Cardiovascular risk factors of Alzheimer’s disease and other neurocognitive disorders in Malaysia

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ABSTRACT
Introduction: Risk factors for cardiovascular disease (CVD) have been increasingly implicated in the development of dementia but little is known about the effects in a Malaysian population. We aimed to determine the interaction between sociodemographic and CVD risk factors among the dementia and mild cognitive impairment (MCI) patients in Malaysia.

Materials and Methods: A cross-sectional study was conducted in the memory clinic at Hospital Kuala Lumpur (HKL). Medical records data from 2014 to 2019 were extracted. Mini Mental State Examination (MMSE) test was used to assess the neurocognitive function of patients.

Results: A total of 298 patients (30 MCI, and 268 dementia) were evaluated, with dementia patients consisting of 78 Alzheimer’s disease (AD), 93 Vascular dementia (VaD), 94 Mixed dementia, 2 early-onset Alzheimer’s disease (EOAD) and 1 Logopenic Progressive Aphasia type of AD (LPA). MCI and dementia were significantly associated with a history of CVD, particularly stroke (p<0.023).

Conclusion: Given that stroke significantly predicted the risk of developing vascular dementia among the patients in a central Malaysian population, lifestyle modifications are recommended to alleviate these risk factors of CVD.

KEYWORDS:
Alzheimer’s disease, vascular dementia, cardiovascular, hypertension, Malaysian

INTRODUCTION
Dementia or major neurocognitive disorders (NCD) refers to the collection of heterogeneous disorders that occur because of progressive neurodegeneration and other pathologies of brain cells. Based on the Diagnostic and Statistical Manual for of Mental Disorders, Fifth Edition (DSM-5), the commonest major NCD is Alzheimer’s disease (AD) that involves disturbances in the cognitive cerebral domains, such as memory, language, and executive functions. On the other hand, mild cognitive impairment (MCI), which is a mild NCD, has been implicated in the spectrum of NCDs, and refers to a transitional state between normal ageing and dementia. MCI is characterised by a decline in one’s cognitive abilities in the memory domain of cognitive functions compared to the previous level of performance, provided the activities of daily living remain intact and the subject does not fulfil the criteria for AD. Typically, AD accounts for more than 70% of all cases of dementia and most patients have late onset AD (LOAD) but some are also identified with early-onset AD (EOAD) that is likely hereditary in aetiology. A survey in 2016, reported that AD affects nearly 40-50 million people worldwide, out of which approximately 23 million live in Asia, and more than 123,000 reside in Malaysia. The second most prevalent form of dementia is vascular dementia (VaD), and the third most common dementia subtype is mixed dementia, which is usually caused by a co-existence of AD and VaD. Other forms of dementias include fronto-temporal dementia (FTD) and Lewy-body dementia (DLB). In addition, atypical AD subtypes such as language variant AD, known as the Logopenic variant of Primary Progressive Aphasia (lv-PPA) also exist.

For VaD, the clinical presentation is dependent on the causative agent. Specifically, a cerebrovascular accident or stroke may localise the area and extent of the brain injury, whereas VaD due to cardiovascular disease (CVD) is highly diffuse in its involvement and presents with a reduced rate of information processing, cognitive dysfunction, and an inability to perform tasks that require complex attention. Apart from memory loss, VaD has been implicated in gait apraxia, and urinary incontinence. Additionally, mixed dementia, presents with a combination of the symptoms of AD and VaD; namely memory loss, together with executive impairment and attention dysfunction.

Clinical conditions such as stroke, atrial fibrillation, coronary heart disease (CHD), and heart failure are examples of CVDs. The CVDs have been increasingly implicated in the development of dementia. It is postulated that there is a direct causal association between CVD and AD as cardiac disease leads to cerebral hypoperfusion and micro-emboli. These mechanisms can cause neuronal damage, which along
with beta amyloid deposition and tau pathology, lead to the 
neurocognitive deficit of AD. Stroke, which is a major type 
of CVD, can lead to ‘post-stroke dem entia’ or VaD. Lacunar 
strokes caused by cerebral small vessels disease are known to 
cause VaD and can also increase the risk of developing AD. Furthermore, ischemic brain damage, which is evidenced by 
white matter lesions on magnetic resonance imaging (MRI), is 
also associated with dementia.  

A previous community-based study conducted among elderly 
Malaysians revealed that the risk factors for dementia 
included older age, lack of formal education, female gender, 
very poor level of self-rated health quality, and Malay or 
Bumiputera ethnicity. There is, however, a lack of 
information regarding the sociodemographic information and 
related risk factors pertaining to dementia patients in a 
hospital-based setup in Malaysia. In particular, it is of 
interest to identify the sociodemographic information and 
associated risk factors for patients having dementia at HKL, 
which is one of the largest tertiary referral centres in Malaysia 
that attends to dementia cases at a regular basis in their 
memory clinic. 

To the best of our knowledge, to date only community-based 
studies pertaining to dementia have been conducted in 
Malaysia. Therefore, the present study is aimed to achieve the 
following objectives i.e., to estimate the frequency of MCI and 
the different subtypes of dementia among Malaysians 
attending the memory clinic HKL, to determine the 
differences in MMSE scores among the MCI and dementia 
patients and to determine the association between MCI or 
dementia with the sociodemographic and CVD risk factors.

MATERIALS AND METHODS

Study design and settings

A retrospective study was carried out using secondary data 
from the medical records of 298 patients (30 MCI and 268 
dementia) attending the memory clinic of HKL between 2014 
and 2019. The patients are residents of an urban region in 
Malaysia, specifically Kuala Lumpur.

The Memory Clinic at the Geriatric Unit, HKL has been 
operating since 2003. Patients who attend the clinic here are 
first screened by nurses who are well-trained in the 
assessment of cognitive function. Several cognitive 
assessment tools such as the Mini Mental State Examination 
(MMSE), Montreal Cognitive Assessment (MoCA), the Saint 
Louis University Mental Status exam (SLUMS) were used to 
assess the level of daily living activities of the patients before 
they were evaluated by the geriatricians. Furthermore, since 
2013, the memory clinic incorporated a multidisciplinary 
approach involving allied health workers in the care of 
patients. For example, occupational therapists, pharmacists, 
speech and language therapist, physiotherapist, dietitians, 
special-need dentists, social workers and neuroradiologist 
were instrumental in providing the necessary services to the 
patients. This kind of multidisciplinary approach is thus 
essential in providing good quality of care for the patients.

Sample size determination

The sample size calculated was estimated based on the 
assumption that retrospective studies use statistical power 
instead of measuring sample sizes (also called post hoc power analysis). Consequently, the GPower software was used to predict the actual sample size needed by choosing the effect 
size of 0.25, power (1-β err prob) of 0.95 and 4 number of 
groups for the ANOVA, the results yielded 280 NCD patients’ 
data was needed to be recorded retrospectively based on the 
a study with similar endpoint. However, during the data 
collection, 298 patients were found in the hospital records and 
hence all were considered for the analysis.

Patients selection

The inclusion criteria included Malaysian patients at the HKL 
memory clinic, having all the relevant clinical data, i.e., the 
diagnosis of the type of NCD was available, the age, gender, 
education level, marriage status, and comorbid disease. 
Foreigners and patients who were not diagnosed with 
dementia between the periods of 2014 to 2019 were excluded 
from the study.

Secondary source of data

The data was collected manually by going through the files of 
the patients that met the inclusion criteria for our study. 
The primary data extracted from the files of patients included 
age, gender, race, marital status, level of education, 
occupation, and the Mini Mental State Examination (MMSE) 
test scores. The MMSE test is an example of a widely used tool 
for the objective assessment of dementia. It is comprised of 
30 questions aimed at evaluating memory, registration, 
recall, calculation, language, attention, and orientation, as 
well as visuospatial abilities. Normally a total score of 24 
and below indicates significant cognitive impairment and 
dementia. However, sociodemographic factors such as age, 
duration of formal education and other factors affect the 
scores at an individual level.

Diagnostic criteria

The patients were diagnosed with the specific subtypes of 
NCDs by the clinicians based on the standardised criteria 
using DSM-5 and MMSE test scores. Although there is no 
consensus for the diagnosis of mixed dementia, several 
international references such as the Alzheimer’s Disease 
Diagnostic and Treatment Centers (ADDTC) and the 
National Institute of Neurological Disorders and Stroke and 
Association Internationale pour la Recherche et l’Enseignement en 
Neurosciences (NINDS-AIREN) have proposed diagnostic 
criteria that differ from each other. Therefore, mixed 
dementia was diagnosed following the harmonization of 
criteria outlined by the ADDTC and NINDS-AIREN, such as 
the presence of focal neurological symptoms and evidence of 
significant CVD.

Ethical Approval

This study was approved by the Medical Research Ethics 
Committee (MREC) of National Medical Registration Registry 
(NMRR) Malaysia (NMRR-19-2719-49105) and the Ethics 
Committee for Research Involving Human Subjects of 
Universiti Putra Malaysia (JEUPM-2019-328)
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Statistical Analysis
All statistical tests were conducted using the Statistical Package for the Social Sciences (SPSS software Version 23.0, SPSS Inc., Chicago, IL, USA) and the level of significant was set at p value less than 0.05. Chi-square test was used to determine the association between socio-demographic risk factors among patients with NCDs while One-way ANOVA test was used to determine the means difference in terms of age of the patients with NCDs. Simple descriptive statistic and one-way ANOVA were employed in analysing the MMSE test scores among various subtypes of NCD patients.

RESULTS
As shown in Figure 1, the distribution of the patients based on the NCDs showed that mixed dementia was the highest type of NCD (Figure 1). This was closely followed by VaD (31.2%), and AD (26.2%). MCI patients made up 10.1% of the patient population. We also identified 2 patients with EOAD and one patient with LPA, respectively. There were no patients diagnosed with FTD during our study period.

To compare the mean MMSE scores among patients with NCDs, One-way ANOVA test was used and revealed a statistical significance [F (3, 263) = 17.28, p < 0.001] mean difference between the scores in the MCI and the dementia groups. Moreover, the results from the post hoc Dunnett’s C test revealed that there is a significant means difference (p < 0.05) between MMSE scores of patients with MCI and those with AD, VaD and mixed dementia. MCI patients had the highest MMSE scores (mean 24.88±4.84), followed by VaD (mean 18.28±6.49), mixed dementia (mean 14.98±7.28), and the lowest score was among the AD (mean 14.81±7.26) as shown in Figure 2.

To determine the association between the sociodemographic and CVD risk factors and NCDs, Chi-square and One-way ANOVA tests were performed. The results indicate that only a history of stroke was significantly associated with NCDs (p=0.023) (Table I). All other factors did not significantly associate with NCDs.

DISCUSSION
We have identified that the frequency of mixed dementia and VaD exceeded that of AD cases and that of EOAD, whereas LPA type of dementia presented with the least frequency in HKL. Hence, it is evident from our study that the

Table I: Association between socio-demographic risk factors and neurocognitive disorders among the memory clinic patients at Hospital Kuala Lumpur, Malaysia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>MCI (n=30)</th>
<th>AD (n=78)</th>
<th>VaD (n=93)</th>
<th>Mixed dementia (n=94)</th>
<th>Total (n=293)</th>
<th>F/X2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>74 (26.2%)</td>
<td>75.47 (8.90)</td>
<td>75.48 (7.77)</td>
<td>77.35 (7.49)</td>
<td>75.93 (7.98)</td>
<td>1.77</td>
<td>0.153</td>
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<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>17 (56.7%)</td>
<td>35 (46.1)</td>
<td>44 (47.3)</td>
<td>36 (40.4)</td>
<td>133 (46)</td>
<td>2.24</td>
<td>0.524</td>
</tr>
<tr>
<td>Female</td>
<td>13 (43.3%)</td>
<td>43 (55.1)</td>
<td>49 (52.7)</td>
<td>53 (59.6)</td>
<td>156 (54)</td>
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<td>Race</td>
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<tr>
<td>Malay/Bumiputera</td>
<td>5 (16.7%)</td>
<td>21 (27.3)</td>
<td>32 (34.8)</td>
<td>27 (28.7)</td>
<td>85 (29)</td>
<td>4.55</td>
<td>0.603</td>
</tr>
<tr>
<td>Chinese</td>
<td>17 (56.7%)</td>
<td>37 (48.1)</td>
<td>37 (40.2)</td>
<td>46 (48.9)</td>
<td>137 (46.8)</td>
<td></td>
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</tr>
<tr>
<td>Indian</td>
<td>8 (26.7%)</td>
<td>19 (24.7)</td>
<td>23 (25)</td>
<td>21 (23.3)</td>
<td>71 (24.2)</td>
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<tr>
<td>Years of education:</td>
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<tr>
<td>≤ 6 years</td>
<td>9 (31.0%)</td>
<td>39 (49.4)</td>
<td>45 (57)</td>
<td>55 (62.5)</td>
<td>148 (56.1)</td>
<td>6.39</td>
<td>0.094</td>
</tr>
<tr>
<td>≥ 6 years</td>
<td>21 (70.0%)</td>
<td>27 (31.2)</td>
<td>22 (25)</td>
<td>25 (27.5)</td>
<td>72 (24.2)</td>
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<tr>
<td>Marital status:</td>
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<tr>
<td>Unmarried</td>
<td>7 (23.3%)</td>
<td>13 (22)</td>
<td>18 (25.4)</td>
<td>28 (35)</td>
<td>66 (22.8)</td>
<td>3.23</td>
<td>0.358</td>
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<tr>
<td>Married</td>
<td>17 (73.7%)</td>
<td>46 (78)</td>
<td>73 (64)</td>
<td>52 (65)</td>
<td>168 (71.8)</td>
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<tr>
<td>Employment</td>
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<tr>
<td>Yes</td>
<td>18 (78.3%)</td>
<td>40 (80.0)</td>
<td>47 (77.0)</td>
<td>52 (75.4)</td>
<td>157 (77.3)</td>
<td>0.369</td>
<td>0.946</td>
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<tr>
<td>No</td>
<td>5 (21.7%)</td>
<td>10 (20.0)</td>
<td>13 (23.0)</td>
<td>17 (24.6)</td>
<td>46 (22.7)</td>
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<tr>
<td>Yes</td>
<td>10 (33.3%)</td>
<td>29 (37.2)</td>
<td>46 (50)</td>
<td>41 (43.6)</td>
<td>126 (42.9)</td>
<td>4.077</td>
<td>0.253</td>
</tr>
<tr>
<td>No</td>
<td>20 (66.7%)</td>
<td>49 (62.8)</td>
<td>46 (50)</td>
<td>53 (56.4)</td>
<td>168 (57.1)</td>
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<tr>
<td>Yes</td>
<td>17 (56.7%)</td>
<td>47 (60.3)</td>
<td>68 (73.9)</td>
<td>64 (68.1)</td>
<td>196 (66.7)</td>
<td>5.051</td>
<td>0.168</td>
</tr>
<tr>
<td>No</td>
<td>13 (43.3%)</td>
<td>31 (39.7)</td>
<td>24 (26.1)</td>
<td>30 (31.9)</td>
<td>98 (33.3)</td>
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<tr>
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<td>1 (3.3%)</td>
<td>3 (2.8)</td>
<td>1 (1.1)</td>
<td>2 (2.1)</td>
<td>7 (2.4)</td>
<td>1.53</td>
<td>0.676</td>
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<tr>
<td>No</td>
<td>29 (96.7%)</td>
<td>75 (96.2)</td>
<td>91 (98.9)</td>
<td>92 (97.9)</td>
<td>287 (97.6)</td>
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<td>Stroke</td>
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<tr>
<td>Yes</td>
<td>1 (3.3%)</td>
<td>3 (3.8)</td>
<td>15 (16.3)</td>
<td>13 (13.8)</td>
<td>32 (10.9)</td>
<td>9.374</td>
<td>0.023</td>
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<tr>
<td>No</td>
<td>29 (96.7%)</td>
<td>75 (96.2)</td>
<td>77 (83.7)</td>
<td>81 (86.2)</td>
<td>262 (89.1)</td>
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<tr>
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<td>0 (0.0%)</td>
<td>1 (1.3)</td>
<td>1 (1.1)</td>
<td>4 (4.3)</td>
<td>6 (2)</td>
<td>3.574</td>
<td>0.311</td>
</tr>
<tr>
<td>No</td>
<td>30 (100%)</td>
<td>77 (98.7)</td>
<td>91 (98.9)</td>
<td>90 (95.7)</td>
<td>288 (98)</td>
<td></td>
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</tbody>
</table>

Note: Data were expressed as n (%) or mean ± SD; Significant difference between risk of MCI and de¬mentia was determined by One-way ANOVA test or Chi-square test (χ2) at 0.05 level of significance; *p<0.05
prevalence of VaD and mixed dementia, i.e., the NCDs with a vascular pathology, are more common than the primary degenerative dementia or AD among the urban Malaysian hospital-based population. Unlike other studies in the Western countries that indicated AD was the more prevalent type of dementia in their population, our results showed that VaD and mixed dementia are more common among Malaysians living in Kuala Lumpur. This may be due to the comorbidity of hypertension as a major risk factor for CVD and the inherent excess dietary salt intake that is prevalent in many Asian populations, specifically in Malaysia.

The MMSE scores of patients with MCI differed significantly (p < 0.001) from those with dementia, whereby MCI patients had overall higher scores compared to patients with dementia. This result agrees with previously published studies proving the usefulness of MMSE test in classifying healthy control from patients with MCI and dementia. The MMSE test is normally administered to patients as the first line screening tool to determine the level of cognitive impairment in patients. Ordinarily, patients with less severe cognitive impairment tend to have higher scores in this neurocognitive test and conversely those at moderate and advanced stage of disease would normally have lower scores. Nevertheless, the interpretation of the test scores also depends on the age and level of education of the patients. Therefore, our result agrees with previous evidence indicating that MMSE test scores, either taken alone or in combination with other tools for testing cognitive impairment, can help clinicians make prompt decisions for the early referral or therapeutic intervention of NCDs.
Our study also revealed that lower levels of education was positively associated with dementia but failed to achieve statistical significance. This may be due to better educated individuals were more likely to seek hospital treatment and thus our patient population was skewed towards urban families with better knowledge and resourcefulness to seek treatment for their afflicted family members. Previously, population-based research supported the understanding that lower level of education correlated with dementia and MCI.\textsuperscript{13,14} It is hypothesised that a lower levels of education, or no formal education, tends to be correlated with dementia due to less involvement in complex brain activity, which affects one’s cognitive reserve and exposes one to early brain cells pathological insult.\textsuperscript{3} However, the association between the level of education and dementia was said to vary between developed and developing countries, whereby low level of education in dementia is more pronounced in the latter countries.\textsuperscript{32}

Moreover, a low level of education (not statistically significant in our study) and a history of stroke (statistically significant in our study) were associated with dementia in our population. These results are comparable with a previous study conducted among the urban population in Beijing China, whereby the elderly people with a lower level of education, having limited physical activity and a history of stroke were noted to have a higher risk for developing dementia.\textsuperscript{31} Furthermore, similar to what has been observed in our study among the urban Malaysian population, a study in China also revealed that multi-infarct dementia or VaD was relatively more common than AD with a ratio of 3:2.\textsuperscript{33}

Low average educational attainment and high CVD risk profile have been postulated to be the cause of VaD being more prevalent in developing countries.\textsuperscript{34} Nevertheless, an excellent explanation for educational level affecting the development of dementia can be derived by the Lifespan Developmental Model proposed by Sharp and Gatz, 2011, whereby educational factor is deemed as a surrogate indicator of cognitive development in a two-stage approach, i.e., (i) pre-education factors, e.g., parental socioeconomic status (SES), genetics, and socio-emotional influences and (ii) post-education factors, e.g., adult SES (particularly in developed regions), which is associated with occupational and environmental exposures, including the type of food intake, exercise and lifestyle habits.\textsuperscript{35} Thus, this model indicates that the level of education does not directly affect the risk for developing dementia directly, but acts as a proxy through its influence on a multitude of factors across the lifespan of the patients.\textsuperscript{35}

Hypertension being one of the modifiable risk factors in the spectrum of CVD, was noted to significantly predicted the development of VaD in our study population. This finding is corroborated by the results from a review conducted by Kalaria et al., 2018 whereby hypertension, diabetes mellitus, and obesity were implicated in the increased risk of developing dementia.\textsuperscript{36} Additionally, a study among patients having VaD in India reported that stroke, hypertension, and diabetes mellitus, acting by the mechanism of causing small vessel disease, were important risk factors that gave rise to predominantly a subcortical type of VaD.\textsuperscript{37} The implication of this study is on improving the healthcare services by educating the public regarding lifestyle modifications and optimising the control of hypertension and diabetes mellitus, which are modifiable risk factors of CVD.

LIMITATIONS
The MMSE was used in this study as a screening tool to identify dementia and MCI among the patient population. However, other studies have suggested that the MoCA is a better screening tool for MCI.\textsuperscript{27,28} Thus, future prospective studies may consider MoCA for evaluating their subjects. Additionally, our study has a relatively small sample size. Thus, future multicentre studies may reveal more significant modifiable risk factors for dementia. Furthermore, comparison with age and gender-matched cognitively healthy controls will more sophisticated statistical evaluation of the predictors of dementia in this population. Another limitation is that the diagnosis of the dementia subtypes was based on the expertise of the clinicians and not by the gold standard such as a biopsy. Alternatively, diagnostic imaging can play a role in the management of dementias, whereby the structural and functional information can be availed to exclude potential secondary causes and offer additional information to differentiate the dementia subtypes, especially in atypical cases.\textsuperscript{39} Nevertheless, our clinicians followed the criteria developed by the ADCTC and NINDS-AIREN. Understanding the mechanisms that lead to dementia is crucial in the planning of interventional strategies, hence futures studies will need to evaluate the complete risk factors profile that includes physical examinations of neuropsychological deficits, food intake, physical activity, biochemical indices, genetic profiling, together with a complete panel of comorbidities and medications.

CONCLUSION
Vascular dementia and mixed dementia are more common than Alzheimer’s disease in our urban HKL population. Modifiable risk factors for cardiovascular disease are significantly associated with dementia. Hence, lifestyle modifications, optimised blood pressure control, and monitoring other CVD risk factors are recommended to delay the development of dementia.

ACKNOWLEDGEMENTS
The authors would like to thank Dr Alan Pok Wen Kin and Dr Elizabeth Chong Gar Mit of the Memory Clinic, Hospital Kuala Lumpur for assisting in the data collection. The authors also thank Mr. Umar Ahmad from the Medical Genetics Unit, Department of Anatomy, Faculty of Basic Medical Sciences, Bauchi State University, Gadau, Nigeria for his assistance in the statistics and data analysis.

FUNDING
We would like to acknowledge the Research Management Centre (RMC) Universiti Putra Malaysia and the Ministry of Education Malaysia in providing the financial support for
this research. This research was financially supported by the Ministry of Education Malaysia research grant, under the Fundamental Research Grant Scheme (FRGS) with the reference code number: FRGS/1/2019/SKK03/UPM/02/4 and project code: 04-01-19-2119FR and project number S540244.

CONFLICT OF INTEREST
All the authors declare that they have no conflict of interest to disclose.

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