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RESEARCH ARTICLE

Mid- and later-life risk factors for predicting neuropathological brain changes associated with Alzheimer's and vascular dementia: The Honolulu Asia Aging Study and the Age, Gene/Environment Susceptibility-Reykjavik Study

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Abstract

Introduction: Dementia prediction models are necessary to inform the development of dementia risk reduction strategies. Here, we examine the utility of neuropathological-based risk scores to predict clinical dementia.

Methods: Models were developed for predicting Alzheimer's disease (AD) and non-AD neuropathologies using the Honolulu Asia Aging neuropathological sub-study (HAAS; $n = 852$). Model accuracy for predicting clinical dementia, over 30 years, was tested in the non-autopsied HAAS sample ($n = 2960$) and the Age, Gene/Environment Susceptibility-Reykjavik Study ($n = 4614$).

Results: Different models were identified for predicting neurodegenerative and vascular neuropathology (c-statistic range: 0.62 to 0.72). These typically included age, APOE, and a blood pressure-related measure. The neurofibrillary tangle and micro-vascular lesion models showed good accuracy for predicting clinical vascular dementia.

Discussion: There may be shared risk factors across dementia-related lesions, suggesting common pathways. Strategies targeting these models may reduce risk or postpone clinical symptoms of dementia as well as reduce neuropathological burden associated with AD and vascular lesions.

KEYWORDS
Alzheimer's disease, dementia, neuropathology, risk prediction, vascular disease

1 | INTRODUCTION

The development of tools to accurately identify individuals at risk of dementia is becoming increasingly important for intervention development and the selective enrichment of clinical trial samples. Numerous dementia risk prediction models exist.[1,2] These typically, with the exception of the Cardiovascular Risk Factors, Aging and Dementia Study (CAIDE) score[3], incorporate known clinical and behavioral risk factors obtained in later-life. A disadvantage of modeling risk based on variables collected in later-life is that the window to intervene becomes narrower and therapeutic strategies less effective once irreversible neuronal damage has occurred.[4] Furthermore, many risk

factors change over time, including cardio-metabolic health status and lifestyle factors, and in late-life may reflect more the presence of dementia than predicting dementia risk.

To date, the outcome tested in dementia prediction models has been a clinical diagnosis of dementia, not the gold standard- neuropathological confirmation of disease. This is largely because of limited availability of brain tissue data. All-cause dementia reflects a wide range and mix of underlying lesions, with examples including neurodegenerative changes (e.g., amyloid plaques and neurofibrillary tangles [NFTs]), vascular abnormalities (e.g., microinfarcts, lacunar infarcts, and white matter lesions), cortical Lewy bodies, hippocampal sclerosis, TDP-43 changes, and generalized brain atrophy. While the overlap between neuropathological changes at death and clinical symptoms in life is imperfect (e.g., due to factors such as cognitive reserve)[5], risk scores based on groups of, or individual neuropathological findings, could increase the accuracy for predicting risk of a clinical diagnosis of dementia and its sub-types such as Alzheimer's disease (AD).

Therefore, the aim of this study was to determine whether risk scores predictive of neuropathologic lesions created using factors measured in mid- to early late life (i.e., age range 45 to 68) improve the accuracy of dementia risk prediction. Data were from the neuropathology sub-sample of the Honolulu Asia Aging Study (HAAS). Risk models were tested for their predictive accuracy of a clinical diagnosis of all-cause dementia, AD, and vascular dementia (VaD) accrued over 30 years of follow-up using the non-autopsied HAAS sample. External validation of the risk scores was also undertaken in participants from the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES–Reykjavik) to test their transportability outside the setting in which they were developed.

RESEARCH IN CONTEXT

Systematic Review: Our group has published numerous systematic reviews synthesizing the literature on dementia risk prediction model development and testing. The findings highlight that those dementia risk models that are available tend to be characterized by poor accuracy, lack of external validity and have limited generalizability due to being developed almost exclusively in Caucasian populations. Furthermore, no model has been developed using the gold standard-neuropathological confirmation of disease.

Interpretation: We found that age, genetic, lifestyle, and blood pressure related variables, collected in mid- to early later-life (i.e., ages 45 to 68 years), predicted neurodegenerative and vascular pathologies at autopsy as well as clinical dementia in life (over approximately 30-years follow-up). Such models could be used to inform the development of dementia prevention and risk reduction strategies.

Future Directions: Strategies targeting health and lifestyle risk factors in mid- to early later-life could impact brain integrity as well as the manifestation of clinical symptoms of dementia. This has important implications for reducing the global burden of disease associated with dementia.

2 | MATERIALS AND METHODS

2.1 | Sample: HAAS

HAAS is a longitudinal population-based study that began in 1991 as an extension of the Honolulu Heart Program (HHP).[6] The HHP included men of Japanese ancestry born between 1900 and 1919, selected from the World War II Selective Service Registration file and living on the Island of Oahu, Hawaii in 1965. In total, 8006 individuals completed the baseline exam (1965 to 1968; age range: 45 to 68 years). These men were invited to repeat exams 2 and 6 years later. In total, 7498 (94% of the original sample) attended the second exam (1967 to 1970), and 6860 (86% of the original sample) attended the third exam (1971 to 1975). Information collected included socio-demographic factors, cardio-metabolic health in addition to blood and urine tests.

Evaluation for HAAS began at the 1991 to 1993 examination (exam 4) and was open to all surviving members of the cohort (n = 4678). In total, 3734 (80%) participants underwent a complete examination.[7] Follow-up interviews were undertaken at exams 5 (1994 to1996; n = 2694), 6 (1997 to 1999; n = 1988) and 7 (1999 to 2000; n = 1500). The autopsy study was initiated in 1992. All HAAS participants were eligible for autopsy, with agreement of family members. The neuropathology analysis is based on the 852 autopsies obtained between April 1992 and August 2013. Participants who were autopsied were similar to non-autopsied participants regarding demographic, social, and health characteristics.[8]

2.2 | Ethics

The Kuakini Medical Center Institutional Review Board, the United States Department of Veterans Affairs, and the National Institute on Aging approved the study. All participants gave written informed consent. Caregivers provided consent when capacity was limited. A next-of-kin family member or legally authorized alternative also provided consent for autopsy.

2.3 | Measurement of risk factors

Mid- to later-life risk factors for dementia were gathered from the HHP baseline (Exam 1) and Exam 3 including: demographics (age, educational attainment), health (history of stroke, diabetes, systolic and diastolic blood pressure, body mass index [BMI]), family history of disease related co-morbidity (stroke), blood-based biomarkers (total cholesterol and triglyceride levels), medication use (antihypertensive and antihyperlipidemic agents), lifestyle factors (smoking, alcohol, physical activity level, diet), and genetics (Apolipoprotein E [APOE] e4

allele status). Some conditions previously associated with dementia, such as myocardial infarction, intermittent claudication, heart attack and coronary heart disease were unusual at that age (< 5% prevalence, at Examinations 1 and 3) and were not included in this analysis. A full description of each risk variable is in Appendix 1.

2.4 | Neuropathology variables

Details of the autopsy procedure and neuropathological examination have been described previously.[9,10] All pathological diagnoses were made blinded to clinical information and final classification made based on consensus. For this analysis, we selected pathological variables that (1) were most prevalent in the sample; and (2) have been consistently associated with the most common phenotypes of dementia including AD and VaD.

Neuropathological markers of AD including neuritic amyloid plaques (NP), diffuse plaques (DP), and NFTs were counted in 8 micron stained sections from multiple brain regions, including four areas of the neocortex: the middle frontal gyrus, inferior parietal lobule, middle temporal gyrus, and occipital cortex. These were stained using a modified Bielschowsky silver stain. All counts were standardized and reported to areas of 1 mm^2. For NP, DP, and NFT counts, five fields from each of the four areas of the neocortex were assessed and averaged to represent the cortical area.

A four-level variable (none/negligible, mild, moderate, and severe) reflecting lesion load and association with cognitive impairment was calculated for each lesion type, based on a previously reported algorithm.[8] Each lesion was considered present if evaluated to be at moderate or severe levels. Each participant was also assigned a Braak NFT stage score from none to VI.[11] Using the Braak NFT staging score together with a semi-quantitative estimate of neuritic plaque density in the neocortex (CERAD amyloid plaque measure) a neuropathological diagnosis of AD was made according to the National Institute on Aging (NIA) Reagan criteria (NIA-Reagan).[12] NIA-Reagan scores were categorized into no AD versus Possible/Probable/High Likelihood of AD combined.

Vascular pathologies included microvascular infarcts defined as micro-infarcts (here referred to as microvascular lesions, MVL) and lacunar infarcts. The MVL variable was based on the total number of micro-infarcts found on examination of sections from 18 brain regions counted in standard screening sections. Previously defined three-level indices were used including: none/negligible (none or one found), mild (2 or 3 found), or moderate/severe (>3 found)[10]. The lacunar infarcts (LI) variable was based on the total number of lacunar infarcts found on gross examination of 30 (15 left and 15 right) coronal brain sections. Scores were coded into three groups: none (none found), mild (1 or 2 found), or moderate/severe (>3 found). For analysis, each variable was dichotomized into none/mild-pathology versus moderate/severe pathology.

A mixed pathology variable was also created for individuals with both neurodegenerative and vascular pathology. See Appendix 2 for a full description of this group.

2.5 | Dementia diagnosis

Clinical dementia was diagnosed by consensus provided by the study neurologist and two physicians with expertise in dementia based on (1) neurological testing, (2) a neurological examination, (3) review of extensive information related to health and functioning prior to the dementia examination, and (4) changes in cognitive function and behavior via an informant interview.[13] Clinical dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) 3rd edition revised criteria.[14] AD was diagnosed using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria.[15] VaD was diagnosed using the State of California Alzheimer's Disease Diagnostic and Treatment Centers criteria.[16] All individuals with a diagnosis of dementia from the start of HAAS (i.e., Wave 4) onwards were classified as having dementia and included in the analysis.

2.6 | External validation

Models were externally validated in the AGES–Reykjavik Study.[17] The AGES–Reykjavik study originates from the Reykjavik Study, which included men and women born in 1907–1935 and living in Reykjavik, Iceland, in 1967. AGES–Reykjavik examinations (2002 to 2006) included 5764 of the surviving Reykjavik Study cohort. Dementia case ascertainment, described previously, was based on a three-step procedure.[18] First, the Mini-Mental State Examination and Digit Symbol Substitution Test were administered to all participants. Persons who screened positive based on a combination of these tests were administered a second, more diagnostic test battery, and a subset of them were selected for a neurologic examination. Proxies for this latter group were interviewed about medical history and social, cognitive, and daily functioning relevant to the diagnosis. A consensus diagnosis according to international guidelines, was made by a panel of experts. The final analytical sample excludes persons with no dementia data (n = 312) and persons with dementia other than AD and VaD (n = 719), leaving an analytical sample of n = 4733. Like HAAS, both prevalent and incident cases of dementia were included in the analysis and risk factor information was collected in mid-life prior to dementia ascertainment.

3 | STATISTICAL ANALYSIS

3.1 | Model development: Neuropathology sample

Models were built using the same procedure as for the CAIDE midlife dementia risk prediction score.[3] Stepwise (backward, p = 0.05) logistic regression analyses, including all seventeen risk variables and time (defined as the interval between baseline interview and death), were implemented to identify the best combination of factors for

predicting each neuropathological variable separately. Results are reported as odds ratios (OR) with 95% confidence intervals (95% CI). Predictive accuracy (discrimination) was assessed using non-parametric receiver operating characteristic analysis to estimate the area under the curve (AUC). Model fit (i.e., calibration) was assessed using the Hosmer–Lemeshow test (H-L test). To correct for optimism bias (i.e., over-fitting) we undertook internal validation using 1000 bootstrap samples. For each logistic regression model, scores were created for each risk factor based on their beta coefficients and summed together.[3] Full details of the scoring system are in Appendix 3.

3.2 | Sensitivity analysis: Value of non-modifiable versus modifiable predictor variables

Given that two of the strongest risk factors for dementia are age and APOE e4 status, we tested the equality of the AUC for each derived neuropathological model to models restricted to (a) age alone; and (b) age and APOE e4 status only. Results are reported as a chi-squared statistic with a p-value.

3.3 | Model testing: Clinical diagnosis (HAAS) and external validation (AGES–Reykjavik Study)

Risk scores were calculated for all individuals using the points-based system developed from the neuropathology analysis above. Separate scores were created for each pathology model ($n = 6$ risk scores for each participant). Logistic regression analysis was used to determine the accuracy of each risk score (continuous) for predicting a clinical diagnosis of dementia (all-cause, AD and VaD) versus no dementia. Discrimination (AUC) and fit (calibration) were again assessed. To allow comparison of the performance of the risk scores when predicting neuropathology verses clinical dementia, we mapped the AUC (and 95% CI) separately for each model in the development and validation samples.

For HAAS, models were run in the sample excluding those from the neuropathology cohort (i.e., $n = 852$) to obtain an independent sample for validation. In the AGES–Reykjavik Study, the models were run in the total sample and stratified by sex.

Missing data were rare and therefore complete case analyses were run (see Appendix 4 for the pattern of missing data for each variable included in the analyses). Analyses were completed using STATA Version 15.1 (StataCorporation, College Station, TX) and SAS Version 9.4 (SAS Institute, Inc., Cary, NC).

4 | DATA SHARING

Anonymized data from both studies analyzed in this manuscript is available for access via request to each study's management committee.

5 | RESULTS

5.1 | HAAS neuropathology sample demographics

The neuropathology sub-sample included 852 individuals (100% male; follow-up range: 21 to 43 years; mean = 31.7 and SD = 4.9 years). Table 1 shows the baseline characteristics of this group.

5.2 | Neurodegenerative pathologies

An NIA-Reagan diagnosis of AD was predicted by a model incorporating age, APOE e4 status, smoking and antihypertensive use (AUC = 0.67; 95% CI: 0.63 to 0.71, $n = 762$). NPs were predicted by a model incorporating age, APOE e4 status and smoking (AUC = 0.71; 95% CI: 0.68 to 0.75, $n = 762$). NFTs were predicted by a model incorporating age, APOE e4 status, stroke, and alcohol use (AUC = 0.68; 95% CI: 0.64 to 0.71, $n = 762$). Across all models, optimism bias was low (range: 0.0049 to 0.0109; for optimism corrected AUCs see Table 2). All models were well calibrated (all H-L test $p > 0.05$, see Table 2).

5.3 | Vascular pathology variables

The best model predicting MVLs included age, education, APOE e4 status, stroke, and systolic blood pressure (AUC = 0.63, 95% CI: 0.59 to 0.67, $n = 762$). The LI model included age, diabetes, systolic blood pressure and antihyperlipidemic medication use (AUC = 0.62; 95% CI: 0.58 to 0.66, $n = 852$). Optimism bias was low (0.0134 and 0.0113 for the LI and MVLs models, respectively); for corrected AUCs see Table 2. Both models were well calibrated (H-L test $p > 0.05$, see Table 2).

5.4 | Neurodegenerative and vascular pathology combined—mixed pathology

The model that best predicted mixed pathology incorporated age, APOE e4 status and systolic blood pressure. Predictive accuracy was high (AUC = 0.72, 95% CI: 0.66 to 0.77, $n = 440$), optimism bias was low (0.0211), and the model was well calibrated (H-L test $p > 0.05$) (see Table 2).

5.5 | Performance of model when predicting a clinical diagnosis of dementia and its subtypes: HAAS non-autopsied participants only

Of the 3734 individuals who successfully completed the cognitive test battery in the HAAS first assessment, $n = 774$ were in the neuropathology analysis and were therefore excluded. This leaving a clinical validation sample of 2960 (non-autopsied) participants (follow-up range: 20.0 to 32.7 years; mean = 27.8 and SD = 2.9). Table 1 shows the baseline characteristics of the sample. As shown, the HAAS non-autopsied sample was similar to the neuropathology sample. Over

TABLE 1 Baseline (Exams 1 and 3) mid- to late-life characteristics of the HAAS neuropathology sub-sample, HAAS non-pathology sample- and the AGES-Reykjavik Study

	Neuropathology Sub-sample (*N* = 852)	Total HAAS Sample (Excluding the neuropathology group) (*N* = 2960)	AGES-Reykjavik Study (*N* = 4733[a])
Demographics			
Mean age (SD), years at mid-age baseline	56.21 (4.86)	55.57 (4.96)	51.41 (7.00)
Mean education (SD), years	10.64 (3.27)	10.40 (3.18)	N/A
0 to 8, *n* (%) Primary	289 (33.90)	1003 (33.90)	1648 (34.82)
9 to 12.5, *n* (%) Secondary or technical	395 (46.40)	1442 (48.70)	2224 (46.99)
13+, *n* (%) College/University	168 (19.70)	515 (17.40)	861 (18.19)
Lifestyle factors			
Ever smoking, *n* (%)	557 (65.38)	2,010 (67.91)	2929 (61.88)
Alcohol use, *n* (%)			
No/Low	412 (48.36)	1455 (49.16)	3943 (90.50)
Moderate	212 (24.88)	758 (25.61)	405 (9.30)
High	212 (24.88)	747 (25.24)	9 (0.21)
Physical activity index (SD) [a]	Mean = 32.85 (SD = 4.72)	Mean = 32.89 (SD = 4.64)	
Diet, n (%)			
Oriental	97 (11.44)	385 (13.06)	0
Western	125 (14.74)	448 (15.19)	4733 (100%)
Mixed	626 (73.82)	2116 (71.75)	0
Health			
Self-reported stroke, n (%)	56 (6.57)	185 (6.25)	681 (14.39)
Diabetes, n (%)	234 (27.46)	783 (26.45)	37 (0.78)
Mean body mass index (SD)	23.95 (2.85)	23.83 (2.77)	25.18 (3.56)
Systolic BP (≥140 mm/Hg), n (%)	233 (27.35)	861 (29.09)	1332 (28.18)
Diastolic BP (≥90 mm/Hg), n (%)	186 (21.83)	642 (21.69)	1090 (23.09)
Mean cholesterol (SD), m/mol	219.86 (32.27)	217.25 (32.08)	248.00 (43.31)
Mean triglycerides (SD), m/mol	234.74 (175.68)	230.13 (181.43)	111.6 (65.03)
Antihypertensive treatment	186 (21.83)	567 (19.20)	301 (6.36)
Antihyperlipidemic treatment	66 (7.75)	205 (6.93)	1085 (22.92)
Genetics and family history			
APOE e4 positive, n (%)	150 (19.69)	520 (18.26)	1,325 (28.11)
Family history of stroke	278 (33.13)	887 (30.50)	583 (12.32)
Dementia cases (prevalent and incident)			
Number of cases (%)	185 (23.9%)	340 (11.5%)	801 (17%)

[a]The analytic sample includes everyone with dementia data at follow-up (including Alzheimer's disease, vascular dementia, and mixed Alzheimer's disease/vascular dementia). People with other dementia sub-types were excluded as they were not the focus of the risk model development analysis.

follow-up (from Exam 4 to Exam 7) there were *n* = 340 (11.5%) cases of dementia including n = 138 (40.6%) with probable-AD and *n* = 88 (25.9%) with probable-VaD. The distribution of the scores for each risk model are shown in Appendix 5.

As shown in Figure 1, both the NIA-Reagan and NFT derived risk scores showed similar levels of accuracy (i.e., the confidence intervals overlapped) for predicting a clinical diagnosis of dementia (including all-cause, AD, and VaD) versus predicting neuropathology outcomes. In contrast, the NP score had poor accuracy at predicting a clinical diagnosis, particularly all-cause dementia and VaD. The mixed pathology risk score also had low accuracy for predicting a clinical diagnosis of all-cause dementia, AD and VaD.

While the vascular pathology derived scores had low accuracy for predicting a clinical diagnosis of dementia (all-cause) and AD, they

TABLE 2 Discriminative accuracy and optimism bias (Bootstrapping, $N = 1000$ samples) of each pathology prediction model: HAAS

	N	AUC (95% CI)	Optimism in AUC (Error)	Optimism corrected AUC	L-H GoF Test results
Neurodegenerative pathologies					
NIA-Reagan	762	0.67 (0.63 to 0.71)	0.0109 (0.0007)	0.66	Chi = 286.57, $p = 0.3969$
NP	762	0.71 (0.68 to 0.75)	0.0049 (0.0006)	0.71	Chi = 228.60, $p = 0.0964$
NFT	762	0.68 (0.64 to 0.72)	0.0083 (0.0006)	0.67	Chi = 317.04, $p = 0.1234$
Vascular pathologies					
MVL	762	0.63 (0.59 to 0.67)	0.0134 (0.0006)	0.62	Chi = 352.85, $p = 0.6388$
LI	852	0.62 (0.58 to 0.66)	0.0113 (0.0006)	0.61	Chi = 257.17, $p = 0.3311$
Mixed dementia					
AD and vascular	440	0.72 (0.66 to 0.77)	0.0211 (0.0009)	0.71	Chi = 155.09, $p = 0.6376$

Abbreviations: 95% CI, 95%, confidence interval; AD, Alzheimer's disease; AUC, area under the curve; GoF, goodness of fit; L-H, Hosmer, Lemeshow test; LI, lacunar infarcts; MVL, micro-vascular lesions; NIA, Reagan National Institutes of Aging Reagan criteria for AD, at autopsy; NFT, neocortical neurofibrillary tangles; NP, neocortical neurotic plaques.

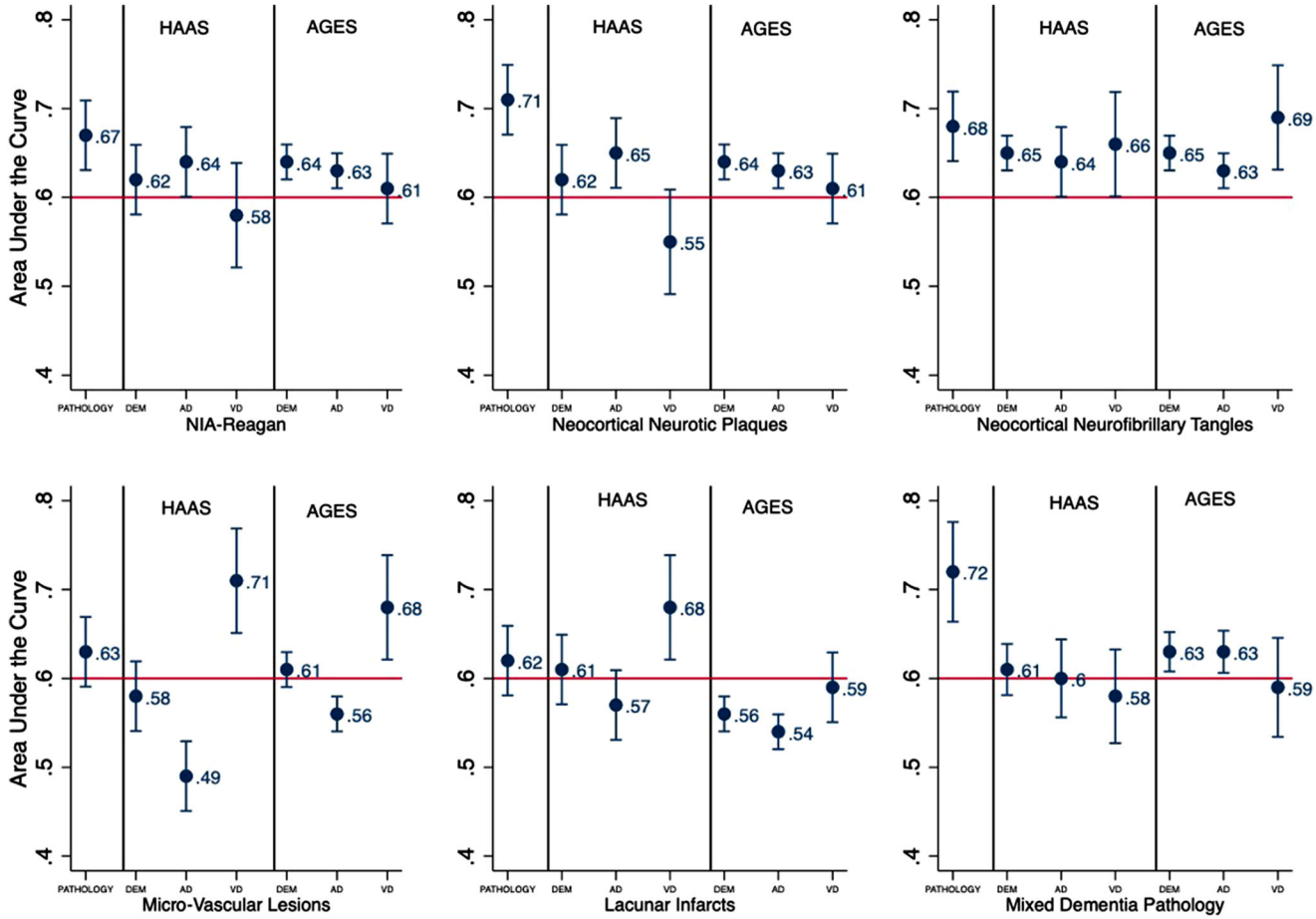

FIGURE 1 Comparison of the discriminative accuracy (AUC and 95% CI) for neurodegenerative derived risk scores when predicting pathology or a clinical diagnosis of dementia (i.e., AD, VaD, or mixed dementia) in HAAS and AGES-Reykjavik. AD, clinical diagnosis of Alzheimer's disease; AGES, Age, Gene/Environment Susceptibility-Reykjavik Study; DEM, clinical diagnosis of dementia (all cause); HAAS, Honolulu Asia Aging Study; NIA-Reagan, National Institutes of Ageing -Reagan derived score; VD, clinical diagnosis of vascular dementia.

TABLE 3 Sensitivity analysis comparing the Area Under the Curve (AUC) values for each neuropathological model compared to models incorporating (a) age only; and (b) age and APOE e4 status only

	AUC full model (95% CI)	AUC age only (95% CI)	AUC Age + APOE e4 status (95% CI)
Neurodegenerative pathologies			
NIA-Reagan	0.67 (0.63 to 0.71)	**0.57 (0.52 to 0.61)**	0.66 (0.62 to 0.71)
NP	0.71 (0.68 to 0.75)	**0.65 (0.61 to 0.69)**	0.71 (0.67 to 0.74)
NFT	0.68 (0.64 to 0.72)	**0.63 (0.59 to 0.67)**	0.67 (0.63 to 0.71)
Vascular pathologies			
MVL	0.63 (0.59 to 0.67)	**0.52 (0.48 to 0.57)**	**0.55 (0.51 to 0.59)**
LI	0.62 (0.58 to 0.66)	**0.59 (0.55 to 0.62)**	**0.58 (0.54 to 0.62)**
Mixed dementia			
AD and vascular	0.72 (0.66 to 0.77)	**0.63 (0.56 to 0.70)**	0.70 (0.65 to 0.76)

Abbreviations: 95% CI, 95% confidence interval; AD, Alzheimer's disease; AUC, area under the curve; LI, lacunar infarcts; MVL, micro-vascular lesions; NIA-Reagan, National Institutes of Aging Reagan criteria for AD at autopsy; NFT, neocortical neurofibrillary tangles; NP, neocortical neurotic plaques.
Note: Bold text indicates where there are significant differences between the full model and partial models (e.g., models including age alone or age + APOE e4 status).

showed good prediction for VaD. However, all scores showed poor calibration (H-L test $p < 0.05$ for all models). Full details of the results are in Appendixes 6 *(discriminative accuracy)* and 7 *(calibration plots)*.

5.6 | Sensitivity analysis: Full models versus restricted models

As shown in Table 3, the derived models for all pathologies had significantly higher discriminative accuracy compared to the model incorporating age as the only predictor variable. However, there was no difference in the discriminative accuracy of the derived models compared to the model incorporating age and APOE e4 status, for predicting neurodegenerative and mixed pathologies. In contrast, for vascular pathologies, the derived models had significantly higher discriminative accuracy compared to the age plus APOE e4 status only model.

5.7 | External validation: AGES—Reykjavik Study

The total sample included 4614 participants (see Table 1 for the baseline sample characteristics). Follow-up ranged from 26 to 4499 days (mean = 2484; SD = 992 days). Over follow-up, there were 801 incident dementia cases including 492 diagnosed with AD (including five with a diagnosis of AD and VaD) and 20 with VaD. The distribution of the scores for each risk model are shown in Appendix 5. As shown in Figure 1, like the results from the HAAS clinical analysis both the NIA-Reagan and NFT derived scores showed comparable levels of predictive accuracy for all-cause dementia, AD and VaD. The NP derived score had poor accuracy for predicting a clinical diagnosis. The vascular pathology derived scores showed good levels of performance for predicting VaD (but not all-cause dementia or AD), particularly the WML risk score. Like the results from HAAS, the mixed pathology risk score was poor at predicting a clinical diagnosis of all-cause dementia, AD and VaD. The calibration results were mixed and generally all models were poorly calibrated with exception of the NIA-Reagan model (for predicting a clinical diagnosis of VaD only), the NP model (for predicting a clinical diagnosis of VaD only), the NFT model (for predicting a clinical diagnosis of all-cause dementia and AD), and the mixed pathology model (for predicting a clinical diagnosis of all-cause dementia, AD and VaD). See Appendixes 8-10 for the discrimination and calibration results.

6 | DISCUSSION

In this study, we derived models based on mid- to later-life health and lifestyle variables to predict neuropathological features representing Alzheimer and vascular dementia pathogeneses. Combinations of variables were identified for predicting each pathology. Although each model differed by one or two specific variables, overall age, APOE e4 status, and a blood pressure-related measure, were common to several lesions. Additionally, the factors included in the models have all be reported to be risk factors for dementia, AD or VaD.[1,2,19] The quality of predictive accuracy of the different models, measured using the AUC, was variable (AUC range: 0.62 to 0.72). Generally higher predictive accuracy was observed for the neurodegenerative compared to the vascular models. While the neurodegenerative lesion derived models and mixed dementia model had poor accuracy for predicting a clinical diagnosis of dementia, reasonable predictive performance was observed for the vascular lesion derived models, particularly for predicting a clinical diagnosis of VaD.

Neuropathology models

Risk of neurodegenerative and mixed pathology was consistently linked to increased age and having the APOE e4 allele in addition

to blood-pressure-related (medication, systolic blood pressure) and/or lifestyle (smoking or drinking) factors. For the vascular models, age and increased systolic blood pressure were the only variables shared by the MVL and LI models. The MVL model tended toward a more similar risk profile to the neurodegenerative models consistent with their cortical location. In contrast, LI included factors related to metabolic dysfunction. Interestingly, education was selected as a predictor only in the MVL model; this possibly because of its association with risk of cardiovascular and cerebrovascular diseases and their risk factors. Indeed, prior reports from HAAS and the Religious Orders Study usually identify education as predicting dementia or poor cognitive test scores, but not the lesions themselves, independent of cognitive function.

External validation: Predicting clinical diagnosis

The results from both HAAS and the AGES-Reykjavik show that the NIA-Reagan model incorporating age, APOE e4 status, midlife smoking, and midlife antihypertensive use had reasonable accuracy for predicting a neuropathological diagnosis of AD as well as a clinical diagnosis of all-cause dementia, AD, and VaD. In contrast, those models derived to predict vascular neuropathology only had reasonable predictive accuracy for a clinical diagnosis of VaD. These results were consistency observed despite differences in the sample characteristics between studies, for example, sex distribution (HAAS was males only) and ethnicity (Japanese American vs. Caucasian) and vascular disease risk factor profile.[20] Overall, the results suggest that risk factors for vascular pathology link well to the clinical syndrome of VaD. However, care must be taken when interpreting the data, as the risk models developed in the neuropathology sample had poor fit (i.e., they were not well calibrated) when predicting a clinical diagnosis. Poor model fit may be due to variability in correspondence between clinical diagnosis and neuropathological data often observed in neuropathological studies.[21] The development of novel and more sensitive protocols for the diagnosis of dementia may improve the agreement between clinical and neuropathological data.

Strengths and limitations

A key strength is that the neuropathology analysis is based on a large autopsy sample from a community-based cohort with detailed health assessment undertaken in mid- to later-life. Furthermore, the scores were externally validated, based on a population with very different characteristics and showed similar results. There are some limitations. First, model development was undertaken in the HAAS Study which are all male and of Japanese ancestry. This may affect generalizability; but as highlighted above the results transported well across different samples, for example, Caucasian men and women in the AGES–Reykjavik Study. Second, predictive accuracy of the models was variable, but similar to the predictive accuracy reported for other scores developed to predict clinical dementia,[1,2,19] and to predict AD (i.e., amyloid plaques and NFTs) and non-AD (i.e., cerebral amyloid angiopathy, cerebral macro- and microinfarcts, and Lewy body pathology) related pathologies in a sample of participants aged ≥ 85 years.[22] Improvements in dementia prediction may require access to more detailed data including for example from brain imaging, cerebrospinal fluid or plasma based variables. However, this information was not available as such variables are expensive and require specialist equipment and would not be currently feasible for calculating in a general clinical or population-based setting. Third, there is the possibility of selection bias for autopsy as families were more likely to give notification of death for those participants who were coming for follow-up contacts due to dementia. Fourth, we only externally validated the models for predicting a clinical diagnosis of dementia, not for the neuropathology outcomes. Population-based neuropathological studies of dementia are rare and to our knowledge only one other study, the Hisayama Study, has similar data (e.g., information on dementia risk factors in mid-life and neuropathological data available in later-life) to allow validation.[23] Last, the neuropathology staining methods and diagnostic criteria for a clinical diagnosis of dementia were based on the criteria available at the time (e.g., DSM-III-R). With the introduction of new methodology and diagnostic criteria (e.g., NIA-AA and DSM-IV), it is unknown whether this would affect predictive accuracy of the models and requires testing in more recent brain banks.

Clinical utility

The NIA-Regan, NFTs, and vascular models showed reasonable accuracy for predicting AD and vascular related neuropathology as well as a clinical dementia. Importantly, the profile of risk variables, including different combinations of age, APOE e4 status, lifestyle factors (alcohol and smoking), and cardio-metabolic health have been highlighted as key intervention targets in the recent Lancet Commission on Dementia Prevention, Intervention, and Care[24]. Our study therefore extends the Lancet Commission to highlight the impact of the different combinations of risk variables on neuropathological brain changes at death. Strategies targeting different health and lifestyle risks early in life could therefore impact not only clinical symptoms but also brain integrity.

7 | CONCLUSION

This is the first study investigating the predictive potential of mid- to later-life demographic, health, and lifestyle status in addition to APOE e4 carriership for neuropathology changes associated with AD and non-AD lesions. The findings highlight that there is some overlap in risk factors for different pathology lesions of dementia and its subtypes. More work needs to be done to disentangle whether the pathogenesis of the individual vascular risk factors (e.g., hypertension, diabetes, and stroke) are specially linked to a given lesion type or whether the cumulative load and/or timing of disease onset may also play a role in the development of neuropathology. While the clinical prediction results were mixed, they suggest the possibility that models developed for predicting vascular lesions and NFTs could be used to inform the development of new strategies to postpone dementia (namely VaD) as well as reduce the neuropathological burden associated with both AD and vascular lesions.

AUTHOR CONTRIBUTIONS

Villi Gudnason, Lenore J. Launer, and Lon R. White were responsible for data acquisition. Blossom Christa Maree Stephan and Denise M. Gaughan were responsible for data analysis; this was overseen by Lon R. White and Lenore J. Launer. Blossom Christa Maree Stephan, Denise M. Gaughan, and Steven Edland were involved in drafting the manuscript. All authors contributed to reviewing and editing the manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest 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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