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by Gea Pandhita S Uploaded By Irfan

Original Paper

Neuroepidemiology
DOI: 10.1159/000503830

Received: March 19, 2019
Accepted: September 28, 2019
Published online: ■■■

Decision Tree Clinical Algorithm for Screening of Mild Cognitive Impairment in the Elderly in Primary Health Care: Development, Test of Accuracy, and Time-Effectiveness Analysis

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Keywords
Mild cognitive impairment · Early detection · Clinical algorithm · Elderly · Screening

Abstract

Mild cognitive impairment (MCI) is predicted to be a common cognitive impairment in primary health care. Early detection and appropriate management of MCI can slow the rate of deterioration in cognitive deficits. The current methods for early detection of MCI have not been satisfactory for some doctors in primary health care. Therefore, an easy, fast, accurate and reliable method for screening of MCI in primary health care is needed. This study intends to develop a decision tree clinical algorithm based on a combination of simple neurological physical examination and brief cognitive assessment for distinguishing elderly with MCI from normal elderly in primary health care. This is a diagnostic study, comparative analysis in elderly with normal cognition and those presenting with MCI. We enrolled 212 elderly people aged 60.04–79.92 years old. Multivariate statistical analysis showed that the existence of subjective memory complaints, history of lack of physical exercise, abnormal verbal semantic fluency, and poor one-leg balance were found to be predictors of MCI diagnosis ($p \leq 0.001$; $p = 0.036$; $p \leq 0.001$; $p = 0.013$). The decision trees clinical algorithm, which is a combination of these variables, has a fairly good accuracy in distinguishing elderly with MCI from normal elderly (accuracy = 89.62%; sensitivity = 71.05%; specificity = 100%; positive predictive value = 100%; negative predictive value = 86.08%; negative likelihood ratio = 0.29; and time effectiveness ratio = 3.03). These results suggest that the decision tree clinical algorithm can be used for screening of MCI in the elderly in primary health care.

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Introduction

The number of the elderly population continues to grow a lot. The increase in the elderly population will have an impact on changing patterns of disease in the community. Mild cognitive impairment (MCI) and major neurocognitive disorder are predicted to be a common cognitive impairment in primary health care [1]. MCI is a transient status between physiologic aging and dementia. The prevalence of MCI in the elderly population aged 60 years and over is 21.3% [2]. Early detection and appropriate management of MCI can slow the rate of deterioration in cognitive deficits and impairment [3–5]. Therefore, MCI screening in the elderly population in primary health care is important.

The current MCI screening method has not been satisfactory for some doctors in primary health care [6, 7]. Brief cognitive assessment instruments and simple neurological physical examination do not have sufficient accuracy [8–10]. In contrast, comprehensive neuropsychological batteries are known to be accurate but cannot be applied due to long examination time. Biomarker measures cannot be applied in primary health care because it requires expensive facilities [11]. An easy, fast, accurate and reliable method for screening of MCI in primary health care is needed.

This study intends to develop a decision tree clinical algorithm, which is a combination of simple neurological physical examination and brief cognitive assessment for distinguishing elderly with MCI from normal elderly. The clinical algorithm is expected to be the right screening method in primary health care.

Materials and Methods

Subjects and Recruitment

This research was conducted from February 2017 to August 2017. The subjects consisted of 212 elderly people who were members of the elderly community in Pondok Kopi and Malaka Jaya, East Jakarta, Indonesia. The sample size was calculated based on $\alpha = 0.05$, deviation = 6.5%, specificity = 90%, and sensitivity = 95% [12]. The inclusion criteria included: age 60 years or older, availability during the testing phases, being literate (reading and writing skills), and presence of a caregiver. The criteria of the elderly in Indonesia based on the Ministry of Health of Indonesia are people aged 60 years and over. Definition of caregiver is a family member or paid helper who regularly looks after the elderly. Exclusion criteria included: history of disturbing odors since childhood, past consumption of drugs affecting brain's function and structure, history of cerebrovascular disease, history of brain tumors, history of severe head injury, Parkinsonism, epilepsy, and presence of serious medical or psychiatric conditions that would prevent participation in the testing.

This is a diagnostic study using a cross-sectional study design, comparative analysis in elderly with normal cognition and those presenting with MCI. Measurement of baseline characteristics of the subjects, simple neurological physical examinations, brief cognitive assessment, and diagnostic of MCI are carried out at relatively the same time, by different examiners, blindly.

Statistical Analysis

All subjects underwent a simple neurological examination, assessment of overall cognitive status, and identified their medical history, functional status, psychosocial aspects, and lifestyle characteristics.

Data were expressed as percentage. Statistical comparisons were performed using chi square test or Fisher's exact test to compare the demographic and clinical factors between elderly with MCI and normal elderly. Any significant variables ($p < 0.25$) were then entered into a multivariate logistic regression.

Multivariate statistical analysis using logistic regression model was performed to obtain an estimate of the independent association between study variables and outcome. A two-tailed p value <0.05 was considered as statistically significant.

Variables that are proven to be potential as a diagnostic predictor of MCI are used to develop a decision tree clinical algorithm for distinguishing elderly with MCI from normal elderly.

Decision tree analyses for disease modeling

Classifier modeling. The Iterative Dichotomiser 3 decision tree classifier software was used. The software RapidMiner Studio version 8.1 copyright (c) 2001–2018 GmbH trial edition was used in this type of decision tree modeling. The placement of each predictor variable in the decision tree clinical algorithm is based on the information gain of each predictor variable [13].

To analyze the validity of the decision tree clinical algorithm, test of accuracy including sensitivity, specificity, likelihood ratio, and predictive value were done. To analyze the applicability of the decision tree clinical algorithm, a time-effectiveness analysis was done.

Instruments

Assessment of MCI

Diagnosis of MCI was based according to "The core clinical criteria for MCI" from "The National Institute on Aging and Alzheimer's Workgroup Association" [14]. The criteria include an absence of dementia, concern regarding a change in cognition, impairment in one or more cognitive domains on the objective cognitive task, and preserved baseline activities of daily living (ADL) or only minimal impairment in complex instrumental functions.

Cognitive assessments were done using CERAD (Consortium to Establish a Registry for Alzheimer's Disease) Neuropsychological Battery [15]. The ADL of Katz and Instrumental ADL of Lawton and Brody were used to assess participants' functional status.

Simple Neurological Examination

All subjects underwent simple neurological examination including primitive reflexes, one-leg balance (OLB), and self-reported olfactory functioning.

The technique's evaluation of primitive reflexes (*palmomental, snout, suck, glabellar, grasp, babinsky*) was based on those used by Damasceno et al. [16].

Participants' status of OLB was measured using the OLB test of Rolland et al. [17] The test was performed by asking the participant to stand unassisted on one leg as long as possible (eyes open, using whichever leg was spontaneously chosen by the participant.). The "OLB" test was reported as abnormal when the participant was unable to stand on one leg for 5 s or more. The test was performed twice, and the best result was used for the analyses.

Self-reported olfactory function was assessed using the method used by Lehrner et al. [18]. Subjects were asked whether in the year there had been a disruption to distinguish the smell of eucalyptus, coffee, tobacco, pandanus leaves, or camphor.

Brief Cognitive Assessment

Brief cognitive assessment including clock drawing test, verbal semantic fluency test (VFT), mental alternation test, alphabetical "WAHYU" test, and subjective memory complaints (SMC).

Clock drawing test. Subjects were instructed to draw a large circle, add the numbers on a clock face, and set the hand at 11:10. The items assessed are: (1) whether the 12 numbers are drawn and placed correctly, (2) whether the minute hand is drawn longer than the hour hand, and (3) whether the short needle is right at number 11. The results of the examination are categorized as abnormal if 2 of the 3 items of assessment are incorrect [19].

VFT. The test is performed by asking the subject to name as many items as he can recall in each of 4 successive categories or sets (colors, animals, fruits, towns). One point is awarded for each correct item offered, with a maximum of 10 in each set and a maximum total score of 40. A total score of under 20 is abnormal [20].

Mental alternation test. Subjects are asked to mention alternating between numbers and letters in the following way: "1-A, 2-B, 3-C, and so on" within 30 s. Assessment is calculated from how many numbers, and letters are correct. The examination results are categorized as abnormal if the subject can only mention <15 correct combinations of numbers and letters [21].

Alphabetical "WAHYU" test. The subject is asked to list the letters of the word "WAHYU," namely, letters "W," "A," "H," "Y," and "U," sorted forward, and then backward. The results of the examination are categorized as abnormal if the subject cannot correctly sequence the letters forward and backward [22].

SMC. The questions are given to the subject: "Are you having a problem with your memory (e.g., repeats the same questions, stories, or statements, over and over)?" The results of the examination are categorized as abnormal if the answer is "Yes."

Results

The subjects consisted of 212 elderly people aged 60.04–79.92 years old. Most of the subjects were women (71.7%). MCI was found in 76 subjects (35.8%), consisting of 62 subjects with multiple-domain amnestic MCI and 14 subjects with multiple-domain non-amnestic MCI. Baseline characteristics and clinical status are shown in Tables 1 and 2.

Multivariate statistical analysis (Table 3) showed that the existence of SMC ($p \leq 0.001$; OR 11.647 [95% CI 2.943–46.095]), history of lack of physical exercise (PE) ($p = 0.036$; OR 3.640 [95% CI 1.089–12.166]), abnormal VFT ($p \leq 0.001$; OR 85.523 [95% CI 16.206–451.317]), and poor OLB ($p = 0.013$; OR 5.222 [95% CI 1.408–19.375]) were found to be predictors of MCI diagnosis. These predictor variables are then combined to make the decision tree clinical algorithm for distinguishing elderly with MCI from normal elderly.

The resulting decision tree is shown in Figure 1. The first splitting parameter is VFT (normal or abnormal), followed by the history of routine PE (positive or negative), existence of SMC (positive or negative), and status of OLB (normal or abnormal). The predicted diagnosis of MCI is shown in probability value.

The Concept of Decision Tree Clinical Algorithm for Screening of MCI is shown in Figure 2. First, VFT is carried out. If the result is abnormal, history of PE is checked. If the history of routine PE is lacking, then the elderly is suspected to be MCI. If the history of routine PE is sufficient, existence of SMC is checked. If there are existences of SMC, then the elderly is suspected to be MCI. If there are no SMC, the elderly may not be MCI.

Table 1. Baseline characteristics of the normal elderly and the elderly with MCI

Variables	MCI (–), *n* (%)	MCI (+), *n* (%)	*p* value
Gender			
Men	36 (60)	24 (40)	0.428
Women	100 (65.79)	52 (34.21)	
Age, years			
60–65	80 (64.52)	44 (35.48)	0.895
>65	56 (63.64)	32 (36.36)	
Education, years			
≥12	76 (70.37)	32 (29.63)	0.054
<12	60 (57.69)	44 (42.31)	
Body mass index			
Normal (<25 kg/m^2)	86 (64.18)	48 (35.82)	0.991
Overweight (≥25 kg/m^2)	50 (64.10)	28 (35.90)	
Hypertension			
No	74 (69.81)	32 (30.19)	0.086
Yes	62 (58.49)	44 (41.51)	
Diabetes mellitus			
No	108 (65.06)	58 (34.94)	0.600
Yes	28 (60.87)	18 (39.13)	
Smoking			
No	130 (63.73)	74 (36.27)	0.714**
Yes	6 (75)	2 (25)	
Physical exercise			
Routine	112 (83.58)	22 (16.42)	**≤0.001**
Not routine	24 (30.77)	54 (69.23)	

** Fisher's exact test.
Bold *p* value indicates statistical significance.
MCI, mild cognitive impairment.

Table 2. Clinical status of the normal elderly and the elderly with MCI

Variables	MCI (–), *n* (%)	MCI (+), *n* (%)	*p* value
Snout reflex			
Negative	136 (65.38)	72 (34.62)	**0.016****
Positive	0 (0)	4 (100)	
Palmomental reflex			
Negative	136 (66.02)	70 (33.98)	**0.002****
Positive	0 (0)	6 (100)	
Glabellar reflex			
Negative	96 (72.73)	36 (27.27)	**0.001**
Positive	40 (50)	40 (50)	
Grasp reflex			
Negative	134 (65.69)	70 (34.31)	**0.026****
Positive	2 (25)	6 (75)	
Babinski reflex			
Negative	136 (65.38)	72 (34.62)	**0.016****
Positive	0 (0)	4 (100)	
One-leg balance			
Normal	122 (69.32)	54 (30.68)	**0.001**
Abnormal	14 (38.89)	22 (61.11)	
Self-reported olfactory function			
Normal	136 (64.45)	75 (35.55)	0.358**
Abnormal	0 (0)	1 (100)	
Clock drawing test			
Normal	112 (67.47)	54 (32.53)	0.056
Abnormal	24 (51.17)	22 (47.82)	
Verbal semantic fluency test			
Normal	132 (84.62)	24 (15.38)	**≤0.001**
Abnormal	4 (7.14)	52 (92.86)	
Mental alternation test			
Normal	64 (78.05)	18 (21.95)	**0.001**
Abnormal	72 (55.38)	58 (44.62)	
Alphabetical "WAHYU" test			
Normal	126 (65.62)	66 (34.38)	0.166
Abnormal	10 (50)	10 (50)	
Subjective memory complaints			
Normal	111 (79.86)	28 (20.14)	**≤0.001**
Abnormal	25 (34.25)	48 (65.75)	

** Fisher's exact test.
Bold *p* values indicate statistical significance.
MCI, mild cognitive impairment.

In the elderly with normal VFT, status of OLB, existence of SMC, and history of PE are checked. If there are existences of SMC, and poor OLB, and history of lack of PE, then the elderly is suspected to be MCI. If one of the examinations shows normal result, the elderly may not be MCI.

The decision trees clinical algorithm has a fairly good accuracy in distinguishing elderly with MCI from normal elderly. The decision trees clinical algorithm of MCI has an accuracy of 89.62% (95% CI 84.71–93.38%), sensitivity = 71.05% (95% CI 59.51–80.89%), specificity = 100% (95% CI 97.32–100%), positive predictive value = 100%, negative predictive value = 86.08% (95% CI 81.30–89.79%), and likelihood ratio (–) = 0.29 (95% CI 0.20–0.41). The value of the time effectiveness ratio = 3.03.

Discussion/Conclusion

This study was conducted at Pondok Kopi and Malaka Jaya, East Jakarta, Indonesia. The subjects were healthy elderly population over 60 years old. The prevalence of MCI in this study was 35.8%. The prevalence is higher

Table 3. Multivariate logistic regression analysis

Dependent variables	*p* value	OR	95% CI	
			lower	upper
Snout reflex	0.999	0.000	0.000	
Palmomental reflex	0.999	0.000	0.000	
Glabellar reflex	0.707	1.229	0.419	3.605
Grasp reflex	0.791	0.403	0.000	331.909
Babinski reflex	0.999	0.000	0.000	
One-leg balance	**0.013**	**5.222**	**1.408**	**19.375**
Clock drawing test	0.755	1.254	0.303	5.195
Verbal semantic fluency test	**≤0.001**	**85.523**	**16.206**	**451.317**
Mental alternation test	0.533	0.632	0.149	2.674
Alphabetical "WAHYU" test	0.518	1.911	0.269	13.580
Subjective memory complaints	**≤0.001**	**11.647**	**2.943**	**46.095**
Physical exercise	**0.036**	**3.640**	**1.089**	**12.166**
Education	0.319	0.555	0.174	1.766
Hipertension	0.991	1.006	0.345	2.933

Bold values indicate statistical significance.

compared to a study by Xu et al. [2] stated that the prevalence of MCI was 21.3% among the urban population aged 60 years or older. The low educational background of the majority in our study population can explain this difference. Xu et al. [2] stated that the higher prevalence of MCI was associated with very old age, male gender, low education level, and poor economic status.

Previous studies have reported that hypertension, diabetes mellitus, PE, and level of education were related to cognitive performance in older adults. However, this study showed that only a history of lack of PE and levels of education were statistically significantly associated with MCI in bivariate statistical analysis. While, hypertension and diabetes mellitus tend to be associated with MCI, but were not statistically significant. This is likely because most participants have long had well-controlled blood pressure and blood sugar with regular therapy.

This study showed that the existence of SMC was statistically significantly associated with MCI. This result is consistent with previous studies. Previous studies have proven that absence of SMC may be a reasonable method of excluding MCI and could be incorporated into short screening programs for MCI. However, it will be more accurate when combined with other examinations [23–25]. SMC are associated with a disruption in the formation of new long-term memory in MCI [4, 23].

This study showed that history of lack of PE was statistically significantly associated with MCI. Previous studies have reported that PE is related to cognitive performance in older adults. PE improves cerebral circulation by increasing the blood flow and oxygen supply to the brain. Regular exercise lowers the blood pressure and lipids, prevents the metabolic syndrome, has a positive effect on inflammatory markers, and improves endothelial function [26]. PE increases the size of the anterior hippocampus, leading to improvements in spatial memory. In addition, the increased hippocampus volume is associated with greater serum levels of BDNF, a mediator of neurogenesis in the dentate gyrus [27]. Elderly that lack PE will increase the risk of MCI. Conversely, the elderly that routinely do PE will be at lower risk of MCI [11, 28, 29]. This statement is in accordance with the results of our study. Our study reveals that history of lack of PE was associated with MCI.

Abnormal VFT result was statistically significantly associated with MCI. This result is similar to previous studies. Previous studies have proven that there are significant differences in the results of verbal fluency test, especially semantic fluency, between normal elderly and elderly with MCI. Elderly with MCI showed lower verbal fluency test results [30–32]. Verbal fluency is a cognitive function that allows retrieval of information from memory stored in the brain by involving executive functions and language skills. Executive function involves the frontal lobe and prefrontal cortex (especially in the left dorsolateral cortex), while language skills involve the left temporal lobe [33, 34]. Therefore, verbal fluency test can be used to assess executive function and language skills.

DOI: 10.1159/000503830

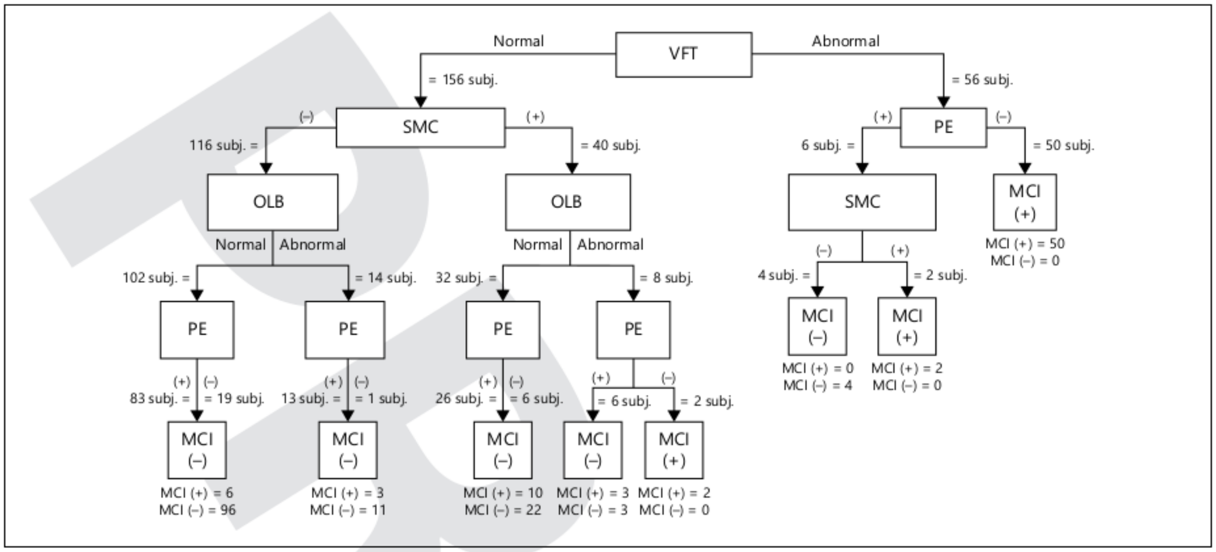

Fig. 1. Decision tree. VFT, verbal semantic fluency test; SMC, subjective memory complaints; OLB, one-leg balance; MCI, mild cognitive impairment; PE, physical exercise; subj., subject.

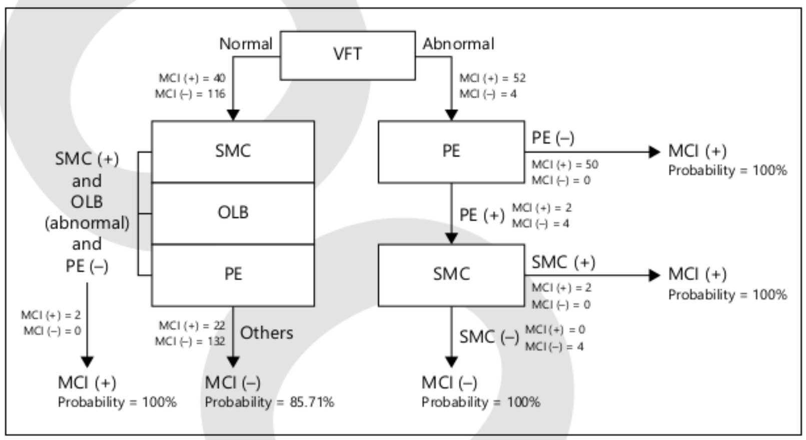

Fig. 2. The concept of decision tree clinical algorithm for screening of MCI. PE, physical exercise; VFT, verbal semantic fluency test; SMC, subjective memory complaints; OLB, one-leg balance; MCI, mild cognitive impairment.

Poor OLB was significantly associated with MCI. This result is consistent with several previous studies [17, 35]. Previous study reveals that the presence of parietal lobe dysfunction and hippocampus dysfunction not only can lead to decreased memory function but also result in a deficit of visuospatial orientation. This visuospatial deficit will result in impaired balance function.

Early detection and appropriate management of MCI can slow cognitive impairment to worse. Some previous studies have shown that the level of progression of MCI to dementia is around 10–12% per year, while the progression of the incidence of dementia in the normal population is only around 1–2% per year [36, 37]. However, if MCI can be detected early and get adequate therapy, it can return to have normal aging cognitive function. Some studies reveal that the percentage of MCI conversion to normal aging cognitive function is around 25–40% [38, 39]. Therefore, an easy, fast, accurate and reliable method for MCI screening is very important so that adequate therapy can be carried out immediately. The decision trees clinical algorithm is expected to be the right method for MCI screening in primary health care. This screening method is the initial method before further examination in a referral hospital to establish a diagnosis of MCI.

The clinical algorithm is a text format that is specially suited for representing a sequence of clinical decisions and for guiding patient care [40]. This algorithm recursively selects the best attribute as the current node using top down induction. Then the child nodes are generated for the selected attribute. It uses an information gain as an entropy-based measure to select the best splitting attribute, and the attribute with the highest information gain is selected as best splitting attribute. The decision trees clinical algorithm has been found useful in classification and prediction modeling due to the fact that it has the capability to accurately discover hidden relationships between variables, it is capable of removing insignificant attributes within a data set, and also presents knowledge in a hierarchical structure which makes it to be knowledge to be understandable.

The decision trees clinical algorithm is in principle simple to understand and also easy to interpret, use, and validate using common statistical techniques. The decision trees clinical algorithm for screening of the MCI made use of a combination of VFT, history of routine PE, existence of SMC, and status of OLB, in a sequential order.

The accuracy of the decision tree clinical algorithm for distinguishing elderly with MCI from normal elderly was fairly good with sensitivity = 71.05% and specificity = 100%. The decision trees clinical algorithm also has a fairly balanced ratio between the length of time examination and the level of accuracy (time effectiveness ratio = 3.03).

Our study represents the first to demonstrate that the decision tree algorithms for the screening of the MCI can be developed for clinical use. If the results of screening indicate the presence of MCI, the subjects can be referred to the hospital for a complete examination to establish a diagnosis of MCI. While a large multicenter study will be needed for these algorithms to be applied globally, our analysis indicates that a decision tree approach distinguishing elderly with MCI from normal elderly in primary health care.

Acknowledgments

The authors sincerely thank all the subjects who participated in this study and the management of the senior club "Gerak Latih Otak" in the Pondok Kopi Jakarta Islamic Hospital who helped us to identify the studied subjects.

Statement of Ethics

The study was approved by the Ethics Committee for Research and Community Health Services, Faculty of Public Health, University of Indonesia (370/UN2.F10/PPM.00.02/2017). Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

G.P.S. is the principal researcher. B.S. is a contributor to research topics and clinical epidemiological aspects. S.W. is a contributor to the neurological aspects specifically about molecular biology of cognitive function. A.C.A. is a contributor to research methodology and clinical epidemiological aspects. T.B.W.R. is a contributor to the health aspects of the elderly, especially related to cognitive function of the elderly. N.A. is a contributor to psychiatric aspects of cognitive function. R.R. is a contributor related to aspects of government policy on primary health care. S.K. is a contributor related to aspects of government policy on public health and epidemiological aspects. S.S. is a contributor to epidemiological aspects of cognitive function. B.R.W. is a contributor to the neurological aspects specifically about screening method of cognitive impairment.

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