Received: 28 October 2024 | Revised: 14 January 2025 | Accepted: 17 January 2025

DOI: 10.1002/alz.14601

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

A deep-learning retinal aging biomarker for cognitive decline and incident dementia

Ming Ann Sim[1,2] | Yih Chung Tham[3,4,5] | Simon Nusinovici[4] | Ten Cheer Quek[4] | Marco Yu[4] | Can Can Xue[4] | Miao Li Chee[4] | Qing Sheng Peng[3] | Eugene S. J. Tan[6] | Siew Pang Chan[6] | Yuan Cai[7] | Eddie Jun Yi Chong[1] | Boon Yeow Tan[8] | Narayanaswamy Venketasubramanian[9] | Saima Hilal[10] | Mitchell K. P. Lai[1] | Hyungwon Choi[11] | Arthur Mark Richards[11,12] | Ching-Yu Cheng[3,4,5] | Christopher L. H. Chen[1]

[1]Memory Aging and Cognition Centre, Departments of Pharmacology and Psychological Medicine, National University of Singapore, Singapore, Singapore

[2]Department of Anesthesia, National University Health System and National University of Singapore, Yong Loo Lin School of Medicine, Singapore, Singapore

[3]Centre for Innovation and Precision Eye Health, and Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[4]Ocular Epidemiology Research Group, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore, Singapore

[5]Ophthalmology and Visual Science Academic Clinical Program, Duke-NUS Medical School, Singapore, Singapore

[6]National University Heart Centre, National University Hospital, Singapore, Singapore

[7]Division of Neurology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Ma Liu Shui, Hong Kong

[8]St Luke's Hospital, Singapore, Singapore

[9]Raffles Neuroscience Centre, Raffles Hospital, Singapore, Singapore

[10]Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

[11]Cardiovascular Metabolic Disease Translational Research Program, National University of Singapore, Singapore, Singapore

[12]Christchurch Heart Institute, University of Otago, Dunedin North, Dunedin, New Zealand

Correspondence
Christopher Li-Hsian Chen, 5 Lower Kent Ridge Road S119074, Singapore.
Email: phccclh@nus.edu.sg

Ming Ann Sim, 5 Lower Kent Ridge Road S119074, Singapore.
Email: ming_ann_sim@nuhs.edu.sg

Yih Chung Tham and Ching-Yu Cheng, Centre for Innovation and Precision Eye Health, and Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
Email: thamyc@nus.edu.sg; chingyu.cheng@nus.edu.sg

Abstract

INTRODUCTION: The utility of retinal photography-derived aging biomarkers for predicting cognitive decline remains under-explored.

METHODS: A memory-clinic cohort in Singapore was followed-up for 5 years. RetiPhenoAge, a retinal aging biomarker, was derived from retinal photographs using deep-learning. Using competing risk analysis, we determined the associations of RetiPhenoAge with cognitive decline and dementia, with the UK Biobank utilized as the replication cohort. The associations of RetiPhenoAge with MRI markers(cerebral small vessel disease [CSVD] and neurodegeneration) and its underlying plasma proteomic profile were evaluated.

Ming Ann Sim and Yih Chung Tham, contributed equally as co-first authors to this work.

Ching-Yu Cheng and Christopher L. H. Chen, contributed equally as co-senior authors to this work.

Funding information
National University Health System (NUHS) Clinician Scientist Academy, Grant/Award Number: NCSP2.0/2023/NUHS/SMA; CSDU Collaborative Grant by the National University of Singapore Yong Loo Lin School of Medicine, Grant/Award Number: KCG/2023/NUSMED; National Medical Research Council, Grant/Award Numbers: MOH-000707, CG21APR2010, NMRC/OFLCG/2019, MH095003/008-340, NMRCCSA-SI/007/2016, NMRC/CG/M006/2017, NMRC/CIRG/1485/2018

RESULTS: Of 510 memory-clinic subjects(N = 155 cognitive decline), RetiPhenoAge associated with incident cognitive decline (subdistribution hazard ratio [SHR] 1.34, 95% confidence interval [CI] 1.10–1.64, $p = 0.004$), and incident dementia (SHR 1.43, 95% CI 1.02–2.01, $p = 0.036$). In the UK Biobank ($N = 33\,495$), RetiPhenoAge similarly predicted incident dementia (SHR 1.25, 95% CI 1.09–1.41, $p = 0.008$). RetiPhenoAge significantly associated with CSVD, brain atrophy, and plasma proteomic signatures related to aging.

DISCUSSION: RetiPhenoAge may provide a non-invasive prognostic screening tool for cognitive decline and dementia.

KEYWORDS
biomarker, cognitive decline, deep-learning, dementia, prognostic, retinal age, retinal photography, Southeast-Asian

Highlights

- RetiPhenoAge, a retinal aging marker, was studied in an Asian memory clinic cohort.
- Older RetiPhenoAge predicted future cognitive decline and incident dementia.
- It also linked to neuropathological markers, and plasma proteomic profiles of aging.
- UK Biobank replication found that RetiPhenoAge predicted 12-year incident dementia.
- Future studies should validate RetiPhenoAge as a prognostic biomarker for dementia.

1 | BACKGROUND

Chronological age remains one of the greatest risk factors for dementia, which is associated with high socioeconomic costs, and reduction in health-span.[1] However, it has been increasingly evident that the trajectory of aging can vary among individuals with similar chronological age.[2,3] Indeed, it is recognized that biological age, an integrated construct reflecting the accumulation of age-related pathology, may provide greater value than chronological age in the prediction of accelerated aging processes and pathological disease phenotypes.[4] Therefore, biomarkers reflective of biological aging may be potential predictors of future cognitive decline.[5–7]

However, current modalities for the measurement of biological age such as epigenetic alterations, brain age, and telomere length are costly and require specialized analytical platforms.[6–8] In comparison, retinal photography is an attractive modality for the assessment of biological age, in view of its accessible, non-invasive nature, and lower cost.[9] The retina has additionally been hypothesized to be the "window" into the brain, considering its shared diencephalic origins, and homology of vasculature with the central nervous system.[10] Therefore, retinal photography may serve as an easily accessible platform to study neuropathological disorders within the central nervous system, shedding insight into accelerated aging processes related to neuropathological disease burden.[11,12]

Complementing the accessibility of retinal photography, the advent of deep-learning has allowed for the development of algorithms to extract known and unknown features from retinal images, which may facilitate increased accuracy in predicting multisystemic morbidity.[13–17] More recently, "RetiPhenoAge," an established non-invasive retinal aging biomarker trained on the ground truths of PhenoAGE (a validated aging marker, derived from a composite of phenotypic biomarkers including glucose, C-reactive protein, albumin, and chronological age), has been successfully applied for the improved prediction of morbidity and mortality.[18,19] However, the prognostic utility of RetiPhenoAge for cognitive decline and incident dementia remains unexplored.

In this study, we evaluated the prognostic utility of RetiPhenoAge for cognitive decline and conversion to dementia, within a Southeast-Asian memory clinic cohort, with replication in a majority Caucasian cohort. To study the neuropathological and biological underpinnings of older RetiPhenoAge, we investigated cross-sectional associations of RetiPhenoAge with neuroimaging measures of cerebral small vessel disease (CSVD) and brain atrophy, as well as plasma proteomic biomarkers. We hypothesized that RetiPhenoAge is associated with increased risk of future cognitive decline and incident dementia, likely related to its associations with CSVD, neurodegeneration, and biological processes of aging.

2 | METHODS

2.1 | Study population – Southeast-Asian memory clinic cohort

The Memory Aging and Cognition Center (MACC) Harmonisation cohort is a longitudinal memory clinic-based cohort of subjects recruited from two Singaporean study sites (St Luke's Hospital and National University Hospital Singapore). This longitudinal memory clinic cohort was followed for up to 5 years. Subjects had to be aged ≥50 years, with sufficient language skills to participate in neuropsychological assessments. Exclusion criterion included the presence of substance abuse disorder, major psychiatric illness, tumors, multiple sclerosis, epilepsy, and traumatic brain injury resulting in cognitive impairment. Informed consent was obtained from all subjects prior to recruitment. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (NHG DSRB reference numbers 2018/01098 and 2010/00017). An overview of the study is presented in Figure 1.

2.2 | Assessment of subject clinical demographics

Data regarding age, education, and gender were collected via detailed questionnaires administered in a standardized manner to all subjects. Clinical history including hypertension, diabetes, and hyperlipidaemia were recorded from subjects and verified from their medical records.

2.3 | Neurocognitive assessments

Neurocognitive diagnoses of all study subjects were discussed at regular consensus meetings attended by study clinicians and neuropsychologists.[20] Yearly cognitive assessments administered included the Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR) score, and a locally validated neuropsychological test battery, which was administered by trained research psychologists in the participants' native language (English, Mandarin, or Malay) as previously described.[20] Subjects without objective cognitive impairment were categorized as no cognitive impairment (NCI). Cognitive impairment no dementia (CIND) was determined by the presence of impairment in one or more cognitive domains (defined by a score of at least 1.5 standard deviations below established education-adjusted cutoff values on any test) without the loss of independent daily function.[20] The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition was utilized in the diagnosis of dementia at baseline.

CDR scores were also assigned to each patient at baseline, and at every subsequent follow-up visit so as to stage the severity of cognitive impairment and dementia.[21] The primary outcome was cognitive decline defined by a longitudinal increment in CDR Sum of Boxes (CDR-SB) score of ≥3 points at any annual follow-up assessment, compared with the baseline. The CDR-SB was utilized as a patient-important indicator of cognitive decline, due to its validation as a marker of longitudinal cognition and function, as well as being aligned with minimal clinically important differences.[21,22] The secondary outcome was the incidence of conversion from CIND to incident dementia, defined by a change in CDR Global score (CDR-GS) from < 1 to ≥ 1 at any annual follow-up.

RESEARCH IN CONTEXT

1. **Systematic review**: Non-invasive biomarkers derived from the integration of retinal photography with deep-learning, have been successfully applied for the prediction of morbidity, mortality and biological aging. However, the utility of deep-learning derived retinal aging biomarkers for predicting cognitive decline and incident dementia remains under-explored.
2. **Interpretation**: RetiPhenoAge, a retinal aging biomarker derived from retinal photographs using deep-learning, was applied to a Singaporean memory clinic cohort. We found that RetiPhenoAge predicted future cognitive decline and incident dementia over 5 years of follow-up. RetiPhenoAge also closely associated with neuroimaging markers of cerebral small vessel disease, brain atrophy as well as plasma proteomic signatures related to aging. Findings were replicated within the UK Biobank, demonstrating that RetiPhenoAge significantly predicted incident dementia over 12 years.
3. **Future directions**: Our study highlights the potential of integrating digital technology with retinal photography, providing a non-invasive biomarker for the prognostication of cognitive decline and dementia.

2.4 | Assessment of retinal aging (RetiPhenoAge) scores

The details of the development of RetiPhenoAge have been previously described.[19] In brief, RetiPhenoAge was previously developed using a VGG-16 deep learning regression model, on eligible subjects from the UK Biobank trained on the ground truths of PhenoAGE. A data-driven, hypothesis-free approach for the development of RetiPhenoAge was employed within retinal images, without the pre-specification of any recognizable retinal features. PhenoAGE was built with nine blood biomarkers plus chronological age, with more details presented in methods S1.

Within the MACC cohort, baseline retinal photography was performed at recruitment. Following standardized pupillary dilation, retinal photographs centered at the optic disc and macula were captured using a 45-degree digital retinal camera (Canon CR-DGi 10D or Canon CR-1-40D). The full methodology of retinal image acquisition has been described previously.[23,24] The validated RetiPhenoAge algorithm was

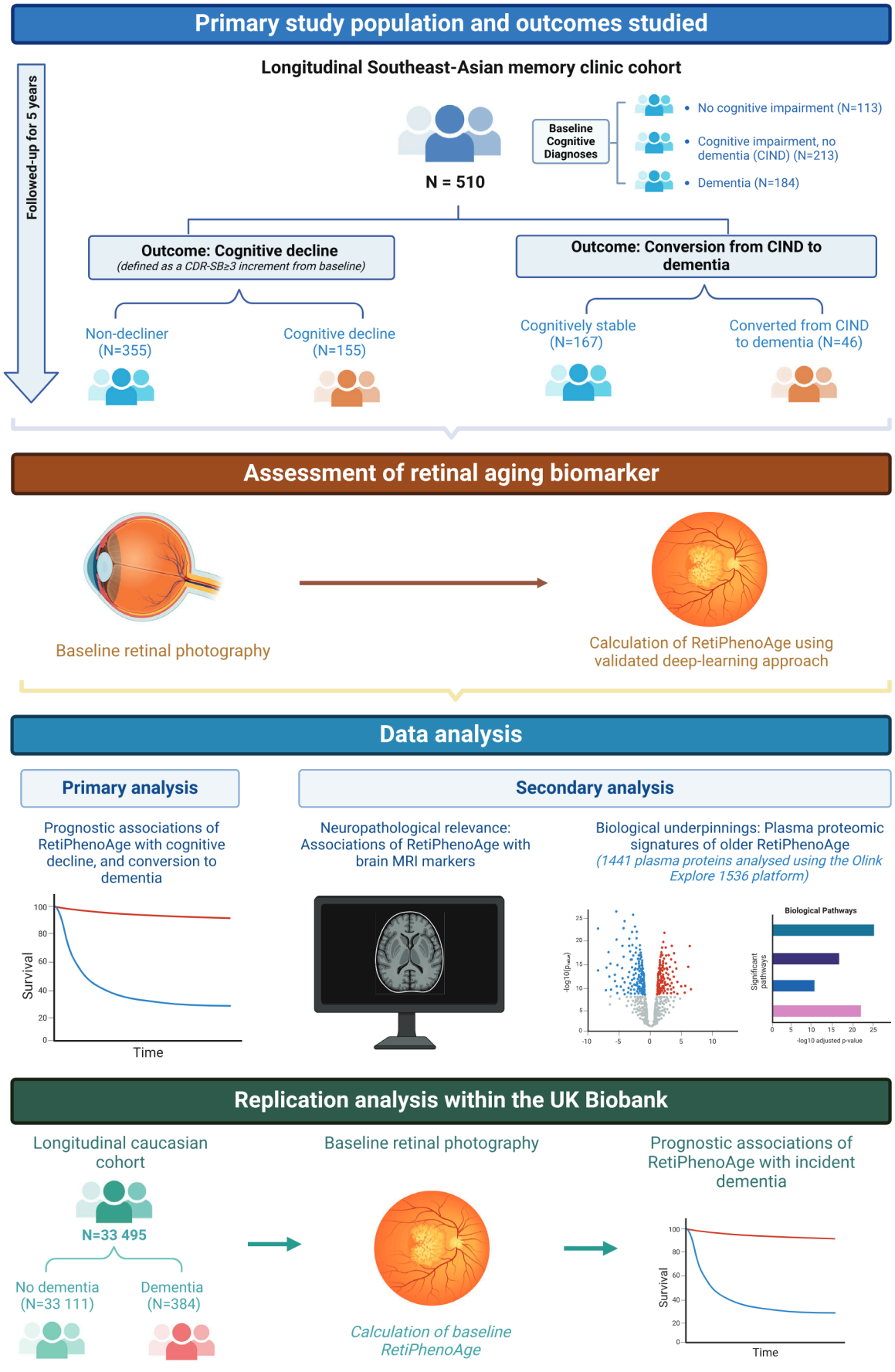

FIGURE 1 Overview of study design (created with biorender.com).

then applied to the MACC cohort retinal photographs, without fine tuning. RetiPhenoAge scores were then subject to *z*-score transformation. Saliency maps were generated to localize anatomy contributing to RetiPhenoAge (methods S1).

2.5 | Neuroimaging assessments

Brain magnetic resonance imaging (MRI) scans were performed using a 3T Siemens Magnetom Trio Tim Scanner comprising a 32-channel head receive coil. Neuroimaging protocols were standardized and included three-dimensional T1-weighted, T2-weighted fluid-attenuated inversion recovery and susceptibility-weighted images, as per our previously published approach.[20,25]

The AccuBrain (IV2.0) software was utilized for automated brain volumetric analysis, to obtain quantitative MRI markers of neurodegeneration (gray matter volume) and CSVD (white matter hyperintensity [WMH] volume). The AccuBrain platform has been previously validated and found to have comparable accuracy with commonly used volumetric analytical platforms including FreeSurfer.[26]

In addition, MRI structural markers of CSVD including lacunes, cortical infarcts and cerebral microbleeds were graded by an expert clinical researcher (S.H.), in accordance with the Standards for Reporting Vascular Changes on Neuroimaging criteria, as previously described (methods S2).[25,27]

2.6 | Profiling of plasma proteomic biomarkers

The Olink Explore 1536 platform (Thermo Fisher Scientific, Waltham, MA, USA) was employed for the profiling of plasma proteins within a subset of 358 subjects with paired RetiPhenoAge scores, and available plasma samples.

A total of 1441 proteins were used for analysis after stringent quality control of the data. Protein levels were then expressed as Normalized Protein eXpression (NPX) values, a relative quantification unit which relates logarithmically to protein concentration. Further details on the experimental protocol and proteins assayed are presented in the methods S3, and Table S1, respectively.

2.7 | Statistical analysis

Statistical analysis was performed using R version 4.3.2 (R Core Team. 2023. R Foundation for Statistical Computing, Vienna, Austria) and STATA (StataCorp. 2023. Release 18. College Station, TX: Statacorp LLC). All statistical tests were conducted at a significance level of 0.05 unless otherwise stated.

Patient characteristics were expressed as frequency and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Chi-squared test was used in the comparison of categorical data. The independent t-test was used for the comparison of continuous variables. RetiPhenoAge values were subject to *z*-score transformation prior to analysis, to express its effects as change per SD increase.

2.7.1 | Primary analysis

Competing risks regression was used to evaluate longitudinal associations of baseline RetiPhenoAge values with cognitive decline. Mortality before the onset of cognitive decline was defined as the competing event. Competing risks regression was employed due to the older age of our memory-clinic population, with 74 of 510 subjects developing mortality over up to 5 years of follow-up.[28] The first model (Model 1) was adjusted for chronological age, while the second model (Model 2) adjusted for chronological age, education, hypertension, hyperlipidemia, diabetes, gender, and baseline MoCA scores. To evaluate the associations of baseline RetiPhenoAge values with progression from CIND to dementia, competing risks regression was performed, adjusted first for chronological age (Model 1), and then for chronological age, gender, and education (Model 2). Sensitivity analysis was performed, additionally adjusting for hypertension, hyperlipidemia, and diabetes to evaluate the effect of RetiPhenoAge on conversion to dementia, independent of these clinical covariates (presented within the Model S3). Mortality before the onset of conversion to dementia was defined as the competing event. Results were presented as subdistribution hazards ratio (SHR) and accompanying 95% confidence intervals (CIs). Kaplan–Meier curves were constructed to visualize cognitive decline and progression from CIND to dementia, stratified by RetiPhenoAge expressed as quartiles. Log-rank *p*-values were calculated to compare survival distribution across RetiPhenoAge quartiles.

2.7.2 | Secondary analysis

Evaluation of associations of RetiPhenoAge with neuroimaging markers

Cross-sectional analysis of RetiPhenoAge with volumetric neuroimaging indices (WMH volume and gray matter volume) was performed with multivariable linear regression models adjusted for age and gender, normalized to intracranial volume. Multivariable Poisson regression was employed to study associations of RetiPhenoAge with the burden of cerebral microbleeds, cortical infarcts and lacunes by counts, adjusted for relevant covariates including age, gender, hypertension, hyperlipidaemia, diabetes. Results were presented as adjusted relative risk (RR) and accompanying 95% CIs.

Identification of plasma proteomic signatures underpinning RetiPhenoAge

To evaluate the biological underpinnings of RetiPhenoAge, exploratory analysis was conducted in a subset of 358 subjects with paired plasma proteomic data. Linear regression analysis was used to study cross-sectional associations of the circulating proteins with RetiPhenoAge scores (expressed as *z*-scores). To account for false discovery rate, correction for multiple testing was performed with a q-value threshold of < 0.05 considered to be statistically significant.[29] The top 20 most

significantly associative proteins for RetiPhenoAge were visualized using volcano plots.

Over-representation analyses among all significant (q-value < 0.05) proteins associated with RetiPhenoAge was performed and mapped to Reactome, Gene Ontology Biological Processes, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways using the DAVID bioinformatics resource.[30] The most significantly over-represented pathways within all proteins significantly associated with Retiphenoage were visualized as bar plots. Wherever applicable, *p*-values were further subjected to multiple testing correction using the Benjamini-Hochberg (BH) procedure.

2.8 | Replication within the UK Biobank cohort

Replication analysis within eligible subjects from the UK biobank cohort was conducted with a similar approach. Competing risks regression was used to evaluate longitudinal associations of baseline RetiPhenoAge with incident all-cause dementia. Mortality before the onset of incident dementia was defined as the competing event. The first model (Model 1) was adjusted for chronological age, while the fully adjusted model (Model 2) comprised adjustments for chronological age, education, hypertension, hyperlipidemia, diabetes, and gender. Subjects with dementia at baseline were excluded from the analysis. Results were presented as SHRs and their accompanying 95% CIs. Kaplan–Meier dementia survival curves were constructed for the association of RetiPhenoAge expressed as quartiles, and the survival distributions were compared using Log-rank test. Details of clinical and cognitive data acquisition within the UK biobank are presented in the Supplemental methods S4.

3 | RESULTS

3.1 | Subject characteristics: Southeast-Asian memory clinic cohort

The flowchart of subject recruitment is presented in Figure 2. Of the 622 subjects within the Southeast-Asian memory clinic cohort with available retinal photographs, 96 subjects failed quality control for retinal images. RetiPhenoAge scores were assessed for 526 subjects, of which 16 subjects did not have follow-up data. Of the 510 subjects with longitudinal follow-up (43.9% male, mean age 72.4 ± 7.8 years), 155 (30.4%) developed cognitive decline, while 355 (69.6%) remained cognitively stable over 3.9 ± 1.5 years of follow-up.

3.2 | Prognostic associations of RetiPhenoAge with cognitive decline and conversion to dementia

Subjects who developed cognitive decline were more likely to be of older age ($p < 0.001$), female gender ($p = 0.019$), lower education ($p < 0.001$), diabetic ($p = 0.011$), and had poorer MoCA scores ($p < 0.001$) at baseline (Table 1). Competing risks regression was used to evaluate the associations of baseline RetiPhenoAge *z*-scores with future cognitive decline. In the age-adjusted model (Model 1), subjects with higher RetiPhenoAge *z*-scores at baseline were more likely to develop cognitive decline (SHR 1.42, 95% CI 1.17–1.72, $p < 0.001$). Similar associations were observed after adjustment for age, education, gender, hypertension, hyperlipidemia, diabetes, and baseline cognition (Model 2). That is, higher RetiPhenoAge *z*-scores associated with greater hazard of cognitive decline (SHR 1.34, 95% CI 1.10–1.64, $p = 0.004$, Table 2). Kaplan–Meier curves of cognitive decline stratified by RetiPhenoAge quartiles are presented in Figure 3A. Significant separation between the quartiles was observed (log-rank $p < 0.001$).

Of 213 subjects with CIND, 46 (21.6%) converted to dementia, while 167 (78.4%) subjects did not. Subjects who converted to dementia were older ($p = 0.015$) (Table S2). Using competing risks regression, higher RetiPhenoAge *z*-scores were associated with significantly increased hazard of progression from CIND to dementia. This was observed on age-adjusted analysis (SHR 1.44, 95% CI 1.03–2.01, $p = 0.034$), and the fully adjusted analysis for age, gender, and years of education (SHR 1.43, 95% CI 1.02–2.01, $p = 0.036$, Table 3). Similar findings were observed on sensitivity analysis with additional model adjustment for hypertension, hyperlipidemia, and diabetes (SHR 1.43, 95% CI 1.02–2.02, $p = 0.038$, Model S3, Table S3). Significant separation between RetiPhenoAge quartiles was observed on Kaplan–Meier curves constructed for the progression from CIND to dementia (Figure 3B, log-rank p = 0.001).

3.3 | Replication analysis: Prognostic associations of RetiPhenoAge with incident dementia within the UK Biobank Cohort

A flowchart of subject inclusion within the replication cohort from the UK Biobank are presented in Figure 2. Of the final 33 495 subjects eligible for final analysis, 33 111 remained cognitively stable, while 384 (1.1%) developed incident dementia, over 11.9 ± 1.7 follow-up years. Subject demographics of eligible subjects from the UK Biobank cohort are presented in Table S4. Of 33 495 subjects (45.7% male, mean age 56.8 ± 8.3 years), subjects with incident dementia were more likely to be older, hypertensive, and diabetic (all $p < 0.05$, refer to Table S4). Results of competing risks regression for associations of RetiPhenoAge *z*-scores with incident dementia are presented in Table 4. In the age adjusted model, higher RetiPhenoAge *z*-scores were associated with increased hazards of incident dementia (SHR 1.31, 95% CI 1.15–1.47, $p = 0.001$). Within the fully adjusted model, higher RetiPhenoAge *z*-scores similarly associated with increased hazard of incident dementia (SHR 1.25, 95% CI 1.09–1.41, $p = 0.008$). Kaplan–Meier curves of incident dementia stratified by RetiPhenoAge quartiles are presented in Figure 3C. Significant separation of the survival curves was observed among the quartiles of RetiPhenoAge (log-rank $p < 0.001$).

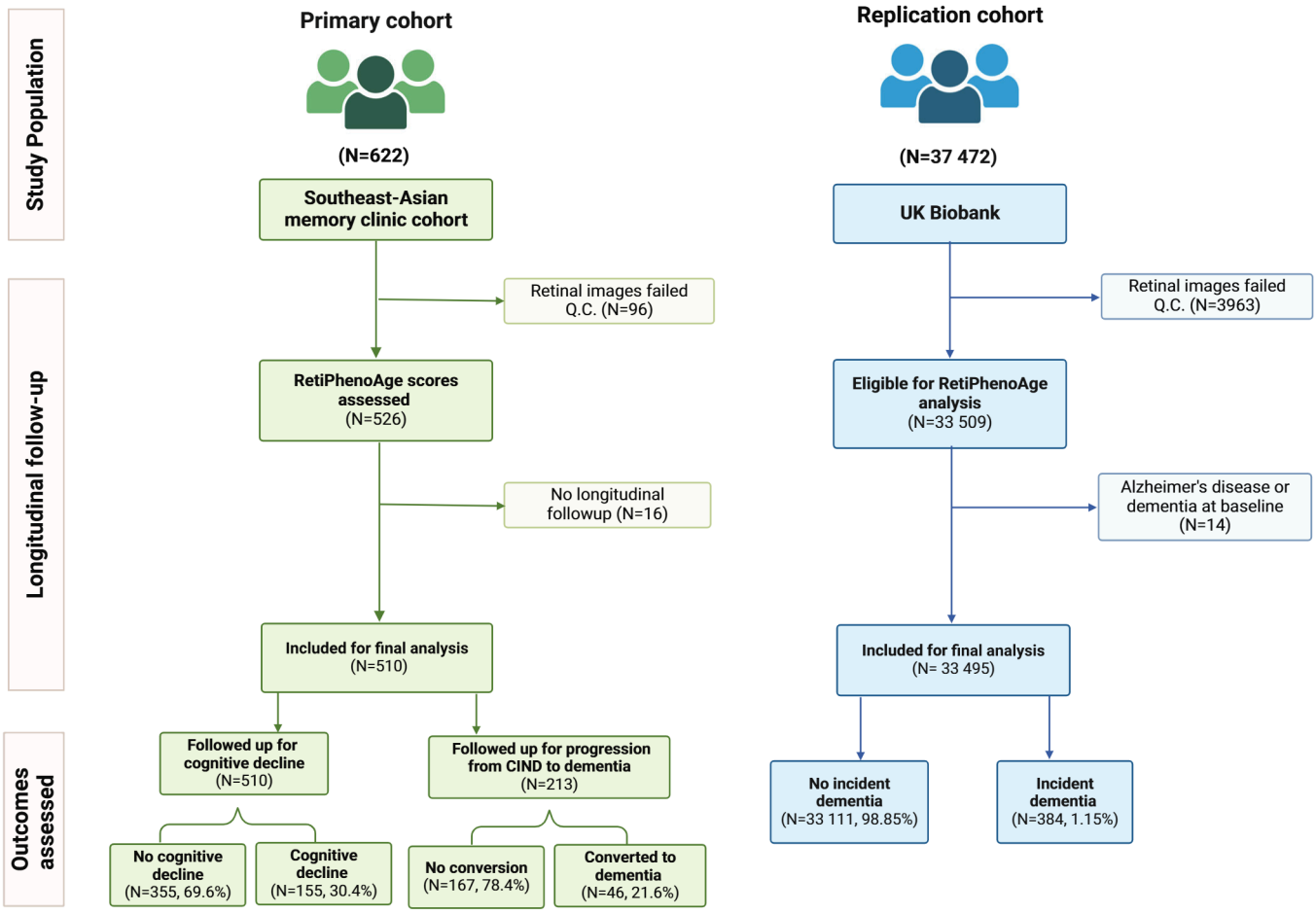

FIGURE 2 Flowchart of subject recruitment within the Asian memory clinic cohort and UK Biobank cohort (created with biorender.com). CIND refers to cognitive impairment, no dementia. Cognitive decline was defined as a longitudinal increment in Clinical Dementia Rating scale Sum of Boxes score of 3 points and above, at any annual follow-up. Q.C. refers to quality control.

TABLE 1 Subject demographics of the Southeast-Asian memory clinic cohort.

Characteristic	All subjects ($N = 510$) / N (%)	No cognitive decline ($N = 355$) / N (%)	Cognitive decline ($N = 155$) / N (%)	p-value
Chronological age, years	72.4 ± 7.8	71.3 ± 8.0	74.8 ± 7.0	<0.001
Male gender, N (%)	224 (43.9)	168 (47.3)	56 (36.1)	0.019
Education, years	7.2 ± 5.1	7.7 ± 5.1	6.1 ± 4.7	<0.001
Hypertension, N (%)	357 (70.6)	243 (69.0)	114 (74.0)	0.257
Hyperlipidaemia, N (%)	375 (73.7)	263 (74.3)	112 (72.3)	0.631
Diabetes, N (%)	182 (35.7)	114 (32.1)	68 (43.9)	0.011
MoCA	18.1 ± 7.0	20.1 ± 6.6	13.6 ± 5.4	<0.001
Baseline cognitive diagnoses				
Dementia, N (%)	184 (36.1)	78 (22.0)	106(68.4)	<0.001
CIND, N (%)	213 (41.8)	168 (47.3)	45 (29.0)	
NCI, N (%)	113 (22.2)	109 (30.7)	4 (2.6)	

Abbreviations: CIND, cognitive impairment no dementia; MoCA, Montreal Cognitive Assessment; NCI, no cognitive impairment.

TABLE 2 Associations of RetiPhenoAge with cognitive decline within the Southeast-Asian memory clinic cohort.

Model	No cognitive decline / *N* (%)	Cognitive decline / *N* (%)	SHR	95% CI	*p*-value
Model 1	355/510 (69.6)	155/510 (30.4)	1.42	1.17–1.72	<0.001
Model 2			1.34	1.10–1.64	0.004

Note: Model 1: Competing risks regression for cognitive decline, adjusted for chronological age and RetiPhenoAge expressed as z-scores, with mortality as the competing event.
Model 2: Competing risks regression for cognitive decline, adjusted for chronological age, gender, years of education, hypertension, hyperlipidemia, diabetes, baseline cognition, and RetiPhenoAge expressed as z-scores, with mortality as the competing event.
Number of competing events (mortality): *N* = 47.
Abbreviations: CI, confidence interval; SHR, subdistribution hazard ratio.

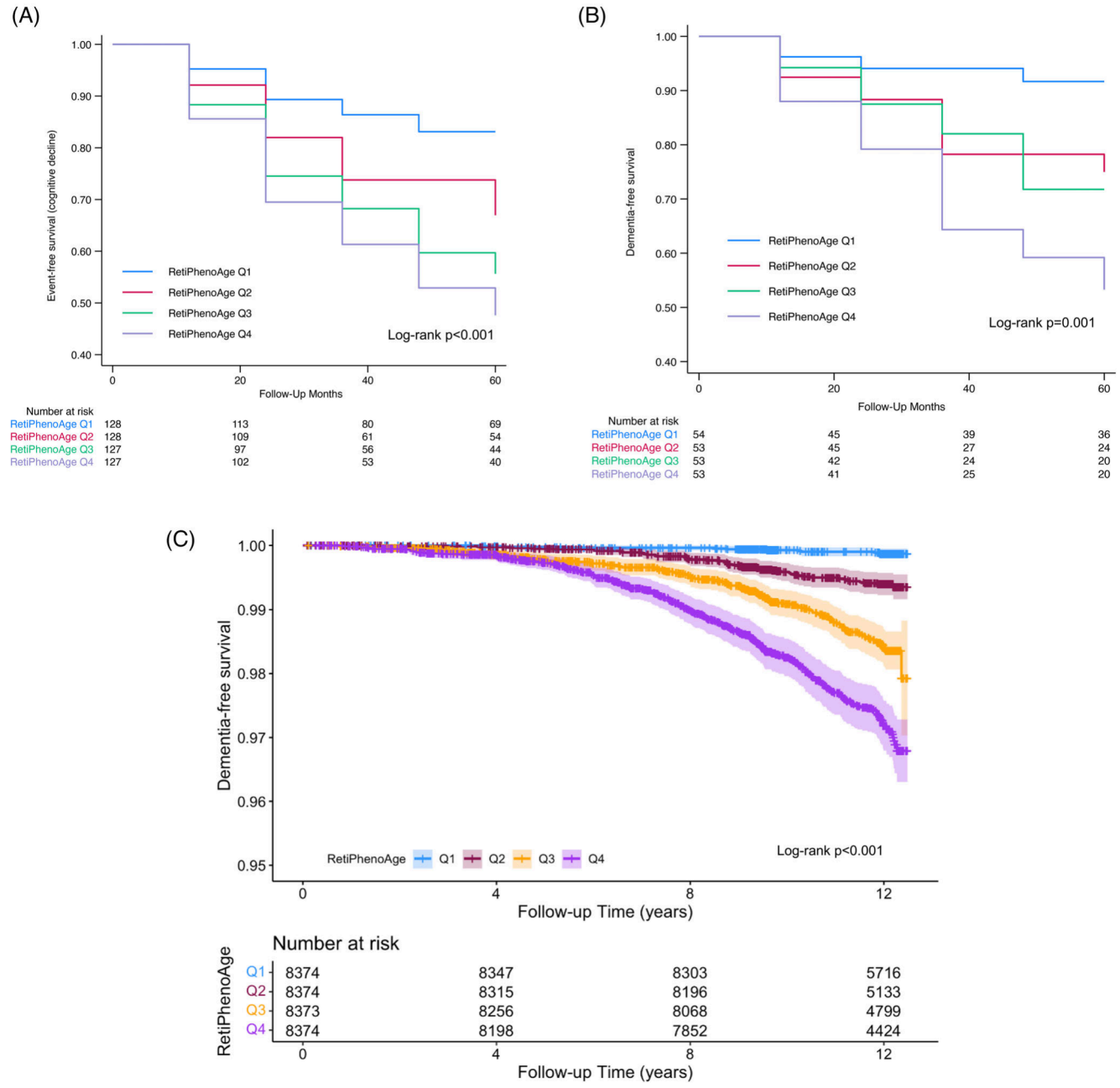

FIGURE 3 Kaplan–Meier curves of (A) cognitive decline, and RetiPhenoAge stratified by quartiles (Southeast-Asian memory clinic cohort); (B) conversion to dementia, and RetiPhenoAge stratified by quartiles (Southeast-Asian memory clinic cohort); (C) incident dementia and RetiPhenoAge stratified by quartiles (UK Biobank cohort). *p*-values presented were derived from log-rank tests of cognitive decline or incident dementia respectively, stratified by RetiPhenoAge quartiles.

TABLE 3 Associations of RetiPhenoAge with progression from CIND to incident dementia within the Southeast-Asian memory clinic cohort.

Model	No incident dementia / *N* (%)	Incident dementia / *N* (%)	SHR	95% CI	*p*-Value
Model 1	167/213 (78.4)	46/213 (21.6)	1.44	1.03-2.01	0.034
Model 2			1.43	1.02-2.01	0.036

Note: Model 1: Competing risks regression for progression from CIND to dementia, adjusted for chronological age and RetiPhenoAge expressed as z-scores, with mortality as the competing event.
Model 2: Competing risks regression for progression from CIND to dementia, adjusted for chronological age, gender, years of education, and RetiPhenoAge expressed as z-scores, with mortality as the competing event.
Number of competing events (mortality): *N* = *10*.
Abbreviations: CI, confidence interval; CIND, cognitive impairment no dementia; SHR, subdistribution hazard ratio.

TABLE 4 Replication analysis: Associations of RetiPhenoAge with incident dementia within the UK Biobank cohort.

Model	No incident dementia	Incident dementia	SHR	95% CI	*p*-Value
Model 1	33 111 / 33 495 (98.9%)	384/ 33 495 (1.1%)	1.31	1.15–1.47	0.001
Model 2			1.25	1.09–1.41	0.008

Note: Model 1: Competing risks regression for incident dementia, adjusted for chronological age and RetiPhenoAge expressed as z-scores, with mortality as the competing event.
Model 2: Competing risks regression for incident dementia, adjusted for chronological age, gender, years of education, hypertension, hyperlipidemia, diabetes, and RetiPhenoAge expressed as z-scores, with mortality as the competing event.
Number of competing events (mortality): *N* = 1728.
Abbreviations: CI, confidence interval; SHR, subdistribution hazard ratio.

3.4 | Secondary analyses

3.4.1 | Association of RetiPhenoAge with MRI markers of CSVD and neurodegeneration

Forest plots of the associations of RetiPhenoAge with cross-sectional MRI brain markers are presented in Figure 4A. Higher RetiPhenoAge scores were associated with greater cross-sectional burden of CSVD (WMH volume (β 0.16, 95% CI 0.03, 0.30, Exp (β) 1.17, $p = 0.015$), cerebral microbleeds (adjusted RR 1.88, 95% CI 1.42–2.48, $p < 0.001$)), and neurodegeneration indices (gray matter volume (β -0.34, 95% CI -0.62, -0.05, Exp (β) 0.71, $p = 0.023$)). No significant associations were found between RetiPhenoAge and baseline lacunes (adjusted RR 1.25, 95% CI 0.97–1.61, $p = 0.090$) and cortical infarcts (adjusted RR 1.22, 95% CI 0.84–1.77, $p = 0.302$).

3.4.2 | Plasma proteomic signatures underpinning RetiPhenoAge

Of the 1441 plasma proteins studied, 345 proteins significantly associated with RetiPhenoAge (q-value < 0.05). Of these, 51 proteins negatively associated with RetiPhenoAge, while 294 were positively associated. The top 20 most significantly predictive proteins for older RetiPhenoAge are presented visualized in volcano plots (Figure 4B). All 345 significant proteins associated with older RetiPhenoAge are presented in Table S5.

The most significant biological pathways identified through over-representation analysis of all 345 proteins associated with Retiphenoage are presented in Figure 4C. All pathways over-represented within the plasma proteomic profile for RetiPhenoAge are presented in Table S6.

3.4.3 | RetiPhenoAge saliency maps

Saliency maps to localize the anatomy which contributed to RetiPhenoAge scores within the memory clinic cohort, indicated abnormalities within the epiretinal, macula, optic disc, and retinal vessels (Figure S1). Details on the generation of the saliency maps are presented in methods S1.

4 | DISCUSSION

In this study, we demonstrated significant associations of RetiPhenoAge – a deep-learning derived retinal aging marker – with future cognitive decline and progression to dementia in a Southeast-Asian memory clinic cohort. On a neuropathological level, this was likely related to neurodegeneration and CSVD, as greater RetiPhenoAge was also found to associate with greater cross-sectional WMH, cerebral microbleeds, and gray matter atrophy. Plasma proteomic analysis identified aging-related pathways underpinning older RetiPhenoAge including inflammation, immune dysregulation, extracellular matrix disruption, and insulin-like growth factor (IGF) signaling. Replication analysis within the Caucasian UK Biobank found that greater RetiPhenoAge similarly associated with the future risk of incident dementia in a younger Caucasian community cohort. Demonstrating

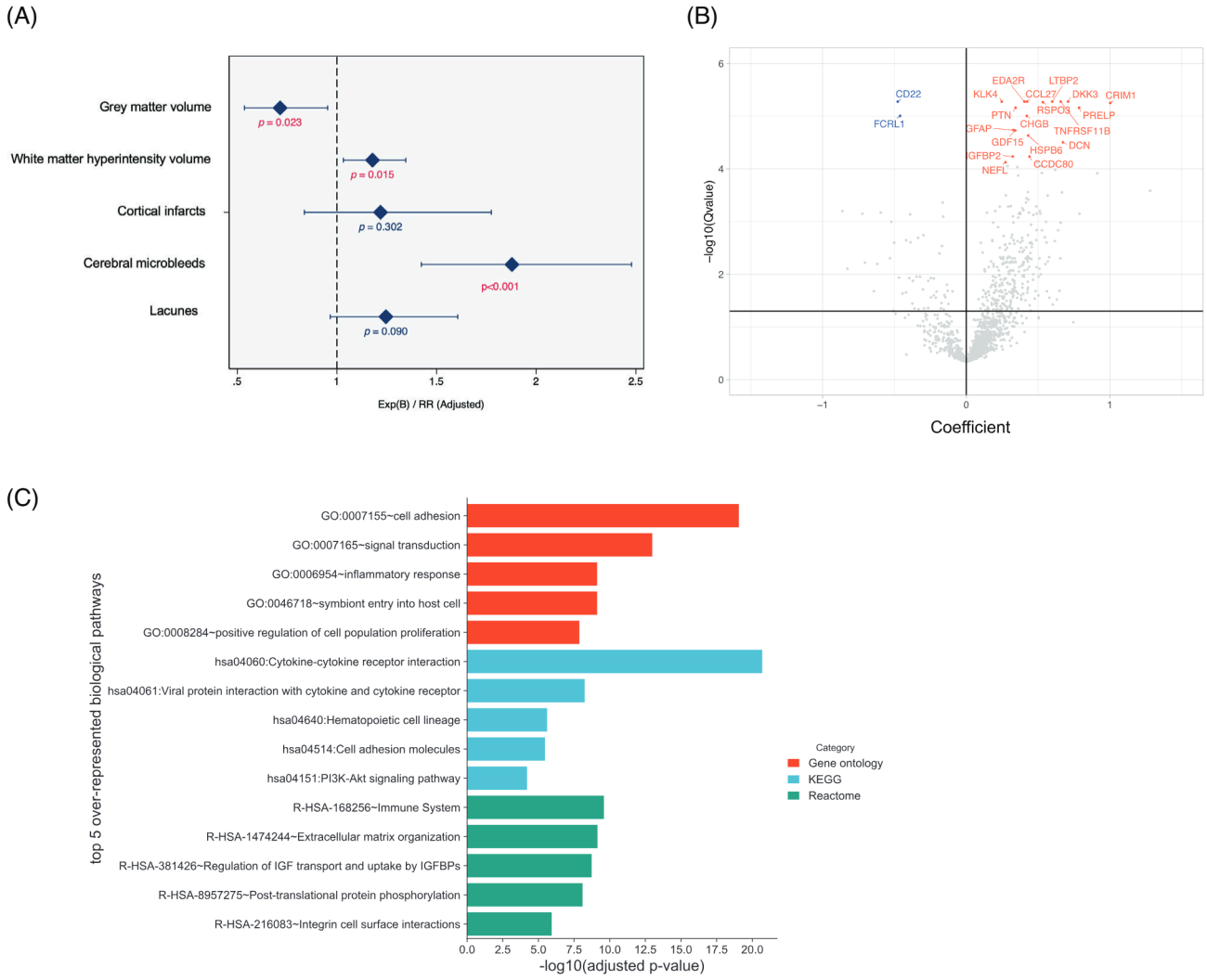

FIGURE 4 (A) Cross-sectional associations of RetiPhenoAge with brain MRI markers of cerebral small vessel disease and neurodegeneration. Forest plots depict Exp(β) and adjusted relative risk (RR), with 95% confidence intervals derived from multivariable linear or Poisson regression, respectively. (B) Top 20 most significantly associative plasma proteins for older RetiPhenoAge. Regression coefficients and corrected p-values (q-values) were derived from linear regression of plasma proteins and RetiPhenoAge. (C) Top five most significant Gene Ontology (biological process), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome pathways over-represented within the associative plasma proteins for RetiPhenoAge.

reproducibility and validation in both cohorts and ethnicities, RetiPhenoAge may thus be an opportunistic, non-invasive prognostic screening tool for cognitive decline and dementia.

Our findings of the predictive utility of deep-learning retinal aging markers for longitudinal age-related pathology such as cognitive decline, are consistent with previous work demonstrating associations of retinal photograph-based deep learning indices, with biological age, morbidity and mortality risk within the UK Biobank.[16,19] Previous studies have similarly reinforced the predictive utility of deep-learning derived retinal photographic indices of aging as biomarkers for arterial stiffness, Parkinson's disease, kidney failure cardiovascular risk, incident stroke, and mortality.[31–34] However, evidence regarding the predictive ability of a deep-learning derived retinal biomarker of biological age, for progression to dementia and cognitive decline remains unclear.

Earlier studies evaluating the associations of conventionally measured retinal features with longitudinal cognitive change have yielded conflicting findings. Studies helmed by the Rotterdam and Lothian-Birth Cohort groups demonstrated no significant associations of conventional retinal vascular features and retinopathy with longitudinal cognitive change.[35–37] By contrast, several longitudinal cohort studies have reported significant associations of midlife retinal vascular perturbations and retinopathy with cognitive decline as well as incident dementia.[38–40] These discrepant findings may perhaps reflect between-study differences in age, prevalence of comorbidities, cognitive disease burden, and duration of cognitive follow-up.[23,35–40] However, it is also plausible that the advent of deep-learning has allowed for the feature extraction of information from retinal images which may not be readily apparent with previously utilized conventional assessment methods. Indeed, the ocular features identified to be

associated with RetiPhenoAge within our saliency maps also included the epiretinal membrane, macula, optic disc, and vessels, which have individually been known to associate with cognitive outcomes.[38–42]

These associations of older retinal age with poorer cognitive outcomes may be explained by several mechanisms. The cerebral and retinal circulatory systems are thought to be contiguous, exhibiting similar age-related changes in blood flow, morphology, and metabolic demands.[31,43] These vascular changes may be contributed by the shared mechanisms of vascular aging including endothelial dysfunction, inflammation, and oxidative stress.[31,44,45] Additionally, risk factors of cognitive decline such as cardiovascular disease, neurodegeneration, and other age-related processes may manifest as detectable features within the retina such as retinopathy, age-related macular degeneration, and vascular alterations.[46–48] Collectively, these retinal features may provide added insight into disease severity and its end-organ effects, which may not be entirely reflected within chronological age.[47,48] Our saliency maps support these conclusions, by highlighting pathology within the retinal vessels, optic disc, and macula which contributed to RetiPhenoAge.

At a neuropathological level, the associations of RetiPhenoAge with cognitive decline and incident dementia were likely linked to both neurodegenerative and CSVD etiologies. This was supported by the significant associations found between RetiPhenoAge with gray matter atrophy, cerebral microbleeds, and WMH. These observations are consistent with previously reported associations of retinal photographic features (vessel alterations, retinopathy, and age-related macular degeneration) with CSVD and brain atrophy.[49–52] Plasma proteomic analysis additionally identified diverse biological pathways related to aging, which underpinned older RetiPhenoAge. These biological pathways included processes related to inflammation, IGF signaling, cellular adhesion, and extracellular matrix disruption.[53–57] The top 20 most significant proteins associated with RetiPhenoAge encapsulated diverse pathobiological processes including cellular adhesion (CD22), extracellular matrix disruption (KLK4, TNFRSF11B, DCN, CCDC80), inflammation (EDA2R, CCL27, FCRL1[58]), transforming growth factor-beta (TGF-beta) receptor signaling (LTBP2,[59] DKK3), angiogenesis (RSPO3, HSPB6,[60] CRIM1[61]), IGF and IGF binding protein axis (CHGB, IGFBP2), neurodegeneration or neuroinflammation (PTN,[62] GFAP, NEFL) and cellular senescence (PRELP, GDF-15[63]).[64] Amongst these, several proteins (GDF15, LTBP2, EDA2R, NEFL, and GFAP) were also featured within recently validated proteomic aging clocks.[55,57] These findings suggest links between age-related biological processes and older RetiPhenoAge. Taken together, our findings highlight the potential role of RetiPhenoAge as a prognostic biomarker for cognitive decline which may relate to CSVD, neurodegeneration, and the pathobiological changes of aging.

The initial associations identified in this study suggest that older RetiPhenoAge may serve as a potential prognostic biomarker of cognitive decline and dementia – offering utility as a non-invasive screening tool for future cognitive outcomes. Further study is needed to explore the biological mechanisms linking older RetiPhenoAge with cognitive outcomes. This would yield deeper insights into the aging processes reflected in the retina and determine its viability as a surrogate endpoint in clinical trials targeting cognitive decline. The utility of RetiPhenoAge as a risk stratification tool for the identification of subjects at risk of cognitive decline should also be evaluated in clinical settings, potentially facilitating early targeted interventions. Lastly, future efforts should be targeted at improving the accessibility and integration of deep-learning and retinal imaging within clinical care settings. Taken together, this may augment current clinical and biomarker approaches for the prognostication of cognitive decline and dementia.

4.1 | Limitations

Our study has several limitations. Firstly, we only utilized good quality retinal photos which passed quality control checks. As such, inter-operator variability in image acquisition could conceivably affect the reproducibility of retinal photography measurements in the community setting. Secondly, inter-ethnic variations in retinal photography features have also been previously reported, which may raise concerns as the predominantly Caucasian UK Biobank cohort was used for the development of RetiPhenoAge.[65] However, our validation of the prognostic utility of RetiPhenoAge across both the Southeast-Asian memory clinic cohort, and UK Biobank suggests robustness of the algorithm across both cohorts and ethnicities, for the prediction of cognitive outcomes. Lastly, the differential associations of RetiPhenoAge with subtypes of cognitive decline (such as vascular or Alzheimer's dementia phenotypes) within larger neurocognitive cohorts require future study.

5 | CONCLUSIONS

A retinal aging marker derived by deep-learning from retinal photography may provide a prognostic non-invasive biomarker for cognitive decline and incident dementia. Future studies should be undertaken to evaluate its feasibility and scalability in community-care as well as specialized clinical settings. Our findings reinforce the utility of digital technology as a promising modality which can be effectively applied to retinal photos for the prognostication of future cognitive outcomes.

ACKNOWLEDGMENTS

The work is supported by funding from the National Medical Research Council (NMRC) Singapore (NMRC/CSA-SI/007/2016, NMRC/CIRG/1485/2018, NMRC/OFLCG/2019, NMRC/CG/M006/2017, CG21APR2010, MOH-000707), awarded to Prof Chen. The work is supported by funding from the National University Health System (NUHS) Clinician Scientist Academy (NCSP2.0/2023/NUHS/SMA), and the NMRC (MH 095:003/008-340) awarded to Dr Sim; as well as the CSDU collaborative grant by the National University of Singapore Yong Loo Lin School of Medicine (KCG/2023/NUSMED) awarded to Drs Sim and Tham. The funders had no role in the design, analysis or conception of the study and the work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Informed consent was obtained from all human subjects.

REFERENCES

1. International AsD. *World Alzheimer Report 2018, The state of the art of dementia research*: New frontiers. 2018;
2. Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol*. 2019;15(10):565-581. doi: 10.1038/s41582-019-0244-7
3. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217. doi: 10.1016/j.cell.2013.05.039
4. Hamczyk MR, Nevado RM, Barettino A, Fuster V, Andres V. Biological versus chronological aging: JACC focus seminar. *J Am Coll Cardiol*. 2020;75(8):919-930. doi: 10.1016/j.jacc.2019.11.062
5. Matt Kaeberlein P. Time for a new strategy in the war on Alzheimer's disease. *Public Policy & Aging Report*. 2019;29(4):119-122. doi: 10.1093/ppar/prz020
6. Sugden K, Caspi A, Elliott ML, et al. Association of pace of aging measured by blood-based DNA methylation with age-related cognitive impairment and dementia. *Neurology*. 2022;99(13):e1402-e1413. doi: 10.1212/wnl.0000000000200898
7. Elliott ML, Belsky DW, Knodt AR, et al. Brain-age in midlife is associated with accelerated biological aging and cognitive decline in a longitudinal birth cohort. *Mol Psychiatry*. 2021;26(8):3829-3838. doi: 10.1038/s41380-019-0626-7
8. Mahoney ER, Dumitrescu L, Seto M, et al. Telomere length associations with cognition depend on Alzheimer's disease biomarkers. *Alzheimers Dement (N Y)*. 2019;5:883-890. doi: 10.1016/j.trci.2019.11.003
9. Snyder PJ, Alber J, Alt C, et al. Retinal imaging in Alzheimer's and neurodegenerative diseases. *Alzheimers Dement*. 2021;17(1):103-111. doi: 10.1002/alz.12179
10. Rifai OM, McGrory S, Robbins CB, et al. The application of optical coherence tomography angiography in Alzheimer's disease: a systematic review. *Alzheimers Dement (Amst)*. 2021;13(1):e12149. doi: 10.1002/dad2.12149
11. Cheung CY, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. *Prog Retin Eye Res*. 2017;57:89-107. doi: 10.1016/j.preteyeres.2017.01.001
12. Cheung CY, Ran AR, Wang S, et al. A deep learning model for detection of Alzheimer's disease based on retinal photographs: a retrospective, multicentre case-control study. *Lancet Digit Health*. 2022;4(11):e806-e815. doi: 10.1016/s2589-7500(22)00169-8
13. Bahr T, Vu TA, Tuttle JJ, Iezzi R. Deep learning and machine learning algorithms for retinal image analysis in neurodegenerative disease: systematic review of datasets and models. *Transl Vis Sci Technol*. 2024;13(2):16. doi: 10.1167/tvst.13.2.16
14. Cheung CY, Ran AR, Wang S, et al. A deep learning model for detection of Alzheimer's disease based on retinal photographs: a retrospective, multicentre case-control study. *The Lancet Digital Health*. 2022;4(11):e806-e815. doi: 10.1016/S2589-7500(22)00169-8
15. Sabanayagam C, Xu D, Ting DSW, et al. A deep learning algorithm to detect chronic kidney disease from retinal photographs in community-based populations. *Lancet Digit Health*. 2020;2(6):e295-e302. doi: 10.1016/s2589-7500(20)30063-7
16. Nusinovici S, Rim TH, Yu M, et al. Retinal photograph-based deep learning predicts biological age, and stratifies morbidity and mortality risk. *Age Ageing*. 2022;51(4):afac065. doi: 10.1093/ageing/afac065
17. Ting DSW, Cheung CY, Lim G, et al. Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes. *JAMA*. 2017;318(22):2211-2223. doi: 10.1001/jama.2017.18152
18. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY)*. 2018;10(4):573-591. doi:10.18632/aging.101414
19. Nusinovici S, Rim TH, Li H, et al. Application of a deep-learning marker for morbidity and mortality prediction derived from retinal photographs: a cohort development and validation study. *The Lancet Healthy Longev*. 2024;5(10):100593. doi: 10.1016/S2666-7568(24)00089-8
20. Wu LY, Kan CN, Cheah IK, et al. Low plasma ergothioneine predicts cognitive and functional decline in an elderly cohort attending memory clinics. *Antioxidants (Basel)*. 2022;11(9):1717. doi: 10.3390/antiox11091717
21. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr*. 1997;9(1):173-176. doi: 10.1017/s1041610297004870. discussion 177-8.
22. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*. 2019;5:354-363. doi: 10.1016/j.trci.2019.06.005
23. Cheung CY, Wong WLE, Hilal S, et al. Deep-learning retinal vessel calibre measurements and risk of cognitive decline and dementia. *Brain Commun*. 2022;4(4):fcac212. doi: 10.1093/braincomms/fcac212
24. Chua J, Zhang Z, Wong D, et al. Age-related eye diseases in individuals with mild cognitive impairment and Alzheimer's Disease. *Front Aging Neurosci*. 2022;14:933853. doi: 10.3389/fnagi.2022.933853
25. Robert C, Ling LH, Tan ESJ, et al. Effects of carotid artery stiffness on cerebral small-vessel disease and cognition. *J Am Heart Assoc*. 2022;11(23):e027295. doi: 10.1161/JAHA.122.027295
26. Zhao L, Luo Y, Mok V, Shi L. Automated brain volumetric measures with AccuBrain: version comparison in accuracy, reproducibility and application for diagnosis. *BMC Med Imaging*. 2022;22(1):117. doi: 10.1186/s12880-022-00841-2
27. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838. doi: 10.1016/S1474-4422(13)70124-8
28. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. *J Am Geriatr Soc*. 2010;58(4):783-787. doi: 10.1111/j.1532-5415.2010.02767.x
29. Storey JD, Tibshirani R. Statistical significance for genomewide studies. *Proc Natl Acad Sci U S A*. 2003;100(16):9440-9445. doi: 10.1073/pnas.1530509100
30. Sherman BT, Hao M, Qiu J, et al. DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update). *Nucleic Acids Res*. 2022;50(W1):W216-w221. doi: 10.1093/nar/gkac194
31. Zhu Z, Hu W, Chen R, et al. Retinal age gap as a predictive biomarker of stroke risk. *BMC Med*. 2022;20(1):466. doi: 10.1186/s12916-022-02620-w
32. Zhu Z, Chen Y, Wang W, et al. Association of retinal age gap with arterial stiffness and incident cardiovascular disease. *Stroke*. 2022;53(11):3320-3328. doi: 10.1161/strokeaha.122.038809
33. Zhang S, Chen R, Wang Y, et al. Association of retinal age gap and risk of kidney failure: a UK Biobank Study. *Am J Kidney Dis*. 2023;81(5):537-544.e1. doi: 10.1053/j.ajkd.2022.09.018
34. Hu W, Wang W, Wang Y, et al. Retinal age gap as a predictive biomarker of future risk of Parkinson's disease. *Age Ageing*. 2022;51(3). doi: 10.1093/ageing/afac062
35. McGrory S, Ballerini L, Okely JA, et al. Retinal microvascular features and cognitive change in the Lothian-Birth Cohort 1936. *Alzheimers Dement (Amst)*. 2019;11:500-509. doi: 10.1016/j.dadm.2019.04.012
36. McGrory S, Taylor AM, Kirin M, et al. Retinal microvascular network geometry and cognitive abilities in community-dwelling older

people: the Lothian Birth Cohort 1936 study. *Br J Ophthalmol*. 2017;101(7):993-998. doi: 10.1136/bjophthalmol-2016-309017

37. Schrijvers EM, Buitendijk GH, Ikram MK, et al. Retinopathy and risk of dementia: the Rotterdam Study. *Neurology*. 2012;79(4):365-370. doi: 10.1212/WNL.0b013e318260cd7e
38. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. *Neurology*. 2009;73(11):862-868. doi: 10.1212/WNL.0b013e3181b78436
39. Deal JA, Sharrett AR, Rawlings AM, et al. Retinal signs and 20-year cognitive decline in the atherosclerosis risk in communities study. *Neurology*. 2018;90(13):e1158-e1166. doi: 10.1212/WNL.0000000000005205
40. de Jong FJ, Schrijvers EM, Ikram MK, et al. Retinal vascular caliber and risk of dementia: the Rotterdam study. *Neurology*. 2011;76(9):816-821. doi: 10.1212/WNL.0b013e31820e7baa
41. Kravets S, Rupnow RA, Sethi A, et al. Association between cognitive function and large optic nerve cupping, accounting for cup-disc-ratio genetic risk score. *PLoS One*. 2022;17(10):e0258564. doi: 10.1371/journal.pone.0258564
42. Keenan TD, Goldacre R, Goldacre MJ. Associations between age-related macular degeneration, Alzheimer disease, and dementia: record linkage study of hospital admissions. *JAMA Ophthalmol*. 2014;132(1):63-68. doi: 10.1001/jamaophthalmol.2013.5696
43. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. 2005;206(4):319-348. doi: 10.1111/j.1469-7580.2005.00395.x
44. Xu X, Wang B, Ren C, et al. Recent progress in vascular aging: mechanisms and its role in age-related diseases. *Aging Dis*. 2017;8(4):486-505. doi:10.14336/ad.2017.0507
45. Sierra C, Coca A, Schiffrin EL. Vascular mechanisms in the pathogenesis of stroke. *Curr Hypertens Rep*. 2011;13(3):200-207. doi: 10.1007/s11906-011-0195-x
46. McGrory S, Cameron JR, Pellegrini E, et al. The application of retinal fundus camera imaging in dementia: a systematic review. *Alzheimers Dement (Amst)*. 2017;6:91-107. doi: 10.1016/j.dadm.2016.11.001
47. Cheung CY, Ikram MK, Sabanayagam C, Wong TY. Retinal microvasculature as a model to study the manifestations of hypertension. *Hypertension*. 2012;60(5):1094-1103. doi: 10.1161/hypertensionaha.111.189142
48. Kim YD, Noh KJ, Byun SJ, et al. Effects of hypertension, diabetes, and smoking on age and sex prediction from retinal fundus images. *Sci Rep*. 2020;10(1):4623. doi: 10.1038/s41598-020-61519-9
49. Hilal S, Cheung CY, Wong TY, Schmetterer L, Chen C. Retinal parameters, cortical cerebral microinfarcts, and their interaction with cognitive impairment. *Int J Stroke*. 2023;18(1):70-77. doi: 10.1177/17474930221097737
50. Czakó C, Kovács T, Ungvari Z, et al. Retinal biomarkers for Alzheimer's disease and vascular cognitive impairment and dementia (VCID): implication for early diagnosis and prognosis. *Geroscience*. 2020;42(6):1499-1525. doi: 10.1007/s11357-020-00252-7
51. Ge QM, Shen YK, Pan YC, et al. Decreased gray matter volume and increased white matter volume in patients with neovascular age-related macular degeneration: a voxel-based morphometry study. *Aging (Albany NY)*. 2021;13(19):23182-23192. doi:10.18632/aging.203610
52. Biffi E, Turple Z, Chung J, Biffi A. Retinal biomarkers of cerebral small vessel disease: a systematic review. *PLoS One*. 2022;17(4):e0266974. doi: 10.1371/journal.pone.0266974
53. Teuscher AC, Statzer C, Goyala A, et al. Longevity interventions modulate mechanotransduction and extracellular matrix homeostasis in C. elegans. *Nature Communications*. 2024;15(1):276. doi: 10.1038/s41467-023-44409-2
54. Tanaka T, Basisty N, Fantoni G, et al. Plasma proteomic biomarker signature of age predicts health and life span. *Elife*. 2020;9. doi: 10.7554/eLife.61073
55. Argentieri MA, Xiao S, Bennett D, et al. Proteomic aging clock predicts mortality and risk of common age-related diseases in diverse populations. *Nature Medicine*. 2024;30(9):2450-2460. doi: 10.1038/s41591-024-03164-7
56. Moaddel R, Ubaida-Mohien C, Tanaka T, et al. Proteomics in aging research: a roadmap to clinical, translational research. *Aging Cell*. 2021;20(4):e13325. doi: 10.1111/acel.13325
57. Johnson AA, Shokhirev MN, Wyss-Coray T, Lehallier B. Systematic review and analysis of human proteomics aging studies unveils a novel proteomic aging clock and identifies key processes that change with age. *Ageing Research Reviews*. 2020;60:101070. doi:10.1016/j.arr.2020.101070
58. Leu CM, Davis RS, Gartland LA, Fine WD, Cooper MD. FcRH1: an activation coreceptor on human B cells. *Blood*. 2005;105(3):1121-1126. doi: 10.1182/blood-2004-06-2344
59. Bashir MM, Han MD, Abrams WR, et al. Analysis of the human gene encoding latent transforming growth factor-beta-binding protein-2. *Int J Biochem Cell Biol*. 1996;28(5):531-542. doi: 10.1016/1357-2725(95)00167-0
60. Zhang X, Wang X, Zhu H, et al. Hsp20 functions as a novel cardiokine in promoting angiogenesis via activation of VEGFR2. *PLoS One*. 2012;7(3):e32765. doi: 10.1371/journal.pone.0032765
61. Glienke J, Sturz A, Menrad A, Thierauch KH. CRIM1 is involved in endothelial cell capillary formation in vitro and is expressed in blood vessels in vivo. *Mech Dev*. 2002;119(2):165-175. doi: 10.1016/s0925-4773(02)00355-6
62. Tanga N, Kuboyama K, Kishimoto A, et al. The PTN-PTPRZ signal activates the AFAP1L2-dependent PI3K-AKT pathway for oligodendrocyte differentiation: targeted inactivation of PTPRZ activity in mice. *Glia*. 2019;67(5):967-984. doi: 10.1002/glia.23583
63. Wedel S, Martic I, Guerrero Navarro L, et al. Depletion of growth differentiation factor 15 (GDF15) leads to mitochondrial dysfunction and premature senescence in human dermal fibroblasts. *Aging Cell*. 2023;22(1):e13752. doi: 10.1111/acel.13752
64. Gaudet P, Livstone MS, Lewis SE, Thomas PD. Phylogenetic-based propagation of functional annotations within the Gene Ontology consortium. *Brief Bioinform*. 2011;12(5):449-462. doi: 10.1093/bib/bbr042
65. Li X, Wong WL, Cheung CY, et al. Racial differences in retinal vessel geometric characteristics: a multiethnic study in healthy Asians. *Invest Ophthalmol Vis Sci*. 2013;54(5):3650-3656. doi: 10.1167/iovs.12-11126

SUPPORTING INFORMATION

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

How to cite this article: Sim MA, Tham YC, Nusinovici S, et al. A deep-learning retinal aging biomarker for cognitive decline and incident dementia. *Alzheimer's Dement*. 2025;21:e14601. https://doi.org/10.1002/alz.14601