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Original Article

A point-based cognitive impairment scoring system for southeast Asian adults☆

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ABSTRACT

Background: Cognitive impairment is a growing concern in Southeast Asian populations, where the burden of cerebrovascular disease (CeVD) is high. Currently, there is no point-based scoring system for identifying cognitive impairment in these populations.

Objective: To develop and validate a simple point-based Cognitive Impairment Scoring System (CISS) for identifying individuals with cognitive impairment no dementia (CIND) and concomitant CeVD in Southeast Asian populations.

Design: A cross-sectional study using data from two population-based studies.

Setting: Community-based setting in Southeast Asia.

Participants: 1,511 Southeast Asian adults (664 with CIND, 44.0 %).

Measures: Two CISS measures were developed: a basic measure including 11 easily assessable risk factors, and an extended measure incorporating seven additional neuroimaging markers. Performance was evaluated using receiver operating characteristic analysis (AUC) and calibration plots.

Results: The AUC for CISS-basic and CISS-extended were 0.81 (95 %CI, 0.76–0.86) and 0.85 (95 %CI, 0.81–0.89), respectively. Calibration plots indicated satisfactory fit for both the basic measure (p=0.82) and the extended measure (p=0.17). The basic measure included age, gender, ethnicity, education, systolic blood pressure, BMI, smoking history, diabetes, hyperlipidemia, stroke history, and mild/moderate depression. The extended measure added neuroimaging markers of CeVD and brain atrophy.

Conclusion: The CISS provides a quick, objective, and clinically relevant tool for assessing cognitive impairment risk in Southeast Asian populations. The basic measure is suitable for initial community-based screenings, while the extended measure offers higher specificity for probable diagnosis. This point-based system enables rapid estimation of cognitive status without requiring complex calculations, potentially improving early detection and management of cognitive impairment in clinical practice.

Abbreviations: AD, Alzheimer's disease; ARWMHC, Age-related white matter changes; BMI, Body mass index; CeVD, Cerebrovascular disease; CIND, Cognitive impairment no dementia; CISS, Cognitive impairment risk score; EDIS, Epidemiology of Dementia in Singapore study; ICS, Intracranial stenosis; ML, Machine learning; MRI, Magnetic resonance imaging; MTA, Medial-temporal atrophy; NCI, No cognitive impairment; NEURO-BMC, Neurological biomarkers of Blood MRI and Cognition; RF, Random forest; ROC, Receiver operating characteristic curve; VaD, Vascular dementia; WMH, White matter hyperintensities.

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1. Introduction

Dementia prevalence is on the rise worldwide, particularly in Asia due to increased longevity and aging populations. Alzheimer's disease (AD) and Vascular dementia (VaD) have traditionally been regarded as the predominant forms of dementia. However, recent studies have reported a growing trend, in dementia characterized by mixed pathology, such as AD combined with cerebrovascular disease (CeVD) [1,2]. Cardiovascular diseases including CeVD may contribute independently or additively to cognitive decline, often stemming from common risk factors like hypertension, hyperlipidemia, and diabetes [3,4]. Previous studies have shown the frequent occurrence of cerebrovascular lesions, such as white matter hyperintensities (WMH), lacunar infarcts, and cerebral microbleeds (CMB), alongside medial temporal lobe and hippocampal atrophy, all of which contribute to cognitive impairment and dementia [5,6]. These vascular lesions and brain atrophy are detectable through brain magnetic resonance imaging (MRI) [7].

Several risk scores have been developed to assess the risk of dementia in community-based settings. These include the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) score, the Australian National University–Alzheimer Disease Risk Index (ANU-ADRI), and the Lifestyle for Brain Health (LIBRA) index, all of which have undergone validation across diverse samples and cohorts [8–11]. While some of these risk scores have been validated in various Asian cohorts, their specific applicability to Southeast Asian populations necessitates further investigation [10]. A recent systematic review highlighted a geographical imbalance in Asian dementia research, with studies predominantly focusing on East Asian populations and limited data available from Southeast Asian communities [12]. This gap is particularly significant given the high cerebrovascular disease burden in Southeast Asia and evidence suggesting that the predictive performance of existing risk scores varies across different ethnic populations [1,13,14]. Furthermore, most of the existing risk scores were developed and weighted based on Western populations with predominantly Alzheimer's pathology [15,16]. A systematic review of prognostic models for dementia prediction identified 14 tools, of which CAIDE was the most extensively validated [17]. However, CAIDE showed limited predictive accuracy and was primarily validated in Western populations (USA, UK, and Finland), making its generalizability to Southeast Asian populations uncertain. While a validated Visual Cognitive Assessment Test screening tool exists for this population, this tool focuses solely on cognitive testing performance without incorporating vascular risk profiles [18]. Given the high prevalence of vascular pathology in Southeast Asian populations, there remains a critical need for comprehensive risk assessment tools that can effectively capture both VaD and mixed pathology (i.e., AD with CeVD).

Currently, the lack of appropriate measures for assessing cognitive profile in community-based settings may lead to underdiagnosis or delayed identification of cognitive impairment in Southeast Asian populations. Evidence suggests that early intervention through the management of modifiable risk factors may prevent dementia [19]. For individuals with mild cognitive impairment (MCI), previous studies have shown that some individuals may revert to normal cognition, with reported reversion rates ranging from 2.1 % to 53 % [20]. Therefore, early identification of individuals in preclinical and prodromal states is crucial for implementing timely interventions and risk factor management strategies to delay or prevent progression to dementia.

Many machine learning (ML) based models for assessing dementia and cognitive impairment have been proposed, but they have faced significant hurdles in clinical settings. These models often included complex variables, such as polygenic risk scores or time-consuming, invasive, or expensive tests, making them impractical for quick evaluation in primary care [21,22]. Additionally, their "black-box" nature and lack of interpretability hindered their widespread adoption in clinical practice. However, simplifying the outputs of these ML models into easy-to-understand scores could facilitate their integration into clinical practice. Clinicians generally favor tools that provided a clear, transparent method for evaluating risk and could be easily incorporated into their workflows.

Hence, the aim of this study was to develop a Cognitive Impairment Scoring System (CISS) for identifying individuals with cognitive impairment, no dementia (CIND) in the Southeast Asian population. The basic measure of the CISS used primarily vascular risk factors; the extended measure added neurodegenerative markers. The CISS was intended to simplify the assessment of cognitive impairment by providing a rapid and objective evaluation of an individual's cognitive impairment profile through a weighted composite of risk factors. This point-based scoring approach was user-friendly for clinicians, requiring no calculator or computer. This was particularly valuable in primary care settings where physician-patient contact time was limited [23,24].

2. Methods

2.1. Study population

This study used cross-sectional data collected from two studies (1) the Epidemiology of Dementia in Singapore study (EDIS) and (2) the Neurological biomarkers of Blood, MRI and Cognition (NEURO-BMC). Our cohort primarily comprised a multiethnic composition of individuals from Singapore. Each study obtained local ethical approval and all participants provided written informed consent. Participants from the EDIS and NEURO-BMC studies were drawn from larger population-based Singapore Epidemiology of Eye Disease (SEED) study and the Singapore Population Health Studies Multi-Ethnic Cohort (MEC), respectively [25,26]. Both SEED and MEC studies employed random sampling and recruited individuals who were Singapore citizens or long-term residents from the three major ethnic groups: Chinese, Malay, and Indian. Details of the EDIS, SEED and MEC study recruitment and cohort profile have been described previously [5,25,26]. Briefly, individuals were screened using several brief cognitive screenings tools (i.e. the Abbreviated Mental Test and Progressive Forgetfulness Test for EDIS study; the Everyday Cognition scale for NEURO-BMC study [27]) to ensure enrichment with individuals exhibiting some forms of cognitive and functional decline. In total, 1511 (EDIS: 911, NEURO-BMC: 600) participants, aged 45–88 years recruited from the community were included in the study. All participants completed a standardized questionnaires on sociodemographic, medical history and functional ability, clinical laboratory investigations, neuropsychological test battery, and interviews with the participant and an informant. The interview consisted of Clinical Dementia Rating questionnaires covering memory, orientation, judgment, problem-solving, community participation, housework, hobbies, and personal care [28]. Additionally, the Neuropsychiatric Inventory was administered to informant to assess the psychological and behavioral symptoms [29]. The informant was defined as an individual with frequent interactions with the study participant. Most informants were spouses, children, or close relatives. Informants answered questions related to the cognitive and neuropsychiatric functioning of the participants. Details of the Clinical Dementia Rating questionnaires are included in the supplementary materials **Supplement eText 1**, and the neuropsychological battery has been published elsewhere [30].

Among the 1511 participants, 1026 (68.0 %) underwent brain magnetic resonance imaging (MRI) scans at the Clinical Imaging Research centre of the National University of Singapore. Due to limited resources, brain MRI scans were offered to a sub-sample (n = 200) of participants in the NEURO-BMC study who reported subjective cognitive complaints and/or showed borderline or impaired performance on one or more objective neuropsychological test batteries.

The scans were performed using a 3-Tesla (3T) Siemens Magnetom Trio Tim scanner with a 32-channel head coil. The MRI protocol included T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery (FLAIR), and Susceptibility Weighted Imaging (SWI). Only individuals with MRI scans (n = 1026) were included for development of the CISS extended measure. The Fig. 1 flowchart summarizes the participants from

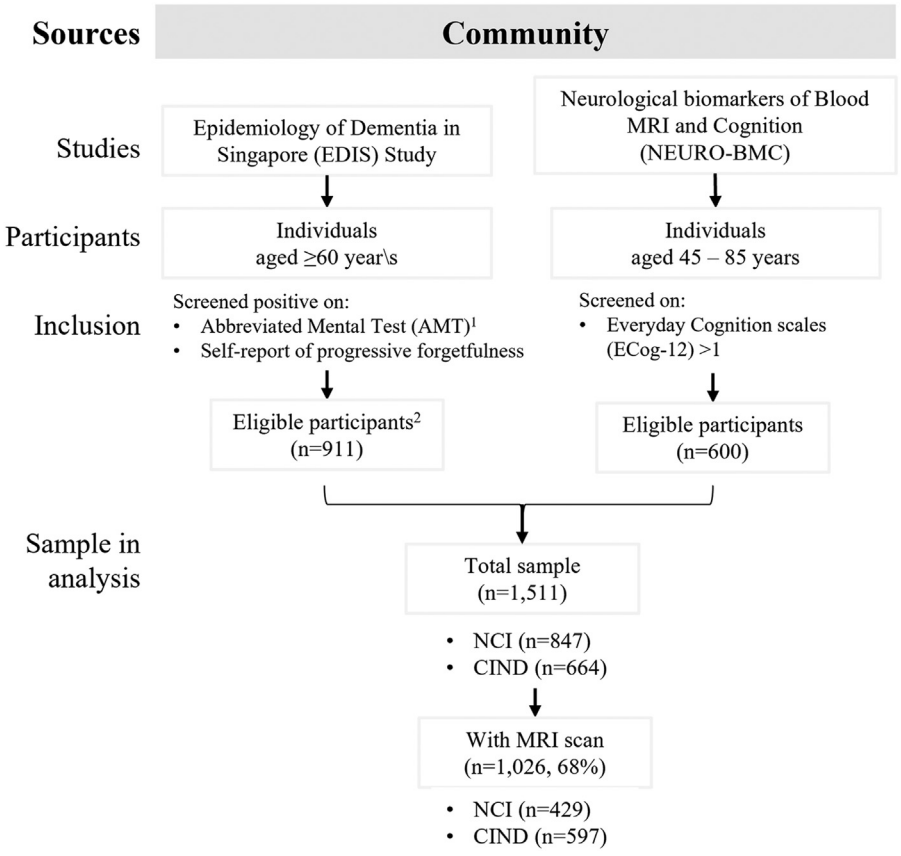

Fig 1. Flowchart detailing the study design and participant flow for the development of the Cognitive Impairment Screening System (CISS)
[1]Inclusion based on an education-adjusted cut-off: AMT≤6 for individuals with below 6 years of formal education, or ≤8 for individuals above 6 years of formal education; Mini-Mental State Examination (MMSE) ≥23 for individuals with above secondary education) or ≥21 for individuals with primary or no education. [2]Excluded participants diagnosed with dementia at baseline (n = 46 EDIS). NCI and CIND denotes no cognitive impairment and cognitive impairment no dementia respectively.

the two studies and the sample included in the current analysis. **Supplement eText 2** provides further details on EDIS and NEURO-BMC study recruitment and examination protocol.

2.2. Candidate variables

The selection of sociodemographic and vascular risk factors for the development of CISS was guided by literature, clinical consensus, and availability within the two studies. Detailed methods of data collection and variable definitions were described in the **Supplement eText 3**. For the basic measure, we considered the following variables: age, sex, ethnicity, years of education, smoking, diabetes, hypertension, hyperlipidemia, blood pressure, body mass index (BMI), stroke history, presence or absence of depressive symptoms, atrial fibrillation, and heart diseases (encompassing the current or past occurrence of myocardial infarction, congestive heart failure, and intervention procedures like angioplasty or stenting).

For the extended measure, we included neuroimaging markers of brain atrophy and markers of CeVD. Brain atrophy was assessed in the central, cortical, and medial temporal (MTA) regions. Cortical atrophy (CA) was graded on the Global Cortical Atrophy Scale [31], and medial temporal atrophy (MTA) was graded on the Scheltens Scale [32]. The extent of atrophy was graded on the scale from 0 to 4, where higher scores indicate more severe atrophy. The five CeVD markers included in this study were graded according to established criteria [5]. These markers were: lacunar infarcts (focal lesions, hyperintense rim on T2 FLAIR based STRIVE criteria[33]); cortical infarcts (focal lesions involving cortical gray matter, following hyperintense rim on FLAIR [33]); cerebral microbleeds (CMBs) (focal rounded areas of hypointensity, blooming effects on SWI sequences using Brain Observer Micro Bleed Scale [34]); intracranial stenosis (ICS) (narrowing of the luminal diameter in any of the intracranial vessels); and white matter hyperintensities (WMH) (graded by the Age-Related White Matter Changes scale). **Supplement eText 4** provides further details on the CeVD markers gradings [35].

For a more detailed assessment of brain atrophy, we conducted an analysis using volumetric measurements (including gray matter, white matter, hippocampal, and intracranial volumes) as an alternative to the visual rating scale. These volumetric measurements were extracted using the automated imaging processing pipeline FreeSurfer v6.0 "recon-all" on T1-weighted images [36]. For a full description of the FreeSurfer processing steps, see Fischl et al. [36].

2.3. Ascertainment of cognitive impairment

Diagnoses of cognitive impairment were determined during weekly consensus meetings attended by a team consisting of clinicians, researchers, and study coordinators. The team reviewed clinical data, blood investigations, informant notes, and neuroimages to adjudicate the validity of results from cognitive performance testing. Cognitive testing was based on a locally validated neuropsychological test battery administered to all participants by trained research personnel in their preferred language. This battery covered seven cognitive domains: five non-memory domains and two memory domains. Further details about the neuropsychological test battery can be found in **Supplement eText 5**. The diagnosis of CIND was given to participants who demonstrated cognitive impairment (>1.5 SD below age-and-education-adjusted norms) in at least one domain while maintaining general functional independence [5]. Functional status was assessed using the Instrumental Activities of Daily Living Scale (IADL) and the Clinical Dementia Rating (CDR) scale. The IADL evaluates eight domains: telephone use, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for medications, and handling finances. The CDR evaluates six domains: memory, orientation, judgment & problem solving, community affairs, home & hobbies, and personal care [37–39]. The majority of study participants (70 %) reported high functional independence, while

30 % reported some functional difficulties, primarily in housekeeping and transportation. CIND was further classified into CIND-mild (impairment in one or two domains) and CIND-moderate (impairment in three or more domains) on the neuropsychological test. In this study, we consolidated the stages of cognitive impairment—mild and moderate—into a single category: CIND.

2.4. Statistical analysis

The characteristics of participants were described by their cognitive status (i.e., NCI or CIND). Continuous variables in baseline data were presented as means ± standard deviation (SD); categorical variables were presented as frequencies and percentages. For descriptive analysis purposes, comparisons were made between individuals with and without cognitive impairment using Chi-square test for categorical variables, Student's *t*-tests for continuous variables with normal distributions, and Mann–Whitney *U* tests for continuous variables with skewed distribution. Missing data were assumed to be missing at random and imputed using multiple imputation (i.e. Iterative Imputer from the 'sklearn.impute' package in Python), using all variables and outcome status [40,41].

2.5. CISS development

A clinical risk scoring framework, AutoScore, was used to develop CISS. AutoScore is an automatic clinical score generator that integrates ML-based variable ranking with multivariable logistic regression. Details regarding the AutoScore framework have been described previously [21,24,42].

The data was first divided into three non-overlapping sets: a training set (60 %): generating feature importance scores and selecting optimal features; a validation set (20 %): for deriving scores, fine-tuning, and conducting intermediate evaluations; and a test set (20 %): for assessing the model's performance. Three ML classifiers were trained separately on all variables to identify CIND, and feature importance scores were generated by averaging the normalized scores derived from these classifiers. The purpose of generating the feature scores was to identify the most informative subset of available features to ensure model parsimony and improve performance. A detailed description of ensemble feature ranking can be found in the **Supplement eText 6** and **eFigure 1** Parsimony plot for variable selection. Next, variables were ranked based on their feature importance scores, and one variable was incrementally added to the AutoScore model to evaluate the resulting enhancement in model performance, as measured by the Area Under the Curve (AUC) on the validation set. The optimal set of predictors was determined by selecting the top N variables with the highest AUC and a percentage change in AUC exceeding 1 %.

Following this, continuous variables were categorized into three groups (0–25th, 25–75th, 75–100th) or based on predefined groups according to local clinical practice guidelines [43] (e.g., BMI based on guidelines on obesity). Categorization facilitated modeling potential non-linear relationships and enhanced interpretability. Subsequently, logistic regression was applied on the categorized variables for score derivation and fine-tuning. Each variable and its categorized values were assigned scores to reflect their contribution to the cognitive impairment estimate. These individual scores were then aggregated to derive the overall cognitive impairment score. The maximum total score attainable was set to 100, with higher scores indicating a greater likelihood of belonging to the CIND group.

2.6. Performance evaluation

Robustness of the CISS was evaluated using bootstrap samples of 100 on the test set. The discriminative ability of the CISS was quantified using receiver operating characteristic analysis with AUC values as the primary metric. AUC values range from 0 to 1, and a value higher than 0.70 indicates that the model exhibits a good discriminatory ability [44]. We reported the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) at optimal threshold (i.e., maximizes the Youden's J statistic (sensitivity + specificity - 1) on the ROC curve). Calibration was evaluated using calibration plots. The Hosmer-Lemeshow χ^2 test was used to assess the goodness-of-fit, where a p-value ≥0.05 indicated a satisfactory fit between the observed and predicted cognitive impairment. All performance metrics were calculated based on the test set, where bootstrapped samples of 100 were applied to calculate 95 % confidence intervals (CI).

All analysis were performed using open-source Python software (version 3.8.8) with the tableone (0.7.12), scikit-learn (1.1.1) and pycaret (3.0) libraries. The point-based scoring was derived using the AutoScore package in R [23,45].

3. Results

3.1. Characteristics of the study participants

Table 1 presents the characteristics of the study sample. Missing data on the included predictors for this study were low (<5 % missing) except for alcohol dependency (60.4 %). Among the 1511 individuals, 664 (44.0 %) were diagnosed as CIND. The CIND group was characterized by older age, a higher proportion Malay, Indian, and other ethnic backgrounds, and a greater prevalence of current/former smokers, depressive symptoms, chronic conditions, and a history of heart disease and stroke compared to the NCI group. Among individuals (n = 1026) with brain MRI scans, the presence of lacunes and ICS was more prevalent among the CIND compared to NCI group. Brain atrophy assessed using the visual ratings and volumetric measures showed a higher degree of atrophy (i.e. more severe gradings, lower brain volume) in the CIND compared to the NCI group (p-value <0.001).

3.2. Selected variables and performance evaluation

Feature importance scores were generated using the top three ML algorithms –logistic regression, random forest (RF), and gradient boosting machine– based on the best AUC. For logistic regression, features were scored based on the magnitude of coefficients. In contrast, for RF and the gradient boosting machine, scores were determined by the mean decrease in impurity measure, the Gini index. **Supplement eTable 1** shows the feature importance scores for the ML algorithms. The basic measure included 11 sociodemographic and vascular risk factors (age, gender, ethnicity, years of education, systolic blood pressure, BMI, ever smoking, diabetes, hyperlipidemia, stroke history, and mild/moderate depression). The extended measure included variables from the basic measure along with seven additional neuroimaging markers (ARWMC, atrophy in central, cortical, and medial temporal areas (MTA), presence of lacunes, cortical infarcts and ICS).

The AUC values and 95 %CI of the CISS were presented in **Supplement eFigures 2A and B**. The discriminative accuracy measured with the AUC of the CISS-basic was 0.81 (95 %CI, 0.76–0.86). Adding visual grading and CeVD markers to the basic model resulted in a higher discriminative ability of 0.85 (95 %CI, 0.80–0.89) for the extended model. In terms of sensitivity (basic: 0.81; extended: 0.77) and NPV (basic: 0.72; extended: 0.70), both CISS measures demonstrated a comparable ability to identify individuals with CIND (true positive cases) and NCI (true negative cases). However, for specificity and PPV, the CISS extended measure exhibited higher specificity (basic: 0.67; extended: 0.75) and PPV (basic: 0.77; extended: 0.81). **Supplement eTable 2** detailed the sensitivity, specificity, PPV and NPV of the two measures. The calibration plots in **Supplement eFigure 3A** and **B** indicated satisfactory fit for both the basic measure (p = 0.82) and the extended measure (p = 0.17) across the decile groups.

Table 1
Participants characteristics according to the presence of cognitive impairment.

	No cognitive impairment (NCI) n = 847	Cognitive impairment no dementia (CIND) n = 664	P-Value
Age	61.1 ± 8.0	70.7 ± 6.8	**<0.001**
Sex (Male)	373 (44.0)	299 (45.0)	0.739
Race			**<0.001**
Chinese	637 (75.2)	198 (29.8)	
Malay	81 (9.6)	237 (35.7)	
Indian	123 (14.5)	229 (34.5)	
Other	6 (0.7)	-	
Years of education	12.3 ± 4.6	5.7 ± 4.6	**<0.001**
Smoker (Ever)	146 (17.2)	181 (27.3)	**<0.001**
Clinical data			
Body mass index (BMI), kg/m^2	24.4 ± 4.1	25.5 ± 4.8	**<0.001**
Blood pressure systolic (SBP), mmHg	130.3 ± 20.5	146.0 ± 19.6	**<0.001**
Blood pressure diastolic (DBP), mmHg	78.0 ± 10.2	76.9 ± 10.8	**0.039**
Diabetes	134 (15.8)	254 (38.3)	**<0.001**
Hyperlipidemia	420 (49.6)	551 (83.0)	**<0.001**
Hypertension	411 (48.5)	578 (87.0)	**<0.001**
Atrial fibrillation (AF)	20 (2.4)	8 (1.2)	0.144
History of heart problem	53 (6.3)	101 (15.2)	**<0.001**
History of stroke	12 (1.4)	36 (5.4)	**<0.001**
Mild/moderate depression	46 (5.4)	69 (10.4)	**<0.001**
Neuroimaging markers			
Intracranial volume, mm^3	1401.0 ± 141.4	1344.6 ± 160.4	**<0.001**
white matter volume, mm^3	426.4 ± 50.3	390.7 ± 49.9	**<0.001**
gray matter volume, mm^3	577.8 ± 52.1	532.3 ± 49.0	**<0.001**
Hippocampal volume, mm^3	7.5 ± 0.9	6.9 ± 0.9	**<0.001**
Lacune (present/absent)	21 (4.6)	123 (18.9)	**<0.001**
Microbleed (present/absent)	18 (3.9)	42 (6.5)	0.086
Intracranial stenosis (present/absent)	26 (5.6)	81 (12.4)	**<0.001**
Cortical infarct (present/absent)	3 (0.7)	20 (3.1)	**0.01**
Age-related white matter changes	4.3 ± 3.5	6.3 ± 4.6	**<0.001**
Central atrophy			**<0.001**
None	63 (13.7)	63 (9.7)	
grade 1	306 (66.4)	363 (55.8)	
grade 2	77 (16.7)	163 (25.0)	
grade 3	15 (3.3)	62 (9.5)	
Cortical atrophy			**<0.001**
None	30 (6.5)	3 (0.5)	
grade 1	303 (65.7)	314 (48.2)	
grade 2	108 (23.4)	259 (39.8)	
grade 3	20 (4.3)	75 (11.5)	
Medial temporal atrophy			**<0.001**
None	152 (33.0)	74 (11.4)	
grade 1	188 (40.8)	309 (47.5)	
grade 2	105 (22.8)	226 (34.7)	
grade 3	16 (3.5)	42 (6.5)	

Continuous variables were expressed as mean (±SD), while categorical variables expressed as number (percentage %). Tests of association with cognitive impairment status for normally distributed continuous variables and categorical variables were performed using student's t-test and chi-square respectively. A two-tailed p-value (≤0.05) was considered statistically significant.

3.3. Score generation and application

The point-based scoring table was presented in Table 2, and the probability of CIND was shown in Table 3. Most individuals had scores ranging between 1 and 80. Variables such as age, ethnicity, years of education, presence of depressive symptoms, presence of lacunes, and a higher degree of brain atrophy were assigned higher score values, indicating their greater contributions to the likelihood of being CIND. The following illustrates the estimation of CIND for two hypothetical individuals:

Case 1: A 75-year-old (=15) Chinese male with six years of education (=4), a BMI of 20.8 kg/m^2 (=0), systolic blood pressure of 130 mmHg, a former smoker (=5) with hyperlipidemia (=7), a history of stroke (=9), no diabetes and depressive symptoms. This individual would have a score of 40 (15 + 4 + 5 + 7 + 9), with an estimated 70.0 % likelihood of being CIND (Fig. 2A).

Case 2: A 60-year-old, non-Chinese (=10) female (=3), with 15 years of education a BMI at 26.3 kg/m^2 (=0), a systolic blood pressure of 155 mmHg (=4), with mild/moderate depression (=9), but no smoking history, diabetes or hyperlipidemia. This individual would have a score of 26 (10 + 3 + 4 + 9) with a 37.0 % likelihood of being CIND (Fig. 2B).

4. Discussion

This study developed a CISS for identifying individuals with CIND in a Southeast Asian community, with our cohort primarily comprising a multiethnic composition of individuals from Singapore. The basic measure included 11 sociodemographic, lifestyle, and vascular risk factors. With comparable sensitivity to the extended measure and easily assessable predictors, the basic measure is ideal for use in initial health assessments or community screenings. In these settings, the priority is to identify as many individuals with CIND as possible for preventive strategies and future monitoring. The extended measure incorporated an additional seven neurodegeneration and CeVD markers. With higher specificity and PPV, the CISS extended measure was more effective for ruling out individuals with no cognitive impairment (NCI), making it appropriate for probable diagnosis. These composite measures were partic-

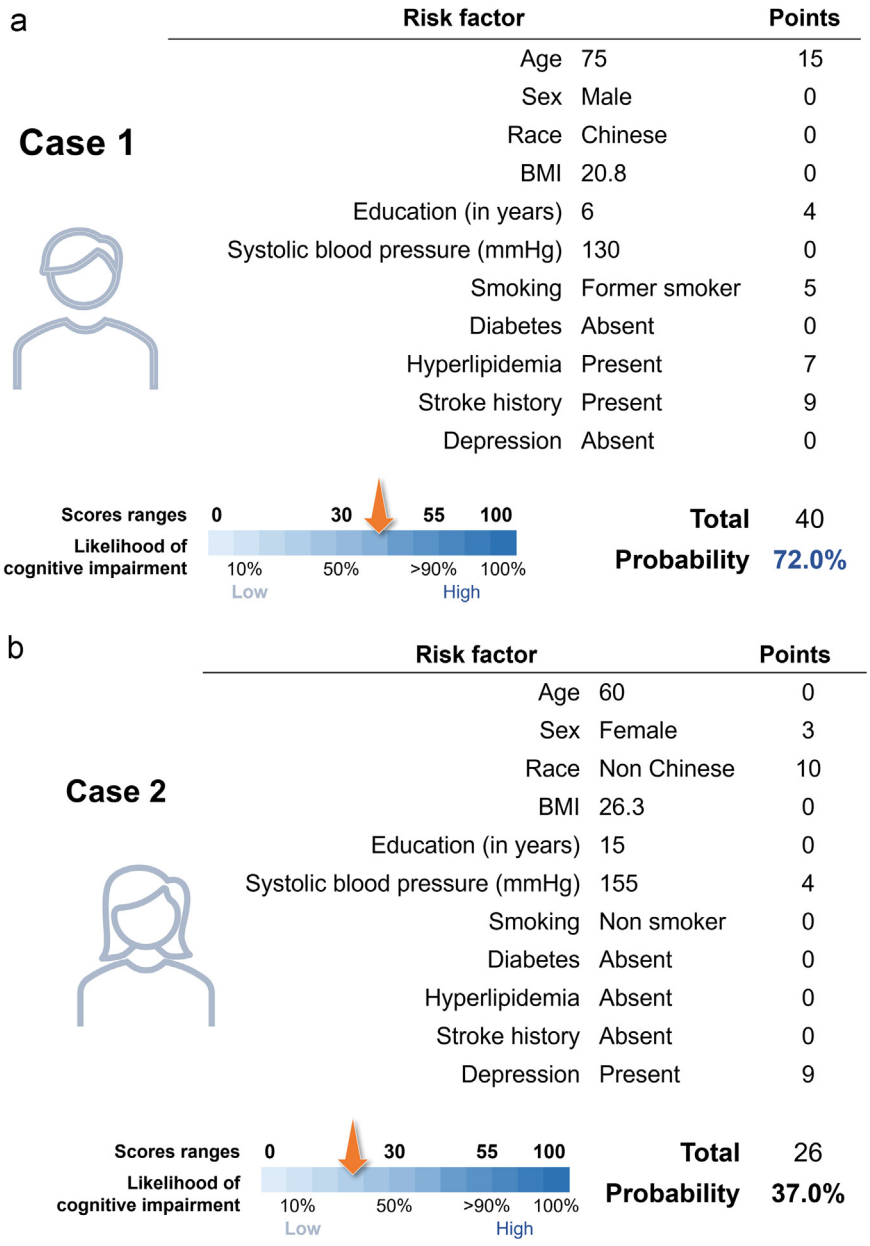

Fig 2. Case examples illustrating the estimation of Cognitive Impairment, No Dementia (CIND) for two hypothetical individuals.

ularly well-suited for identifying individuals with cognitive impairment in Southeast Asia, where VaD or dementia due to mixed pathology (i.e. AD+CeVD) is common. The point-based scoring approach simplified the assessment of cognitive impairment by summing all points for the risk factor profile, without the need for a calculator or computer.

To date, the development of population-specific cognitive assessment tools for Asian populations, particularly Southeast Asian communities, remained limited. While several dementia risk prediction tools developed in Western populations have been validated in Asian cohorts, particularly East Asian populations, these validation studies have shown variable predictive performance (AUC: 0.52–0.78) [10,46]. Moreover, most existing tools focused on dementia risk prediction rather than cognitive impairment assessment. Findings from multidomain prevention trials such as the Multidomain Alzheimer Preventive Trial (MAPT study) and the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [47,48], suggested that interventions are most effective when implemented before substantial cognitive impairment developed. While biomarkers such as cerebrospinal fluid analysis and amyloid-positron emission tomography could identify at-risk individuals, their application outside specialized memory clinics was constrained by cost and practical considerations [49,50]. Therefore, developing a simple cognitive impairment measure could provide a cost-effective solution for early identification of at-risk individuals in broader clinical settings.

The discriminative ability of our basic measure (AUC: 0.81) was comparable to previously reported Western population-based dementia risk scores (AUC: 0.65–0.80) [8,10,11,51]. Comparable studies in Asian populations have shown promising results. For instance, a ML model predicting cognitive impairment in older Chinese adults achieved an AUC of 0.81, although this model incorporated functional disability and cognitive test performance rather than neurodegenerative or cerebrovascular disease markers [52]. Similarly, a Korean study using national health examination data reported an AUC of 0.81 for dementia prediction [53]. Notably, the risk factors identified in these studies—including hypertension, diabetes, a BMI $\leq$18.5 kg/m^2, a history of stroke, and depression—were consistent with those incorporated in our CISS-basic measure, supporting their crucial roles in assessing cognitive impairment.

Table 2
Scoring table for cognitive impairment scoring system (CISS). The table presents the points assigned to demographic, vascular, lifestyle factors, and neuroimaging markers for both the basic and extended measure.

CISS	Value Range	Points	
		Basic	Extended
Age	<60	0	0
	60 – 75	9	7
	>75	15	14
Sex	Male	0	0
	Female	3	3
Ethnicity	Chinese	0	0
	Non-Chinese	10	5
Body mass index (BMI) (kg/m^2)	<18.5	11	4
	18.5 – 30	0	0
	>30	6	2
Years of education	<4	12	8
	4 – 11	4	2
	>11	0	0
Blood Pressure Systolic (mmHg)	<140	0	0
	140 – 160	4	1
	≥160	11	4
Diabetes	Absent	0	0
	Present	8	2
Hyperlipidemia	Absent	0	0
	Present	7	2
Smoking	Never	0	0
	Ever	5	2
Stroke history	Absent	0	0
	Present	9	2
Depression	Absent	0	0
	Present	9	4
Lacune	Absent		0
	Present		5
Cortical infarct	Absent		0
	Present		5
Intracranial stenosis	Absent		0
	Present		2
Age-related white matter changes	<8		0
	8 – 15		2
	>15		7
Central atrophy	Grade 0		0
	Grade 1 and 2		2
	≥ Grade 3		10
Cortical atrophy	Grade 0		0
	Grade 1 and 2		6
	≥ Grade 3		11
Medial temporal atrophy	Grade 0		0
	Grade 1 and 2		4
	≥ Grade 3		10
Maximum points		100	100

Table 3
Probability of cognitive impairment no dementia (CIND) based on cognitive impairment scoring system (CISS) basic and extended measures.

Scores	Basic Probability of CIND (%)	Scores	Extended Probability of CIND (%)
0–4	6	0–4	2
5–10	8	5–10	4
10–14	13	10–14	7
15–19	19	15–19	14
20–24	28	20–24	25
25–29	38	25–29	41
30–34	50	30–34	59
35–39	61	35–39	75
40–44	72	40–44	86
45–49	80	45–49	93
50–54	87	≥ 50	> 95
≥ 55	> 90		

In addition, our study found that ethnicity and years of education significantly influenced CIND diagnosis, given their notable weighting in the CISS measure. Although existing evidence consistently links lower educational attainment to an increased risk of cognitive impairment and dementia in both Western and Asian populations, our research highlighted ethnic disparities [54]. Compared to participants of Chinese ethnicity, those with other ethnicities (i.e., Malays and Indians) had a higher prevalence of vascular risk factors and greater burden of CeVD. These associations were consistent with previous longitudinal studies that have established temporal relationships between vascular risk factors and cognitive decline [55,56].

In this study, smoking contributed to the likelihood of having a CIND diagnosis. However, evidence regarding associations with CIND was weak for other risk factors such as alcohol dependency, AF, and a history of heart disease. We did not include these risk factors in our CISS measure because they had low feature importance scores. For example, over 90 % of the sample analyzed did not report alcohol dependency or AF condition, which limited our ability to detect significant associations due to these small number of cases.

Notably, when neuroimaging markers were added to the basic measure, the specificity improved 14.0 % (from 0.67 to 0.77). This suggested that neuroimaging markers were potentially helpful for ruling out individuals with NCI. We also observed that the influence of blood pressure, presence of diabetes, hyperlipidemia, and stroke history on CIND diagnosis was attenuated in the extended measures. We reasoned that neurodegeneration and CeVD burden conferred an independent effects on cognitive impairment diagnosis, providing additional discriminative utility beyond the sociodemographic, vascular, and lifestyle risk factors used in the basic measure.

In our evaluation of the discriminative accuracy between visual rating scales and volumetric measurements for assessing neurodegeneration, we found that both approaches exhibited comparable performance. Previous research on brain atrophy had yielded mixed results regarding the discriminatory power of visual rating scales vs volumetric measurements. While one study found that volumetric measures offer enhanced discriminatory power and display a stronger correlation with memory and functional scores, others have reported similar discriminatory power between the two methods [57,58]. Nonetheless, the measure using the visual rating scales was chosen because of its brevity and ease of interpretation for use in clinical practice.

Although existing works have considered the contribution of vascular and lifestyle factors to the cognitive impairment and dementia, our study is unique for several reasons. First, the derivation of the CISS weighted each sociodemographic, vascular and lifestyle risk factor, as well as neurodegeneration and CeVD marker, based on its relevance to cognitive diagnosis in the Southeast Asian population. Second, existing works primarily focused on traditional risk factors of dementia, which may not fully capture the vascular brain injury and CeVD burden best evaluated by MRI (when available) to identify relevant lesions (i.e., lacunes and WMH) in vivo [4,59]. Our CISS-extended measure integrated neurodegenerative and CeVD markers into a single conceptual framework closely reflecting VaD, and/or dementia of mixed pathology. Additionally, we utilized multiple neuroimaging markers, which provide an integrated measurement of vascular brain damage and abnormalities. Visual grading of brain atrophy can be performed quickly and does not require specialized equipment, unlike volumetric measures. This makes it suitable for use in clinical practice and applicable in population-based settings. Third, we were able to simplify the evaluation of CIND and translate our findings into a simple point-based scoring. These measures can effectively differentiate between individuals with normal cognition and those with CIND in a community-based setting.

Our study had several limitations. First, its cross-sectional design prevented assessment of the impact of vascular and lifestyle risk factors, as well as neurodegenerative and CeVD burden, on cognitive decline over time. However, both NEURO and EDIS studies have ongoing longitudi-

nal follow-up visits that will enable future examination of these temporal relationships. Second, in this study, the diagnoses of CIND-mild and CIND-moderate were combined under CIND to focus on early identification of cognitive impairment rather than stratifying by impairment severity. This decision was also due to the relatively low prevalence of CIND-moderate cases in the NEURO-BMC cohort (aged ≥45 years), which would have limited statistical power for separate analyses. While this approach aligned with our primary objective of identifying individuals at earlier stages of cognitive decline where interventions might be most effective, it precludes examination of how the CISS measure performs across different severity levels of cognitive impairment. Future studies with larger samples could help evaluate the tool's utility across the full spectrum of cognitive decline. Third, factors such as lifestyle and psychosocial influences, which are associated with cognitive impairment and dementia, were not included in the development of the CISS due to their unavailability in the baseline EDIS dataset. Notably, the EDIS follow-up assessments now include additional lifestyle variables such as diet and physical activity, which will provide a more comprehensive understanding of these factors' contributions in future analyses. Fourth, while continuous predictors generally provided more granular information for modeling complex relationships, our CISS measure converted several continuous variables into categories to enhance clinical utility. Although the categorizations for blood pressure and BMI followed the recommended national guidelines for clinical thresholds, age and years of education were categorized using tertiles derived cutpoints, which may have introduced some information loss. Nevertheless, similar approaches have been successfully implemented in widely-used clinical risk scores such as the Singapore-modified Framingham Risk Score, where categorical point allocation has proven effective for rapid risk stratification in clinical practice [60]. In addition, efforts were made to mitigate potential bias by performing the categorization after feature selection. We also conducted additional analyses comparing visual grading variables against continuous neuroimaging markers when assessing brain atrophy in the extended CISS measure. Fifth, the screening criteria (i.e., ECog-12 for NEURO-BMC and Abbreviated Mental Test and Progressive Forgetfulness Test for the EDIS study) warrant consideration when interpreting the findings. The generalizability of the findings may be limited by selection criteria. For instance, the EDIS study may have missed individuals with very mild symptoms who screened negative, while the NEURO-BMC study's targeted recruitment approach may have selected individuals with higher cognitive concerns. Future validation studies in broader community-based samples would help confirm the tool's generalizability. Lastly, further validation with other Southeast Asian populations is necessary to replicate these findings and reinforce the utility of the CISS measure in identifying individuals with CIND across various racial and ethnic communities. This will ensure that the measure is robust and applicable to diverse sub-ethnic groups within the Southeast Asian region.

In conclusion, the CISS measures offer a means to identify CIND in Southeast Asian communities. The basic measure, tailored for a broader range of clinical settings, addresses the practical demands of everyday clinical practice, while the extended measure meets the need for precise evaluations in specialized settings. Its point-based scoring system simplifies the assessment of the multifactorial nature of cognitive impairment and dementia, enabling clinicians to rapidly evaluate an individual's cognitive status during routine clinical visits.

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Consent statement

Subjects were recruited from the community, and all signed Institutional Review Board-approved consent forms.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI and AI-assisted technologies were in the writing process.

Conflicts of Interest

The authors have no conflicts of interest to report.

CRediT authorship contribution statement

Wei Ying Tan: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiangyuan Huang:** Data curation. **Caroline Robert:** Data curation. **Mervin Tee:** Data curation. **Christopher Chen:** Writing – review & editing. **Gerald Choon Huat Koh:** Writing – review & editing, Investigation. **Rob M. van Dam:** Writing – review & editing, Investigation. **Nagaendran Kandiah:** Writing – review & editing. **Saima Hilal:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100069.

References

[1] Lam BYK, Yiu B, Ampil E, et al. High burden of cerebral white matter lesion in 9 Asian cities. Sci Rep 2021;11(1):11587.
[2] Zhao D. Epidemiological features of cardiovascular disease in Asia. JACC: Asia 2021;1(1):1–13.
[3] Ji F, Chai YL, Liu S, et al. Associations of blood cardiovascular biomarkers with brain free water and its relationship to cognitive decline: a diffusion-MRI study. Neurology 2023;101(2):e151–63.
[4] Chen C, Homma A, Mok V, et al. Alzheimer's disease with cerebrovascular disease: current status in the Asia–Pacific region. J Intern Med 2016;280(4):359–74.
[5] Hilal S, Liu S, Wong TY, et al. White matter network damage mediates association between cerebrovascular disease and cognition. J Cereb Blood Flow Metab 2021;41(8):1858–72.
[6] Sun W, Huang L, Cheng Y, et al. Medial temporal atrophy contributes to cognitive impairment in cerebral small vessel disease. Front Neurol 2022;13:858171.
[7] Chung CP, Ihara M, Saima H, Chen L-K. Targeting cerebral small vessel disease to promote healthy aging: preserving physical and cognitive functions in the elderly. Arch Gerontol Geriatr 2023:104982.
[8] Stephan BC, Pakpahan E, Siervo M, et al. Prediction of dementia risk in low-income and middle-income countries (the 10/66 Study): an independent external validation of existing models. The Lancet Global Health 2020;8(4):e524–35.
[9] Deckers K, Barbera M, Köhler S, et al. Long-term dementia risk prediction by the LIBRA score: a 30-year follow-up of the CAIDE study. Int J Geriatr Psychiatry 2020;35(2):195–203.
[10] Chosy EJ, Edland SD, Gross N, et al. The CAIDE dementia risk score and the honolulu-asia aging study. Dement Geriatr Cogn Disord 2019;48(3–4):164–71.
[11] Anstey KJ, Cherbuin N, Herath PM. Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. Prev Sci Aug 2013;14(4):411–21.
[12] Islam B, Li T, Xu M, et al. Emerging trends in cognitive impairment and dementia among older populations in Asia: a systematic review. J Glob Health Nov 8 2024;14:04233.
[13] Andrews SJ, Boeriu AI, Belloy ME, et al. Dementia risk scores, APOE, and risk of Alzheimer disease: one size does not fit all. medRxiv Aug 16 2024.
[14] Venketasubramanian N, Yoon BW, Pandian J, Navarro JC. Stroke epidemiology in South, East, and South-East Asia: a review. J Stroke Sep 2017;19(3):286–94.
[15] Low A, Prats-Sedano MA, Stefaniak JD, et al. CAIDE dementia risk score relates to severity and progression of cerebral small vessel disease in healthy midlife adults: the PREVENT-Dementia study. J Neurol Neurosurg Psychiatry 2022;93(5):481–90.
[16] Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Prevalence Chen CL-H. risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. J Neurol Neurosurg Psychiatry 2017.

[17] Mohanannair Geethadevi G, Quinn TJ, George J, et al. Multi-domain prognostic models used in middle-aged adults without known cognitive impairment for predicting subsequent dementia. Cochrane Database Syst Rev Jun 2 2023;6(6) CD014885.
[18] Soo SA, Kumar D, Leow YJ, Koh CL, Saffari SE, Kandiah N. Usefulness of the visual cognitive assessment test in detecting mild cognitive impairment in the community. J Alzheimers Dis 2023;93(2):755–63.
[19] Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. Lancet Aug 8 2020;396(10248):413–46.
[20] Qin Y, Han H, Li Y, et al. Estimating bidirectional transitions and identifying predictors of mild cognitive impairment. Neurology Jan 17 2023;100(3):e297–307.
[21] Xie F, Ong MEH, Liew JNMH, et al. Development and assessment of an interpretable machine learning triage tool for estimating mortality after emergency admissions. JAMA Network Open 2021;4(8) e2118467-e2118467.
[22] Tan WY, Hargreaves C, Chen C, Hilal S. A machine learning approach for early diagnosis of cognitive impairment using population-based data. J Alzheimers Dis 2023;91(1):449–61.
[23] Xie F, Chakraborty B, Ong MEH, Goldstein BA, Liu N. AutoScore: a machine learning-based automatic clinical score generator and its application to mortality prediction using electronic health records. JMIR Med Inform Oct 21 2020;8(10):e21798.
[24] Ren L, Liang J, Wan F, Wang Y, Dai XJ. Development of a clinical risk score prediction tool for 5-, 9-, and 13-year risk of dementia. JAMA Network Open 2022;5(11) e2242596-e2242596.
[25] Majithia S, Tham YC, Chee ML, et al. Cohort Profile: the singapore epidemiology of eye diseases study (SEED). Int J Epidemiol Mar 3 2021;50(1):41–52.
[26] Liew SJ, Lee JT, Tan CS, Koh CHG, Van Dam R, Muller-Riemenschneider F. Sociodemographic factors in relation to hypertension prevalence, awareness, treatment and control in a multi-ethnic Asian population: a cross-sectional study. BMJ Open May 19 2019,;9(5):e025869.
[27] Farias ST, Mungas D, Harvey DJ, Simmons A, Reed BR, DeCarli C. The measurement of everyday cognition: development and validation of a short form of the Everyday cognition scales. Alzheimer's Dementia 2011;7(6):593–601.
[28] Hilal S, Cheung CY, Wong TY, Schmetterer L, Chen C. Retinal parameters, cortical cerebral microinfarcts, and their interaction with cognitive impairment. Int J Stroke Jan 2023;18(1):70–7.
[29] Cummings J. The Neuropsychiatric Inventory: development and Applications. J. Geriatr Psychiatry Neurol Mar 2020;33(2):73–84.
[30] Zhang H, Wang Y, Zhang Y, et al. Housing status is protective of neuropsychiatric symptoms among dementia-free multi-ethnic Asian elderly. BMC Geriatr Aug 23 2024;24(1):698.
[31] Wattjes MP, Henneman WJ, van der Flier WM, et al. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64–detector row CT. Radiology 2009;253(1):174–83.
[32] Korf ES, Wahlund L-O, Visser PJ, Scheltens P. Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. Neurology 2004;63(1):94–100.
[33] 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):822–38.
[34] Cordonnier C, Potter GM, Jackson CA, et al. Improving interrater agreement about brain microbleeds: development of the brain observer MicroBleed scale (BOMBS). Stroke 2009;40(1):94–9.
[35] Wahlund L-O, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32(6):1318–22.
[36] Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33(3):341–55.
[37] Yemm H, Robinson DL, Paddick SM, et al. Instrumental activities of daily living scales to detect cognitive impairment and dementia in low- and middle-income countries: a systematic review. J Alzheimers Dis 2021;83(1):451–74.
[38] Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology Nov 1993;43(11):2412–14.
[39] Nosheny RL, Yen D, Howell T, et al. Evaluation of the electronic clinical dementia rating for dementia screening. JAMA Netw Open Sep 5 2023;6(9):e2333786.
[40] Pedregosa F, Varoquaux G, Gramfort A, et al. Scikit-learn: machine learning in Python. J. Mach. Learn. Res 2011;12:2825–30.
[41] Van Buuren S, mice Groothuis-Oudshoorn K. Multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67.
[42] Saffari SE, Ning Y, Xie F, et al. AutoScore-Ordinal: an interpretable machine learning framework for generating scoring models for ordinal outcomes. BMC Med Res Methodol 2022;22(1):1–13.
[43] Obesity Clinical practice guidelines. Ministry of health (MOH) Singapore. Accessed Jan 24, 2024. https://www.moh.gov.sg/docs/librariesprovider4/guidelines/obesity-cpg_summary.pdf.
[44] Fangyu L, Hua H. Assessing the accuracy of diagnostic tests. Shanghai Arch Psychiatry 2018;30(3):207.
[45] Nan L. AutoScore. Github. Accessed 24 Jan, 2024. https://github.com/nliulab/AutoScore.
[46] Licher S, Yilmaz P, Leening MJG, et al. External validation of four dementia prediction models for use in the general community-dwelling population: a comparative analysis from the Rotterdam Study. Eur J Epidemiol Jul 2018;33(7):645–55.
[47] Deckers K, Zwan MD, Soons LM, et al. A multidomain lifestyle intervention to maintain optimal cognitive functioning in Dutch older adults-study design and baseline characteristics of the FINGER-NL randomized controlled trial. Alzheimers Res Ther Jun 13 2024;16(1):126.
[48] Vellas B, Gillette-Guyonnet S, Touchon J, et al. Mapt Study: a multidomain approach for preventing Alzheimer's Disease: design and baseline data. J Prev Alzheimers Dis 2014:1–10.
[49] Solomon A, Stephen R, Altomare D, et al. Multidomain interventions: state-of-the-art and future directions for protocols to implement precision dementia risk reduction. A user manual for Brain Health Services-part 4 of 6. Alzheimers Res Ther Oct 11 2021;13(1):171.
[50] Wisch JK, Gordon BA, Boerwinkle AH, et al. Predicting continuous amyloid PET values with CSF and plasma Abeta42/Abeta40. Alzheimers Dement (Amst) Jan-Mar 2023;15(1):e12405.
[51] Geethadevi GM, Peel R, Bell JS, et al. Validity of three risk prediction models for dementia or cognitive impairment in Australia. Age Ageing 2022;51(12):afac307.
[52] Hu M, Shu X, Yu G, Wu X, Välimäki M, Feng H. A risk prediction model based on machine learning for cognitive impairment among Chinese community-dwelling elderly people with normal cognition: development and validation study. J Med Internet Res 2021;23(2):e20298.
[53] Park KM, Sung JM, Kim WJ, et al. Population-based dementia prediction model using Korean public health examination data: a cohort study. PLoS ONE 2019;14(2):e0211957.
[54] Naheed A, Hakim M, Islam MS, et al. Prevalence of dementia among older age people and variation across different sociodemographic characteristics: a cross-sectional study in Bangladesh. Lancet Reg Health-Southeast Asia 2023:17.
[55] Ou YN, Kuo K, Yang L, et al. Longitudinal associations of cardiovascular health and vascular events with incident dementia. Stroke Vasc Neurol Aug 27 2024;9(4):418–28.
[56] Song R, Pan KY, Xu H, et al. Association of cardiovascular risk burden with risk of dementia and brain pathologies: a population-based cohort study. Alzheimers Dement Dec 2021;17(12):1914–22.
[57] Lin Y, Fu Y, Zeng YF, et al. Six visual rating scales as a biomarker for monitoring atrophied brain volume in Parkinson's disease. Aging Dis 2020;11(5):1082.
[58] Ingala S, van Maurik IS, Altomare D, et al. Clinical applicability of quantitative atrophy measures on MRI in patients suspected of Alzheimer's disease. Eur Radiol 2022;32(11):7789–99.
[59] Ranson JM, Rittman T, Hayat S, et al. Modifiable risk factors for dementia and dementia risk profiling. A user manual for brain health services—Part 2 of 6. Alzheimers Res Ther 2021;13(1):1–12.
[60] Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: the framingham study risk score functions. Stat Med May 30 2004,;23(10):1631–60.