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RESEARCH ARTICLE

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Polygenic score integrating neurodegenerative and vascular risk informs dementia risk stratification

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Abstract

INTRODUCTION: An integrative polygenic risk score (iPRS) capturing the neurodegenerative and vascular contribution to dementia could identify high-risk individuals and improve risk prediction.

METHODS: We developed an iPRS for dementia (iPRS-DEM) in Europeans (aged 65+), comprising genetic risk for Alzheimer's disease (AD) and 23 vascular or

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neurodegenerative traits (excluding apolipoprotein E [*APOE*]). iPRS-DEM was evaluated across cohorts comprising older community-dwelling people (N = 3702), a multi-ancestry biobank (N = 130,797 Europeans; 105,404 non-Europeans), and dementia-free memory clinic participants (N = 2032).

RESULTS: iPRS-DEM was associated with dementia risk independently of *APOE* in the elderly (subdistribution hazard ratio [sHR]$_{per1SD}$ = 1.15, 95% confidence interval [CI]: 1.03 to 1.28), which generalized to Europeans (EUR-sHR$_{per1SD}$ = 1.28, 95% CI: 1.09 to 1.51]), East-Asians (EAS-sHR$_{per1SD}$ = 5.29, 95% CI: 1.43 to 34.36), and memory-clinic participants (sHR$_{per1SD}$ = 1.25, 95% CI: 1.11 to 1.42). Prediction was comparable to clinical risk factors in older community-dwelling people, with improved performance among memory-clinic patients. Risk stratification was enhanced by defining four genetic risk groups with iPRS-DEM and *APOE* ε4, reaching five-fold increased risk in *APOE* ε4+/iPRS-DEM+ memory-clinic participants.

DISCUSSION: Alongside *APOE* ε4, iPRS-DEM may refine risk stratification for the enrichment of dementia clinical trials and prevention programs.

KEYWORDS
apolipoprotein E genotype, community-dwelling elderly, competing risk analysis, dementia prevention, incident dementia, longitudinal study, memory clinic, multi-ancestry biobank, polygenic risk score, transportability of PRS, vascular cognitive impairment

Highlights

- iPRS-DEM reflects neurodegenerative and vascular contribution to dementia.
- We show iPRS-DEM captures additional dementia genetic risk beyond *APOE* and AD-PRS.
- iPRS-DEM, in combination with *APOE* ε4, shows promise for dementia risk stratification.
- Our results generalize across both population-based and memory-clinic settings.
- We show transportability of iPRS-DEM to East Asian ancestry.

1 | BACKGROUND

Dementia, arising from a complex interplay of genetic and environmental factors, is a major contributor to disability and dependency among older persons, affecting over 55 million people worldwide.[1] Most dementia cases in the population exhibit "mixed" pathology, with co-occurrence of neurodegenerative (predominantly due to Alzheimer's disease [AD]) and vascular brain injury, including those due to clinical stroke and, more frequently, covert cerebral small vessel disease (cSVD).[2–5] This vascular contribution has been sparsely accounted for in dementia trials, and the failure to develop disease-modifying therapies has been partly attributed to over-reliance on imprecise AD biomarkers used to enroll at-risk patients.[6] Yet, approximately 40% of dementia burden is attributable to modifiable risk factors, many of vascular origin (including hypertension, physical inactivity, obesity, smoking, and diabetes).[7] Multimodal interventions, including management of vascular risk factors in midlife, have shown promise in preventing dementia, particularly among high-risk groups.[8–10]

Polygenic risk scores (PRS), derived from large genome-wide association studies (GWAS), capture genetic risk for complex conditions by combining the effects of many independent risk variants on a given phenotype. They have a demonstrated ability to identify individuals at a high genetic risk of multifactorial diseases, with effect sizes approaching those of monogenic disease mutations in the top percentiles of PRS.[11] As PRS can be measured at low cost and early in life, they could be important tools to tailor preventive interventions for high-risk individuals[12,13] and for predictive and prognostic enrichment of clinical trials.[14] PRS derived from AD GWAS (AD-PRS) that combine the effects of common genetic risk variants other than apolipoprotein E epsilon 4 (*APOE* ε4) were shown to predict AD beyond *APOE* ε4 and are associated with neuroimaging markers of neurodegeneration and amyloid and tau burden.[15,16] However, while some studies have described AD-PRS to also predict all-cause and vascular dementia,[17–21] recruitment in AD GWAS is likely biased toward patients with less extensive contribution of vascular brain disease than in the general population.[22]

We sought to more comprehensively capture polygenic risk of all-cause dementia by applying a novel integrative PRS (iPRS) approach, combining AD-PRS with PRS for stroke, MRI markers of cSVD, vascular risk factors, and neurodegenerative processes. The iPRS model is based on the assumption that the majority of genetic variants exert their effects on a given disease by affecting intermediate traits and was successfully applied to coronary artery disease (CAD) and stroke.[23–26] A similar approach was recently applied to AD,[27] but this included a heterogeneous set of traits (eg, PRS for psychiatric conditions and sensory deficits) and did not comprehensively capture genetic susceptibility to vascular brain disease. Moreover, published AD-PRS were typically trained and evaluated in case–control datasets and have not explicitly investigated association with the probability of dementia over time (ie, cumulative incidence) while accounting for the competing risk of death.

Here, we trained an iPRS for all-cause dementia (iPRS-DEM), excluding the *APOE* locus, in a population-based, longitudinal cohort of older community-dwelling persons. Using competing risk models, we characterized the relationship of iPRS-DEM with cumulative incidence of all-cause dementia and evaluated the predictive performance of iPRS-DEM against single-trait AD-PRS, in comparison and combination with *APOE* and clinical risk factors. We explored the ability of iPRS-DEM to stratify dementia risk alongside *APOE* ε4 carrier status and validated it in memory clinic patients with cognitive complaints or mild cognitive impairment (MCI) to inform utility of iPRS-DEM to different stages of dementia prevention. Finally, we investigated the transportability of iPRS-DEM in a large, prospective cohort comprising participants of diverse socioeconomic background and ancestries (Europeans, East Asian, African-American, and Hispanic).

RESEARCH IN CONTEXT

1. **Systematic review**: Using PUBMED and similar sources, we identified studies investigating dementia PRS. There were limited studies demonstrating PRS association with all-cause dementia in longitudinal cohorts. Additionally, PRS studies focused primarily on AD and have yet to incorporate genetics reflecting the vascular contribution to dementia risk.
2. **Interpretation**: In longitudinal population-based and memory-clinic cohorts, we found an integrative PRS comprising multiple vascular and neurodegenerative traits, beyond AD-PRS alone, to be associated with risk of all-cause dementia independent of *APOE* and clinical risk factors and to refine stratification of dementia risk. An integrative PRS for all-cause dementia may capture additional risk above and beyond AD polygenic risk, *APOE*, and clinical risk factors and has potential to identify high-risk individuals in multiple dementia prevention settings.
3. **Future directions**: Future studies integrating PRS with clinical prediction models and further development of dementia PRS in non-Europeans are warranted.

2 | METHODS

2.1 | Study populations

The 3C and Memento studies were used to train and validate the iPRS-DEM. 3C is a population-based cohort comprising community-dwelling people aged ≥ 65 years from the French cities of Dijon, Montpellier, and Bordeaux, recruited in 1999 to 2001 and followed every 2 to 3 years over 12 to 17 years.[28] We split 3C by center into a training (Bordeaux and Montpellier [3C-BM]) and validation set (3C-Dijon). Memento participants were recruited from 26 French memory clinics based on subjective cognitive complaints or MCI in 2011 to 2014, with a follow-up every 6 to 12 months over 5 years.[29] The National Institutes of Health's All of Us (AoU) is a large ongoing prospective cohort study of American adults (aged 18+) aiming to enroll up to one million participants and welcoming participants from all backgrounds to reduce disparities in medical research.[30] Among those who consent, AoU collects survey questionnaires capturing detailed past and present medical history data, electronic health records, physical measurements (ie, blood pressure, height, weight), and genomic information (ie, whole genome sequencing).[31] Data were available from all participants who enrolled from the beginning of the program in May 2018 to June 2022 (release version 7). Participants without viable genome-wide genotype data, with prevalent dementia at baseline, or no follow-up were excluded. Genome-wide genotyping and imputation are described in the eMethods 1.

2.2 | Dementia diagnosis

In 3C, diagnosis of dementia followed a three-step procedure at baseline and at each follow-up visit.[28] First, all participants underwent a battery of neuropsychological tests at baseline and each follow-up visit by a trained psychologist. Second, a neurologist examined all the participants in Montpellier and in Bordeaux at baseline. In Dijon, participants screening positive for dementia based on their neuropsychological performance underwent further clinical examination. At each follow-up, all participants with suspected dementia were examined by a neurologist to establish provisional diagnosis. In Memento, trained neurologists administered a battery of neuropsychological tests at baseline and assessed dementia status at each follow-up visit.[29] In both cohorts, an independent panel of expert neurologists reviewed and validated all possible dementia cases according to the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* criteria. In AoU, dementia was ascertained from individual-level electronic health records, clinical notes, and self-report data using a combination of Systematized Nomenclature of Medicine (SNOMED)[32] and International Statistical Classification of Diseases and Related Health Problems, Ninth and Tenth Revisions (ICD-9 and 10)[33] codes shown in eTable 1.

2.3 | Generation of iPRS

An overview of the derivation and validation of iPRS-DEM is given in Figure 1. We identified large-scale GWAS summary statistics for 27 dementia-related traits aiming to comprehensively capture both neurodegenerative and vascular contribution to dementia, including AD, stroke (subtypes), vascular risk factors, MRI markers of cSVD, hippocampal volume, and cerebrospinal fluid levels of phosphorylated tau and amyloid beta (references for included GWAS in eTable 2). We performed standard quality control recommended for PRS,[34] including addressing sample overlap of 3C or Memento in GWAS meta-analyses (eMethods 1). As recommended, the *APOE* region (chromosome 19: 44.4 to 46.5 Mb) was excluded from the AD-PRS.[35]

In 3C-BM, we generated 148 candidate PRS models per trait using three validated PRS methods: the "clumping and thresholding" approach[36] and two Bayesian approaches, LDPRED2[37] and PRS-CS[38] (eMethods 2). Each candidate PRS model was evaluated in a Fine-Gray regression (FGR) model for cumulative incidence of all-cause dementia with time since baseline (years) as a time scale and considering death as a competing event.[39] Models were adjusted for age at baseline, age squared (to account for non-linearity), study center, sex, the first 10 genetic principal components (PCs) of population stratification,[40] and dosage of *APOE* ε4 and *APOE* ε2 alleles. Dementia onset was imputed as the midpoint between the time of diagnosis and last dementia-free visit. Non-demented individuals, including those who died more than two and a half years since their last visit, were censored at their last dementia-free visit. We performed a systematic procedure to select and integrate the best PRS for each trait and construct iPRS-DEM (Figure 1, eMethods 3). Briefly, we evaluated each candidate PRS model based on the lowest integrated Brier score[41] across 5, 7.5, and 10 years and then inputed the best PRS for each trait in Fine-Gray elastic-net regression[42] to address overfitting and correlation between PRS using the glmnet R package[43,44] (eMethods 3). Training weights were extracted from elastic-net for each sPRS and used to re-weight SNP effect sizes in the iPRS-DEM (eMethods 3).

2.4 | Validation of iPRS-DEM

We estimated the effect of iPRS-DEM and AD-PRS (included in iPRS-DEM) per 1 SD increment on the cumulative incidence of dementia (referred to interchangeably as dementia risk) in 3C-Dijon using FGR and the same time scale, censoring, and adjustment variables as for 3C-BM. We also partitioned each PRS into quintiles, estimating subdistribution hazard ratios [sHRs] relative to the middle 20%, and ran sensitivity analyses with cause-specific hazard (Cox) models for dementia and death.[45] As complementary analyses, we assessed dichotomized versions of each PRS at progressive percentile cutoffs against the rest of the sample. We verified if iPRS-DEM was associated with dementia risk independently of clinical risk factors (hypertension, smoking, dyslipidemia, diabetes, obesity, history of cardiovascular disease, and low education; definitions in eMethods 4) and calculated the percentage change in the FGR coefficient after adjustment (removing those with missing data; $n = 26$). Of note, FGR coefficients correspond to sHR, which only approximate the magnitude of effect on the cumulative incidence of dementia[46] (eMethods 5). Lastly, we performed subgroup analyses of the association between iPRS-DEM and dementia risk, stratifying by sex and looking at differential associations depending on age at onset (<80, ≥80 years, eMethods 6).

We also assessed risk stratification ability of iPRS-DEM alongside *APOE* ε4 after removing participants with *APOE* ε2/ε4 genotypes ($n = 70$). We first tested the interaction of iPRS-DEM with *APOE* ε4 carrier status and obtained *APOE* ε4 strata-specific sHRs. Then, through a factorial design, we categorized individuals into four genetic risk groups based on their *APOE* ε4 status (*APOE* ε4+/*APOE* ε4−) and the presence of high iPRS-DEM (iPRS-DEM+/iPRS-DEM−) (eMethods 7 for threshold selection). In non-parametric analysis, we compared the cumulative incidence of dementia at different ages in each genetic risk stratum, accounting for death as a competing event and left truncation with the etm R package (etmCIF function)[47,48] (eMethods 8). We also estimated the sHR in each genetic risk stratum relative to non-*APOE* ε4 carriers with low iPRS-DEM (*APOE* ε4−/iPRS-DEM−) as the reference group.

Finally, in FGR models, we compared prediction performance of iPRS-DEM against AD-PRS, *APOE* ε4 and ε2 dosage, clinical risk factors (showing significant association with increased dementia risk), and a reference model containing age at baseline, sex, and 10 PCs (eMethods 9). We calculated the time-dependent area under the curve (AUC)[49] and Index of Prediction Accuracy (IPA),[50] a rescaling of the Brier score against a null model with no covariates, at 10-year follow-up over 2000 bootstrap replications in 3C-Dijon using the riskRegression R package.[51] Twenty-six individuals with missing clinical risk factor data were also removed from these analyses.

2.5 | External validation in Memento

The iPRS-DEM was generated in Memento and validated by applying the same methods as described previously. FGR models were similar to 3C-Dijon validation, except for including only a linear term for age at baseline. We investigated approximately similar risk factors in Memento, including family history of dementia (eMethods 10). To estimate cumulative incidence in genetic risk strata, we used time since baseline assessment, adjusted for baseline covariates (adjustedCurves R package[52]) since progression from cognitive complaints or MCI to dementia is of interest in this clinical population (eMethods 11). Again, we performed complete case analysis for analyses including clinical risk factors and removed those with *APOE* ε2/ε4 genotype ($n = 39$) from *APOE* ε4 stratified analyses (eFigure 1). All statistical analyses were carried out in R version 4.1.0.[53]

2.6 | Transportability of iPRS-DEM across ancestries in AoU

We investigated the transportability of iPRS-DEM across ancestries in the US population-based All of Us research program. Here,

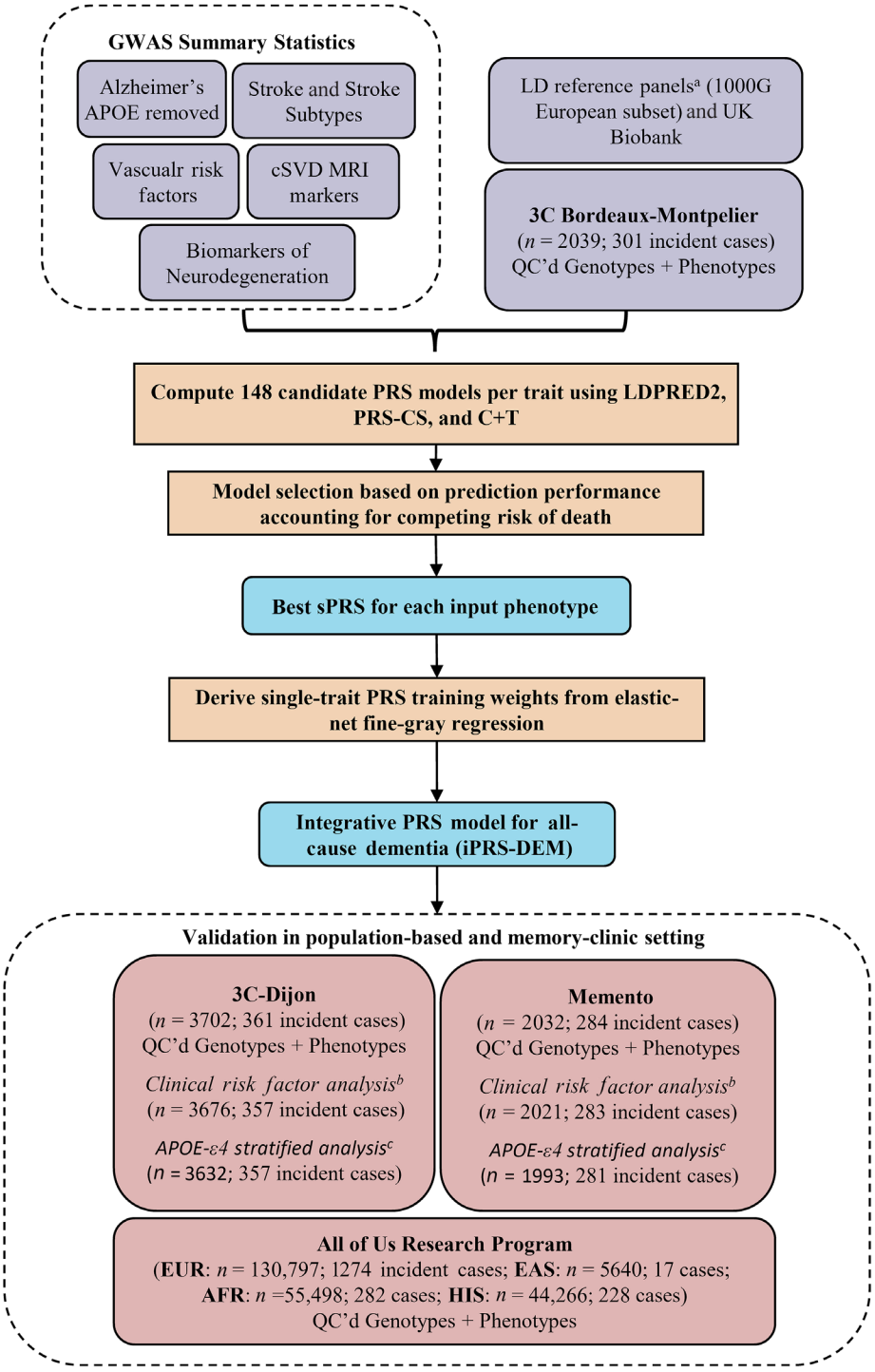


FIGURE 1 Overview of derivation and validation of iPRS-DEM. At each step of iPRS-DEM generation, we used Fine-Gray regression models. LDPRED2, PRS-CS, and C+T are validated methods to derive PRS using distinct combinations of tuning parameters. Candidate PRS models for each trait were selected based on integrative Brier score across 5-, 7.5-, and 10-year horizons. For each selected single-trait PRS the penalized coefficients from elastic-net were divided by the empirical standard deviation to derive training weights. Training weights were used to re-weight the effect size of SNPs included in their respective single-trait PRS. [a]UK Biobank was used as a reference panel for LDPRED2 PRS models as provided by the software. The 1000G European Subset was used as a reference panel for both PRS-CS and C+T. [b]Clinical risk factor analyses included assessing the change in the estimate of iPRS-DEM after adjustment for risk factors and prediction performance at 10-year follow-up in 3C and 5-years in Memento. In Memento, 1,952 participants had complete clinical risk factor data; however, only family history of dementia and low education were used in prediction models (positively associated with dementia risk) corresponding to 2,021 individuals in this analysis. [c]In analyses stratified by *APOE* ε4, we removed those with *APOE* ε2/ε4 genotype. These analyses included interaction models and stratifying individuals into genetic risk groups. AFR, African-American ancestry; C+T, clumping and thresholding; cSVD, cerebral small vessel disease; EAS, East Asian ancestry; EUR, European ancestry; HIS, Hispanic ancestry; LD, linkage disequilibrium; PRS, polygenic risk score(s); QC, quality control; sPRS, single-trait polygenic risk score(s).

we estimated the association of iPRS-DEM (per 1 SD) with cumulative incidence of dementia across European (EUR), East Asian (EAS), African-American (AFR), and Hispanic (HIS) ancestries, adjusting for baseline variables (age, sex, 5 PCs, and *APOE* ε4 and ε2 dosage).

3 | RESULTS

3.1 | Description of study populations

After excluding participants without viable genotyping, with prevalent dementia at baseline, or no follow-up (eFigure 1), study populations comprised 5741 3C participants, 236,201 in AoU, and 2032 Memento participants. 3C-BM (N = 2039; mean age ± SD = 73.9 ± 5.1 years; 60% women) had 301 (14.8%) incident dementia cases over median (interquartile range [IQR]) years of follow-up of 9.77 (IQR: 5.7 to 11.6), while 3C-Dijon (N = 3702; 74.2 ± 5.5 years; 61.8% women) had 361 (9.8%) incident dementia cases over 8.4 (IQR: 4.0 to 10.7) years follow-up. 3C-Dijon participants were slightly more educated than 3C-BM participants, but other baseline characteristics, including clinical risk factors and *APOE* genotype, were similar (Table 1). Memento (N = 2032; 70.9 ± 8.6 years; 61.5% women) had 284 (14.0%) dementia cases over 5.0 (IQR: 3.0 to 5.1) years follow-up and had a wider age range, higher education levels, and proportionally more *APOE* ε4 carriers than 3C (Table 1). Per ancestry, AoU had a sample size of 130,797 Europeans (1274 incident dementia cases; 56 ± 17 years, 59.8% women), 5640 East Asians (17 incident dementia cases; 44 ± 17 years; 63.7% women), 55,498 African-Americans (282 incident dementia cases; 49 ± 15 years; 57.6% women), and 44,266 Hispanics (228 incident dementia cases; 45 ± 16 years; 66.8% women). AoU had a larger age range than 3C-Dijon or Memento, and follow-up time was shorter (median of 3 years in each ancestry group, Table 2). In AoU Europeans, the *APOE* genotype distribution was similar to 3C-Dijon, while it was markedly different in other ancestries (*APOE* ε4 being less common in EAS and more common in AFR participants, Table 2).

3.2 | Construction of iPRS-DEM

We selected the best PRS for 27 dementia-related traits (AD, stroke, vascular risk factors, MRI markers of cSVD, and biomarkers of neurodegeneration), based on their ability to predict dementia risk in 3C-BM, and removed three traits whose best PRS did not improve prediction beyond *APOE* (eTable 3). Expectedly, there was considerable correlation between some of the sPRS in the training dataset (eFigure 2). Following elastic-net regression, 12 of 24 sPRS, including a substantial vascular component, had a non-zero training weight and were included in the final iPRS-DEM (eTable 4, eFigure 3, weights of top 250 SNPs are available in eTable 5).

3.3 | Association of iPRS-DEM with cumulative incidence of all-cause dementia in 3C-Dijon

In 3C-Dijon, a 1 SD increase in iPRS-DEM was associated with dementia risk independent of *APOE* ε4 and ε2 dosage (sHR_{per1SD} = 1.15, 95% CI: 1.03 to 1.28; p = .01), and participants in the highest iPRS-DEM quintile had significantly higher dementia risk relative to the middle 20% (sHR = 1.48, 95% CI: 1.08 to 2.05; p = .016). The AD-PRS was not significantly associated with dementia risk for both per 1 SD increase (sHR_{per1SD} = 1.11, 95% CI: 1.00 to 1.23; p = .06) and comparing the upper to middle quintiles (sHR = 1.21, 95% CI: 0.88 to 1.67; p = .25). Sensitivity analysis in cause-specific Cox models revealed similar associations between iPRS-DEM and dementia incidence (eTable 6). The sHR increased when dichotomizing iPRS-DEM at increasing percentiles, reaching sHR = 1.36 (95% CI: 1.09 to 1.68) in the top 30%, sHR = 1.53 (95% CI: 1.04 to 2.26) in the top 5% and sHR = 1.82 (95% CI: 0.92 to 3.62) in the top 1% compared to the rest of the sample (Figure 2A), while no such trend was observed for AD-PRS, with sHRs of 1.37 (95% CI: 1.11 to 1.70), 1.32 (95% CI: 0.86 to 2.01), and 0.77 (95% CI: 0.24 to 2.42) for AD-PRS in the top 30%, 5%, and 1% (eFigure 4). The iPRS-DEM sHR per 1 SD was comparable to that of associated clinical risk factors (sHR_{per1SD} range: 1.14 to 1.24, eTable 7). Adjusting for education and vascular risk factors only modestly attenuated the association of iPRS-DEM with cumulative incidence of dementia (by 27%, eTable 8).

In sex-stratified analyses, we found iPRS-DEM tended to be associated more strongly with dementia risk in women than in men, though interaction was non-significant (iPRS per 1 SD sHR_{Women} = 1.23, 95% CI: 1.07 to 1.41; sHR_{Men} = 1.04, 95% CI: 0.88 to 1.23; interaction p = .13) (Figure 3, eTable 9). iPRS-DEM showed no difference in association with earlier- versus later-onset dementia (< vs ≥ 80 years) (Figure 3, eTable 9).

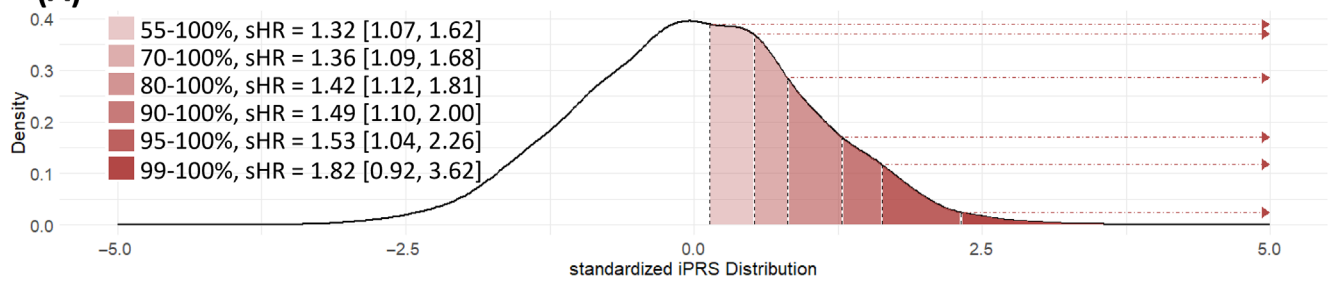
Next, we explored the risk stratification ability of iPRS-DEM alongside *APOE* ε4. Across *APOE* ε4 carriers and non-carriers there were similar sHRs of iPRS-DEM per 1 SD increase with dementia risk in 3C-Dijon ($sHR_{APOE\,\varepsilon4-}$ = 1.130, 95% CI: 0.99 to 1.28; $sHR_{APOE\,\varepsilon4+}$ = 1.194, 95% CI: 0.98 to 1.46; interaction p = .648). We then stratified individuals into four genetic risk groups by *APOE* ε4 carrier status and iPRS-DEM+/iPRS-DEM−. The optimal cutoff to dichotomize iPRS-DEM was at the 56th percentile in *APOE* ε4+ (sHR = 1.71, 95% CI: 1.11 to 2.62) and at the 94th percentile in *APOE* ε4− (sHR = 1.95, 95% CI: 1.33 to 2.86). In non-parametric estimation of cumulative incidence, iPRS-DEM+ had a significantly higher cumulative incidence of dementia than iPRS-DEM−, in both *APOE* ε4 carriers and non-carriers by age 85 (eTable 10a-c). Overall, cumulative incidence increased with age and greater burden of genetic risk; by age 90 cumulative incidence estimates reached 20.8% (18.0% to 23.6), 24.18% (15.8% to 32.6%), 37.3% (25.6% to 48.7%), and 40.1% (30.7% to 49.4%) in *APOE* ε4-/iPRS-DEM-, *APOE* ε4+/iPRS-DEM-, *APOE* ε4+/iPRS-DEM+, and *APOE* ε4+/iPRS-DEM+, respectively (Figure 2B1, eTable 10a-b). In FGR models, compared to *APOE* ε4-/iPRS-DEM-, both *APOE* ε4+/iPRS-DEM+

TABLE 1 Baseline characteristics of 3C-Bordeaux-Montpellier, 3C-Dijon, and Memento.

Baseline variables	3C BM (*N* = 2039)	3C Dijon (*N* = 3702)	Memento (*N* = 2032)
Follow-up time (years) Median [IQR]	9.77 [5.66 to 11.6]	8.36 [3.96 to 10.7]	5.00 [3.03 to 5.09]
Status at end of follow-up			
Censored	1427 (70.0%)	2910 (78.6%)	1700 (83.7%)
Demented	301 (14.8%)	361 (9.8%)	284 (14.0%)
Deceased (w/o dementia)	311 (15.3%)	431 (11.6%)	48 (2.4%)
Age at baseline assessment			
Mean (SD)	73.9 (5.09)	74.2 (5.50)	70.9 (8.62)
Median [min, max]	73.3 [65.0 to 92.2]	73.4 [65.0 to 94.6]	71.7 [32.5 to 92.7]
Sex			
Male	816 (40.0%)	1414 (38.2%)	782 (38.5%)
Female	1223 (60.0%)	2288 (61.8%)	1250 (61.5%)
APOE genotype			
ε2/ε2	9 (0.4%)	24 (0.6%)	9 (0.4%)
ε2/ε3	249 (12.2%)	444 (12.0%)	200 (9.8%)
ε2/ε4	21 (1.0%)	70 (1.9%)	39 (1.9%)
ε3/ε3	1383 (67.8%)	2460 (66.5%)	1218 (59.9%)
ε3/ε4	364 (17.9%)	664 (17.9%)	495 (24.4%)
ε4/ε4	13 (0.6%)	40 (1.1%)	71 (3.5%)
Low education (primary education only or no formal)	643 (31.5%)	761 (20.6%)	242 (11.9%)
Missing	5 (0.2%)	1 (0.0%)	0
Hypertension	1559 (76.5%)	2946 (79.6%)	1221 (60.1%)
Missing	0	0	39 (1.9%)
Smoking status			
Never smoker	1921 (94.2%)	3513 (94.9%)	1892 (93.1%)
Current smoker	117 (5.7%)	188 (5.1%)	139 (6.8%)
Missing	1 (0.0%)	1 (0.0%)	1 (0.0%)
Obesity (> 30 kg/m^2)	296 (14.5%)	497 (13.4%)	265 (13.0%)
Missing	23 (1.1%)	9 (0.2%)	36 (1.8%)
Diabetes	209 (10.3%)	332 (9.0%)	177 (8.7%)
Missing	11 (0.5%)	9 (0.2%)	8 (0.4%)
History of CVD	201 (9.9%)	342 (9.2%)	380 (18.7%)
Missing	0 (0%)	2 (0.1%)	8 (0.4%)
Dyslipidemia	1140 (55.9%)	2174 (58.7%)	581 (28.6%)
Missing	2 (0.1%)	5 (0.1%)	0
Family history of dementia[a]	N/A	N/A	850 (41.8%)
Missing	N/A	N/A	11 (0.5%)

Note: Definitions of clinical risk factors differ slightly between cohorts, see eMethods 4 and 10 for details.
Abbreviations: 3C, Three-Cities study; BM, Bordeaux and Montpellier; CVD, cardiovascular disease; IQR, interquartile range.
[a]Family history of dementia was not ascertainable in 3C.

(A)



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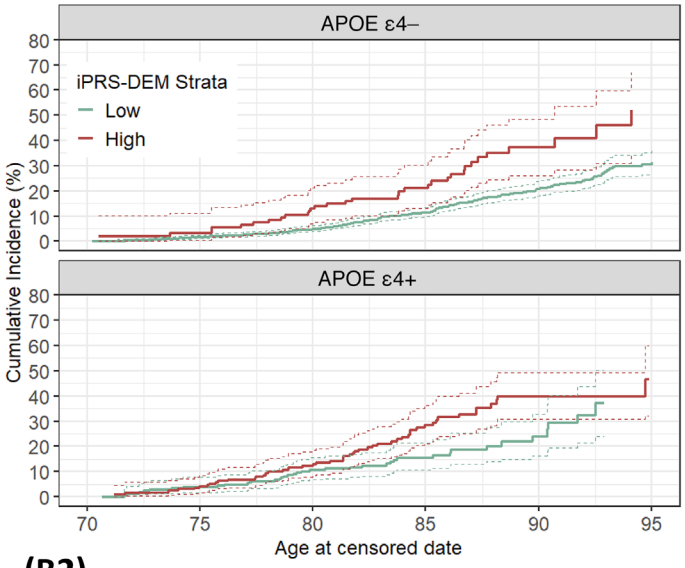


Genetic risk group	Age in years	Estimated cumulative incidence	Number at risk
APOE ε4– and Low PRS (< 93.8th percentile)	75	1.7% [0.9 to 2.4]	1359
	80	4.9% [3.8 to 6.1]	1247
	85	11.5% [9.7 to 13.3]	601
	90	20.8% [18 to 23.6]	199
APOE ε4– and High PRS (> 93.8th percentile)	75	3.5% [-1.4 to 8.4]	81
	80	13.2% [6 to 20.4]	89
	85	21.1% [12.4 to 29.7]	46
	90	37.3% [25.9 to 48.6]	13
APOE ε4+ and Low PRS (< 55.6th percentile)	75	4.1% [1.1 to 7]	211
	80	10.7% [6.3 to 15]	160
	85	15.5% [10.1 to 20.9]	74
	90	24.2% [15.8 to 32.6]	17
APOE ε4+ and High PRS (> 55.6th percentile)	75	4.3% [0.9 to 7.6]	165
	80	12.4% [7.4 to 17.4]	135
	85	28.5% [21 to 36.1]	53
	90	40.1% [30.7 to 49.4]	10

(B2)

Genetic risk strata	*N*	No. cases	sHR (95% CI)	*P*
APOE ε4– and Low iPRS-DEM	2741	234	Reference	Reference
APOE ε4– and High iPRS-DEM	187	33	1.972 [1.361 to 2.858]	0.00033
APOE ε4+ and Low iPRS-DEM	388	38	1.29 [0.909 to 1.832]	0.15
APOE ε4+ and High iPRS-DEM	316	52	2.233 [1.644 to 3.032]	2.7E-07

(C)

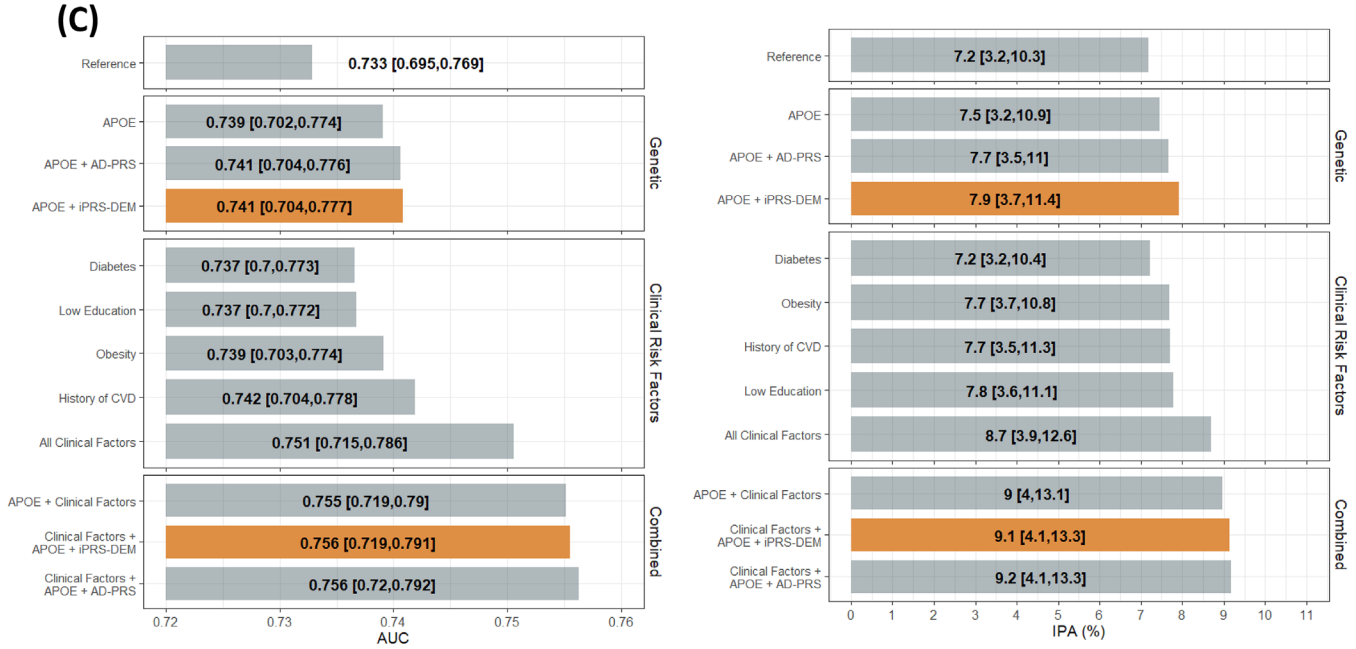


TABLE 2 Per ancestry baseline characteristics of All of Us.

Baseline variables	EAS (*N* = 5640)	AFR (*N* = 55,498)	HIS (*N* = 44,266)	EUR (*N* = 130,797)
Follow-up time (years)*				
Median [IQR]	3.05 (2.04 to 4.05)	3.05 (3.05 to 3.05)	3.05 (2.04 to 3.05)	3.05 (2.04 to 4.05)
Status at end of follow-up				
Censored	5595 (99.2%)	54,760 (98.7%)	43,828 (99.0%)	128,337 (98.1%)
Demented	17 (0.3%)	282 (0.5%)	228 (0.5%)	1274 (1.0%)
Deceased (w/o dementia)	28 (0.5%)	456 (0.8%)	210 (0.5%)	1186 (0.9%)
Age at baseline				
Mean (SD)	44 (17)	49 (15)	45 (16)	56 (17)
Median [IQR]	42 (29 to 58)	52 (38 to 60)	44 (31 to 57)	59 (42 to 69)
Sex				
Male	2050 (36.3%)	23,521 (42.4%)	14,705 (33.2%)	52,559 (40.2)
Female	3590 (63.7%)	31,977 (57.6%)	29,561 (66.8%)	78,238 (59.8%)
APOE Genotype				
ε2/ε2	41 (0.7%)	66 (1.2%)	94 (0.2%)	840 (0.6%)
ε2/ε3	760 (13.5%)	7969 (14.4%)	3161 (7.1%)	16,092 (12.3%)
ε2/ε4	100 (1.8%)	2492 (4.5%)	479 (1.1%)	2791 (2.1%)
ε3/ε3	3827 (67.9%)	25,638 (46.2%)	31,082 (70.2%)	80,765 (61.7%)
ε3/ε4	859 (15.2%)	16,251 (29.2%)	8799 (19.9%)	27,855 (21.4%)
ε4/ε4	53 (0.9%)	2484 (4.5%)	651 (1.5%)	2454 (1.9%)

Abbreviations: AFR, African; EAS, East Asian; EUR, European; HIS, Hispanic.
*Follow-up time is only given on a per-year basis, and not coded as a continuous variable.

and *APOE* ε4−/iPRS-DEM+ conveyed substantially higher dementia risk ($sHR_{APOE\ \varepsilon4+/IPRS\text{-}DEM+}$ = 2.23, 95% CI: 1.64 to 3.03; $sHR_{APOE\ \varepsilon4-/IPRS\text{-}DEM+}$ = 1.97, 95% CI: 1.36 to 2.86]), while the *APOE* ε4+/iPRS-DEM− group was not significantly associated with dementia risk (HR = 1.29, 95% CI: 0.91 to 1.83, Figure 2B2).

3.4 | Predictive performance of iPRS-DEM in 3C-Dijon

At the 10-year follow-up, there was no discernible difference in the prediction of dementia between iPRS-DEM and AD-PRS, both of which performed less well than a model with all clinical factors associated with increased dementia risk in 3C-Dijon (Figure 2C). Combining all clinical risk factors, *APOE ε4* and *ε2* dosage, and iPRS-DEM slightly improved prediction (AUC = 0.756, 95% CI: 0.72 to 0.792; IPA = +9.2% [4.1% to 13.3%]) over a model comprising clinical factors only (AUC = 0.751, 95% CI: 0.715 to 0.786; IPA = +8.7% [3.9 to 12.6%]).

3.5 | External validation of iPRS-DEM in Memento

The iPRS-DEM in Memento included 1,270,010 of 1,320,229 SNPs (96.2%). A 1-SD increase in iPRS-DEM was associated with dementia risk independently of *APOE* ε4 and ε2 dosage (sHR_{per1SD} = 1.25, 95% CI: 1.11 to 1.42; p = .0003, eTable 11). Adjusting for family history of dementia and education, the two clinical risk factors associated with increased all-cause dementia risk in Memento, resulting in negligible

FIGURE 2 Validation of iPRS-DEM in 3C-Dijon. (A) Association of iPRS-DEM with cumulative incidence of dementia across percentile groups. Subdistribution hazard ratios for dementia are per percentile cutoffs relative to the rest of the sample as derived from Fine-Gray regression models. (B) Comparison of genetic risk strata defined by *APOE* ε4 status and iPRS-DEM. (B1) Estimated cumulative incidence curves at ages 75 to 95 years across genetic risk strata. (B2) Association across *APOE* ε4 and iPRS-DEM defined genetic risk strata with cumulative incidence of dementia. All models in each analysis were adjusted for age at baseline (including age-squared), sex, and 10 principal components, as well as *APOE* ε2 and *APOE* ε4 dosage (except for *APOE* ε4 stratified analysis). AD-PRS, Alzheimer's disease polygenic risk score; *APOE*4-, *APOE* ε4 non-carriers; *APOE*4+, *APOE* ε4 carriers; AUC, area under the curve; CVD, cardiovascular disease; IPA, index of prediction accuracy; iPRS, integrative polygenic risk score; sHR, subdistribution hazard ratio. (C) Comparison of prediction performance at 10 years of iPRS-DEM against *APOE*, AD-PRS, and clinical risk factors* based on time-dependent AUC and index of prediction accuracy over 2000 bootstrap replications (*only risk factors showing significant association with increased cumulative incidence of all-cause dementia in 3C-Dijon are used here).

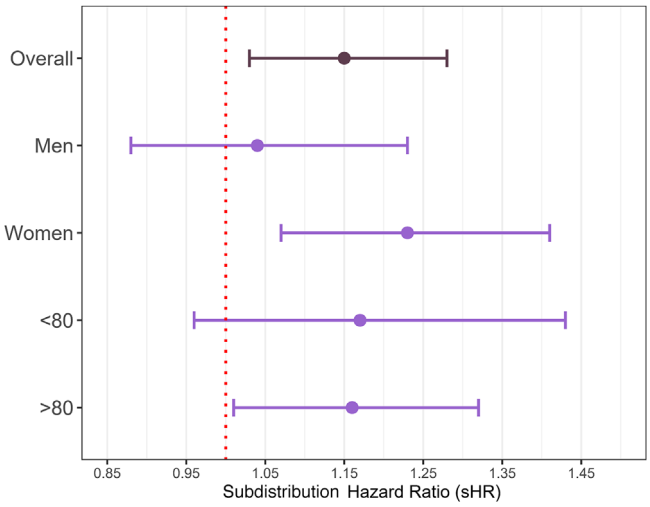


FIGURE 3 iPRS-DEM association with cumulative incidence of dementia in 3C-Dijon, including age and sex subgroups. Error bars represent 95% confidence intervals. All Fine-Gray models are adjusted for age at baseline, sex, 10 genetic principal components, and *APOE* ε2 and *APOE* ε4 dosage. <80 refers to analysis censoring at 80 years old, >80 refers to analysis excluding data before age 80; see eMethods 6 for details.

changes in estimates for the association of iPRS-DEM with dementia risk (4.4%, eTables 12 and 13). Individuals in the highest quintile of iPRS-DEM showed a significant increase in dementia risk relative to the middle 20% (sHR = 1.58, 95% CI: 1.10 to 2.27; $p = .01$). Further, iPRS-DEM showed non-linearly increasing association with dementia risk across higher percentile thresholds, reaching sHRs of 1.79 (95% CI: 1.04 to 2.26), 1.24 (95% CI: 0.74 to 2.09), and 2.28 (95% CI: 0.82 to 6.33) in the top 30%, 5%, and 1% compared to the rest of the sample (Figure 4A). Similar to 3C-Dijon, sex-stratified analyses revealed a non-significant trend toward a stronger association of iPRS-DEM with dementia risk in women than in men (iPRS per 1SD $sHR_{Women} = 1.30$, 95% CI: 1.10 to 1.54; $sHR_{Men} = 1.17$, 95% CI: 0.97 to 1.40; interaction $p = .37$) (Figure 5, eTable 14). Unlike 3C-Dijon, iPRS-DEM showed an association with earlier-onset dementia cases (<80 years) but not in later onset (≥80 years) ($sHR_{<80years} = 1.30$, 95% CI: 1.11 to 1.52; $sHR_{\geq 80years} = 1.13$, 95% CI: 0.92 to 1.38), although, again, confidence intervals overlap (Figure 5, eTable 14).

As in 3C-Dijon, the association of iPRS-DEM per 1 SD increase with dementia risk did not differ significantly between *APOE* ε4 carriers and non-carriers ($sHR_{APOE\,\varepsilon4+} = 1.33$, 95% CI: 1.12 to 1.58; $sHR_{APOE\,\varepsilon4-} = 1.15$, 95% CI: 0.96 to 1.37; $p_{interaction} = .25$). For risk stratification by *APOE* ε4 carrier status and iPRS-DEM+/iPRS-DEM−, the optimal cutoff for iPRS-DEM was at the 69.9th percentile in *APOE* ε4+ ($sHR_{iPRS\text{-}DEM+} = 2.16$, 95% CI: 1.54 to 3.02) and at the 74.1th percentile in *APOE* ε4− ($sHR_{iPRS\text{-}DEM+} = 1.49$, 95% CI: 1.02 to 2.18). Notably, iPRS-DEM+ had a significantly higher cumulative incidence of dementia than iPRS-DEM− by the 3-year follow-up in *APOE* ε4 carriers and by the 4-year follow-up in non-carriers (eTable 15a-c). Estimated cumulative incidence of dementia in each genetic risk strata at the 5-year follow up was 9.8% (7.9% to 11.7%), 13.8% (9.7% to 17.8%), 22.1% (17.8% to 26.4%), and 41.3% (32.9% to 49.8%), in *APOE* ε4-/iPRS-DEM−, *APOE* ε4−/iPRS-DEM+, *APOE* ε4+/iPRS-DEM+, and *APOE* ε4+/iPRS-DEM+, respectively (Figure 4B1). Compared to the *APOE* ε4−/iPRS-DEM− reference group, all genetic risk groups conveyed a significant increase in dementia risk ($sHR_{APOE\,\varepsilon4-/iPRS\text{-}DEM+} = 1.49$, 95% CI: 1.03 to 2.15; $sHR_{APOE\,\varepsilon4+/iPRS\text{-}DEM-} = 2.62$, 95% CI: 1.93 to 3.54; $HR_{APOE\,\varepsilon4+/iPRS\text{-}DEM+} = 5.72$, 95% CI: 4.15 to 7.87, Figure 4B2).

At the 5-year follow-up, iPRS-DEM modestly improved prediction (AUC = 0.758, 95% CI: 0.715 to 0.800; IPA = +10.1% [3.6% to 15.6%]) beyond *APOE* ε4 and ε2 dosage (AUC = 0.751, 95% CI: 0.707 to 0.793; IPA = +9.1% [2.6% to 14.4%]) (Figure 4C). Overall, genetic risk (*APOE* with and without iPRS-DEM) improved dementia prediction above the reference model (age, sex, 10PCs) (AUC = 0.682, 95% CI: 0.636 to 0.727) substantially more than known risk factors, education level and family history, in this setting (AUC = 0.686, 95% CI: 0.641 to 0.731) (Figure 4C).

TABLE 3 Association of iPRS and with dementia within ancestry sub-groups in All of Us.

Ancestry	sHR (95% CI)	*p*
Europeans	1.28 (1.09 to 1.51)	.003
East Asians	5.29 (1.43 to 34.36)	.016
African Americans	1.06 (0.75 to 1.45)	.79
Hispanics	1.09 (0.78 to 1.68)	.48

Fine-Gray models are adjusted for baseline covariates (age, sex, five genetic principal components) and *APOE* dosage.

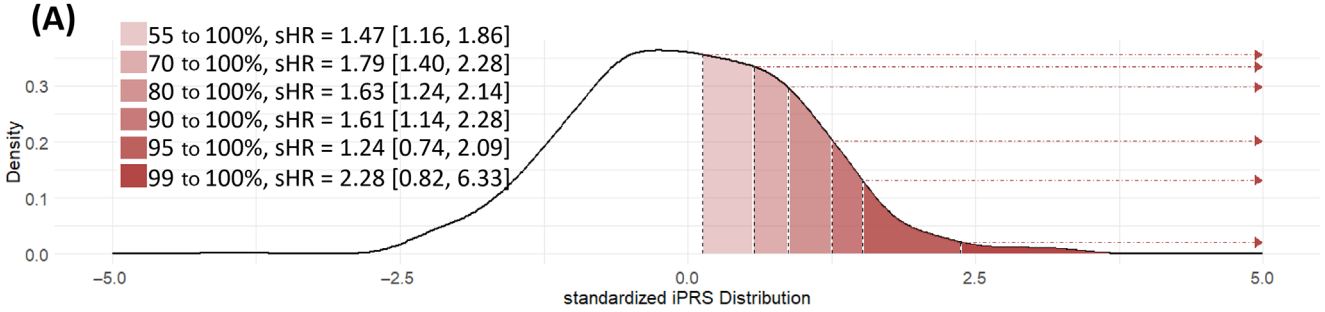
3.6 | Transportability of iPRS-DEM across ancestries in AoU

The iPRS-DEM in AoU included 1,318,697 of 1,320,229 SNPs (99.9%). 1 SD increase in iPRS-DEM was associated with dementia risk independently of *APOE* ε4 and ε2 dosage in both EUR ($sHR_{per1SD} = 1.28$, [1.09 to 1.51]; $p = .003$) and EAS participants ($sHR_{per1SD} = 5.29$, 95% CI: 1.43 to 34.36; $p = .016$), but not in AFR or HIS, although the direction of effect (+) was consistent (Table 3, Cox model sensitivity in eTable 16).

4 | DISCUSSION

We developed a novel integrative PRS for all-cause dementia encompassing genetic risk for multiple traits, in addition to AD, reflecting the neurodegenerative and vascular contribution to dementia risk. We trained iPRS-DEM in an elderly longitudinal population-based cohort and validated it in older community-dwelling people, across ancestries in a large-scale population-based cohort, and in dementia-free memory clinic patients, while accounting for competing risk of death. In older community-dwelling people, iPRS-DEM was associated with dementia risk independently of *APOE* and only modestly attenuated by clinical risk factors, while a single-trait AD-PRS was non-significant. Though improvement in overall prediction was limited, we demonstrated the

(A)



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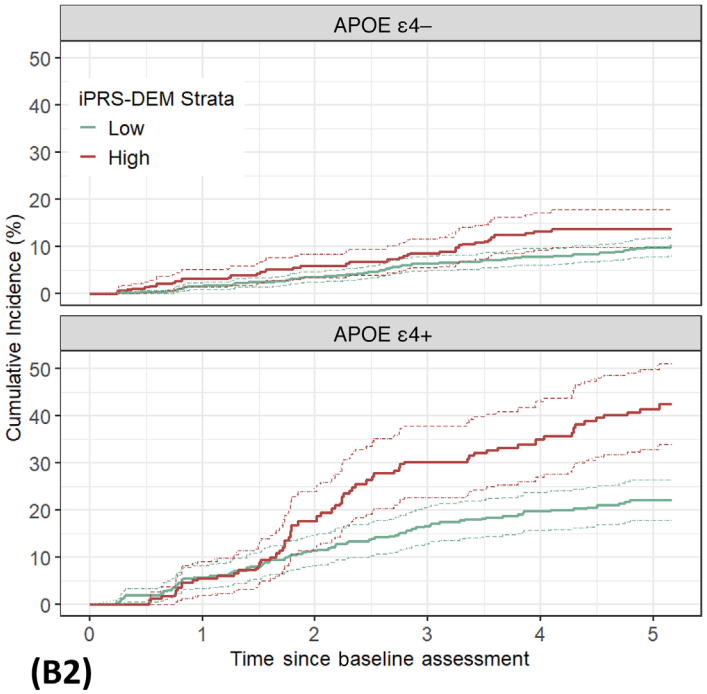
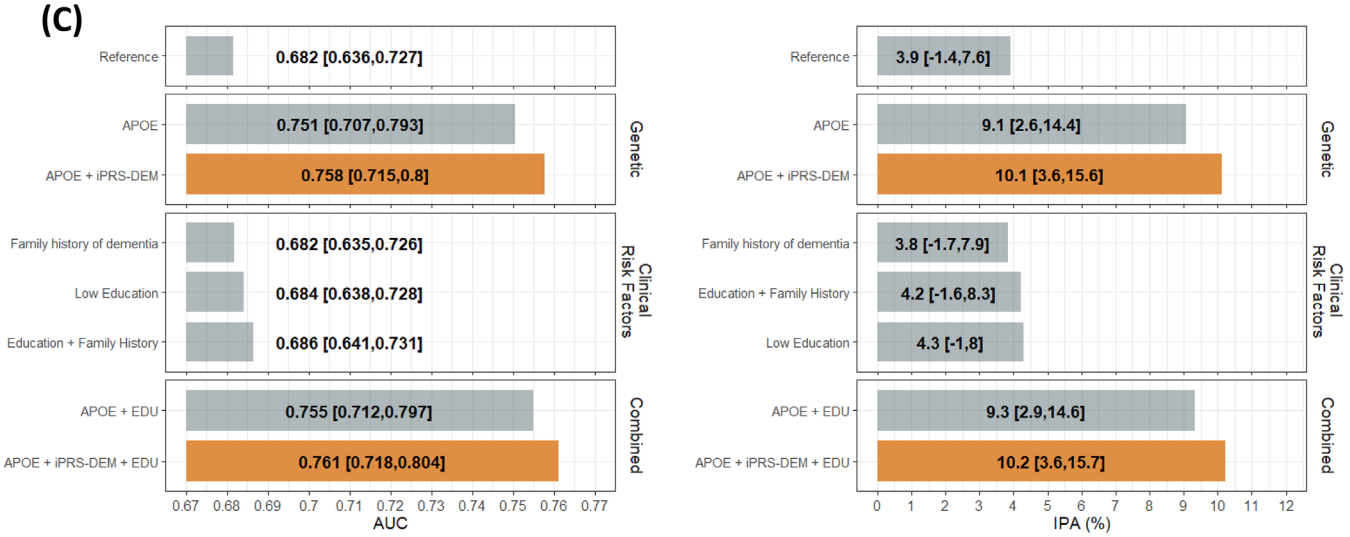


Genetic risk group	Years since baseline	Estimated cumulative incidence	Number at risk
APOE ε4– and Low iPRS-DEM (<74.1th percentile)	1	1.6% [0.8 to 2.4]	1007
	2	3.6% [2.4 to 4.7]	931
	3	6.4% [4.8 to 7.9]	843
	4	7.8% [6.1 to 9.5]	785
	5	9.8% [7.8 to 11.7]	675
APOE ε4– and High iPRS-DEM (>74.1th percentile)	1	3.3% [1.4 to 5.1]	335
	2	5.8% [3.3 to 8.4]	300
	3	8.5% [5.4 to 11.6]	273
	4	13.1% [9.2 to 17]	240
	5	13.8% [9.7 to 17.8]	204
APOE ε4+ and Low iPRS-DEM (<69.9th percentile)	1	5.7% [3.2 to 8.1]	357
	2	11.3% [8.1 to 14.6]	317
	3	16.6% [12.8 to 20.4]	284
	4	19.7% [15.6 to 23.8]	248
	5	22.1% [17.8 to 26.4]	215
APOE ε4+ and High iPRS-DEM (>69.9th percentile)	1	5.5% [1.9 to 9.1]	158
	2	17.5% [11.3 to 23.8]	134
	3	30.1% [22.5 to 37.7]	105
	4	35% [27 to 43]	96
	5	41.3% [32.9 to 49.7]	72

(B2)

Genetic risk strata	*N*	No. cases	sHR (95% CI)	*P*
APOE ε4– and Low iPRS-DEM	1060	91	Reference	Reference
APOE ε4– and High iPRS-DEM	367	45	1.488 [1.028 to 2.154]	0.035
APOE ε4+ and Low iPRS-DEM	393	81	2.616 [1.933 to 3.54]	4.7E-10
APOE ε4+ and High iPRS-DEM	173	64	5.717 [4.151 to 7.874]	1.3E-26

(C)



importance of iPRS-DEM to stratify dementia risk in combination with *APOE* ε4 status. Having a high iPRS-DEM, regardless of *APOE* ε4 status (*APOE* ε4+/iPRS-DEM+ or *APOE* ε4−/iPRS-DEM+) was associated with an approximate two-fold increased risk of dementia compared with *APOE* ε4−/iPRS-DEM−, while *APOE* ε4+/iPRS-DEM− did not convey significantly greater dementia risk. We further validated iPRS-DEM in the memory-clinic setting, showing significant association with dementia risk independent of *APOE* and clinical risk factors and also improving risk prediction and stratification. Particularly in the memory clinic, iPRS-DEM captured substantial genetic risk among *APOE* ε4 carriers, distinguishing cumulative incidence of dementia by the 3-year follow-up, while those with *APOE* ε4+/iPRS-DEM+ had a 5-year cumulative incidence of dementia of 40% and nearly six-fold increased dementia risk compared to the *APOE* ε4−/iPRS-DEM−. We also show strong validation of iPRS-DEM in European adults of all ages and diverse socioeconomic backgrounds. Importantly, we attempted to validate iPRS-DEM across diverse ancestry groups (EAS, AFR, and HIS) and demonstrated transportability to East Asians despite a small sample size. Our findings suggest a promising ability of iPRS-DEM to identify persons at highest genetic risk for dementia in both population and clinical settings.

Polygenic scores may inform dementia prevention strategies by identifying high-risk individuals for either clinical trials or future interventions in the general population.[9,54] However, previous AD-PRS did not explicitly account for the vascular contribution to dementia risk and showed inconsistent relation with all-cause dementia across *APOE* genotypes in population-based cohorts.[19,21,55,56] Our investigations reveal the utility of more comprehensive polygenic risk prediction encompassing genetically determined vascular risk over a single-trait AD-PRS, particularly for all-cause dementia risk stratification in combination with *APOE* ε4.

A recent iPRS for AD did not suggest any benefit over an AD-PRS.[27] However, integrative PRS are sensitive to selection of input traits, methodological choices in PRS derivation, training population, and phenotype definition. The published iPRS focused on AD risk, included a heterogeneous set of traits incompletely capturing vascular risk, and was trained and evaluated in AD case–control datasets that do not consider competing risk of death. In contrast, iPRS-DEM includes input traits specifically focused on neurodegenerative and vascular origins and was trained and evaluated using a longitudinal population-based cohort to predict the probability of all-cause dementia over time using Fine-Gray models to account for competing risk.

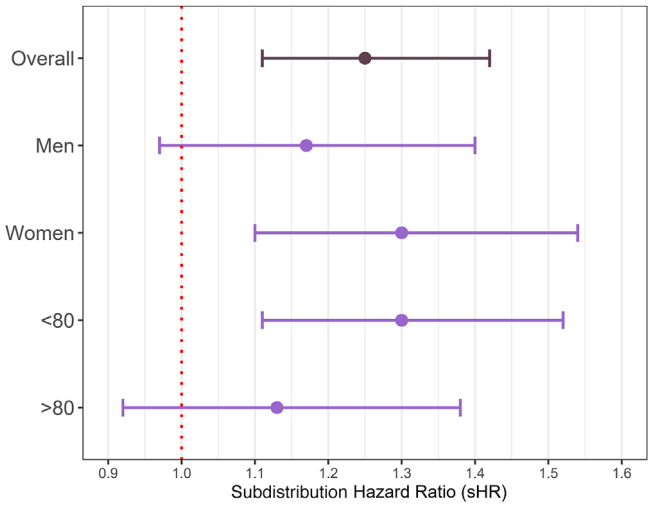


FIGURE 5 iPRS-DEM association with cumulative incidence of dementia in Memento including age and sex subgroups. Error bars represent 95% confidence intervals. All Fine-Gray models are adjusted for age at baseline, sex, 10 genetic principal components, and *APOE ε2* and *APOE ε4* dosage. <80 refers to analysis censoring at 80 years old, >80 refers to analysis excluding data before age 80, see eMethods 6 for details.

Moreover, the previous integrative AD-PRS[27] did not explore risk stratification in combination with *APOE* ε4 that highlighted potential utility of iPRS-DEM in our study.

The limited improvement in prediction performance for all-cause dementia above and beyond clinical factors in a population-based setting is comparable to PRS for other common age-related neurological conditions, like stroke,[24–26] but overall lags behind cardiovascular conditions such as CAD or atrial fibrillation.[11,57] This could be attributed, at least in part, to greater disease heterogeneity. However, iPRS-DEM could potentially still be informative for early preventive interventions at the population level as genetic risk is stable from birth, whereas clinically defined risk factors such as high blood pressure are often detected in mid to late life and may be subject to measurement variability.[58] Further, for population-level risk stratification, we showed the ability of iPRS-DEM to stratify dementia risk in both *APOE* ε4 carriers and non-carriers, with dementia risk in *APOE* ε4 non-carriers with extreme iPRS-DEM being nearly equivalent to that of *APOE* ε4 carriers with high iPRS-DEM.

FIGURE 4 External validation of iPRS-DEM in Memento. (A) Association of iPRS-DEM with cumulative incidence of dementia across percentile groups. Subdistribution hazard ratios for dementia are per percentile cutoffs relative to the rest of the sample as derived from Fine-Gray regression models. Models are adjusted for age at baseline, sex, and 10 principal components, as well as *APOE* ε4 and ε2dosage. (B) Comparison of genetic risk strata defined by *APOE* ε4 status and iPRS-DEM. (B1) Estimated cumulative incidence curves at up to 5-year follow-up across genetic risk strata. (B2) Association across *APOE* ε4 and iPRS-DEM defined genetic risk strata with cumulative incidence of dementia. All models in each analysis are adjusted for age at baseline, sex, and 10 principal components, as well as *APOE* ε2 and *APOE* ε4 dosage (except for *APOE* ε4 stratified analysis). AUC, area under the curve; *APOE*4−, *APOE* ε4 non-carriers; *APOE*4+, *APOE* ε4 carriers; EDU, low education; IPA, index of prediction accuracy; iPRS, integrative polygenic risk score; sHR, subdistribution hazard ratio. (C) Comparison of prediction performance at 5 years of iPRS-DEM against *APOE*, AD-PRS, and clinical risk factors* based on time-dependent area under the curve and index of prediction accuracy over 2000 bootstrap replications (*only risk factors showing significant association with increased cumulative incidence of all-cause dementia in Memento are used here).

Originally, we extended iPRS-DEM to the memory-clinic setting, exploring its potential to inform dementia risk assessment in persons with MCI or subjective cognitive complaints.[13] Studies investigating PRS in a memory clinic setting are scarce, with one study showing that low single-trait AD-PRS mitigated AD risk in *APOE* ε4 carriers, although it was not associated with all-cause dementia.[59] We provide initial evidence that iPRS-DEM, despite being trained in a population-based setting, is associated with and improves prediction of all-cause dementia in a memory-clinic population. Notably, high iPRS-DEM was associated with dementia risk in both *APOE* ε4 strata and was particularly strong among *APOE* ε4 carriers, distinguishing risk by the 3-year follow-up. Taken together, *APOE* ε4 carriers with high iPRS-DEM approximated a nearly six-fold increased dementia risk compared to *APOE* ε4 non-carriers with "low" iPRS-DEM representing the majority of the population. These results support the idea that iPRS-DEM alongside *APOE* could be a powerful tool to identify memory-clinic patients for targeted preventive interventions or enrollment in clinical trials.

There is mounting, cross-domain evidence for sex differences in AD pathogenesis,[60] which likely extends to polygenic risk.[61] Here, we found in both 3C-Dijon and Memento that iPRS-DEM was associated with dementia risk more strongly (and, significantly, in part due to larger sample size) in women than in men, which is congruent with a recent study investigating AD-PRS in a population-based German cohort (ESTHER).[21] Incidence of AD is known to be higher in women among older adults likely due to greater longevity in women and men having healthier cardiovascular risk profiles at older ages.[62] Given both 3C and Memento have a higher proportion of women (~60%) and comprise largely older individuals, PRS for vascular traits included in iPRS-DEM may, to some extent, capture genetic risk predominantly expressed in women. These findings highlight the need for sex-stratified GWAS of dementia (as well as other relevant traits included in the iPRS) and that future PRS for dementia should consider training models separately in women and men.

Lastly, iPRS-DEM association with dementia risk strongly replicated in European ancestry participants of AoU, importantly spanning a wide age range and with substantial geographical and socioeconomic diversity. We also leveraged the unique genetic diversity in AoU to assess the transportability of iPRS-DEM to non-Europeans, demonstrating a significant association with dementia risk in East Asians. These results did not translate to African American or Hispanic ancestry, although the directionality of effect was consistent. We suggest that different translatability of iPRS-DEM in EAS compared to AFR or HIS ancestry could be driven by increased genetic diversity in AFR[63] and admixture effects in HIS.[64] A recent study in AoU proposed a framework to develop translatable PRS for non-Europeans across multiple conditions, although AD/dementia was not investigated.[65] Further, recent developments in PRS methods that leverage cross-ancestry reference panels (PRSCS-X) and admixture mapping (GAUDI) propose to enhance PRS transportability.[64] Most importantly, our results highlight the crucial need to increase diversity in GWAS used to generate PRS,[26,66] especially for neurodegenerative traits and MRI-based endophenotypes.

We acknowledge the limitations of this study. For certain traits, such as MRI markers of cSVD and other biomarkers, their contribution to iPRS-DEM was likely limited by underpowered GWAS. Of note, 3C was restricted to participants >65 years, stipulating that those at highest risk (ie, high genetic burden) of developing earlier-onset dementia are less likely to be selected for the study. Indeed, *APOE* ε4 homozygosity has been shown to represent a distinct genetic form of AD, with an average age of symptom onset of 65.1 years.[67] Retraining in cohorts spanning wider age ranges would help address this selection issue. Further, we cannot rule out possible bias introduced by interval censoring or selective survival common to dementia studies such as 3C or Memento.[68] We did not investigate the association of iPRS-DEM with dementia subtypes due to limited sample size. Comparison of iPRS-DEM with more comprehensive risk factors for dementia and standard neuropsychological assessment should be considered in future work on larger samples.[7] Ultimately, translation into clinical practice may be optimized by the integration of iPRS-DEM with both clinical variables and other biomarkers, especially novel plasma AD biomarkers,[69] into risk prediction models based on global, multimodal biomarker measurements. Promisingly, CAD PRS have shown benefit alongside clinical risk prediction models to inform statin use in primary prevention.[70]

By accounting for the vascular contribution to dementia risk, iPRS-DEM may provide useful guidance for trial enrichment designs that are more representative of global dementia risk. Our results suggest that in combination with *APOE* ε4, it could offer substantial predictive enrichment by identifying participants at high likelihood of developing dementia.[71] Whether iPRS-DEM could inform prognostic enrichment as well remains unclear. It will also be interesting to examine whether iPRS-DEM can help identify individuals especially predisposed to vascular brain disease who are at high risk of developing amyloid-related imaging abnormalities from amyloid immunotherapy, currently considered for AD prevention in asymptomatic persons with high amyloid burden.[72]

Overall, we provide evidence that an iPRS-DEM incorporating both neurodegenerative and vascular contributions to dementia is a powerful genetic risk stratification tool in addition to *APOE* ε4 that could be applied in both population-based and memory-clinic settings for dementia precision prevention. Future studies refining and validating iPRS-DEM in additional, especially non-European, populations are warranted.

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CONFLICT OF INTEREST STATEMENT

The authors of this manuscript have no competing interests to declare. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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