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RESEARCH PAPER

Validity of three risk prediction models for dementia or cognitive impairment in Australia

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Abstract

Background: no studies have compared the predictive validity of different dementia risk prediction models in Australia.
Objectives: (i) to investigate the predictive validity of the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI), LIfestyle for BRAin Health (LIBRA) Index and cardiovascular risk factors, ageing and dementia study (CAIDE) models for predicting probable dementia/cognitive impairment in an Australian cohort. (ii) To develop and assess the predictive validity of a new hybrid model combining variables from the three models.
Methods: the Hunter Community Study (HCS) included 3,306 adults aged 55–85 years with a median follow-up of 7.1 years. Probable dementia/cognitive impairment was defined using Admitted Patient Data Collection, dispensing of cholinesterase inhibitors or memantine, or a cognitive test. Model validity was assessed by calibration and discrimination. A hybrid model was developed using deep neural network analysis, a machine learning method.
Results: 120 (3.6%) participants developed probable dementia/cognitive impairment. Mean calibration by ANU-ADRI, LIBRA, CAIDE and the hybrid model was 19, 0.5, 4.7 and 3.4%, respectively. The discrimination of the models was 0.65 (95% CI 0.60–0.70), 0.65 (95% CI 0.60–0.71), 0.54 (95% CI 0.49–0.58) and 0.80 (95% CI 0.78–0.83), respectively.
Conclusion: ANU-ADRI and LIBRA were better dementia prediction tools than CAIDE for identification of high-risk individuals in this cohort. ANU-ADRI overestimated and LIBRA underestimated the risk. The new hybrid model had a higher predictive performance than the other models but it needs to be validated independently in longitudinal studies.

Keywords: dementia risk, cognitive impairment, prognostic models, risk assessment, risk prediction, older people

Key Points

- This is the first study to compare predictive validity of three dementia risk prediction models in an Australian cohort.
- The three models had moderate-to-low ability to discriminate those who developed dementia versus those who did not.
- A new hybrid model developed using machine learning showed better discrimination power than the three models.
- There is a need to further develop and validate models to improve their predictive accuracy.

Introduction

The World Health Organization estimates that the global prevalence of dementia will increase from 55 million in 2021 to 139 million by 2050 [1]. Dementia is characterised by a long preclinical phase of neurological degeneration followed by symptomatic cognitive impairment before the diagnostic criteria are fulfilled. Modifiable risk factors for dementia include low education, hypertension, obesity, hearing loss, traumatic brain injury, alcohol misuse, smoking, depression, physical inactivity, social isolation, diabetes and air pollution [2]. Estimates suggest that even a 10% reduction of

modifiable risk factors through effective interventions can reduce the global burden of dementia by more than a million by 2050 [3].

Risk scores or clinical prediction models assign a probability for developing dementia based on the presence of risk and protective factors [4]. Prediction models can be used by clinicians, researchers and policymakers to identify people most likely to benefit from preventive measures. Unlike diagnosis or case finding models, risk prediction models seek to identify people at high future risk of dementia [5]. The cardiovascular risk factors, aging and dementia (CAIDE) prediction model was developed in 2006 using data from 1,449 Finnish participants [6]. The discrimination power (area under the receiver-operating characteristic curve [AUROC]) was 0.78. Those classified at high risk versus low risk had a 16.4 versus 1.0% risk of developing dementia over 20 years. The AUROC for CAIDE ranged from 0.64 to 0.78 in validation studies [7–9]. Newer prediction models such as the LIfestyle for BRAin Health (LIBRA) Index and the Australian National University-Alzheimer's Disease Risk Index (ANU-ADRI) have a greater number of predictive factors but similar predictive performance to CAIDE in other cohorts [10, 11].

Early identification of individuals at high risk of developing dementia and who may benefit from targeted risk reduction is a public health priority. Dementia-specific population-wide risk reduction, without risk stratification, may be unrealistic and too resource intensive. The predictive power of models varies considerably across settings and countries, and it is imperative that they are validated for use in local contexts. To date, no study has compared the performance of dementia risk prediction models head-to-head in an Australian cohort.

The aim of this study was to directly compare the validity of CAIDE, ANU-ADRI and LIBRA for predicting probable dementia/cognitive impairment. A further objective was to develop a new hybrid model for predicting probable dementia/cognitive impairment by combining relevant variables from the three models and to assess its performance using a machine learning method of deep neural network analysis.

Methods

Study population and data sources

The Hunter Community Study (HCS) included community-dwelling adults aged 55–85 years who resided in Newcastle, New South Wales (NSW), Australia, and commenced in 2004 [12]. Eligible participants were randomly selected from the electoral roll and contacted by post or telephone for consent. Those who could not speak English or were already living in an aged-care facility at the time of recruitment were excluded. Participants ($n = 3,253$) had to self-complete four sets of questionnaires and attended an HCS clinic for baseline clinical measurements. There were three waves of data collection: wave 1 (2004–07), wave 2 (2010) and wave 3 (2013).

A separate consent was obtained to link participant data from Medicare Benefits Schedule, Pharmaceutical Benefits Scheme and the NSW Admitted Patient Data Collection (APDC). The linkage was performed by the Centre for Health Record Linkage [13–15]. The databases link medication claims subsidised by the Australian Government, inpatient and emergency department admissions of the participants.

The current study was approved by the Monash University Human Research Ethics Committee and the results have been reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement [16] (Supplementary Table 1).

Dementia risk prediction model variables

CAIDE includes age, sex, education, hypertension, body mass index, cholesterol, physical activity and APOE ε4 genotype status. ANU-ADRI includes age, gender, educational level, body mass index, history of diabetes, symptoms of depression, high cholesterol, history of traumatic brain injury, smoking, alcohol consumption, social engagement, physical activity, involvement in cognitive activities, fish intake and pesticide exposure [17]. The LIBRA index includes age, gender, education level, depression, hypertension, obesity, smoking, hypercholesterolemia, diabetes, physical inactivity, coronary artery disease (CAD) and alcohol use [18].

Assessment of predictors

In the current study, the variables tested for predictive validity included: age, sex, education, medical and surgical conditions (including history of head injury), food frequency questionnaire for capturing the frequency of fish intake [19], physical activity measured using a pedometer, symptoms of depression assessed using the CES-D scale [20], self-report of smoking status and alcohol intake (the number of standard drinks/week), social interaction assessed using Duke's Social Support Index (DSSI) [21], and cognitive activity recorded using frequency of reading activity. The biometric/clinical measures included were height, weight, blood pressure, Audio Recorded Cognitive Screen (ARCS) (Supplementary Table 2) [22, 23], cholesterol profile and APOE ε4 status.

Outcome definition

The composite outcome of the study was probable dementia or cognitive impairment, defined as having a history of cholinesterase inhibitor or memantine dispensing, had a dementia diagnosis recorded in the APDC (ICD-10 codes G30.0, G30.1, G30.8 and G30.9) or the final ARCS score below 85 (out of 140) at the end of 7 years. Dispensing cholinesterase inhibitors or memantine was ascertained through linkage to the PBS. Several studies have utilised PBS dispensing records to define mild-to-moderate Alzheimer's

disease [24, 25]. APDC has been studied for predictors of hospitalisation and health service utilisation [26–28].

Statistical analysis

We performed multiple imputation (number of iterations = 10) for the missing data using the fully conditional specification method (Supplementary Table 3) [29]. Participant characteristics were described using mean and standard deviation (SD), median and interquartile range (IQR) or numbers and percentages as appropriate. Pearson's χ^2 tests were used to compare the scores of participants with and without dementia. The level of statistical significance was set at $P \leq 0.05$ for all analyses.

The predictive performance of the models was analysed based on discrimination and calibration methods. Discrimination (ability to distinguish between the person who will and will not develop dementia during the entire follow-up) was assessed using AUROC, also known as the concordance statistic (c-statistic). The c-statistic ranges from 0.5 to 1; a value of 1 denotes perfect predictive ability and 0.5 represents prediction no better than chance [5].

Calibration (agreement between the observed and expected frequency of dementia) is presented as calibration plots. We calculated the intercept and slope of the calibration models to assess whether the prediction under-or-overestimated the risk of dementia [30]. The equation for calculation was available only for the CAIDE model and for other models we estimated the probability based on the incidence of dementia in each quartile or tertiles of scores reported in previously published studies [17, 18].

We subsequently developed a hybrid model from variables used in all the above models for prediction of the outcome using deep learning—a subset of machine learning utilising neural networks [31]. There were 17 nodes (number of variables) in input layers, two hidden layers of 50 and 25 nodes (experimentally chosen), and one node output layer (binary outcome) [32, 33]. The data set was split into two; 80% of the data were used for training the model and 20% were used to test the calibration and discrimination performances of the model. The rectified linear unit activation function was used in each layer of the model, and sigmoid activation function for binary classification was used in the last layer [34]. The loss was calculated by binary cross entropy. We did not categorise the continuous variables to reduce their loss of predictive ability [35].

We tested the minimum sample size (post hoc) requirement based on the expected c-statistic of 0.78 (0.72–0.84) as in the development study of CAIDE [6]. The targeted standard error was 0.0306, with an expected 95% confidence interval width of 0.12, and assuming normal distribution of the scores, we calculated that we needed a minimum of 2,125 participants and 85 events to achieve the desired precision of the c-statistic [36, 37].

To estimate the possible number of dementia cases that may have been missed, we used the dementia transition probabilities during each year of life as reported by Nguyen *et al*. [38] from Alzheimer's Australia [39]. We calculated the age-based expected prevalence of all cause-dementia in the HCS cohort to be 182–302 (5.5–9.4%), if all participants had completed their 6–10 years of follow-up (Supplementary Table 4 and Figure 1).

The analysis was performed using Statistical Analysis Software (SAS) version 9.4, SAS Institute and Statistical Package for the Social Sciences version 28.0, IBM. The development analysis was done using TensorFlow (version 2.0) provided by Google using Keras (version 2.3.1) for training and testing a deep neural network model in Python (version 3.7.7). Sample size calculation was performed using Software for Statistics and Data Science version 17.0, StataCorp.

Results

A total of 3,306 participants were followed up for a median (IQR) of 7.1 (1.8) years. The mean (SD) age of the cohort on enrolment was 63.8 (7.8) years and 53% were females (Table 1). More than half of the cohort had 10 or more years of formal education, more than one-third had hypertension, over half were physically inactive, one-third had obesity, more than one-third smoked, 27.7% had at least one allele of APOE ε4, 15% had a history of CAD, 15% had symptoms of depression and 12% had diabetes. A total of 120 (3.6%) participants were deemed to have developed probable dementia/cognitive impairment during the follow-up (45 participants based on the PBS, 55 based on diagnoses recorded in the APDC, 33 based on the ARCS and 13 based on both PBS and APDC).

Those who developed dementia were significantly older (69.4 [7.9] versus 63.6 [7.8], $P < 0.001$). There was no difference in the other risk factors between people who developed and did not develop dementia; diabetes (15 versus 12.2%, $P = 0.332$), history of CAD (18.3 versus 14.7%, $P = 0.270$), symptoms of depression (20 versus 15%, $P = 0.132$), physical inactivity (76.7 versus 68.2%, $P = 0.051$) and presence of APOE ε4 (31.7 versus 27.6%, $P = 0.327$). All three models gave higher risk scores for those who developed dementia: ANU-ADRI (2 [17] versus −4 [11], $P < 0.001$), LIBRA (6.8 [7.6] versus 4.1 [5.4], $P < 0.01$) and CAIDE (9.63 versus 9.32, $P = 0.139$). The standardised mean difference of the three models for people with and without outcome was 0.627, 0.620 and 0.124 for ANU-ADRI, LIBRA and CAIDE, respectively. The complete ARCS data were available only for 297 participants; those who developed dementia ($n = 55$) had a significant decrease in the ARCS score over time with a mean reduction of 30.1 (1.9).

Discriminant validity of models

The AUROC was 0.54 (95% CI 0.49–0.58) for CAIDE, 0.65 (95% CI 0.60–0.71) for LIBRA and 0.65 (95% CI 0.60–0.70) for ANU-ADRI (Figure 1). The CAIDE score had a sensitivity of 69.2% and specificity of 39.7% at a cut-off of 8.5, ANU-ADRI had a sensitivity of 71.7% and

Table 1. Baseline characteristics of the HCS cohort (n = 3,306)

Age in years, mean (SD)	63.8 (7.8)
Female sex, *n* (%)	1,753 (53%).
≥10 years of education, *n* (%)	2,081 (62.9%)
Systolic blood pressure in mm of Hg, mean (SD)	136 (18.7)
Body mass index (kg/m ^{2}), mean (SD)	28.7 (5.04)
Daily step count using pedometer, median (IQR)	6,514 (4153)
Total cholesterol in mmol/L, mean (SD)	5.05 (1.03)
History of head injury, *n* (%)	573 (17.3%)
Depressive symptoms (CESD) *n* (%)	501 (15.1%)
Type 2 diabetes mellitus, *n* (%)	402 (12.2%)
Smoking status, *n* (%)	
Ex-smoker	1,257 (38%)
Current smoker	254 (7.7%)
Alcohol consumption, *n* (%)	2,432 (73.5%)
DSSI, mean (SD)	28.18 (3.2)
Number of days of reading activity/week, median (IQR)	4 (0.37)
Fish intake per day in grams, mean (SD)	34.6 (39)
History of CAD, *n* (%)	490 (14.8%)
APOE ε4, *n* (%)	917 (27.7%)
CAIDE score, mean, SD	9.32 (2.48)
ANU-ADRI score, median (IQR)	−4 (11)
LIBRA score, median (IQR)	4.2 (5.6)

ANUADRI; Australian National University- Alzheimer's disease Risk Index, LIBRA; LIfestyle for BRAin Health Index, CAIDE; Cardiovascular risk factors, aging, and dementia study; CAD- Coronary Artery Disease; SD- Standard Deviation; IQR- Inter Quartile Range; CESD-Centre for Epidemiologic Studies Depression

specificity of 46.8% at −4.5 and LIBRA had a sensitivity of 73.3% and specificity of 48% at 3.9 for the outcome. The positive predictive values were 4.1% for CAIDE, 4.9% for ANU-ADRI and 5% for LIBRA. The negative predictive values were 97.2, 97.7 and 97.9%, for CAIDE, ANU-ADRI and LIBRA, respectively.

Calibration

The mean estimated risk (mean calibration) by CAIDE was 4.7% (4.0), ANU-ADRI was 19.0% (5.0) and LIBRA was 0.5% (0.2). The calibration intercept and slope were as follows: CAIDE (0.024 and 0.42), ANU-ADRI (−0.036 and 0.381) and LIBRA (0.015 and 4.01).

Hybrid model

The variables in the hybrid model were age, sex, education, systolic blood pressure, BMI, physical activity, total cholesterol, history of head injury, depression, diabetes mellitus, smoking status, alcohol consumption, social activity, cognitive activity, fish intake, history of CAD and APOE ε4. The AUROC of the hybrid model was 0.80 (95% CI 0.78–0.83), and the mean calibration was 3.4%.

The risk in the validation cohort (20% subgroup) was 3.4% (24 of 661 participants). The model had a slope of 0.96 and intercept of 0.016 (Figure 2).

Discussion

Head-to-head comparison of three dementia risk prediction models in the same cohort has highlighted the variability in predictions. Although all three models assigned a higher mean score for people who developed probable dementia/cognitive impairment at the end of follow-up, the absolute risk assigned to the cohort varied from 0.5 to 19%. ANU-ADRI covered more of the risk and protective factors related to dementia, followed by the LIBRA and the CAIDE models. ANU-ADRI may be highly sensitive to risk modification in intervention studies, which can motivate behavioural change.

Higher mean age, higher percentage of APOE ε4 allele, lower physical activity levels and a slightly higher percentage of diabetes and CAD than expected were observed in people with dementia. At least one of these variables was present in all the three models. There was no difference in other risk factors such as hypertension and hypercholesterolemia. This may reflect clinical practice within Australia and subsidised access to pharmacological management. We could not find any difference in BMI, alcohol intake, smoking, social activity, cognitive activity or education level between those people with and without dementia.

The discriminative accuracy of dementia prediction models varied from 0.49 to 0.89 in previous studies [40]. A recent systematic review of dementia prediction models used a cut-off for predictive capacity based on AUC values of 0.9–1.0, 0.7–0.9 and < 0.7 as high, moderate and low, respectively [41]. Thus, the predictive performances of the three models were moderate to low in the HCS. The discriminative power of ANU-ADRI and LIBRA was better than that of CAIDE, despite some previous studies demonstrating moderate predictive power for CAIDE [8, 42]. This could be because of the smaller number of factors included in the CAIDE model, and the differences in categorising the same variable between models, e.g. fewer and wider categories of BMI may attenuate any actual associations with the outcome. Nevertheless, it is also important to note that large studies that attempted adding more factors to the original CAIDE model have shown no improved predictive power [8]. Poor predictive ability of CAIDE has been evident while validating across multiple cohorts [43].

The new hybrid model had better discrimination compared with all the three models. This may have been because of the use of additional variables compared with any one model or the use of continuous variables, which is the recommended best practice and also simpler to apply in a clinical context. However, developmental models tend to be optimistic in predicting the outcome and this result needs to be validated in other cohorts and longitudinal studies [44].

The overall sensitivity and specificity of the models were poor and many of those who are truly at risk may not be identified correctly. The sensitivity and specificity were better for ANU-ADRI and LIBRA compared with CAIDE. The low PPV for all the models suggests that more individuals at high risk will be categorised as low risk, whereas the high

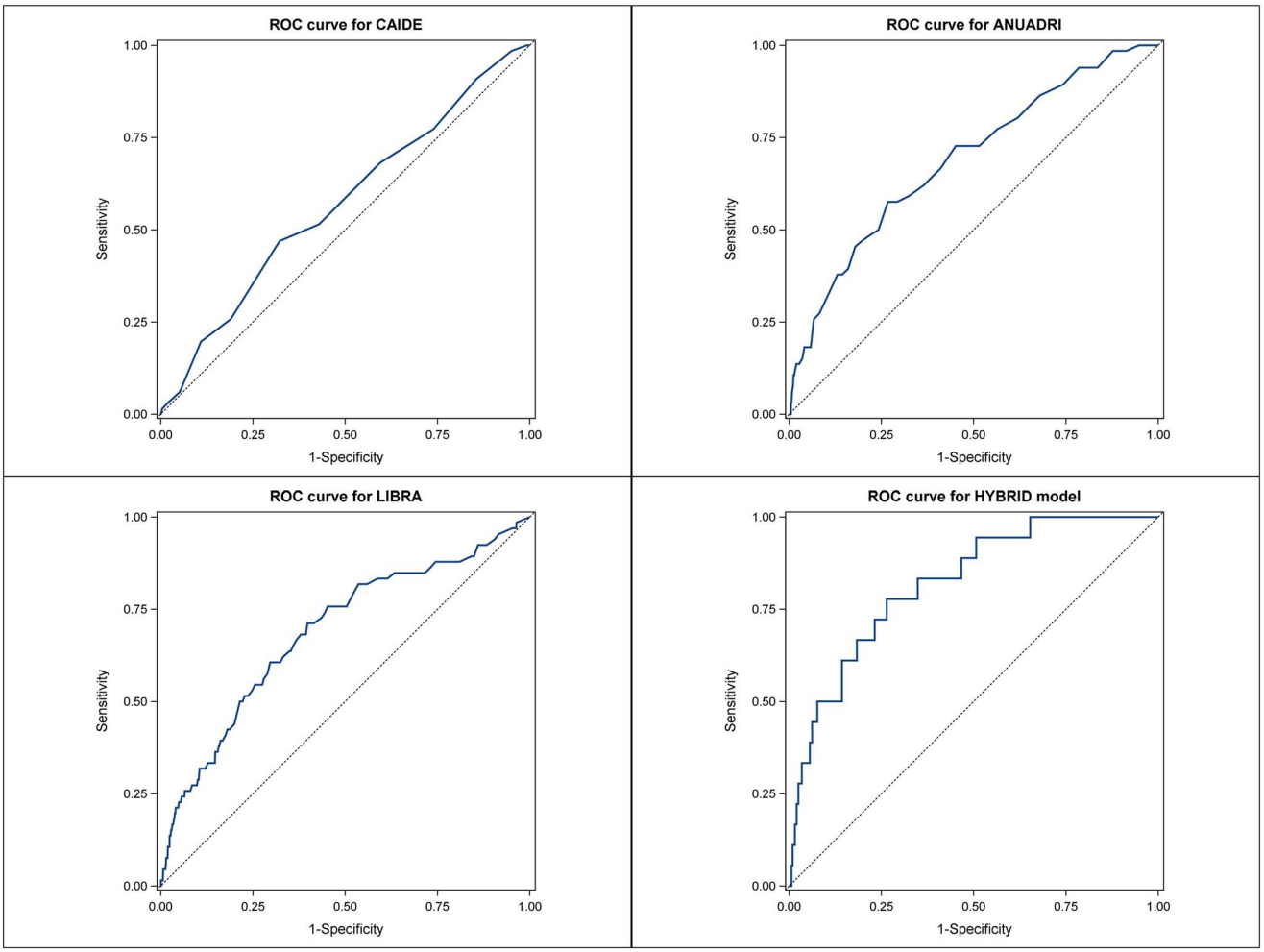

Figure 1. The discrimination of the models. ANUADRI, Australian National University- Alzheimer's disease Risk Index; LIBRA, LIfestyle for BRAin Health Index; CAIDE, Cardiovascular risk factors, aging, and dementia study.

NPV suggests that most low-risk individuals will be rightly classified.

The average predicted risk is higher than the actual dementia rate, indicating that ANU-ADRI overestimated the risk, whereas LIBRA underestimated the risk. Part of the reason for the poor prediction would have been the short follow-up timeframe involved. The CAIDE and LIBRA were developed in studies with follow-up over 16 years [6, 45]. HCS being a population-based study, future cross-sectional analysis of dementia events may help to assess the change in predictive capacity of the models. The mean prediction of the CAIDE model was nearly the same as the actual proportion of dementia cases observed in the population. The slope of CAIDE and ANU-ADRI models was <1, suggesting that the estimated risks were too extreme; higher for high-risk and lower for low-risk individuals. The expected value of calibration intercept is 0, with negative values indicating overestimation (ANU-ADRI) and positive values (LIBRA and CAIDE) indicating underestimation of risks. A calibration curve close to the reference line suggests that predicted risk corresponds well to the observed risk proportions, which was not seen in any of the models.

Our study had a number of strengths and limitations. This is the first study to directly compare multiple dementia prediction models in an Australian cohort. We analysed data from a well-characterised and representative community cohort of middle age adults with a median follow-up of over 7 years. Previous models have focused on validation in an older adult population [41]; however, consistent with an ongoing Cochrane review [46], we focused on the performance of the models in middle age as dementia has a long preclinical phase and many of the risk factors have greater relevance in middle age compared with older age [3]. Some risk factors have been found to even lose their significant association with dementia in the older age [47, 48].

We expected a higher number of dementia cases in the cohort than found; the low incidence observed was potentially because of: (i) dependence on contact with the health system to ascertain dementia (admission to hospital or prescription of a drug) and (ii) potential participation bias

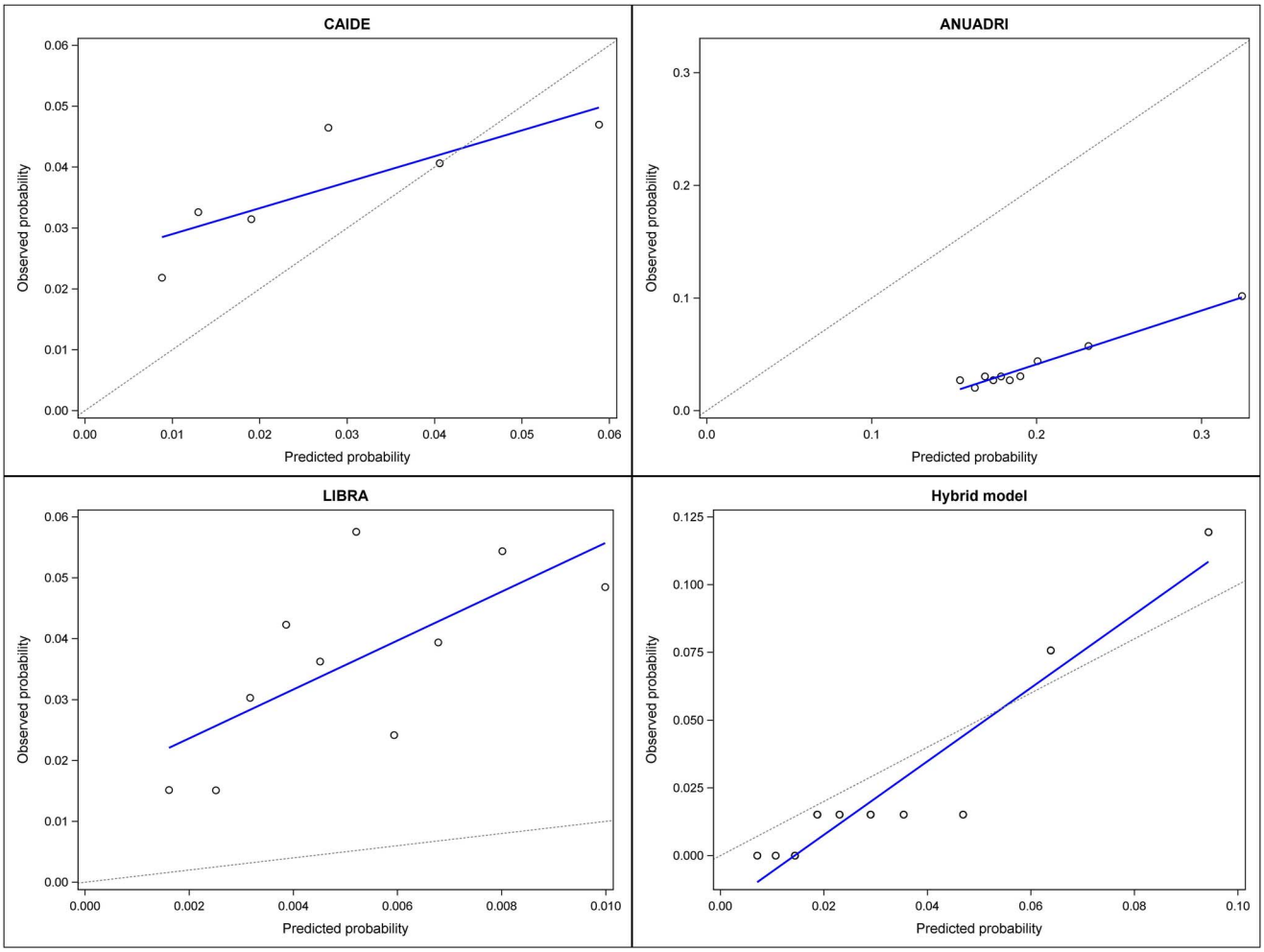

Figure 2. The linear calibration of the prediction models. ANUADRI, Australian National University- Alzheimer's disease Risk Index; CAIDE, Cardiovascular risk factors, Aging, and Dementia; LIBRA, LIfestyle for BRAin Health Index.

given that well-educated and health-conscious people may volunteer and follow through with a cohort study. There was no detailed clinical assessment for diagnosis of dementia in our study, unlike in the developmental studies of the three models. Moreover, studies have shown that the rate of undiagnosed dementia in the community in high-income countries can be as high as 61% [49]; undetected dementia could be greater in the early ages seen in our cohort (mean age of 63 years).

There were limitations associated with our composite outcome measure for dementia. History of cholinesterase inhibitor or memantine has a low sensitivity for detecting all-cause dementia as they are mainly used for mild–moderate Alzheimer's disease (sensitivity of 80%) in Australia [50, 51]. ICD codes from APDC have a sensitivity of >60% for detection of dementia [52]. ARCS cut-off of 85 has a sensitivity of 92% for the diagnosis of dementia, but unfortunately was not available for all patients [22]. By combining multiple outcome measures, as is consistent with previous studies [18, 45], we aimed to improve the overall sensitivity of the outcome measures. Since we used multiple databases, and a cognitive screening tool, it was not possible to know the type of dementia. We also used a number of self-reported measures rather than objective measures, which may have reduced the sensitivity of the risk factors. However, self-report of risk factors is preferred in a setting where the cost of score estimation can be reduced. Another limitation to note is that these tools were primarily designed to identify people with risk factors for dementia that may benefit from interventions and did not include biomarkers which may improve statistical goodness of fit. ANU-ADRI was designed to be solely self-reported, LIBRA focused on modifiable risk factors and CAIDE to identify individuals who may benefit from intensive lifestyle consultations, which may have impacted their overall predictive ability for dementia.

Our study emphasises the predictive capacity of the available models and highlights the importance of developing models with better predictive accuracy. Risk scores are important as they highlight relevant risk and protective factors before the development of actual disease. This provides an opportunity for prevention and to abort or slow the trajectory of dementia. The continuous scores from the model can

also be used to give a personalised target for an individual and to motivate behaviour change. Identifying the best model that correctly predicts the dementia risk in the community is important to address the global burden of dementia.

Conclusion

ANU-ADRI and LIBRA were better dementia prediction tools than CAIDE in an Australian cohort for risk stratification. The predictive validities of all three dementia prediction models were moderate to low. A hybrid model developed using deep neural network analysis performed better than the validated models, but it needs to be tested in future studies.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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Data Availability Statement: The data that support the findings of this study are available from the author, J.A, upon reasonable request.

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