ORIGINAL ARTICLE

Predictors of Mild Cognitive Impairment in a Hypertensive Population

Predictores de riesgo de deterioro cognitivo leve en una población de hipertensos

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ABSTRACT

Background: Cognitive status is considered a biomarker of vascular brain damage caused by hypertension (HTN). Screening for mild cognitive impairment (MCI) is essential in patients with HTN.
Objective: The aim of this study was to evaluate the presence of predictors of MCI in hypertensive patients.
Methods: We conducted an observational and cross-sectional study between 2015 and 2023. All the patients > 18 years treated in a clinic and who were evaluated with the Montreal Cognitive Assessment (MoCA) were included. A score < 24 in the MoCA test was considered abnormal. Patients with motor or sensory impairment, psychiatric disorders, or illiteracy were excluded. Qualitative variables are presented as absolute frequencies and percentages, and the chi-square test was used to analyze their association. Quantitative variables are expressed as mean ± standard deviation and were compared with the independent samples t-test. All the variables with statistical significance in the univariate analysis through forward selection were included in the multiple logistic regression analysis. A p value < 0.05 was considered statistically significant.
Results: A total of 129 patients were included (women-to-men ratio 2:1; mean age 60 years); 79.1% had stage 3 HTN, time from HTN diagnosis was > 20 years in 30.4%, 52.7% had complete primary education, 89.4% had overweight/obesity, 36.4% were smokers and 29.7% had mixed dyslipidemia. A score ≥ 24 in the MoCA was present in 65.1% and 34.9% had a score < 24. The logistic predictor model identified time from HTN diagnosis, mixed dyslipidemia and cerebrovascular disease as predictors of abnormal MoCA. A tertiary educational level had a protective effect.
Conclusions: Identifying predictors of cognitive impairment is a priority to take preventive actions. In this study, time from HTN diagnosis, mixed dyslipidemia, cerebrovascular disease and educational level were associated with cognitive impairment.

Key words: Mild cognitive impairment - Hypertension - Montreal Cognitive Assessment

RESUMEN

Introducción: El estatus cognitivo es considerado un biomarcador del daño vascular encefálico en la hipertensión arterial (HTA). Es fundamental en pacientes con HTA la pesquisa del deterioro cognitivo leve (DCL).
Objetivo: Valorar la presencia de factores predictores de DCL en pacientes hipertensos.
Material y métodos: Estudio observacional, transversal, en el periodo 2015-2023. Se incluyeron pacientes mayores de 18 años, asistidos en policlínica que hubieran realizado la Evaluación Cognitiva de Montreal (MoCA). Se consideró valor de MoCA alterado uno < 24. Se excluyeron pacientes con dificultades motoras, sensoriales, enfermedad psiquiátrica, analfabetismo. Las variables cualitativas se presentan como frecuencias absolutas y relativas, y para el estudio de asociación se utilizó test de Chi cuadrado. Las variables cuantitativas se presentan como media y desviación estándar, y el estudio de diferencias se realizó con test T de Student para muestras independientes. En el análisis de regresión logística múltiple se colocaron aquellas variables significativas en el análisis univariado por el método Forward. Nivel de significación alfa = 0,05.
Resultados: 129 pacientes, mujeres: hombres 2:1; edad promedio 60 años. El 79,1 % tenía HTA grado 3, 30,4 % presentaban más de 20 años de evolución de HTA. El 52,7% tenía escolarización primaria. Un 89,4 % presentaba sobrepeso-obesidad, el 36,4 % tabaquismo, 29,7 % dislipidemia mixta. Un 65,1% presentó un valor de MoCA ≥ 24 y el 34,9 % un valor < 24. En el modelo predictor logístico, las variables evolución en años de HTA, dislipidemia mixta, y enfermedad cerebrovascular fueron predictoras de riesgo de MoCA alterado. El nivel educativo terciario fue factor protector.
Conclusiones: La identificación de factores predictores de daño cognitivo es prioritaria para una acción preventiva. En este estudio las variables tiempo de evolución de la HTA, dislipidemia mixta, enfermedad cerebrovascular y nivel educativo permitieron predecir mayor riesgo de DCL.

Palabras clave: Deterioro cognitivo leve - Hipertensión arterial - Evaluación cognitiva de Montreal

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INTRODUCTION

Most countries worldwide are experiencing growth in both the size and the proportion of older persons in the population. According to the United Nations, population aging is poised to become one of the most significant social transformations of the 21st century, affecting all sectors of society. Uruguay began its aging process at the beginning of the 20th century, earlier than other countries in the region. Nowadays, along with Cuba they are the two countries in the region with the highest incidence of elderly population. (1).

The World Health Organization (WHO) has been leading international action plans under the framework of the "United Nations 2021–2030 Decade of Healthy Aging" program. The goal is to promote healthy aging, which aims to develop and maintain functional capacity to enable well-being in old age. Functional ability is closely related to intrinsic capacity, defined as "composite of all physical and mental capacities of an individual". (2) The intrinsic capacity framework includes cognitive ability and is a significant aspect of the "WHO Integrated Care for the Elderly" (ICOPE) program. (3)

Dementia, a major neurocognitive disorder, is one of the leading causes of disability and dependency among older people worldwide. In high-income countries, individuals with dementia face a mortality risk that is two-and-a-half times higher. Nonetheless, it is underdiagnosed, and when it is diagnosed, it is typically in advanced stages. Lack of understanding of the disease, combined with stigma, creates barriers to early diagnosis and the immediate care that patients need. There is a misconception that memory problems are a normal part of aging and that nothing can be done about them. (4)

The onset of dementia is preceded by mild cognitive impairment (MCI) and subjective memory or cognitive complaint (CC). Mild clinical impairment is a clinical syndrome characterized by impairment in memory or other cognitive function, without significant impairment in the ability to perform activities of daily living. It is a defined clinical-pathological entity, which identifies subjects who are in an intermediate state between normal aging and dementia. The course of MCI is variable and can progress to dementia, remain stable or regress, which defines it as an important diagnostic and therapeutic target. (5-7)

The criteria for the diagnosis of MCI are frequent memory complaints, abnormal memory on cognitive testing (adjusted for age and education level), normal activities of daily living, and absence of dementia. (5,6)

The Montreal Cognitive Assessment (MoCA) is a screening tool for MCI with good results in the international literature that has been translated into several languages and validated in numerous countries. The results have shown high internal consistency and predictive validity. (8) This tool evaluates 6 cognitive domains (memory, visuospatial skills, executive functions, attention/concentration/working memory, language, and orientation). The total possible score is 30 points. A score < 26 indicates MCI, with a sensitivity of 89 % and specificity of 75%. In a cohort of 137 patients treated at Hospital Maciel in Montevideo, Uruguay, a MoCA cut-off point < 24 was associated with a sensitivity of 88.9% and specificity of 78.9% to detect MCI. (9)

Environmental and genetic factors have been described in the pathogenesis of MCI, both in its onset and progression. Environmental factors include low educational level, depression in the elderly, hearing loss, social isolation, and cardiovascular risk factors (CRF) such as hypertension (HTN). It is estimated that over 80% of patients with HTN are not adequately controlled. Uncontrolled and untreated HTN is associated with cognitive impairment and dementia. (10,11)

Cognitive status is internationally considered a biomarker of vascular brain damage caused by HTN. The 2023 European Society guidelines for the management of HTN recommend performing cognitive function testing as part of the clinical evaluation of hypertensive patients. Therefore, it is important to have appropriate screening tests available during medical visits. Thirty percent of hypertensive patients without involvement of other organs present vascular brain damage and cognitive impairment. The time from HTN diagnosis, HTN stage and variability of blood pressure levels, and the loss of the physiological dipper pattern are associated with impaired cognitive function. (12,13)

For this reason, the aim of this study was to evaluate the presence of predictors of MCI in a hypertensive population.

METHODS

We conducted a descriptive, observational, and cross-sectional study between May 2015 and January 2023 at the Hypertension Clinic of Hospital Maciel in Montevideo, Uruguay. Patients treated in the Clinic sign a general informed consent form, which is then recorded anonymously in the database.

All the patients > 18 years evaluated with the MoCA were included. Patients with motor or sensory impairment, psychiatric disorders, or illiteracy were excluded.

The following variables were analyzed:

- Sex: men and women.
- Age: in years
- Educational level: defined by the years of education completed. The educational levels are categorized as follows: incomplete primary education (less than 6 years completed), complete primary education (6 years completed), incomplete secondary education (between 7 and 11 years completed), complete secondary education (12 years completed), incomplete tertiary education, and complete tertiary education (depending on whether the corresponding syllabus has been completed).
- HTN: systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg.
- Time from HTN diagnosis: in years.
- Stage of HTN (according to ESC 2018): stage 1, SBP 140-159 and/or DBP 90-99 mm Hg; stage 2, SBP 160-179

and/or DBP 100-109 mm Hg; and stage 3, SBP > 179 and/or DBP > 109 mm Hg.
- Weight: in kg, measured with office scale.
- Height: in cm, measured with portable stadiometer.
- Overweight: body mass index (BMI) between 25 and 30 kg/m^2.
- Obesity: BMI > 30 kg/m^2.
- Diabetes mellitus (DM): fasting glycemia ≥ 126 mg/dl or incidental finding of glycemia > 200 mg/dL.
- Mixed dyslipidemia: total cholesterol > 190 mg/dL and/or LDL cholesterol > 115 mg/dL and/or HDL cholesterol < 40 mg/dL in men or 46 mg/dL in women and triglycerides > 150 mg/dL. (14)
- Pre-existing cardiovascular disease: history of ischemic heart disease (IHD), heart failure (HF), lower extremity peripheral artery disease, stroke and/or transient ischemic attack (TIA), documented in the medical record.
- CC: frequent memory loss reported by patients or caregivers.
- Cognitive impairment: according to the optimal cut-off point for the study population.
  A score < 24 in the MoCA was considered abnormal.

Statistical analysis

Qualitative variables are presented as absolute frequencies and percentages, and the chi-square test was used to analyze their association. Quantitative variables are expressed as mean ± standard deviation and were compared with the independent samples t-test. All the variables with statistical significance in the univariate analysis through forward selection were included in the multiple logistic regression analysis. All statistical calculations were performed using STATA 17.0 software package. A p value < 0.05 was considered statistically significant.

Ethical considerations

The study was evaluated and approved by the Institutional Review Board of Hospital Maciel and was conducted following the National Statement 158/19 for research on human subjects and the Declaration of Helsinki revised in 2000. Data confidentiality was maintained, and all the patients signed an informed consent form to be included in the database.

RESULTS

A total of 129 patients were included. Mean age was 60.0 ± 1.1 years and 68.2% (n = 88) were women. The majority of patients (79.1%) had HTN stage 3, and time from HTN diagnosis was > 20 years in 30.4%.

In terms of educational levels, 52.7% reported incomplete or complete primary education. Regarding CRF, 89.4% had overweight or obesity, 36.4% were smokers, and 29.7% had dyslipidemia. A score ≥ 24 in the MoCA test was present in 65.1% and 34.9% had a score < 24 points.

On univariate analysis, there were no differences between the two groups, abnormal MoCA and normal MoCA, in terms of sex, HTN stage, overweight or obesity, smoking habits, peripheral artery disease, IHD, HF, and atrial fibrillation.

The variables with statistically significant differences on univariate analysis are presented in Table 1. Multivariate logistic regress analysis identified the independent predictor variables that are shown in Table 2.

The final predictor model was made up of time from HTN diagnosis > 20 years, the presence of mixed dyslipidemia, stroke/TIA, and tertiary education level. The presence of a subjective complaint was only observed in the univariate model, but it lost statistical significance in the multivariate model.

DISCUSSION

Hypertension is the primary CRF for cognitive impairment. The age at diagnosis and the time from HTN diagnosis are significant predictors of cognitive impairment. The longer the time from HTN diagnosis, the worse the performance in both executive functions and immediate logical memory. (15-17) In the study population, time from HTN diagnosis >20 years was the main predictor of abnormal MoCA.

Hypertension has been associated with reduced abstract reasoning (executive dysfunction), slowing of mental processing speed, and, less frequently, memory deficits. (18)

Muela et al. reported that the HTN stage and educational level were the best predictors of MCI in patients with hypertension. The most affected cognitive domains were language, processing speed, visuospatial abilities, and memory. (19)

The 2023 European Society guidelines for the management of HTN recommend screening hypertensive patients > 65 years using short cognitive screening tests, such as the Mini-Mental State Examination. However, the guidelines place greater emphasis on the MoCA. A MoCA score below 24, or below 26 and subjective complains of memory loss should lead to referral to a neurologist or a geriatrician. (12)

Most of the population included in this study has stage 3 hypertension according to the 2018 ESC guidelines, probably because they are treated in clinic specialized in managing difficult cases of hypertension. However, in this study HTN stage had no significant differences between the groups with normal and abnormal MoCA. A tertiary educational level had a protective effect is this study. A high level of education is widely used as an indicator of "cognitive reserve", defined as individual ability to make flexible and efficient use of available neuronal networks in the active model (10) to cope with pathology. Patients with cognitive impairment with higher cognitive reserve have an increased capacity to cope with reduced white matter integrity and thus modulate structural brain changes. (20)

The prevalence of CRF is higher in patients with cognitive impairment compared to those who are cognitively normal. There is significant evidence linking CRF and subclinical atherosclerosis to brain health. This evidence suggests that cerebrovascular and neurodegenerative diseases often coexist and contribute to the development of dementia. Therefore, a history of stroke or TIA can be a predictor of increased risk.

Variables	Abnormal MoCA < 24 (n = 45)	Normal MoCA ≥ 24 (n = 84)	p
Educational level, n (%)			
Incomplete primary education	16 (35.6)	13 (15.5)	
Complete primary education	9 (20.0)	30 (35.7)	
Incomplete secondary education	10 (22.2)	22 (26.2)	<0.001
Complete secondary education	2 (4.4)	2 (2.4)	
Incomplete tertiary education	1 (2.2)	5 (6.0)	
Complete tertiary education	2 (4.4)	7 (8.3)	
No data	5 (11.1)	5 (6.0)	
Age, years, mean ± SD	66.1 ± 1.6	56.8 ± 1.3	<0.001
Time from HTN diagnosis, years, n (%)			
< 5 years	6 (18.9)	18 (31.6)	
5 to 10 years	7 (21.9)	12 (21.1)	<0.001
11 to 20 years	2 (6.3)	17 (29.8)	
> 20 years	17 (53.1)	10 (17.5)	
Mixed dyslipidemia, n (%)	14 (37.8)	25 (6.4)	<0.001
Diabetes, n (%)	16 (41.0)	22 (26.5)	0.029
Established CV disease, n (%)	20 (55.6)	28 (38.4)	0.003
Stroke/TIA, n (%)	12 (33.3)	14 (19.2)	0.004
Cognitive complaint, n (%)	21(56.8)	30(40.5)	0.047

CV: cardiovascular; HTN: hypertension; MoCA: Montreal Cognitive Assessment; SD: standard deviation; TIA: transient ischemic attack

Table 1. Differences between patients with abnormal MoCA and normal MoCA.

Table 2. Multivariate model to predict MCI. Independent predictors

Variable	OR	95% CI
Tertiary educational level	0.43	(0.19 - 0.71)
Time from HTN diagnosis > 20 years	5.33	(2.28 - 7.31)
Mixed dyslipidemia	2.07	(1.06 - 4.89)
Stroke/TIA	1.82	(1.25 - 3.89)

CI: confidence interval; HTN: hypertension; MCI: mild cognitive impairment; OR: odds ratio; TIA: transient ischemic attack

(21) In this population, only mixed dyslipidemia was found to be a cardiovascular risk factor to predict worse cognitive function. This may be due to the relatively low number of patients.

Cognitive complaints are a common reason for consultation, representing a significant number of patients treated in memory care units worldwide. Jonker et al. (2000) found an incidence of 25-56%. In 2005, the percentage of CC at Karolinska Memory Clinic in Huddinge, Sweden, was 38%. (22,23) Cognitive complaints are considered a stage preceding MCI and a risk factor for dementia. In a Japanese cohort of 3672 participants, CC were associated with a higher risk of dementia in cognitively intact participants but not in those with cognitive impairment (HR 4.95, 95% CI 1.52–16.11, p = 0.008). (24)

In the study population, CC only appeared as a predictor in the univariate model but lost statistical significance in the multivariate model. Wang et al. did not find any association between CC and dementia. They evaluated 543 individuals from a rural area twice during a 3-year period. In both evaluations, CC was associated with poorer performance on neuropsychological tests but not with cognitive impairment over time. (25) Based on the evidence provided by the Rotterdam study, it is possible that the characteristics of a population living in a rural setting with a low level of education may have reduced the predictive value of CC. Overall, most longitudinal studies suggest a modest positive association between CCs and future deterioration. (26) Identifying subjects at this preclinical stage would have dual utility: developing new therapeutic strategies to delay the onset of the disease and reducing the worldwide prevalence of dementia in the next 40 years. (27)

Study limitations

The study population may be biased because they are patients attending a specialized clinic with a high percentage of patients who have stage 3 hypertension and are overweight or obese.

CONCLUSIONS

Identifying predictors of cognitive impairment is a priority in preventing the development and progression of vascular dementia. Time from HTN diagnosis, mixed dyslipidemia, cerebrovascular disease, and educational level were associated with cognitive impair-

ment. In the future, it will be necessary to determine which group of individuals would be candidates for early intervention.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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REFERENCES

1. Brunet N. Márquez C. Envejecimiento y personas mayores en Uruguay. En: Calvo J. Atlas sociodemográfico y de la desigualdad del Uruguay. 1era ed. Montevideo: Ediciones Trilce; 2016:5-22

2. Sum G, Lau LK, Jabbar KA, Lun P, George PP, Munro YL, et al. The World Health Organization (WHO) Integrated Care for Older People (ICOPE) Framework: A Narrative Review on Its Adoption Worldwide and Lessons Learnt. Int J Environ Res Public Health. 2022;20:154. https://doi.org/10.3390/ijerph20010154

3. Atención integrada para las personas mayores (ICOPE). Guía sobre la evaluación y los esquemas de atención centrados en la persona en la atención primaria de salud. Washington, D.C.: Organización Panamericana de la Salud; 2020.

4. Demencia: una prioridad de salud pública. Organización Mundial de la Salud & Organización Panamericana de la Salud. Recuperado a partir de: https://apps.who.int/iris/handle/10665/98377.

5. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. J Alzheimers Dis. 2009;18:11-30. https://doi.org/10.3233/JAD-2009-1120

6. Michon A. The concept of mild cognitive impairment: relevance and limits in clinical practice. Front Neurol Neurosci. 2009;24:12-9. https://doi.org/10.1159/000197880.

7. De León L, Rivero C, Escovar L, Guerrini V. Trastornos cognitivos: diagnósticos diferenciales. Arch Med Int. 2013;35:27-9.

8. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc.
2005;53:695-9. https://doi.org/10.1111/j.1532-5415.2005.53221.x

9. Spósito P, Llorens M. Utilidad del MoCa (Montreal Cognitive Assessment) como test de cribado para el deterioro cognitivo leve en población de hipertensos. Rev Urug Med Interna. 2022;7:44-52.

10. Vicario A, Vainstein NE, Zilberman J, Del Sueldo M, Cerezo GH. Hipertensión arterial: otro camino hacia el deterioro cognitivo, la demencia y las alteraciones conductuales. NEUROL ARG. 2010;2:226-33. https://doi.org/10.1016/S1853-0028(10)70070-7

11. Stuhec M, Keuschler J, Serra-Mestres J, Isetta M. Effects of different antihypertensive medication groups on cognitive function in older patients: A systematic review. Eur Psychiatry. 2017;46:1-15. https://doi.org/10.1016/j.eurpsy.2017.07.015

12. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 20231;41:1874-2071. https://doi.org/10.1097/HJH.0000000000003480.

13. Vicario A, Cerezo HG. Why should we must evaluate cognitive function in hypertensive patients? Brain Disorders & Therapy. 2021;10:1000135.

14. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111-88. https://doi.org/10.1093/eurheartj/ehz455

15. Goldstein FC, Levey AI, Steenland NK. High blood pressure and cognitive decline in mild cognitive impairment. J Am Geriatr Soc. 2013;61:67-73. Httops://doi.org/10.1111/jgs.12067

16. de Heus RAA, Tzourio C, Lee EJL, Opozda M, Vincent AD, Anstey KJ, et al. VARIABLE BRAIN Consortium; Claassen JAHR, Tully PJ. Association Between Blood Pressure Variability With Dementia and Cognitive Impairment: A Systematic Review and Meta-Analysis. Hypertension. 2021;78:1478-89. https://doi.org/10.1161/HYPERTENSIONAHA.121.17797

17. Paradela R, Martino L, Torres L. Ferreira N, Cabella B, Detogni A, et al. Time of hypertension is differently associated with cognitive impairment. J Am Coll Cardiol. 2020,75 (11_Supplement_1) 2023

18. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. American Heart Association Council on Hypertension; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. Hypertension. 2016;68:e67-e94. https://doi.org/10.1161/HYP.0000000000000053

19. Muela HC, Costa-Hong VA, Yassuda MS, Moraes NC, Memória CM, Machado MF, et al. Hypertension Severity Is Associated With Impaired Cognitive Performance. J Am Heart Assoc. 2017;6:e004579. https://doi.org/10.1161/JAHA.116.004579.

20. Mortamais M, Portet F, Brickman AM, Provenzano FA, Muraskin J, Akbaraly TN, Berr C, et al. Education modulates the impact of white matter lesions on the risk of mild cognitive impairment and dementia. Am J Geriatr Psychiatry. 2014;22:1336-45. https://doi.org/10.1016/j.jagp.2013.06.002

21. Parikh NS, Gottesman RF. Midlife Cardiovascular Risk Factors, Subclinical Atherosclerosis, and Cerebral Hypometabolism. J Am Coll Cardiol. 2021;77:899-901. https://doi.org/10.1016/j.jacc.2020.12.046

22. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry. 2000;15:983-91.
https://doi.org/10.1002/1099-1166(200011)15:11<983::aid-gps238>3.0.co;2-5

23. Andersson C. Predictors of cognitive decline in memory clinic patients. [Doctoral thesis]. Stockholm: Karolinska Institutet, Karolinska University; 2007.

24. Tsutsumimoto K, Makizako H, Doi T, Hotta R, Nakakubo S, Makino K, et al. Subjective Memory Complaints are Associated with Incident Dementia in Cognitively Intact Older People, but Not in Those with Cognitive Impairment: A 24-Month Prospective Cohort Study. Am J Geriatr Psychiatry.
2017;25:607-16. https://doi.org/10.1016/j.jagp.2016.12.008

25. Wang PN, Wang SJ, Fuh JL, Teng EL, Liu CY, Lin CH, et al. Subjective memory complaint in relation to cognitive performance and depression: a longitudinal study of a rural Chinese population. J Am Geriatr Soc. 2000;48:295-9. https://doi.org/10.1111/j.1532-5415.2000.tb02649.x

26. Verhaaren BF, Vernooij MW, de Boer R, Hofman A, Niessen WJ, van der Lugt A, et al. High blood pressure and cerebral white matter lesion progression in the general population. Hypertension. 2013;61:1354-9. https://doi.org/10.1161/HYPERTENSIONAHA.111.00430

27. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers Dement. 2007;3:186-91. https://doi.org/10.1016/j.jalz.2007.04.381