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Ischemic cerebrovascular burden evaluated by magnetic resonance imaging in an elderly Brazilian community: The Pietà study

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ABSTRACT

In developing countries, cardiovascular risk factors are poorly controlled, leading to high prevalence of cerebrovascular diseases. The aim of the study was to evaluate the burden of white matter lesions in magnetic resonance through the Fazekas scale in a population aged 75+ years living in the community, and to investigate possible associations between vascular lesions, cardiovascular risk factors and cognitive status. Subjects were selected from a community-based study on brain aging conducted in Caeté (Minas Gerais state), Brazil. Overall, 177 participants (112 cognitively healthy, 36 with cognitive impairment-no dementia and 29 with dementia), being 108 women, aged 79.3 ± 3.8 years, with 3.1 ± 2.9 years of educational level, underwent a 3 Tesla magnetic resonance scanner with fluid attenuated image recovery acquisition. Severity of white matter lesions was assessed through the Fazekas scale. Severe white matter lesions were present in 31.1% of the whole sample and in 25.0% of the cognitively healthy individuals. A significant association was found between severe white matter lesions and cognitive impairment (OR = 2.20, 95% CI 1.17–6.53; p = 0.021), as well as with hypertension (OR = 1.92, 95% CI 1.03–7.39; p = 0.043). In conclusion, a high prevalence of severe white matter lesions was observed in this elderly Brazilian population sample, and white matter lesions were associated with hypertension and cognitive status. Importantly, the prevalence of white matter lesions was also high in cognitively healthy subjects.

1. Introduction

Aging and brain vascular disease share reciprocal relationships: at one side, cerebral small vessel disease (SVD) is a common finding in aging; on the other hand, aging is a risk factor for cerebral SVD [1]. Such changes appear as white matter hyperintensities (WMH) on T2 weighted magnetic resonance imaging (MRI) and are called leukoaraiosis when detected by computed tomography. The clinical meaning of these findings is a matter of debate as cerebral SVD can be related either to pathological conditions, such as stroke or cognitive decline, or can be observed in asymptomatic individuals [2]. Whilst cerebral SVD is considered the most common cause of vascular dementia [3], it also frequently coexists with neurodegenerative disorders, sharing risk factors with Alzheimer"s disease (AD) [4], and constitutes an important determinant of age-associated functional impairment [5].

As defined by an international consensus, MRI-visible WMH are markers of cerebrovascular disease [6] and are considered imaging-based biomarkers of vascular lesions [7,8]. Studies have shown that their pathologic correlates are arteriosclerosis [9] and its consequences, vasogenic edema [10] and cerebral amyloid angiopathy [11].

Studies from developed countries have shown that prevalence of cerebral SVD, as assessed by MRI, is high. For instance, in a North-American study the overall prevalence of white matter lesions was 15.8%, increasing from 7.9% in the 55 to 59 year-old age group to 22.9% in the 65 to 72-year-old age group [12]. In United Kingdom, the prevalence of white matter lesions assessed by post-mortem MRI in the elderly was 94% [13]. In Latin America, a histopathological study showed that 16.8% of cognitively healthy individuals had cerebral SVD. Furthermore, cerebral SVD was significantly associated with different causes of dementia: AD, vascular dementia and mixed dementia [14,15].

Elderly inhabitants from developing countries usually have on average low educational levels, which might compromise access to better health care services and to a healthier life style. Therefore, these populations are exposed to poor control of cardiovascular risk factors, and

Abbreviations: AD, Alzheimer's disease; CIND, cognitive impairment-no dementia; FAQ, Functional Activity Questionnaire; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; MMSE, Mini-Mental Status Examination; SVD, small vessel disease; WMH, white matter hyperintensities.

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display an elevated prevalence of cerebrovascular disease [14]. In addition, there is convincing evidence from the Brazilian brain bank of the Brazilian Aging Study indicating that even a few years of education, when compared to illiteracy, provide resilience against neuropathological burden, in accordance with the cognitive reserve hypothesis [16]. Therefore, the combined large burden of cardiovascular disorders and lower cognitive reserve background suggests that cerebrovascular disease may play a major role in cognitive decline and dementia in developing countries [17]. Accordingly, recent results from the long-term follow-up of the Framingham cohort have shown a suggestive decline in dementia incidence across a three decade span, especially in highly educated participants, which is supposed to be associated with a better control of cardiovascular risk factors or conditions [18,19].

Previous studies assessed the prevalence of cerebral SVD in developed countries, but very few focused on individuals older than 75 years. One study in Europe reported WMH in 68.2% of subjects aged 75 + years [20], while another described the presence of severe lesions in 50% of those aged 85 + years [21]. As far as we are aware, no previous study in Latin America evaluated cerebral SVD in a community setting using MRI. In the present study we investigated WMH burden assessed through MRI in a community-based sample of individuals aged 75 + years with low educational level. We hypothesized that prevalence of cerebral SVD would be high in this population regardless of reported symptoms, and its' severity would be associated with cognitive impairment.

2. Methods

2.1. Population

The participants were selected from the Pietà study, a community-based investigation on brain aging conducted in Caeté (Minas Gerais state), Southeast of Brazil [22]. Elderly individuals aged 75 + years, targeted in this study, were 1251 (3.2% of the total population) according to the Brazilian Institute of Geographic and Statistics [23]. They were actively searched through community-health program agents from the local government; announcements on local radios and newspapers were also strategically posted. As for institutionalized elderly, the research team visited the two existing long-term care institutions in the town. Overall, 639 individuals, corresponding to 51.1% of the city population aged 75 + years were evaluated. Participants were submitted to a thorough clinical, neurological and functional evaluation. Blood samples were collected for routine laboratory tests, including TSH, B12 vitamin and VDRL to rule out reversible causes of cognitive impairment. The clinical, functional, neurological and psychiatric status of the participants was established according to the performance on the cognitive tests and on careful group discussions and consensus agreement among the examining physicians. Participants were submitted to the Mini-Mental Status Examination MMSE [24,25] and to a Brief Cognitive Screening Battery [26]. Functional performance was assessed with the Functional Activity Questionnaire (FAQ) [27]. Individuals were considered to be cognitively efficient when they had a performance in the MMSE and in the Brief Cognitive Battery above the 25th percentile according to age and educational level, in agreement with previous Brazilian reports [28–31]. A cut-off of 5 points on the FAQ was set to define a significant level of functional impairment [32]. For the purpose of the present study, the participants were classified into cognitively healthy when they had the expected performance for age and education in the tests and no functional impairment. When there was cognitive impairment, but functional independence (FAQ ≤ 5), they were classified as cognitive impairment-no dementia (CIND) [33,34]. As this was a population-based study, the CIND concept [35] was preferred instead of mild cognitive impairment (MCI) because it is a broader concept and it is not necessarily associated with cognitive complaint. This latter feature is particularly relevant given the sociodemographic profile of the study population (advanced age and low schooling). Indeed, most CIND subjects and/or their relatives did not have cognitive complaints, and cognitive impairment was identified only after clinical and neuropsychological evaluation. Finally, the diagnosis of dementia was made based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria [36].

Antecedents of myocardial infarction and dyslipidemia were assessed with a standardized medical questionnaire administered to the individuals or to their relatives, whenever necessary. Diabetes mellitus was considered to be present if the subject had a previous diagnosis and/or was taking oral antidiabetics or insulin. Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. A subject was considered to have hypertension if he/she provided a compatible medical history of hypertension or when he/she was taking antihypertensive drugs.

2.2. Standard protocol approvals, registrations, and patient consents

This study was approved by the Ethics Committee of the Federal University of Minas Gerais. All participants or their legally acceptable representatives signed the written informed consent.

2.3. Neuroimaging data acquisition, processing and analysis

A random subsample of the individuals from the Pietà study (n = 200) was asked to take part in the MRI examination. The effective sample used in this study (n = 177) included participants with acceptable quality of the fluid attenuated inversion recovery (FLAIR) images acquired in a 3 Tesla Philips Achieva scanner. The FLAIR images were obtained in axial plane with a single-shot, spin-echo echoplanar sequences in the axial plane (TR/TE = 10,000/140 ms, Inversion time: 2800 ms, Echo train length: 27 mm, FOV = 240 mm, matrix = 352 × 212 (reconstructed 512 × 512), slice thickness = 5.0 mm with 0.5 mm gap between slices).

An experienced radiologist (LCS), blind to all clinical information, centrally performed the assessment of the severity of WMH on axial FLAIR images using the Fazekas scale. The Fazekas score is rated according to the presence of WMH in FLAIR images: zero refers to no white matter lesions (including symmetrical, well-defined caps or bands), one refers to the presence of focal lesions, two refers to the presence of beginning confluent lesions, and three refers to the presence of diffuse involvement of the entire white matter, with or without involvement of U fiber [37,38]. Deep and periventricular white matter were separately considered for the analysis. Brainstem hyperintensities were excluded. This scale does not evaluate acute vascular lesions or lacunes. According to WMH severity, patients were subdivided into three groups: absent/mild changes (Fazekas 0 and 1), moderate changes (Fazekas 2) and severe changes (Fazekas 3) [37].

2.4. Statistical analysis

Absolute frequencies of different levels of WMH were measured as total numbers of mild intensity (Fazekas 0 and 1), moderate intensity (Fazekas 2), and severe intensity (Fazekas 3). The frequencies were also divided by sex, age and cognitive status: cognitively healthy, CIND and dementia. Age was divided into three groups: 75 to 79, 80 to 84 and 85 and older. Koromogov-Smirnov test was used to check the normality of the sample. The chi-square test or Fisher's exact test, when appropriate, was used for categorical variables. Kruskal-Wallis test was used for quantitative variables.

Logistic regression analysis was employed to evaluate the association between severe WMH group and the following variables: cognitive impairment (dementia and CIND), history of myocardial infarction, hypertension, diabetes and dyslipidemia, adjusted for age, sex, and schooling. SPSS (version 22; Statistical Package for the Social Sciences, Chicago, IL) was employed, and the value of significance was accepted as a p-value < 0.05 in two-tailed tests.

3. Results

The absolute proportion of cognitively healthy individuals was 63.3% (n = 112), CIND 20.3% (n = 36) and dementia 16.4% (n = 29). The mean age was 79.3 ± 3.8 years, being 61.0% (n = 108) female, with 3.1 ± 2.9 years of schooling. Overall, 74.6% of the sample had history of hypertension, 14.7% had history of diabetes, and 20.3% had history of dyslipidemia. History of myocardial infarction was present in 3.4%.

White matter hyperintensities (Fazekas ≥ 1) were present in 97.7% (n = 173) of the whole sample, while Fazekas 2 occurred in 29.9% (n = 53) and severe WMH (Fazekas 3) occurred in 31.1% (n = 55) of the sample.

There was no difference between age, education, gender, cognitive status, cardiovascular risk factors or conditions among WMH severity groups (Table 1). In a logistic regression analysis, considering age, sex and education as covariates, there was a significant association between severe WMH and cognitive impairment (CIND plus dementia) (OR = 2.20, 95% CI 1.17–6.53; p = 0.021). Additionally, severe WMH were also associated with hypertension (OR = 1.92, 95%CI 1.03–7.39; p = 0.043). Performances on cognitive tests, namely the MMSE and the memory test from the Brief Cognitive Battery, were not significantly different among WMH severity groups.

4. Discussion

In this population-based study, a high prevalence of white matter lesions, as assessed by WMH on MRI, was observed. Moreover, we found that 31.1% of this elderly sample had severe WMH, and 25.0% of cognitively healthy individuals also had severe WMH. Moreover, we found that severe WMH was associated with cognitive impairment (CIND and dementia), as previously reported [39].

In the first Rotterdam study in the 1990's, the prevalence of severe white matter lesions was 10% among subjects with mean age of 55 years [40]. In the Leukoaraiosis and Disability Study, a European multicenter study which examined nondisabled elderly subjects aged 65 to 85 years old, 22.6% of the population had Fazekas 3 [41]. Some most recent studies quantified white matter lesions in volumetric approaches with specific software, and not through visual scale. However, there is conflicting evidence whether volumetric measures are more sensitive than visual scales [42]. Also, there is a good correspondence between visual scales and volumetric approach [39]. Nonetheless, even studies that assessed white matter lesions using volumetric measures have shown mild to moderate densities of white matter lesions in the populations studied. It ranged from 0.7 ± 2.2 mm^3 (mild lesions) in healthy controls selected under highly restricted criteria [43] to 11.7 ± 6.7 mm^3 (moderate lesions) in a population based study [44]. Outside Europe and North America, there are few population-based studies assessing white matter lesions. The Personality & Total Health Through Life Longitudinal Relatively Young (60–64 years) cohort study in Australia reported an average WMH volume of 4.8 ± 4.7 mm^3 (moderate lesions) [45]. The Clinical Research Center for Dementia of South Korea, a multisite elderly cohort study, reported an average WMH volume of 10.8 ± 18.4 mm^3 (moderate lesions) [46].

Table 1
Frequencies of white matter hyperintensities severity distributed by age, sex and diagnosis.

	WMH severity			
	Absent/mild (n = 69)	Moderate (n = 53)	Severe (n = 55)	p-Value
Age (%)				0.065
75–79	41.9%	36.5%	21.6%	
80–84	40.3%	19.4%	40.3%	
≥85	30.5%	36.1%	33.3%	
Gender				n.s.
Female (%)	37.0%	28.7%	34.2%	
Cognitive category				0.092
Cognitively healthy	42.8%	32.1%	25.0%	
CIND	38.9%	27.7%	33.3%	
Dementia	24.1%	24.1%	51.7%	
Clinical comorbidities				
History of MI (n = 6)	33.3%	33.3%	33.3%	n.s.
Hypertension (n = 132)	36.4%	30.3%	33.3%	n.s.
Diabetes (n = 26)	30.8%	30.8%	38.5%	n.s.
Dyslipidemia (n = 36)	36.1%	30.6%	33.3%	n.s.

WMH: white matter hyperintensities; CIND: cognitive impairment no dementia; MI: myocardial infarction; n.s.: not significant.

We found a high prevalence of white matter lesions in our study. Despite of the increasing access to health system in the last years, the cerebrovascular disease risk factors, such as arterial hypertension, diabetes mellitus, and hyperlipidemia, are still not adequately treated in Brazil [47,48]. Probably, this lack of appropriate control of risk factors might have been the main cause of this high prevalence.

Interestingly, there was a high prevalence of severe white matter lesions in cognitively healthy subjects. This supports the fact that, at least in some individuals, there are other factors that influences the way that brain damage turns out into cognitive impairment. One example of a protective factor is the educational level. Some studies suggest that the higher the educational level, less cognitive symptoms emerge with the same white matter burden [16,49]. On the other hand, AD pathology seems to reduce the threshold to the onset of symptoms. A recent study has shown that in asymptomatic carriers of AD mutations, the WMH volume is significantly higher than in non-carriers. Even more intriguing is that such changes can occur about six years before the age of expected Alzheimer's symptoms' onset [50]. It has also been recently demonstrated that the amount of cerebral vessel pathology (atherosclerosis and arteriolosclerosis) increases the risk of sporadic AD [51], thus suggesting that vascular factors are pathophysiological features of AD. Actually, the exact role of white matter lesions in cognition and its relation to neurodegeneration is still not completely understood.

As previously reported [41,52], we also found association between severe WMH and hypertension. In Brazil the prevalence of hypertension in the elderly ranges from 28.7% to 62.7% [53] being 39.1% in Latin America, considering all ages [54]. In our sample we found 74.6% of the population studied being hypertensive. This feature was probably due to the advanced age of the sample, and although the study has taken place in a city in the Southeast region (the wealthiest country's region), this city is small and has a considerable rural area, where the control of cardiovascular risk factors is poor. On the other hand, the prevalence of diabetes in our study was slightly inferior to other Brazilian studies, 14.7% against 17.6% in a self-reported study in Brazil in individuals aged 75+ years [55]. This finding may be explained by differences in criteria to define the disease and to the fact that since we have classified diabetes based on previous medical history, the disease was probably underdiagnosed, due to limitations in the access to public health care in the country.

Although some studies have found association between severity of WMH and age [40,56], we did not find this association, possibly due to the fact that our sample is already very old and that we did not include subjects younger than 75 years old.

In this study there was no significant association between severity of white matter lesions and performance in tests of global cognition and episodic memory. Although some studies described associations between cognitive performance and WMH [41,43,57,58], these associations mainly occur with tests that assess executive functions and mental processing speed, which are cognitive aspects more associated with white matter integrity [44,49,58,59]. It should be pointed out that other factors which have not been assessed in the present study such as brain atrophy, lacunar infarcts [60] and diffusion measures [61], are also determinants of cognitive performance. Finally, the longitudinal effect of WMH is less detectable in cross-sectional studies [39].

There are several limitations in this study. First, not all individuals from the community-based study undergone brain MRI. Subjects who had MRI performed were younger, with higher educational level and with higher MMSE. This happened because we did not propose the exam to very frail individuals, once the exam was conducted in another city. Conversely, the sample analyzed with neuroimaging was still very old and with low educational level, allowing the conclusions made about this type of population. Secondly, the visual scale was rated by only one radiologist, which could have a potential bias. However, this methodological design has been employed before [56]. Moreover, as the rater has >10 years of experience and was completely blind for all the clinical information, we consider that this possible bias did not affect the results significantly. Thirdly, we did not use specific tests for executive function or mental processing speed, preventing association analysis between WMH and these cognitive aspects. Finally, the diagnosis of cardiovascular risk factors was assessed through primarily direct questioning the individuals and the sensitivity and specificity of this method is not ideal [62]. However, many epidemiological surveys also employ self-reported diagnosis [63–65].

In conclusion, we found a high prevalence of severe white matter lesions in this elderly population sample living in community. These lesions were associated with cognitive impairment and hypertension. However, severe WMH were also prevalent in cognitively healthy individuals. These findings might also apply for other developing countries, where clinical control of vascular risk factors is still insufficient. Public health policies to improve the assistance to better control the cardiovascular risk factors should be prioritized in order to reduce dementia burden.

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Conflict of interest

The authors declare they have no conflict of interest related to this research.

References

[1] M.H. Chowdhury, A. Nagai, H. Bokura, et al., Age-related changes in white matter lesions, hippocampal atrophy, and cerebral microbleeds in healthy subjects without major cerebrovascular risk factors, J. Stroke Cerebrovasc. Dis. 20 (4) (2011) 302–309, http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2009.12.010.
[2] L. Pantoni, A. Poggesi, D. Inzitare, Cognitive decline and dementia related to cerebrovascular diseases: some evidence and concepts, Cerebrovasc. Dis. 27 (Suppl. 1) (2009) 191–196.
[3] L. Pantoni, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (7) (2010) 689–701, http://dx.doi.org/10.1016/S1474-4422(10)70104-6.
[4] M. Dichgans, V. Zietemann, Prevention of vascular cognitive impairment, Stroke 43 (11) (2012) 3137–3146, http://dx.doi.org/10.1161/STROKEAHA.112.651778.
[5] B.T. Baune, W.P. Schmidt, A. Roesler, et al., Functional consequences of subcortical white matter lesions and MRI-defined brain infarct in an elderly general population, J. Geriatr. Psychiatry Neurol. 22 (4) (2009) 266–273, http://dx.doi.org/10.1177/0891988709342722.
[6] J.M. Wardlaw, E. SE, G.J. Biessels, et al., Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration, Lancet Neurol. 12 (2013) 822–838 (1474–4465 (Electronic)) http://dx.doi.org/10.1016/S1474-4422(13)70124-8.
[7] S. Artero, H. Tiemeier, N.D. Prins, et al., Neuroanatomical localisation and clinical correlates of white matter lesions in the elderly, J. Neurol. Neurosurg. Psychiatry 75 (9) (2004) 1304–1308, http://dx.doi.org/10.1136/jnnp.2003.023713.
[8] P. Scheltens, F. Barkhof, J. Valk, et al., White matter lesions on magnetic resonance imaging in clinically diagnosed Alzheimer's disease. Evidence for heterogeneity, Brain 115 (Pt 3) (1992) 735–748, http://dx.doi.org/10.1093/brain/115.3.735.
[9] A.A. Gouw, A. Seewann, W.M. van der Flier, et al., Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations, J. Neurol. Neurosurg. Psychiatry 82 (2) (2011) 126–135, http://dx.doi.org/10.1136/jnnp.2009.204685.
[10] S. Black, F. Gao, J. Bilbao, Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment, Stroke 40 (3 Suppl) (2009) S48–S52, http://dx.doi.org/10.1161/STROKEAHA.108.537704.
[11] M. Haglund, E. Englund, Cerebral amyloid angiopathy, white matter lesions and Alzheimer encephalopathy — a histopathological assessment, Dement. Geriatr. Cogn. Disord. 14 (3) (2002) 161–166.
[12] R.N. Bryan, J. Cai, G. Burke, et al., Prevalence and anatomic characteristics of infarct-like lesions on MR images of middle-aged adults: the atherosclerosis risk in communities study, AJNR Am. J. Neuroradiol. 20 (7) (1999) 1273–1280.
[13] M.S. Fernando, P.G. Ince, Vascular pathologies and cognition in a population-based cohort of elderly people, J. Neurol. Sci. 226 (1–2) (2004) 13–17.
[14] L.T. Grinberg, R. Nitrini, C.K. Suemoto, et al., Prevalence of dementia subtypes in a developing country: a clinicopathological study, Clinics (Sao Paulo) 68 (8) (2013) 1140–1145, http://dx.doi.org/10.6061/clinics/2013(08)13.
[15] K. Nagata, D. Takano, T. Yamazaki, et al., Cerebrovascular lesions in elderly Japanese patients with Alzheimer's disease, J. Neurol. Sci. 322 (1–2) (2012) 87–91, http://dx.doi.org/10.1016/j.jns.2012.07.001.
[16] J.M. Farfel, R. Nitrini, C.K. Suemoto, et al., Very low levels of education and cognitive reserve: a clinicopathologic study, Neurology 81 (7) (2013) 650–657, http://dx.doi.org/10.1212/WNL.0b013e3182a08f1b.
[17] R. Nitrini, C.M. Bottino, C. Albala, et al., Prevalence of dementia in Latin America: a collaborative study of population-based cohorts, Int. Psychogeriatr. 21 (4) (2009) 622–630, http://dx.doi.org/10.1017/S1041610209009430.
[18] K.M. Langa, Is the risk of Alzheimer's disease and dementia declining? Alzheimers Res. Ther. 7 (1) (2015) 34–38, http://dx.doi.org/10.1186/s13195-015-0118-1.
[19] C.L. Satizabal, A.S. Beiser, V. Chouraki, et al., Incidence of dementia over three decades in the Framingham heart study, N. Engl. J. Med. 374 (6) (2016) 523–532, http://dx.doi.org/10.1056/NEJMoa1504327.
[20] C. Wehrberger, S. Jungwirth, P. Fischer, et al., The relationship between cerebral white matter hyperintensities and lower urinary tract function in a population based, geriatric cohort, Neurourol. Urodyn. 33 (4) (2014) 431–436, http://dx.doi.org/10.1002/nau.22419.
[21] T.M. Polvikoski, E.C. van Straaten, F. Barkhof, et al., Frontal lobe white matter hyperintensities and neurofibrillary pathology in the oldest old, Neurology 75 (23) (2010) 2071–2078, http://dx.doi.org/10.1212/WNL.0b013e318200d6f9.
[22] P. Caramelli, M.T. Barbosa, E. Sakurai, et al., The Pietà study. Epidemiological investigation on successful brain aging in Caeté (MG), Brazil. Methods and baseline cohort characteristics, Arq. Neuropsiquiatr. 69 (4) (2011) 579–584.
[23] http://www.ibge.gov.br/cidadesat.
[24] M.F. Folstein, S.E. Folstein, P. McHugh, 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198.
[25] S.M. Brucki, R. Nitrini, P. Caramelli, et al., Sugestões para o uso do Mini-Exame do Estado Mental no Brasil, Arq. Neuropsiquiatr. 61 (2003) 777–781.
[26] R. Nitrini, P. Caramelli, E. Herrera Junior, et al., Performance of illiterate and literate nondemented elderly subjects in two tests of long-term memory, J. Int. Neuropsychol. Soc. 10 (2004) 634–638.
[27] R.I. Pfeffer, T.T. Kurosaki, C.H. Harrah, et al., Measurement of functional activities in older adults in the community, J. Gerontol. 37 (1982) 323–329.
[28] L.T. Takada, P. Caramelli, H.C. Fichman, et al., Comparison between two tests of delayed recall for the diagnosis of dementia, Arq. Neuropsiquiatr. 64 (1) (2006) 35–40, http://dx.doi.org/10.1590/S0004-282X2006000100008.
[29] P. Caramelli, M.T. Carthery-Goulart, C.S. Porto, et al., Category fluency as a screening test for Alzheimer disease in illiterate and literate patients, Alzheimer Dis. Assoc. Disord. 21 (2007) 65–67.
[30] E. Herrera Jr., P. Caramelli, A.S.B. Silveira, et al., Epidemiological survey of dementia in a community-dwelling Brazilian population, Alzheimer Dis. Assoc. Disord. 16 (2002) 103–108.
[31] P. Caramelli, E. Herrera Jr., R. Nitrini, Education-adjusted normative values for the mini-mental state examination (MMSE) in a large elderly cohort, Dementia & Neuropsychologia 1 (Suppl. 2) (2007) 18.
[32] E. Teng, B.W. Becker, E. Woo, et al., Utility of the functional activities questionnaire for distinguishing mild cognitive impairment from very mild Alzheimer's disease, Alzheimer Dis. Assoc. Disord. 24 (2010) 348–353.
[33] E.M. Ebly, D.B. Hogan, I.M. Parhad, Cognitive impairment in the nondemented elderly. Results from the Canadian study of health and aging, Arch. Neurol. 52 (1995) 612–619.
[34] J. Graham, K. Rockwood, B. Beattie, et al., Prevalence and severity of cognitive impairment with and without dementia in an elderly population, Lancet 349 (9068) (1997) 1793–1796.
[35] B. Caracciolo, K. Palmer, R. Monastero, et al., Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study, Neurology 70 (2008) 1778–1785, http://dx.doi.org/10.1212/01.wnl.0000288180.21984.cb.
[36] APA, Diagnostic and Statistical Manual of Mental Disorders, 4rd ed. American Psychiatric Association, Washington, DC, 2000.
[37] L.O. Wahlund, F. Barkhof, F. Fazekas, et al., A new rating scale for age-related white matter changes applicable to MRI and CT, Stroke 32 (2001) 1318–1322.
[38] F. Fazekas, J.B. Chawluk, A. Alavi, et al., Mr signal abnormalities at 1.5 t in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (1987) 351–356.
[39] G.B. Frisoni, S. Galluzzi, L. Pantoni, et al., The effect of white matter lesions on cognition in the elderly—small but detectable, Nat. Clin. Pract. Neurol. 3 (11) (2007) 620–627.

[40] M.M. Breteler, J.C. van Swieten, M.L. Bots, et al., Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam study, Neurology 44 (7) (1994) 1246–1252.
[41] R. Schmidt, S. Ropele, J. Ferro, et al., Diffusion-weighted imaging and cognition in the leukoariosis and disability in the elderly study, Stroke 41 (5) (2010) e402–e408, http://dx.doi.org/10.1161/STROKEAHA.109.576629.
[42] A.A. Gouw, M. VdFW, E.C.W. van Straaten, et al., Simple versus complex assessment of white matter hyperintensities in relation to physical performance and cognition: the LADIS study, J. Neurol. 253 (9) (2006) 1189–1196.
[43] O. Carmichael, C. Schwarz, D. Drucker, et al., Longitudinal changes in white matter disease and cognition in the first year of the Alzheimer disease neuroimaging initiative, Arch. Neurol. 67 (11) (2010) 1370–1378, http://dx.doi.org/10.1001/archneurol.2010.284.
[44] A.C. Birdsill, R.L. Koscik, E.M. Jonaitis, et al., Regional white matter hyperintensities: aging, Alzheimer's disease risk, and cognitive function, Neurobiol. Aging 35 (4) (2014) 769–776, http://dx.doi.org/10.1016/j.neurobiolaging.2013.10.072.
[45] X. Chen, W. Wen, K.J. Anstey, et al., Prevalence, incidence, and risk factors of lacunar infarcts in a community sample, Neurology 73 (4) (2009) 266–272, http://dx.doi.org/10.1212/WNL.0b013e3181aa52ea.
[46] Y. Noh, Y. Lee, S.W. Seo, et al., A new classification system for ischemia using a combination of deep and periventricular white matter hyperintensities, J. Stroke Cerebrovasc. Dis. 23 (4) (2014) 636–642, http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.06.002.
[47] R. Beaglehole, E. S, S. Reddy, et al., Prevention of chronic diseases: a call to action, Lancet 370 (9605) (2007) 2152–2157, http://dx.doi.org/10.1016/S0140-6736(07)61700-0.
[48] A.L. Ribeiro, B.B. Duncan, L.C. Brant, et al., Cardiovascular health in Brazil: trends and perspectives, Circulation 133 (4) (2016) 422–433, http://dx.doi.org/10.1161/CIRCULATIONAHA.114.008727.
[49] C. Dufouil, A. Alperovitch, C. Tzourio, Influence of education on the relationship between white matter lesions and cognition, Neurology 60 (2003) 831–836.
[50] S. Lee, F. Viqar, M.E. Zimmerman, et al., White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network, Ann. Neurol. (2016), http://dx.doi.org/10.1002/ana.24647.
[51] Z. Arvanitakis, A.W. Capuano, S.E. Leurgans, et al., Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study, Lancet Neurol. 15 (9) (2016) 934–943, http://dx.doi.org/10.1016/S1474-4422(16)30029-1.
[52] J.A. Scott, M.N. Braskie, D. Tosun, et al., Cerebral amyloid and hypertension are independently associated with white matter lesions in elderly, Front. Aging Neurosci. 7 (221) (2015), http://dx.doi.org/10.3389/fnagi.2015.00221.
[53] V.M.A. Passos, T.D. Assis, S.M. Barreto, Hipertensão arterial no Brasil: estimativa de prevalência a partir de estudos de base populacional, Epidemiologia e Serviços de Saúde 15 (1) (2006) 35–45.
[54] A.M. Sarki, C.U. Nduka, S. Stranges, et al., Prevalence of hypertension in low- and middle-income countries: a systematic review and meta-analysis, Medicine (Baltimore) 94 (50) (2015), e1959, http://dx.doi.org/10.1097/MD.0000000000001959.
[55] M.I. Schmidt, B.B. Duncan, J.F. Hoffmann, et al., Prevalência de diabetes e hipertensão no Brasil baseada em inquérito de morbidade auto-referida, Brasil, 2006, Rev Saúde Pública 43 (Suppl. 2) (2009) 74–82.
[56] D. Inzitari, P. G, A. Poggesi, et al., Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort, BMJ 6 (339) (2009) b2477, http://dx.doi.org/10.1136/bmj.b2477.
[57] W.T. Longstreth Jr., T.A. Manolio, A. Arnold, et al., Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The cardiovascular health study, Stroke 27 (8) (1996) 1274–1282.
[58] J. Ramirez, A.A. McNeely, C.J. Scott, et al., Subcortical hyperintensity volumetrics in Alzheimer's disease and normal elderly in the Sunnybrook dementia study: correlations with atrophy, executive function, mental processing speed, and verbal memory, Alzheimers Res. Ther. 6 (4) (2014) 49, http://dx.doi.org/10.1186/alzrt279.
[59] N.D. Prins, E.J. van Dijk, T. den Heijer, et al., Cerebral small-vessel disease and decline in information processing speed, executive function and memory, Brain 128 (Pt 9) (2005) 2034–2041, http://dx.doi.org/10.1093/brain/awh553.
[60] M.W. Warren, M.F. Weiner, H.C. Rossetti, et al., Cognitive impact of lacunar infarcts and white matter hyperintensity volume, Dement Geriatr Cogn Dis Extra 5 (1) (2015) 170–175, http://dx.doi.org/10.1159/000370109.
[61] M. O'Sullivan, R.G. Morris, B. Huckstep, et al., Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis, J. Neurol. Neurosurg. Psychiatry 75 (3) (2004) 441–447, http://dx.doi.org/10.1136/jnnp.2003.014910.
[62] A.K. Dey, A. Alyass, R.T. Muir, et al., Validity of self-report of cardiovascular risk factors in a population at high risk for stroke, J. Stroke Cerebrovasc. Dis. 12 (2015) 2860–2865, http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.08.022.
[63] S. de Kort, C.C.J.M. Simons, P.A. van den Brandt, et al., Diabetes mellitus type 2 and subsite-specific colorectal cancer risk in men and women: results from the Netherlands Cohort Study on diet and cancer, Eur J Gastroenterol Hepatol (2016) (Published Ahead of Print) http://dx.doi.org/10.1097/MEG.0000000000000626.
[64] R. Wong-McClure, E. Gregg, A. Barcelo, et al., Prevalence of diabetes and impaired fasting glucose in Costa Rica: Costa Rican National Cardiovascular Risk Factors Survey, 2010, J Diabetes (2015), http://dx.doi.org/10.1111/1753-0407.12348.
[65] S.A. Patel, M. Winkel, M.K. Ali, et al., Cardiovascular mortality associated with 5 leading risk factors: national and state preventable fractions estimated from survey data, Ann. Intern. Med. 163 (4) (2015) 245–253, http://dx.doi.org/10.7326/M14-1753.