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

Chenglong Yu[1], **Joanne Ryan**[1], **Suzanne G. Orchard**[1], **Catherine Robb**[1], **Robyn L. Woods**[1], **Rory Wolfe**[1], **Alan E. Renton**[2,3], **Alison M. Goate**[2,3], **Amy Brodtmann**[4,5], **Raj C. Shah**[6], **Trevor T.-J. Chong**[7,8,9], **Kerry Sheets**[10,11], **Christopher Kyndt**[12,13], **Ajay Sood**[14], **Elsdon Storey**[1], **Anne M. Murray**[10,11,15], **John J. McNeil**[1], **Paul Lacaze**[1]

[1]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[2]Department Genetics and Genomic Sciences and Ronald M. Loeb Center for Alzheimer's Disease, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[3]Departments of Neurology and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[4]Cognitive Health Initiative, Central Clinical School, Monash University, Melbourne, Victoria, Australia

[5]Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia

[6]Department of Family & Preventive Medicine and the Rush Alzheimer's Disease Center, Chicago, Illinois, USA

[7]Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Clayton, Victoria, Australia

[8]Department of Neurology, Alfred Health, Melbourne, Victoria, Australia

[9]Department of Clinical Neurosciences, St. Vincent's Hospital, Melbourne, Victoria, Australia

[10]Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA

[11]Division of Geriatrics, Hennepin Healthcare, Minneapolis, Minnesota, USA

[12]Department of Neurology, Melbourne Health, Parkville, Victoria, Australia

Correspondence: Chenglong Yu, School of Public Health and Preventive Medicine, Monash University, Level 5, 553 St. Kilda Rd, Melbourne, VIC 3004, Australia. chenglong.yu@monash.edu.

[13]Department of Neuroscience, Eastern Health, Box Hill, Victoria, Australia

[14]Department of Neurology and the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, USA

[15]Berman Center for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, Hennepin Healthcare, and University of Minnesota, Minneapolis, Minnesota, USA

Abstract

Introduction: Recent genome-wide association studies identified new dementia-associated variants. We assessed the performance of updated polygenic risk scores (PRSs) using these variants in an independent cohort.

Methods: We used Cox models and area under the curve (AUC) to validate new PRSs (PRS-83SNP, PRS-SBayesR, and PRS-CS) compared with an older PRS-23SNP in 12,031 initially-healthy participants 70 years of age. Dementia was rigorously adjudicated according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.

Results: PRS-83SNP, PRS-SBayesR, and PRS-CS were associated with incident dementia, with fully adjusted (including apolipoprotein E [*APOE*] ε4) hazard ratios per standard deviation (SD) of 1.35 (1.23–1.47), 1.37 (1.25–1.50), and 1.42 (1.30–1.56), respectively. The AUC of a model containing conventional/non-genetic factors and *APOE* was 74.7%. This was improved to 75.7% ($p = 0.007$), 76% ($p = 0.004$), and 76.1% ($p = 0.003$) with addition of PRS-83SNP, PRS-SBayesR, and PRS-CS, respectively. The PRS-23SNP did not improve AUC (74.7%, $p = 0.95$).

Conclusion: New PRSs for dementia significantly improve risk-prediction performance, but still account for less risk than *APOE* genotype overall.

Keywords

1 | BACKGROUND

Dementia results in tremendous medical, economic, and social impact with an increasing global burden.[1,2] Although lifestyle factors form a large part of all-cause dementia risk, the genetic heritability of Alzheimer's disease (AD), the most common form of dementia, is estimated at 58%–79% from twin studies.[3,4] This opens a potential avenue for preventing and treating dementia by targeting high-risk individuals based on genetic predisposition. The apolipoprotein E (*APOE*) gene is the strongest known genetic determinant of common dementia.[5–7] Recent genome-wide association studies (GWASs) have identified many additional dementia-associated risk variants.[8–14] A recent GWAS of AD and related dementias by Bellengeuz et al.[14] involving 39,106 clinically diagnosed cases, 46,828 proxy cases, and 401,577 controls of European ancestry, identified 83 independent dementia-associated variants (excluding the *APOE* region), more than doubling the number of previously identified variants.[15] Updated polygenic risk scores (PRSs) incorporating these variants can now be calculated, which may improve dementia risk prediction.[14] Performance of dementia risk-prediction models, including using these newly associated variants from

outside the *APOE* region, may help identify high-risk individuals with more accuracy.[16–18] This, in turn, may facilitate more targeted prevention and early intervention strategies for individuals or families, and facilitate recruitment into disease-modifying or prevention intervention trials.

There is a requirement to independently assess and validate the performance of newly derived genomic risk scores in external cohorts. Here, we independently assess the performance of three newly derived PRSs[19–21] based on Bellengeuz et al.[14] in the ASPirin in Reducing Events in the Elderly (ASPREE) clinical trial, with extended observational follow-up through the eXTension (ASPREE-XT) study.[22–25] Together, these studies comprise a population of older individuals 70 years of age with no personal history of diagnosed cardiovascular disease events, dementia, or severe physical disability at enrollment, who were followed prospectively with all-cause dementia adjudicated as a primary endpoint. All incident dementia cases in ASPREE were adjudicated by expert panels and used the same standardized protocols. Our study helps assess the future potential utility of genomic risk prediction for all-cause dementia.

2 | METHODS

2.1 | Study population

ASPREE was a randomized double-blind, placebo-controlled clinical trial (2010–2017) to determine whether daily 100-mg aspirin extended disability-free survival in 19,114 healthy adults aged 70 years (65 years for US minorities) with no prior diagnosed cardiovascular diseases, dementia, physical disability, or other life-threatening illness (based on their medical records at the clinics and confirmed with general practitioners) at enrolment. Afterward, an ongoing observational follow-up study (ASPREE-XT), which was established in 2018, continues to collect data from ASPREE participants and investigates long-lasting effects of low-dose aspirin on diseases, such as cancer. In addition, it investigates a broad range of factors that contribute to the maintenance of physical and cognitive health in older adults. The design and protocol of the ASPREE trial and ASPREE-XT study have been reported previously.[22–26] All participants provided written informed consent. The study was approved by the Human Research Ethics Committees at Monash University and Alfred Hospital in Australia and site-specific institutional review boards in the United States.

In this genetic study we included 12,031 genotyped participants from the ASPREE trial and excluded participants with non-European ancestry, who were younger than 70 years at enrollment, and close relatives based on a coefficient of relatedness >0.05 (Figure 1). We excluded ASPREE participants with non-European ancestry from our study because (1) the GWAS performed by Bellengeuz et al.[14] used to derive the PRSs was based predominately on individuals with European ancestry,[27] and (2) there were relatively few participants with non-European ancestry enrolled in the ASPREE trial. The sample size of genotyped non-European participants in the ASPREE trial was $n < 535$ (across multiple ancestries, see Figure 1). This provided insufficient power to test the performance of PRSs in an ancestry-specific manner. All phenotypic data used in this study were collected in person from participants at the time of enrollment.[22]

2.2 | Incident dementia diagnosis

Cognitive assessments were administered by trained and accredited staff at baseline and year 1, and then biennially over the follow-up period. The cognitive battery included the Modified Mini-Mental State (3MS)[28] test to measure global cognition, the Hopkins Verbal Learning Test-Revised (HVLT-R)[29] for episodic memory, the single letter (F) Controlled Oral Word Association Test (COWAT)[30] for language and executive function, and the Symbol Digit Modalities Test (SDMT)[31] to measure psychomotor speed. Participants who had a suspected dementia diagnosis ("trigger") were referred for further standardized cognitive and functional evaluations. Triggers for dementia were defined as a 3MS score <78,[32] which explained ≈50% of the triggers; a drop of >10.15 points from the predicted score based on their own baseline 3MS adjusted for age and education[33]; a report of memory concerns or other cognitive problems to a specialist; clinician diagnosis of dementia as indicated in the participant's medical records; and prescription of a cholinesterase inhibitor.[34–36]

To reduce the likelihood of delirium contributing to the cognitive profile, participants were administered a battery of cognitive tests at least 6 weeks following the initial dementia trigger. These tests included the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) subscale,[37] Color Trails,[38] Lurian overlapping figures,[39] and the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ACL) scale,[40] which was completed by the participant and study partner. Other information relevant to the dementia assessment included laboratory tests, brain imaging (computed tomography or magnetic resonance imaging [CT or MRI]), and clinical case notes. A committee of geriatricians and neurologists assessed each dementia trigger case following the ASPREE methodology for clinical adjudication. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria were used for dementia diagnosis. The dementia diagnosis date was taken as the date of the trigger that resulted in a confirmed dementia diagnosis by the adjudication committee.[34]

2.3 | Genotyping

The peripheral blood samples provided by ASPREE participants at the time of study enrollment were processed to buffy coat within 4 hours of collection and then stored at −80°C. DNA was later purified from the buffy coat via magnetic bead extraction[41] and genotyped using the Axiom 2.0 Precision Medicine Diversity Research Array (Thermo Fisher Scientific, CA). Variant calling used a custom pipeline aligned to the human reference genome GRCh38. The imputation was performed based on the Haplotype Reference Consortium panel for European samples using the Michigan imputation server.[42] Post-imputation quality control removed variants with $r2 < 0.3$. *APOE* genotype was measured directly at two single-nucleotide polymorphisms (SNPs), rs7412 and rs429358, which were included in the Axiom array.

2.4 | Polygenic risk scores

We calculated four different PRSs. Our goal was to investigate the contribution of polygenic risk based on variants outside the *APOE* locus. Therefore, all four PRSs excluded variants in the *APOE* region (44,000,000–46,000,000 bp on chromosome 19 in GRCh38).[14]

1. PRS-83SNP is a new PRS comprising 83 independent genome-wide significant variants ($p < 5 \times 10^{-8}$) at 75 loci from a GWAS of AD and related dementias performed by Bellengeuz et al.[14] The PRS was calculated as the sum of an individual's risk alleles weighted by effect sizes taken from the GWAS summary statistics (Table S1).

2. PRS-SBayesR is a new PRS derived from the SBayesR method that models the genetic architecture with linkage disequilibrium (LD) in a Bayesian framework.[19] The LD matrices provided by SBayesR developers were calculated based on ≈1.1 million HapMap3 common SNPs in a random sample of 50,000 unrelated individuals of European ancestry in the UK Biobank data set.[19] We performed SBayesR (with default parameters that the software recommended[19,21]) using these LD matrices on summary statistics from the aforementioned GWAS[14] and obtained improved effect sizes for 1,081,756 HapMap3 SNPs. The PRS was then calculated using the newly derived effect sizes of the 1,081,756 SNPs.

3. PRS-CS is a new PRS derived from the PRS-CS (continuous shrinkage) method,[20] which infers posterior effect sizes of SNPs using GWAS summary statistics and an external LD reference panel. PRS-CS developers provided the LD reference panel, which was calculated based on ≈1.1 million HapMap3 SNPs in 375,120 unrelated individuals of European ancestry in the UK Biobank data set.[20] We performed PRS-CS (with default parameters that the software recommended[20,21]) using the LD reference panel on summary statistics from the aforementioned GWAS[14] and obtained posterior (improved) effect sizes for 1,103,008 HapMap3 SNPs. The PRS was then calculated using new effect sizes of the 1,103,008 SNPs.

4. PRS-23SNP is an older PRS comprising 23 genome-wide significant ($p < 5 \times 10^{-8}$) AD-associated SNPs, which have recently been used by van der Lee et al.[16] and Riaz et al.[17] These SNPs were identified in previous studies.[8,43,44] The PRS was calculated as the sum of an individual's risk alleles weighted by effect sizes derived by a metaanalysis.[16]

2.5 | Statistical analysis

We used Cox proportional hazard (PH) regression models to estimate the association (hazard ratio [HR] and 95% confidence interval [CI]) between the PRS as a continuous variable (per standard deviation, SD) and the risk of progression to all-cause dementia. In Model 1, we adjusted for age at recruitment, sex, and the first 20 principal components (PCs) of genetic ancestry to account for population stratification. Model 2 was additionally adjusted for the number of *APOE ε*4 and *APOE ε*2 alleles as done previously.[14] We evaluated a third model (Model 3) with adjustment for baseline smoking status, alcohol drinking status, body mass index, living status (alone vs with others), years of education, depressive symptoms (Center for Epidemiological Studies-Depression-10 [CES-D]scale), diabetes status, systolic blood pressure, diastolic blood pressure, dyslipidemia, and dementia family history (father, mother, or siblings) (Table 1). We did not include aspirin treatment as a covariate as we found no evidence that aspirin was associated with risk of dementia in the ASPREE

cohort.[34] The PRS included in the models was also investigated by categorical groups (deciles). As a sensitivity analysis, we also used the Fine-Gray sub-distribution hazard model[45] accounting for a competing risk of mortality, to estimate the association between the PRS as a continuous variable and the risk of progression to all-cause dementia, with the same covariates used in Models 1–3. The results were considered to be significant after Bonferroni correction for multiple comparisons.

To evaluate whether the relevant covariates mentioned above may modify the effect of PRSs on dementia progression, we also used Cox PH models to investigate interactions between PRSs (as continuous variables) and sex, *APOE* genotypes, and other covariates used in Model 3. We then performed subgroup analyses for covariates with significant interactions.

To assess the effects of PRSs on dementia risk prediction, we estimated the area under the receiver-operating characteristic (ROC) curve (AUC) after a mean of 6.5 years follow-up. The baseline model (logistic regression) contained the conventional/non-genetic variables mentioned above (Model 3). Improvement in AUC was assessed after addition of *APOE* genotypes to the baseline model, and then again after addition of the PRSs to the baseline + *APOE* model, using the R package "*pROC*."[46] The DeLong test was used for comparing AUCs of nested models.[47] Statistical analyses were performed using R version 4.0.3.

3 | RESULTS

3.1 | Baseline characteristics and polygenic score calculation

The baseline characteristics of the study population are shown in Table 1. The mean age of the participants was 75.1 years, and 54.9% were female. Only a small proportion were current smokers (3.1%) or had diabetes (9.2%) at baseline.

The distributions of four PRSs (standardized to a mean of 0 and variance of 1) of the 12,031 participants are shown in Figure S1. These distributions are all approximately Gaussian (Kolmogorov–Smirnov test *p*-values for four PRS distributions are all >0.05) but moderately correlated (Table S2).

3.2 | PRS and incident dementia risk

During a mean follow-up of 6.5 years, 505 incident all-cause dementia events were observed. The newly derived PRS-83SNP, PRS-SBayesR, and PRS-CS were significantly associated with incident dementia risk in all models (fully adjusted model, Model 3: HR = 1.35 per SD [95% CI: 1.23–1.47] for PRS-83SNP, HR = 1.37 per SD [1.25–1.50] for PRS-SBayesR, and HR = 1.42 per SD [1.30–1.56] for PRS-CS) (Table 2). The older PRS-23SNP was associated with incident dementia risk, but with a lower effect size (Model 3: HR = 1.12 per SD [1.02–1.22], *p* = 0.02). This association did not remain significant after Bonferroni correction (*p* < 0.05/12 = 0.004). After adjusting for the competing risk of death using the Fine-Gray model, these results remained unchanged (Table S3).

Figure 2 presents associations between different categorical groups of the PRSs (deciles of the PRS distributions) with incident dementia risk during follow-up. Compared with the lowest/1st decile group as a reference (0%–10%), the highest/10th decile group (90%–

100%) had an ≈3-fold higher risk of incident dementia for PRS-83SNP (HR = 3.14 [95% CI: 1.99–4.96]), PRS-SBayesR (HR = 2.44 [1.65–3.62]), and PRS-CS (HR = 3.90 [2.51–6.07]) in the fully adjusted model (Model 3). However, the comparison between the lowest and highest deciles for the older PRS-23SNP resulted in a far lower effect size that was not statistically significant (HR = 1.32 [0.89–1.96] in Model 3).

3.3 | Subgroup analyses

Testing for PRS-by-sex interactions revealed no statistically significant interactions ($p >$ 0.05, Table S4), suggesting that PRS effects on dementia are not sex specific. In PRS-by-covariate interaction analysis (Table S4), we observed evidence of interaction between the PRSs and alcohol drinking status ($p = 0.02$ for PRS-83SNP; $p = 0.001$ for PRS-SBayesR; $p = 0.01$ for PRS-CS; and $p = 0.02$ for PRS-23SNP), PRS-SBayesR and the number of *APOE* ε4 ($p = 0.004$), and PRS-CS and the number of *APOE* ε4 ($p = 0.01$), but no other interaction signals were detected (all $p > 0.05$). Thus we examined the effects of PRSs on incident dementia for subgroups of participants according to their alcohol drinking status and carrying numbers of *APOE* ε4 (Table 3). The PRS effects on incident dementia were stronger in individuals who never drank alcohol (HR = 1.74 [1.40–2.16] for PRS-83SNP, HR = 1.95 [1.56–2.43] for PRS-SBayesR, and HR = 1.84 [1.49–2.28] for PRS-CS) relative to current or former alcohol drinkers. For *APOE* ε4 non-carriers (a large population subgroup), PRS effects on prediction of dementia development were stronger (HR = 1.40 [1.25–1.58] for PRS-83SNP, HR = 1.52 [1.34–1.71] for PRS-SBayesR, and HR = 1.59 [1.40–1.79] for PRS-CS) compared to the general population. However, for participants who carry two copies of *APOE* ε4, PRSs had no effect on dementia risk, as no association was significant after Bonferroni correction ($p < 0.05/12 = 0.004$).

3.4 | AUC estimates and comparisons

Full covariate-adjusted AUC estimates after a mean of 6.5 years of follow-up are shown in Table 4, based on different models examined. This includes changes in the AUC from the baseline model (containing only conventional/non-genetic risk factors), after addition of *APOE* genotypes and the four PRSs. The AUC of the baseline model containing no genetic information was 71.0% (68.7%–73.3%), which upon addition of *APOE* genotypes, improved to 74.7% (72.6%–76.8%) ($p = 3.27 \times 10^{-6}$ by DeLong test). When PRS-83SNP was subsequently added to the model containing *APOE* genotype, the AUC further improved to 75.7% (73.7%–77.8%), a statistically significant improvement ($p = 0.007$). The addition of PRS-SBayesR to the baseline + *APOE* model showed a similar AUC improvement to 76.0% (74.0%–78.0%) ($p = 0.004$). The addition of PRS-CS to the baseline + *APOE* model also showed a similar AUC improvement to 76.1% (74.1%–78.2%) ($p = 0.003$). However, the addition of the older PRS-23SNP to the baseline + *APOE* model showed no evidence of improvement to the AUC, which remained at 74.7% (72.6%–76.8%) ($p = 0.95$). We also examined larger models by adding any two of PRS-83SNP, PRS-SBayesR, and PRS-CS to the baseline + *APOE* model (Table 4); however, no significant improvement was found compared to the addition of a single PRS. For example, although the model of baseline + *APOE* + PRS-83SNP + PRS-CS reached the best estimate of AUC with 76.5% (74.5%–78.5%) and performed a little better than the addition of PRS-83SNP

($p = 0.03$), it was not significantly better than the baseline + *APOE* + PRS-CS model ($p = 0.13$).

4 | DISCUSSION

In this study, we evaluated the performance of three newly derived PRSs, PRS-83SNP, PRS-SBayesR, and PRS-CS, for all-cause dementia in a well-characterized population of older individuals followed prospectively. We found improved performance for the new PRSs, compared to the older PRS-23SNP score, and strong associations between the new PRSs and incident dementia risk during follow-up. The addition of the new PRSs to risk-prediction models containing conventional/non-genetic risk factors and *APOE* genotype improved the AUC. However, AUC improvements after adding the PRSs were modest (≈1% for PRS-83SNP, ≈1.3% for PRS-SBayesR, and ≈1.4% for PRS-CS). Our study provides evidence that if the sample sizes and power of future GWASs for dementia continue to increase, the performance of resulting PRSs based on greater numbers of dementia-associated variants will continue to improve.

Previous studies have assessed effects of the older PRS-23SNP for risk of progression to dementia,[16,17] AD age at onset,[16,48] and other cognitive impairments,[17,49,50] but found limited performance or practical utility for individual patients. For example, van der Lee et al.[16] evaluated the PRS-23SNP on incident dementia in cognitively healthy participants (age >45 years) from the community-based Rotterdam Study. Their results showed that the PRS could significantly modify the risk and age at onset of AD and all-cause dementia beyond the *APOE* genotype.[16] However, this study did not examine the prediction performance of the PRS using AUC or the C-statistic.

A previous study from our group[17] examining the older PRS-23SNP in the ASPREE cohort (using only a mean of 4.5 years of follow-up) found the effect of the PRS on incident dementia risk to be modest, with only a 1.4-fold increase in incident dementia risk between the lowest and the highest PRS-23SNP tertiles. By contrast, in the present study (using the newly derived PRSs and ≈2 additional years of follow-up), the effect sizes per SD increased to HR = 1.41 per SD (PRS-CS), and the increase in risk between the lowest and highest deciles increased to 3.9-fold (PRS-CS). However, the older PRS-23SNP still did not significantly improve dementia risk prediction above the base model (AUC = 74.7%, $p = 0.95$).

Bellengeuz et al. validated the performance of the new PRS-83SNP using a fixed-effect meta-analysis, presenting the results in the same publication as the GWAS.[14] However, the effect size was quite low (HR = 1.08, 95% CI: 1.06–1.09), and the findings required independent assessment in an external cohort. Separately, Stocker et al.[51] investigated the performance of a more recent PRS derived using 72 independent SNPs[9] and *APOE* status to predict clinically diagnosed all-cause dementia in a community-based cohort followed over 17 years. The AUC of predicting all-cause dementia using this PRS, with *APOE* status, age, sex, and education was estimated as 79.2%, which is higher than our results, possibly due to more dementia cases included in a longer follow-up. However, this particular study did not examine the risk of incident dementia using longitudinal analysis. The above studies, taken

together with our study, provide evidence that PRS performance for dementia may continue to improve as a function of larger GWAS. This is consistent with our main results indicating a significant improvement to AUC for a model containing conventional/non-genetic factors and *APOE* (AUC = 74.7%), with the addition of the newer PRS-83SNP (AUC = 75.7%, p = 0.007), PRS-SBayesR (AUC = 76%, p = 0.004), or PRS-CS (AUC = 76.1%, p = 0.003).

However, the concept of PRS performance improving in a linear fashion with more disease-associated variants identified (e.g., by larger GWASs) has been brought into question. A recent study[15] compared SNP-based heritability estimates from different AD GWASs and found a downward trend in heritability estimates with larger GWASs. For example, the most recent GWAS by Bellengeuz et. al.[14] explained only ≈3% heritability, whereas the previous smaller GWAS by Lambert et. al.[8] in 2013 explained ≈9%. Several possible explanations have been provided for this counter-intuitive trend,[15] including the lack of clinical screening and younger average age of controls used in the recent GWAS, and the growing use of "proxy dementia cases" rather than clinically diagnosed AD patients. Nonetheless, despite these discrepancies in heritability estimates, we observed clearly improved PRS performance from newly derived PRSs (from large recent GWAS), compared with the older PRS. Despite the improvement we observed in PRS performance, the newly derived PRSs still confer only modest risk when compared with the *APOE* genotype, and improve risk-prediction models only incrementally (beyond *APOE* genotype). This raises the question of whether a PRS (containing non-*APOE* variants) will ever confer sufficient variation and effect to be considered of clinical or epidemiological utility for dementia risk prediction. Given that the newly derived PRSs can be calculated for the same cost and using similar methods as previous PRSs, it is a logical progression to use them. We argue that continued development of improved PRSs (based on more dementia-associated variants other than *APOE*) is worthwhile, particularly for improved risk prediction and stratification of *APOE* ε4 non-carriers (e.g., ε3/ε3 homozygotes), who comprise a large population sub-group where many individuals will still go on to develop dementia. Furthermore, there is hope that improved early identification of higher-risk individuals for dementia (based on genetic risk scores and also other factors) will promote prevention and early intervention by individuals or their families to minimize the disease progression, such as modifying lifestyles to reduce risk,[52,53] and facilitate more efficient recruitment of clinical trials, especially for new preventive therapies or interventions as they emerge.

In addition, incremental improvements to risk-prediction models (e.g., single-digit AUC) are a common property of PRSs and seen across many disease areas.[54–56] In some cases, this small benefit is translating into clinical utility (e.g., coronary heart disease and breast cancer risk prediction and risk stratification). For dementia, a relatively common disease with increasing prevalence due to aging populations, if risk-prediction models are extrapolated to an entire nation's population, for example, a modest improvement in AUC could result in re-classification of thousands of people into lower- or higher-risk categories. If re-classification determines whether certain interventions will be recommended or not, this may become important, especially if future interventions are particularly expensive or invasive.

Our study found that an updated PRS containing a higher number of dementia-associated common variants identified from GWAS[14] has led to the improved prediction of dementia

risk. However, beyond the identification of more dementia-associated variants from GWASs (most of them are common variants), more studies are required to better understand the role of rare and structural variants for dementia,[57–60] which also need to be incorporated in risk-prediction models. Moreover, the interplay between genes and the environment requires improved understanding with regard to dementia risk.[61]

Strengths of our study include independent validation of PRS performance in a large sample size of well-characterized, initially-healthy older individuals, followed prospectively over a mean of 6.5 years. All incident dementia cases in ASPREE were adjudicated as primary clinical trial endpoints by expert panels, using standardized protocols for data collection and DSM-IV criteria.

Limitations of our study include analyzing participants of European ancestry only to prevent population stratification biases, meaning our conclusions cannot necessarily be generalized to other ancestries. The ASPREE cohort also has an acknowledged healthy survivorship bias, with reduced prevalence of comorbidities at enrollment, and participants were without diagnosed cardiovascular disease events, major physical disability, or dementia. The ASPREE cohort, overall, has a lower incidence of dementia than the general population would at similar ages. This may result in an underestimation of PRS effects. The molecular processes underlying most of the common variants used in the PRSs are still unknown or uncharacterized. Further functional studies are required to understand the underlying mechanisms between these dementia-associated variants, risk, and clinical phenotypes. Another limitation is that the dementia adjudication did not include clinical phenotyping. Thus, although the majority of dementia endpoints were likely due to AD, the endpoint itself captured all-cause dementia.

5 | CONCLUSION

We present, to our knowledge, the first external validation of three newly derived PRSs for dementia, in an independent cohort of older individuals followed prospectively. Our study demonstrates that the newly derived PRSs for dementia provide significantly improved performance and improve risk prediction beyond the use of conventional/non-genetic risk factors and *APOE* genotypes. Our findings have potential implications for the improved risk stratification and prediction of dementia. Further studies will be required to more rigorously assess the clinical utility of genetic risk scores for dementia as new therapeutic and preventive agents become available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

1. Sloane PD, Zimmerman S, Suchindran C, et al. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. Annu Rev Public Health. 2002;23:213–231. [PubMed: 11910061]

2. Takizawa C, Thompson PL, van Walsem A, Faure C, Maier WC. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. J Alzheimers Dis. 2015;43(4):1271–1284. [PubMed: 25159675]

3. Gatz M, Reynolds CA, Fratiglioni L, Johansson B, Mortimer JA, Berg S, et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry. 2006;63(2):168–174. [PubMed: 16461860]

4. Karlsson IK, Escott-Price V, Gatz M, et al. Measuring heritable contributions to Alzheimer's disease: polygenic risk score analysis with twins. Brain Commun. 2022;4(1):fcab308. [PubMed: 35169705]

5. Tudorache IF, Trusca VG, Gafencu AV. Apolipoprotein E-a multifunctional protein with implications in various pathologies as a result of its structural features. Comput Struct Biotechnol J. 2017;15:359–365. [PubMed: 28660014]

6. Qian J, Wolters FJ, Beiser A, et al. APOE-related risk of mild cognitive impairment and dementia for prevention trials: an analysis of four cohorts. PLoS Med. 2017;14(3):e1002254. [PubMed: 28323826]

7. Rasmussen KL, Tybjærg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Absolute 10-year risk of dementia by age, sex and APOE genotype: a population-based cohort study. CMAJ. 2018;190(35):E1033–E1041. [PubMed: 30181149]

8. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet. 2013;45(12):1452–1458. [PubMed: 24162737]

9. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet. 2019;51(3):414–430. [PubMed: 30820047]

10. Moreno-Grau S, de Rojas I, Hernández I, et al. Genome-wide association analysis of dementia and its clinical endophenotypes reveal novel loci associated with Alzheimer's disease and three causality networks: the GR@ ACE project. Alzheimer's Dement. 2019;15(10):1333–1347. [PubMed: 31473137]

11. Wightman DP, Jansen IE, Savage JE, et al. A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease. Nat Genet. 2021;53(9):1276–1282. [PubMed: 34493870]

12. Kunkle BW, Schmidt M, Klein HU, et al. Novel Alzheimer disease risk loci and pathways in African American individuals using the African genome resources panel: a meta-analysis. JAMA Neurol. 2021;78(1):102–113. [PubMed: 33074286]

13. De Rojas I, Moreno-Grau S, Tesi N, et al. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. Nat Commun. 2021;12(1):3417. [PubMed: 34099642]

14. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet. 2022;54(4):412–436. [PubMed: 35379992]

15. Escott-Price V, Hardy J. Genome-wide association studies for Alzheimer's disease: bigger is not always better. Brain Commun. 2022;4(3):fcac125. [PubMed: 35663382]

16. van der Lee SJ, Wolters FJ, Ikram MK, et al. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. Lancet Neurol. 2018;17(5):434–444. [PubMed: 29555425]

17. Riaz M, Huq A, Ryan J, et al. Effect of APOE and a polygenic risk score on incident dementia and cognitive decline in a healthy older population. Aging Cell. 2021;20(6):e13384. [PubMed: 34041846]

18. Leonenko G, Baker E, Stevenson-Hoare J, et al. Identifying individuals with high risk of Alzheimer's disease using polygenic risk scores. Nat Commun. 2021;12(1):4506. [PubMed: 34301930]

19. Lloyd-Jones LR, Zeng J, Sidorenko J, et al. Improved polygenic prediction by Bayesian multiple regression on summary statistics. Nat Commun. 2019;10(1):5086. [PubMed: 31704910]

20. Ge T, Chen CY, Ni Y, Feng YC, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun. 2019;10(1):1776. [PubMed: 30992449]

21. Ni G, Zeng J, Revez JA, et al. A comparison of ten polygenic score methods for psychiatric disorders applied across multiple cohorts. Biol Psychiatry. 2021;90(9):611–620. [PubMed: 34304866]

22. McNeil JJ, Woods RL, Nelson MR, et al. Baseline characteristics of participants in the ASPREE (ASPirin in Reducing Events in the Elderly) study. J Gerontol A Biol Sci Med Sci. 2017;72(11):1586–1593. [PubMed: 28329340]

23. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med. 2018;379(16):1499–1508. [PubMed: 30221596]

24. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379(16):1509–1518. [PubMed: 30221597]

25. McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med. 2018;379(16):1519–1528. [PubMed: 30221595]

26. Nunn JS, Sulovski M, Tiller J, Holloway B, Ayton D, Lacaze P. Involving elderly research participants in the co-design of a future multi-generational cohort study. Res Involv Engagem. 2021;7(1):23. [PubMed: 33941290]

27. Martin AR, Gignoux CR, Walters RK, et al. Human demographic history impacts genetic risk prediction across diverse populations. Am J Hum Genet. 2017;100(4):635–649. [PubMed: 28366442]

28. Ryan J, Woods RL, Britt C, et al. Normative performance of healthy older individuals on the Modified Mini-Mental State (3MS) examination according to ethno-racial group, gender, age, and education level. Clin Neuropsychol. 2021;35(6):1174–1190. [PubMed: 32100619]

29. Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test–revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol. 1998;12(1):43–55.

30. Ross TP. The reliability of cluster and switch scores for the Controlled Oral Word Association Test. Arch Clin Neuropsychol. 2003;18(2):153–164. [PubMed: 14591467]

31. Smith A Symbol Digit Modalities Test (SDMT) Manual (revised). Los Angeles, California: Western psychological services; 1982.

32. Bland RC, Newman SC. Mild dementia or cognitive impairment: the Modified Mini-Mental State examination (3MS) as a screen for dementia. Can J Psychiatry. 2001;46(6):506–510. [PubMed: 11526806]

33. Tombaugh TN. Test-retest reliable coefficients and 5-year change scores for the MMSE and 3MS. Arch Clin Neuropsychol. 2005;20(4):485–503. [PubMed: 15896562]

34. Ryan J, Storey E, Murray AM, et al. Randomized placebo-controlled trial of the effects of aspirin on dementia and cognitive decline. Neurology. 2020;95(3):e320–e331. [PubMed: 32213642]

35. Orchard SG, Polekhina G, Ryan J, et al. Combination of gait speed and grip strength to predict cognitive decline and dementia. Alzheimers Dement (Amst). 2022;14(1):e12353. [PubMed: 36187193]

36. Collyer TA, Murray AM, Woods RL, et al. Association of dual decline in cognition and gait speed with risk of dementia in older adults. JAMA Network Open. 2022;5(5):e2214647. [PubMed: 35639376]

37. Graham DP, Cully JA, Snow AL, Massman P, Doody R. The Alzheimer's Disease Assessment Scale-Cognitive subscale: normative data for older adult controls. Alzheimer Dis Assoc Disord. 2004;18(4):236–240. [PubMed: 15592137]

38. D'Elia LF, Satz P, Uchiyama CL, White T. Color Trails Test: Professional Manual. Odessa, Florida: Psychological Assessment Resources; 1996.

39. Reid W, Broe G, Creasey H, et al. Age at onset and pattern of neuropsychological impairment in mild early-stage Alzheimer disease: a study of a community-based population. Arch Neurol. 1996;53(10):1056–1061. [PubMed: 8859068]

40. Fish J Alzheimer's Disease Cooperative Study ADL Scale. Encyclopedia of Clinical Neuropsychology. Springer; 2011.

41. Pinese M, Lacaze P, Rath EM, et al. The Medical Genome Reference Bank contains whole genome and phenotype data of 2570 healthy elderly. Nat Commun. 2020;11(1):435. [PubMed: 31974348]

42. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. Nat Genet. 2016;48(10):1284–1287. [PubMed: 27571263]

43. Ruiz A, Dols-Icardo O, Bullido MJ, et al. Assessing the role of the TREM2 p. R47H variant as a risk factor for Alzheimer's disease and frontotemporal dementia. Neurobiol Aging. 2014;35(2):444.e1–4.

44. Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. PLoS Med. 2017;14(3):e1002258. [PubMed: 28323831]

45. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.

46. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinf. 2011;12:77.

47. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988:837–45. [PubMed: 3203132]

48. Leonenko G, Sims R, Shoai M, et al. Polygenic risk and hazard scores for Alzheimer's disease prediction. Ann Clin Transl Neurol. 2019;6(3):456–465. [PubMed: 30911569]

49. Marden JR, Mayeda ER, Walter S, et al. Using an Alzheimer's Disease polygenic risk score to predict memory decline in black and white Americans over 14 years of follow-up Running head: AD polygenic risk score predicting memory decline. Alzheimer Dis Assoc Disord. 2016;30(3):195–202. [PubMed: 26756387]

50. Chaudhury S, Brookes KJ, Patel T, et al. Alzheimer's disease polygenic risk score as a predictor of conversion from mild-cognitive impairment. Transl Psychiatry. 2019;9(1):154. [PubMed: 31127079]

51. Stocker H, Perna L, Weigl K, et al. Prediction of clinical diagnosis of Alzheimer's disease, vascular, mixed, and all-cause dementia by a polygenic risk score and APOE status in a community-based cohort prospectively followed over 17 years. Mol Psychiatry. 2021;26(10):5812–5822. [PubMed: 32404947]

52. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14(11):653–666. [PubMed: 30291317]

53. McMaster M, Kim S, Clare L, et al. Lifestyle risk factors and cognitive outcomes from the multidomain dementia risk reduction randomized controlled trial, body brain life for cognitive decline (BBL-CD). J Am Geriatr Soc. 2020;68(11):2629–2637. [PubMed: 32909259]

54. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018;19(9):581–590. [PubMed: 29789686]

55. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet. 2019;28(R2):R133–R142. [PubMed: 31363735]

56. O'Sullivan JW, Raghavan S, Marquez-Luna C, et al. Polygenic risk scores for cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2022;146(8):e93–e118. [PubMed: 35862132]

57. Geier EG, Bourdenx M, Storm NJ, et al. Rare variants in the neuronal ceroid lipofuscinosis gene MFSD8 are candidate risk factors for frontotemporal dementia. Acta Neuropathol. 2019;137(1):71–88. [PubMed: 30382371]

58. Cuyvers E, Bettens K, Philtjens S, et al. Investigating the role of rare heterozygous TREM2 variants in Alzheimer's disease and frontotemporal dementia. Neurobiol Aging. 2014;35(3):726.e11–19.

59. Beck J, Pittman A, Adamson G, et al. Validation of next-generation sequencing technologies in genetic diagnosis of dementia. Neurobiol Aging. 2014;35(1):261–265. [PubMed: 23998997]

60. Qiang W, Yau WM, Lu JX, Collinge J, Tycko R. Structural variation in amyloid-β fibrils from Alzheimer's disease clinical subtypes. Nature. 2017;541(7636):217–221. [PubMed: 28052060]

61. Dunn AR, O'Connell KM, Kaczorowski CC. Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease. Neurosci Biobehav Rev. 2019;103:73–80. [PubMed: 31207254]

RESEARCH IN CONTEXT

Systematic review:

The authors reviewed the literature using PubMed on genome-wide association studies (GWASs) and polygenic risk scores (PRSs) for dementia. Recent GWASs have identified an increased number of dementia-associated variants, and PRSs were updated using these variants. PubMed search did not identify studies on validating these new PRSs in an independent cohort.

Interpretation:

Our study showed that three new PRSs for dementia significantly improved risk prediction performance, which suggested a potential clinical use to facilitate more targeted prevention and early intervention strategies for individuals or families and facilitate recruitment into disease-modifying or preventive intervention trials.

Future directions:

Beyond the identification of more dementia-associated variants from GWAS, more studies are required to better understand the role of rare and structural variants for dementia, which also need to be incorporated in risk-prediction models. Future studies will more rigorously assess the clinical utility of these genetic risk scores.
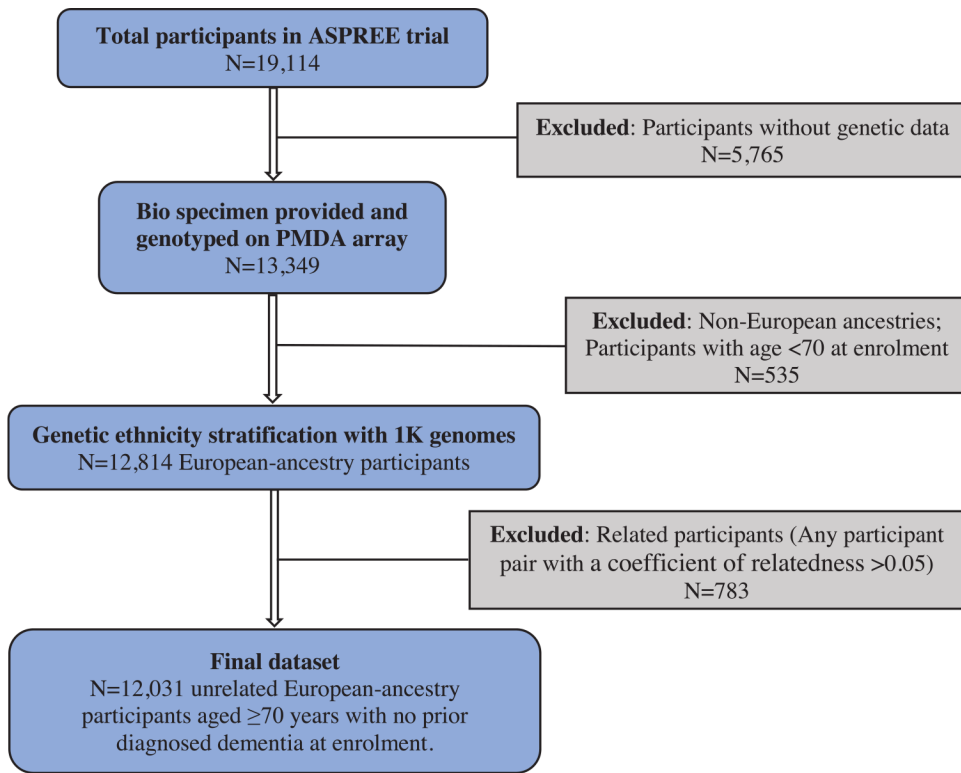
FIGURE 1.
Flow chart of selection of ASPREE participants included in this genetic study.
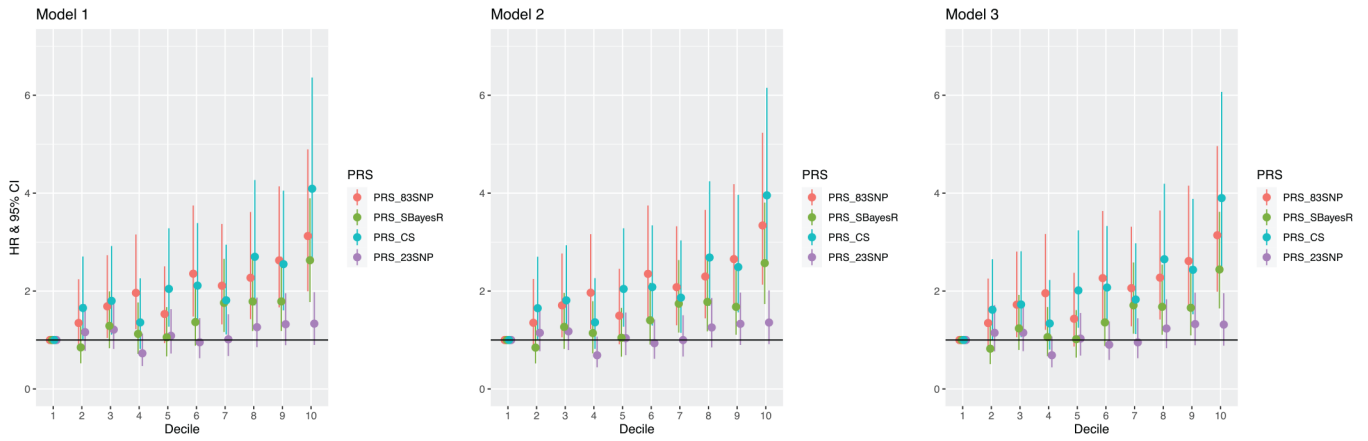
FIGURE 2.

Association of PRS decile groups with incident dementia. Cox proportional hazards (PH) models were used to estimate the hazard ratio (HR) with 95% confidence intervals (CIs). 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 1

Baseline characteristics of ASPREE participants included in this genetic study.

Baseline categories	Overall ($n = 12,031$)
Age, mean (SD), years	75.1 (4.2)
Sex	
Male, n (%)	5425 (45.1%)
Female, n (%)	6606 (54.9%)
Smoking status	
Current, n (%)	367 (3.1%)
Former, n (%)	4990 (41.5%)
Never, n (%)	6674 (55.5%)
Alcohol drinking status	
Current, n (%)	9608 (79.9%)
Former, n (%)	584 (4.9%)
Never, n (%)	1839 (15.3%)
Years of education	
<9 years, n (%)	1840 (15.3%)
9–11 years, n (%)	3781 (31.4%)
12 years, n (%)	1343 (11.2%)
13–15 years, n (%)	1898 (15.8%)
16 years, n (%)	1105 (9.2%)
17–21 years, n (%)	2064 (17.2%)
Living status	
At home alone, n (%)	3813 (31.7%)
At home with family, friends, or others, n (%)	8218 (68.3%)
CES-D-10,[a] mean (SD)	3.1 (3.2)
BMI[b], mean (SD), kg/m^2	28.0 (4.5)
Systolic blood pressure, mean (SD), mm Hg	139.5 (16.3)
Diastolic blood pressure, mean (SD), mm Hg	77.2 (9.9)
Dyslipidemia	
Yes, n (%)	7987 (66.4%)
No, n (%)	4044 (33.6%)
Diabetes status	
Yes, n (%)	1108 (9.2%)
No, n (%)	10,923 (90.8%)
Dementia family history[c], n (%)	3064 (25.5%)
APOE genotype[d]	
$\varepsilon1/\varepsilon3$: $\varepsilon2/\varepsilon4$, n (%)	440 (3.7%)
$\varepsilon1/\varepsilon4$, n (%)	2 (<0.1%)
$\varepsilon2/\varepsilon2$, n (%)	64 (<0.1%)
$\varepsilon2/\varepsilon3$, n (%)	1642 (13.6%)
$\varepsilon3/\varepsilon3$, n (%)	7214 (60.0%)

Baseline categories	Overall (n = 12,031)
$\varepsilon3/\varepsilon4$, n (%)	2459 (20.4%)
$\varepsilon4/\varepsilon4$, n (%)	185 (1.5%)

[a] CES-D-10, Center for Epidemiologic Studies Depression Scale, 10-item version.

[b] BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

[c] Family history of dementia in father, mother, or sibling.

[d] Twenty-five participants had missing *APOE* genotypes due to quality control of genotyping at rs7412 or rs429358.

TABLE 2

Association of four dementia-related polygenic risk scores (as a continuous variable, per SD) with risk of incident dementia.

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	1.35 (1.23–1.47)	2.85E-11	1.37 (1.26–1.50)	3.12E-12	1.35 (1.23–1.47)	5.33E-11
PRS-SBayesR	1.39 (1.27–1.51)	6.48E-13	1.37 (1.26–1.50)	3.07E-12	1.37 (1.25–1.50)	9.51E-12
PRS-CS	1.43 (1.31–1.57)	3.56E-15	1.42 (1.30–1.56)	1.43E-14	1.42 (1.30–1.56)	1.67E-14
PRS-23SNP	1.11 (1.02–1.21)	0.02	1.12 (1.03–1.23)	0.01	1.12 (1.02–1.22)	0.02

Note: Cox PH regression models were used to estimate the hazard ratio (HR) of the PRS per standard deviation, with 95% confidence intervals (CIs). 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 3

Association of four dementia-related polygenic risk scores (as a continuous variable, per SD) with risk of incident dementia for subgroups according to alcohol drinking status and the number of *APOE-ε*4.

Subgroup analysis		PRS-83SNP		PRS-SBayesR		PRS-CS		PRS-23SNP	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Alcohol drinking	Current	1.28 (1.16–1.42)	2.21E-06	1.29 (1.16–1.43)	2.09E-06	1.35 (1.22–1.50)	2.27E-08	1.06 (0.96–1.18)	0.25
	Former	1.26 (0.85–1.88)	0.25	1.08 (0.73–1.62)	0.69	1.24 (0.81–1.89)	0.33	1.07 (0.72–1.58)	0.74
	Never	1.74 (1.40–2.16)	6.58E-07	1.95 (1.56–2.43)	2.84E-09	1.84 (1.49–2.28)	1.43E-08	1.41 (1.14–1.74)	1.75E-03
Number of *APOE-ε*4	0	1.40 (1.25–1.58)	1.53E-08	1.52 (1.34–1.71)	1.69E-11	1.59 (1.40–1.79)	1.12E-13	1.08 (0.96–1.21)	0.22
	1	1.37 (1.18–1.59)	3.13E-05	1.27 (1.10–1.48)	1.44E-03	1.33 (1.15–1.54)	1.64E-04	1.25 (1.07–1.45)	4.31E-03
	2	0.59 (0.35–1.02)	0.06	0.67 (0.41–1.09)	0.11	0.53 (0.30–0.92)	0.02	0.82 (0.50–1.34)	0.43

Note: Cox PH regression models were used to estimate the hazard ratio (HR) of the PRS per standard deviation with 95% confidence intervals (CI), adjusted for age at recruitment, sex, first 20 genetic PCs, the number of *APOE-ε*4 and *APOE-ε*2 alleles, 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 (Model 3).

TABLE 4

AUC estimates at a mean of 6.5 years of follow-up and comparisons for predictions of dementia risk.

Model	AUC (95% CI)	*p*-value
Baseline	71.0% (68.7%–73.3%)	
Baseline + *APOE*	74.7% (72.6%–76.8%)	3.27E-06 (vs Baseline)
Baseline + *APOE* + PRS-83SNP	75.7% (73.7%–77.8%)	0.007 (vs Baseline + *APOE)*
Baseline + *APOE* + PRS-SBayesR	76.0% (74.0%–78.0%)	0.004 (vs Baseline + *APOE)*
Baseline + *APOE* + PRS-CS	76.1% (74.1%–78.2%)	0.003 (vs Baseline + *APOE)*
Baseline + *APOE* + PRS-23SNP	74.7% (72.6%–76.8%)	0.95 (vs Baseline + *APOE)*
Baseline + *APOE* + PRS-83SNP + PRS-SBayesR	76.2% (74.2%–78.2%)	0.06 (vs Baseline + *APOE* + PRS-83SNP)
		0.22 (vs Baseline + *APOE* + PRS-SBayesR)
Baseline + *APOE* + PRS-83SNP + PRS-CS	76.5% (74.5%–78.5%)	0.03 (vs Baseline + *APOE* + PRS-83SNP)
		0.13 (vs Baseline + *APOE* + PRS-CS)
Baseline + *APOE* + PRS-SBayesR + PRS-CS	76.2% (74.2%–78.2%)	0.40 (vs Baseline + *APOE* + PRS-SBayesR)
		0.61 (vs Baseline + *APOE* + PRS-CS)

Note: The baseline model includes the predictors in Model 3, excluding *APOE* genotype variables (the number of $\varepsilon 4$ and $\varepsilon 2$ alleles) and PRS, that is, age at recruitment, sex, first 20 genetic PCs, 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. *p*-value was obtained through the DeLong test by comparing AUCs from two nested models.