------|----------------------------|------------------|
| rs141749679 | 1 | 109345810 | <i>SORT1</i> | C/T | 0.003 | Imputed |
| rs679515 | 1 | 207577223 | <i>CR1</i> | T/C | 0.179 | Imputed |
| rs72777026 | 2 | 9558882 | <i>ADAM17</i> | G/A | 0.141 | Imputed |
| rs17020490 | 2 | 37304796 | <i>PRKD3</i> | C/T | 0.139 | Genotyped |
| rs143080277 | 2 | 105749599 | <i>NCK2</i> | C/T | 0.005 | Imputed |
| rs6733839 | 2 | 127135234 | <i>BIN1</i> | T/C | 0.390 | Genotyped |
| rs139643391 | 2 | 202878716 | <i>WDR12</i> | T/TC | 0.127 | Imputed |
| rs10933431 | 2 | 233117202 | <i>INPP5D</i> | G/C | 0.227 | Imputed |
| rs16824536 | 3 | 155069722 | <i>MME</i> | A/G | 0.056 | Imputed |
| rs61762319 | 3 | 155084189 | <i>MME</i> | G/A | 0.027 | Imputed |
| rs3822030 | 4 | 993555 | <i>IDUA</i> | G/T | 0.430 | Imputed |
| rs6846529 | 4 | 11023507 | <i>CLNK</i> | C/T | 0.270 | Imputed |
| rs2245466 | 4 | 40197226 | <i>RHOH</i> | G/C | 0.332 | Imputed |
| rs112403360 | 5 | 14724304 | <i>ANKH</i> | A/T | 0.072 | Imputed |
| rs62374257 | 5 | 86927378 | <i>COX7C</i> | C/T | 0.232 | Imputed |
| rs871269 | 5 | 151052827 | <i>TNIP1</i> | T/C | 0.326 | Imputed |
| rs113706587 | 5 | 180201150 | <i>RASGEF1C</i> | A/G | 0.102 | Imputed |
| rs6605556 | 6 | 32615322 | <i>HLA-DQA1</i> | G/A | 0.187 | Imputed |
| rs10947943 | 6 | 41036354 | <i>UNC5CL</i> | A/G | 0.152 | Imputed |
| rs143332484 | 6 | 41161469 | <i>TREM2</i> | T/C | 0.010 | Imputed |
| rs75932628 | 6 | 41161514 | <i>TREM2</i> | T/C | 0.003 | Imputed |
| rs60755019 | 6 | 41181270 | <i>TREML2</i> | G/A | 0.001 | Imputed |
| rs7767350 | 6 | 47517390 | <i>CD2AP</i> | T/C | 0.269 | Imputed |
| rs785129 | 6 | 114291731 | <i>HS3ST5</i> | T/C | 0.341 | Imputed |
| rs6943429 | 7 | 7817263 | <i>UMAD1</i> | T/C | 0.412 | Imputed |
| rs10952097 | 7 | 8204382 | <i>ICA1</i> | T/C | 0.105 | Imputed |
| rs13237518 | 7 | 12229967 | <i>TMEM106B</i> | A/C | 0.414 | Imputed |
| rs1160871 | 7 | 28129126 | <i>JAZF1</i> | G/GTCTT | 0.208 | Imputed |
| rs6966331 | 7 | 37844191 | <i>EPDR1</i> | T/C | 0.335 | Imputed |
| rs76928645 | 7 | 54873635 | <i>SEC61G</i> | T/C | 0.104 | Imputed |

| | | | | | | |
|-------------|----|-----------|-------------------------|--------|-------|-----------|
| rs7384878 | 7 | 100334426 | <i>SPDYE3</i> | C/T | 0.323 | Imputed |
| rs11771145 | 7 | 143413669 | <i>EPHA1</i> | A/G | 0.353 | Genotyped |
| rs1065712 | 8 | 11844613 | <i>CTSB</i> | C/G | 0.052 | Imputed |
| rs73223431 | 8 | 27362470 | <i>PTK2B</i> | T/C | 0.365 | Imputed |
| rs11787077 | 8 | 27607795 | <i>CLU</i> | T/C | 0.401 | Imputed |
| rs34173062 | 8 | 144103704 | <i>SHARPIN</i> | A/G | 0.079 | Genotyped |
| rs1800978 | 9 | 104903697 | <i>ABCA1</i> | G/C | 0.128 | Imputed |
| rs7912495 | 10 | 11676714 | <i>USP6NL</i> | G/A | 0.449 | Imputed |
| rs7068231 | 10 | 60025170 | <i>ANK3</i> | T/G | 0.402 | Imputed |
| rs6586028 | 10 | 80494228 | <i>TSPAN14</i> | C/T | 0.201 | Imputed |
| rs6584063 | 10 | 96266650 | <i>BLNK</i> | G/A | 0.041 | Imputed |
| rs7908662 | 10 | 122413396 | <i>PLEKHA1</i> | G/A | 0.470 | Imputed |
| rs10437655 | 11 | 47370397 | <i>SPI1</i> | A/G | 0.386 | Imputed |
| rs1582763 | 11 | 60254475 | <i>MS4A4A</i> | A/G | 0.378 | Genotyped |
| rs3851179 | 11 | 86157598 | <i>EED</i> | T/C | 0.372 | Genotyped |
| rs74685827 | 11 | 121482368 | <i>SORL1</i> | G/T | 0.019 | Genotyped |
| rs11218343 | 11 | 121564878 | <i>SORL1</i> | C/T | 0.037 | Genotyped |
| rs6489896 | 12 | 113281983 | <i>TPCN1</i> | C/T | 0.071 | Imputed |
| rs17125924 | 14 | 52924962 | <i>FERMT2</i> | G/A | 0.094 | Imputed |
| rs7401792 | 14 | 92464917 | <i>SLC24A4</i> | G/A | 0.354 | Imputed |
| rs12590654 | 14 | 92472511 | <i>SLC24A4</i> | A/G | 0.343 | Imputed |
| rs7157106 | 14 | 105761758 | <i>IGH gene cluster</i> | A/G | 0.331 | Imputed |
| rs10131280 | 14 | 106665591 | <i>IGH gene cluster</i> | A/G | 0.125 | Imputed |
| rs8025980 | 15 | 50701814 | <i>SPPL2A</i> | G/A | 0.341 | Imputed |
| rs602602 | 15 | 58764824 | <i>MINDY2</i> | A/T | 0.293 | Imputed |
| rs117618017 | 15 | 63277703 | <i>APH1B</i> | T/C | 0.136 | Genotyped |
| rs3848143 | 15 | 64131307 | <i>SNX1</i> | G/A | 0.208 | Imputed |
| rs12592898 | 15 | 78936857 | <i>CTSH</i> | A/G | 0.128 | Imputed |
| rs1140239 | 16 | 30010081 | <i>DOC2A</i> | T/C | 0.405 | Imputed |
| rs889555 | 16 | 31111250 | <i>BCKDK</i> | T/C | 0.286 | Imputed |
| rs4985556 | 16 | 70660097 | <i>IL34</i> | A/C | 0.120 | Genotyped |
| rs450674 | 16 | 79574511 | <i>MAF</i> | C/T | 0.392 | Imputed |
| rs12446759 | 16 | 81739398 | <i>PLCG2</i> | G/A | 0.399 | Genotyped |
| rs72824905 | 16 | 81908423 | <i>PLCG2</i> | G/C | 0.009 | Imputed |
| rs16941239 | 16 | 86420604 | <i>FOXF1</i> | A/T | 0.021 | Imputed |
| rs56407236 | 16 | 90103687 | <i>PRDM7</i> | A/G | 0.070 | Genotyped |
| rs35048651 | 17 | 1728046 | <i>WDR81</i> | T/TGAG | 0.218 | Imputed |
| rs7225151 | 17 | 5233752 | <i>SCIMP</i> | A/G | 0.117 | Genotyped |
| rs2242595 | 17 | 18156140 | <i>MYO15A</i> | A/G | 0.124 | Genotyped |
| rs5848 | 17 | 44352876 | <i>GRN</i> | T/C | 0.278 | Imputed |
| rs199515 | 17 | 46779275 | <i>WNT3</i> | G/C | 0.217 | Genotyped |
| rs616338 | 17 | 49219935 | <i>ABI3</i> | T/C | 0.008 | Imputed |
| rs2526377 | 17 | 58332680 | <i>TSPOAP1</i> | G/A | 0.436 | Imputed |

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|-------------|----|----------|-----------------|------|-------|---------|
| rs4277405 | 17 | 63471557 | <i>ACE</i> | C/T | 0.381 | Imputed |
| rs12151021 | 19 | 1050875 | <i>ABCA7</i> | A/G | 0.324 | Imputed |
| rs149080927 | 19 | 1854254 | <i>KLF16</i> | G/GC | 0.469 | Imputed |
| rs9304690 | 19 | 49950060 | <i>SIGLEC11</i> | T/C | 0.240 | Imputed |
| rs587709 | 19 | 54267597 | <i>LILRB2</i> | C/T | 0.276 | Imputed |
| rs1358782 | 20 | 413334 | <i>RBCK1</i> | A/G | 0.234 | Imputed |
| rs6014724 | 20 | 56423488 | <i>CASS4</i> | G/A | 0.083 | Imputed |
| rs6742 | 20 | 63743088 | <i>SLC2A4RG</i> | T/C | 0.213 | Imputed |
| rs2154481 | 21 | 26101558 | <i>APP</i> | C/T | 0.483 | Imputed |
| rs2830489 | 21 | 26775872 | <i>ADAMTS1</i> | T/C | 0.275 | Imputed |

^a GRCh38 assembly.

^b Nearest protein coding gene according to Gencode release 33.

^c Effect size (beta) of risk alleles can be found in Bellenguez *et al.* (2022).

^d Minor allele frequency.

Table S2. Correlations between four dementia-related PRS based on the ASPREE participants included in this genetic study.

| Dementia-related polygenic risk score | PRS-83SNP | PRS-SBayesR | PRS-CS | PRS-23SNP |
|---------------------------------------|-----------|-------------|--------|-----------|
| PRS-83SNP | | | | |
| PRS-SBayesR | 0.54 | | | |
| PRS-CS | 0.39 | 0.85 | | |
| PRS-23SNP | 0.56 | 0.42 | 0.32 | |

Table S3. Association of four dementia-related polygenic risk scores (as a continuous variable, per SD) with risk of incident dementia, adjusted for the competing risk of death.

| Dementia-related polygenic risk score | Model 1 | | Model 2 | | Model 3 | |
|---------------------------------------|------------------|----------|------------------|----------|------------------|----------|
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| PRS-83SNP | 1.34 (1.23-1.46) | 1.49E-11 | 1.36 (1.25-1.48) | 2.28E-12 | 1.34 (1.23-1.46) | 4.73E-11 |
| PRS-SBayesR | 1.39 (1.27-1.51) | 9.05E-13 | 1.37 (1.25-1.50) | 8.63E-12 | 1.37 (1.25-1.50) | 2.85E-11 |
| PRS-CS | 1.43 (1.31-1.57) | 1.88E-14 | 1.42 (1.29-1.56) | 1.50E-13 | 1.42 (1.30-1.56) | 1.39E-13 |
| PRS-23SNP | 1.11 (1.01-1.22) | 0.03 | 1.12 (1.02-1.23) | 0.02 | 1.12 (1.02-1.23) | 0.02 |

Note: Fine-Gray subdistribution hazard model accounting for a competing risk of mortality was used to estimate the hazard ratio (HR) of the PRS per standard deviation, with 95% confidence intervals (CI). Model 1 was adjusted for age at recruitment, sex and first 20 genetic PCs. Model 2 was additionally adjusted for the number of *APOE*- ϵ 4 and *APOE*- ϵ 2 alleles. Model 3 was further adjusted for baseline smoking status, alcohol drinking status, BMI, living status, years of education, CES-D-10, diabetes status, systolic blood pressure, diastolic blood pressure, dyslipidemia and dementia family history.

Table S4. P-values in associations between PRS (a continuous variable)-by-covariate interaction and incident dementia using a fully adjusted model (Model 3). Marginally significant signals (P<0.05, bold) were detected for some interactions.

| Covariate | P for PRS-by-covariate interaction | | | |
|--|------------------------------------|--------------|-------------|-------------|
| | PRS-83SNP | PRS-SBayesR | PRS-CS | PRS-23SNP |
| Age at recruitment | 0.22 | 0.71 | 0.25 | 0.38 |
| Sex | 0.88 | 0.83 | 0.96 | 0.87 |
| Smoking status ^a | 0.73 | 0.10 | 0.05 | 0.09 |
| | 0.52 | 0.17 | 0.09 | 0.11 |
| Alcohol drinking status ^b | 0.74 | 0.41 | 0.52 | 0.85 |
| | 0.02 | 0.001 | 0.01 | 0.02 |
| Years of education | 0.22 | 0.50 | 0.35 | 0.30 |
| Living status | 0.45 | 0.52 | 0.97 | 0.27 |
| CES-D-10 | 0.26 | 0.07 | 0.06 | 0.34 |
| BMI | 0.49 | 0.37 | 0.68 | 0.13 |
| Systolic blood pressure | 0.67 | 0.60 | 0.64 | 0.60 |
| Diastolic blood pressure | 0.40 | 0.19 | 0.44 | 0.53 |
| Diabetes status | 0.12 | 0.05 | 0.16 | 0.07 |
| Dyslipidemia | 0.41 | 0.43 | 0.12 | 0.38 |
| Dementia family history | 0.86 | 0.73 | 0.38 | 0.52 |
| the number of <i>APOE</i> - ϵ 2 | 0.61 | 0.42 | 0.34 | 0.92 |
| the number of <i>APOE</i> - ϵ 4 | 0.14 | 0.004 | 0.01 | 0.97 |

^a Using “Current smoking” as a reference, the two P-values were derived by comparing with “Former smoking” and “Never smoking”, respectively.

^b Using “Current alcohol use” as a reference, the two P-values were derived by comparing with “Former alcohol use” and “Never alcohol use”, respectively.

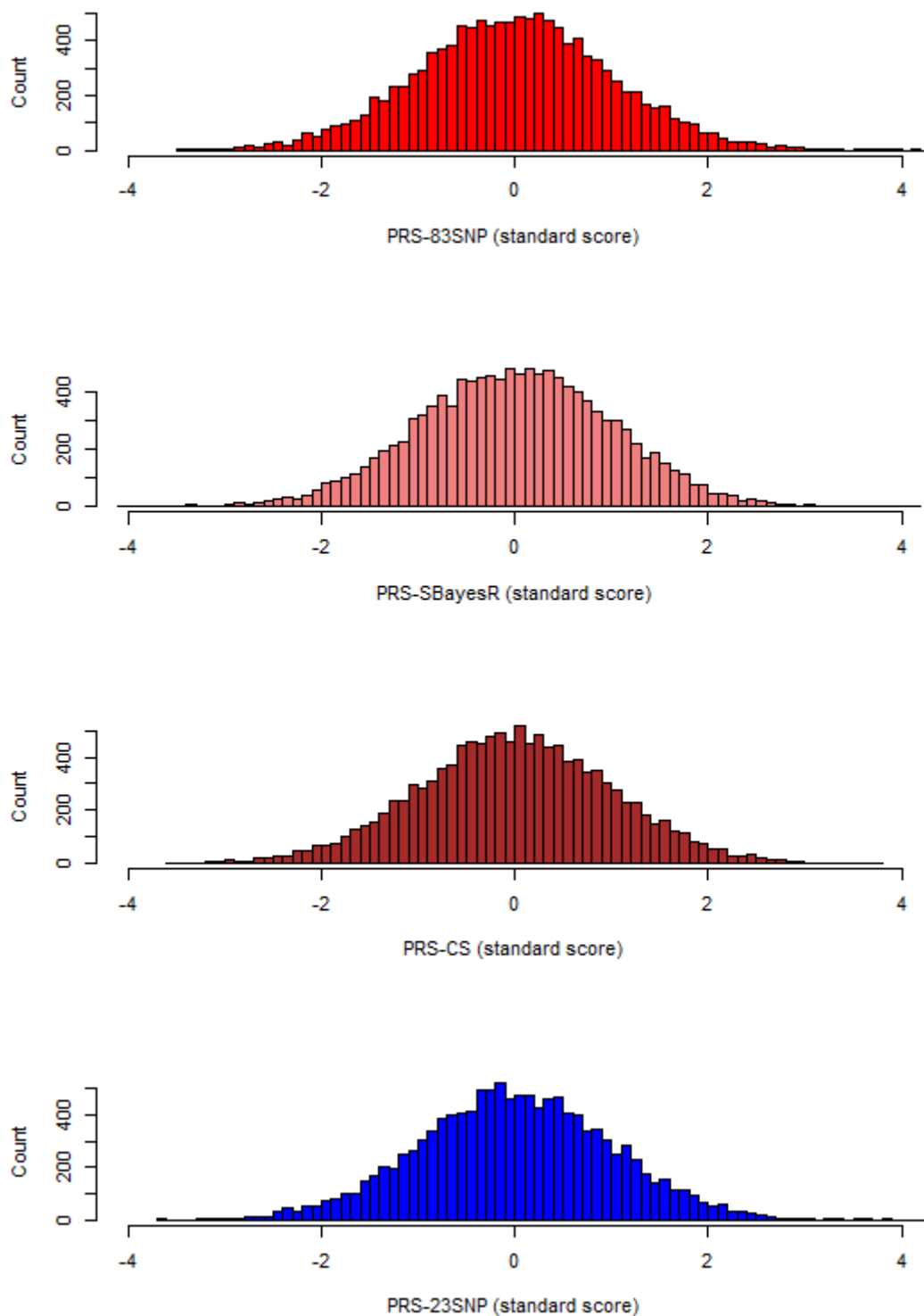


Figure S1: Four PRS distributions of the 12,031 ASPREE participants included in this study. The scores were standardised to a mean of 0 and a variance of 1. These distributions are all approximately Gaussian (Kolmogorov-Smirnov test P value = 0.11 for PRS-83SNP, 0.85 for PRS-SBayesR, 0.75 for PRS-CS, and 0.69 for PRS-23SNP).