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Executive dysfunction in middle-aged hypertensive adults

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Abstract

Objective: *The objective was to compare the executive functions between hypertensive and non-hypertensive middle-aged Mexican adults.* **Methods:** *An observational and analytic study was designed. Participants were men and women residents of Southeastern Mexico, aged between 40 and 60 years, with at least 5 years of hypertension diagnosis. The control group was people without hypertension. All participants completed a digit symbol substitution test (DSST), clinical and epidemiological data. Statistical analysis unpaired Student's t-test, $p < 0.05$.* **Results:** *DSST score in control men was 37.78 ± 11.94, control women: 42.96 ± 11.19, hypertensive men: 16.81 ± 9.82, and hypertensive women: 26.88 ± 12.04. Significant differences were found between hypertensive and non-hypertensive groups. Men had worse scores than women. No difference between normotensive men and women. Inverse correlation was found between DSST score and age, values of systolic and diastolic blood tension in the hypertension group.* **Conclusion:** *Hypertension decreases the executive function in middle-aged people, mainly in men. This dysfunction could be an early indicator of brain deterioration.*

Key words: *Hypertension. Executive cognitive function. Mature age. Brain dysfunction.*

Disfunción ejecutiva en adultos hipertensos de edad madura

Resumen

Objetivo: *comparar la función ejecutiva entre adultos mexicanos de mediana edad, hipertensos y no hipertensos.* **Métodos:** *se diseñó un estudio observacional y analítico. Los participantes eran hombres y mujeres residentes del sureste de México, con edades comprendidas entre 40 y 60 años y al menos cinco años de diagnóstico de hipertensión. Los controles fueron personas sin hipertensión. Todos los participantes completaron la prueba de Sustitución de Símbolo y Dígitos (DSST), datos clínicos y epidemiológicos. Análisis estadístico t-Student no pareada, $p < 0.05$.* **Resultados:** *la puntuación DSST en los hombres control fue de 37.78 ± 11.94 y las mujeres control: 42.96 ± 11.19, los hombres hipertensos: 16.81 ± 9.82 y las mujeres hipertensas: 26.88 ± 12.04. Se encontraron diferencias significativas entre el grupo hipertenso y no hipertenso. Los hombres tuvieron peores puntajes que las mujeres. No hay diferencia entre hombres y mujeres normotensos. Se encontró correlación inversa entre la puntuación DSST y la edad, los valores de tensión arterial sistólica y diastólica en el grupo con*

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hipertensión. **Conclusión:** *la hipertensión disminuye la función ejecutiva en personas de mediana edad, principalmente en hombres. Esta disfunción podría ser un indicador temprano de deterioro cerebral.*

Palabras clave: *Hipertensión. Función cognitiva ejecutiva. Edad madura. Disfunción cerebral.*

Introduction

According to the National Health Survey (ENSANUT MC) 2016, 25.5% of Mexican adults have hypertension[1,2]. Hypertension causes functional and structural alterations in blood vessels, especially affecting arteries of medium and small caliber, which predominate in some organs like brain[3]. Several studies have established a causal relationship between hypertension and brain diseases such as stroke, vascular dementia, and recently Alzheimer's disease[4]. Due to factors that are not yet completely clear, vascular damage induced by hypertension seems to be more aggressive in the frontal lobe, which could lead to executive dysfunction[5].

Executive functions refer to a collection of cognitive abilities that enable and drive adaptive, goal-oriented behavior. These include the ability to generate thought and think flexibly, to update and manipulate information mentally, to inhibit what is irrelevant to current goals, to self-monitor, and to plan and adjust behavior as appropriate to the present context. Executive dysfunction impairs efficient performing of daily activities and increases the risk of morbidity and mortality by accidents inside and outside the home, increases dependence on caregivers, limits productive activities, and reduces quality of life[6,7]. Chronicity and aging can worsen brain damage caused by hypertension[8]. Executive dysfunction may be one of the first manifestations of brain damage[9], especially in patients who do not achieve control despite consuming pharmacological treatment[10].

In most cases, brain damage is irreversible[6], so it is an important early diagnosis. Young and middle-aged hypertensive people usually have not symptoms of a cognitive impairment, however, there are standardized tools to evaluate the executive function[11]. The aim of this study was to compare the executive cognitive function in middle-aged hypertensive and no hypertensive Mexican adults and related with some epidemiological data.

Methods

It is an observational and analytical study.

Patients were recruited at the Unit of Social Insertion (UUIS) of University of Yucatán, México. This institution provides medical care to approximately 1179 users annually. The sample size was non-probabilistic and included all patients with and without hypertension, men and women from 41 to 60 years, with and without diagnosis of hypertension, and with minimum secondary schooling who attended the external consultation from October 2018 to December 2018. All selected patients with hypertension had at least 5 years of diagnosis to ensure chronicity period. To avoid biases on interpretation of cognitive function, results were excluded patients with a history of cerebral vascular event, known brain diseases, with obesity (body mass index [BMI] > 30), dyslipidemias, and hypo or hyperthyroidism. Motor, visual or auditory dysfunction, or under neurological or psychiatric treatment were not included in the study. Ninety-two people agreed to participate and met the selection criteria.

We eliminated patients who at the time of the evaluation had mild cognitive deterioration and/or depressive symptomatology. Seven people were eliminated due to symptoms of depression and/or cognitive impairment. Forty-one hypertensive and 44 normotensive patients were included in final analysis.

Procedures

A physician in a clinic room evaluated patients, during the morning (8-10 am). A brief clinical history was complete emphasizing aspects related to hypertension, time of hypertension evolution, type of treatment it carries, drugs, doses, and achievement of therapeutic goal. All participants in fasting were weighed and measured, without shoes, trousers or skirts, and shirt or blouse. The patients were weighed and measured with Detecto® brand stadiometer and scale; with these values, the BMI was determined, according to the following formula: weight (Kg)/Size (M^2).

Blood pressure (BP) was determined with a Check-ATeK® Baumanometer calibrated according to the official Mexican standard NOM-009-SCFI-1993 with the technique and specifications indicated by NOM-030-SSA2-2017[12]. It was considerate as therapeutic goal if patient at time of measurement systolic BP (SBP) < 140 mmHg and diastolic < 90 mmHg. If in the past 3 months, average arterial BP would not

have exceeded reference values (taken from the clinical record), patients were considerate controlled.

Questionnaires

1. Digit symbol substitution test (DSST) evaluates the working memory, organization of perceived stimuli, visomotor coordination, and selective attention, which are executive cognitive functions. DSST was validated in Europe and the United States, mainly in the older adult population. Due to its iconographic nature, no linguistic translation is required, and the test has been used and validated in multiple contexts, regions, and languages, including Spanish and Mexican population[13-15]. All participants were explained how to respond and used as an example the first 10 boxes with their respective symbols to ensure that patient understood how to perform the test. Participant had to match numbers with their respective symbol in order and without skipping any box, as fast as possible and without any kind of external help. Test had a total duration of 90 s (in triplicate). The number of binomials number-symbol paired correctly constituted score of the participant in the DSST. Blank space between two completed items does not invalidate the test; however, two or more consecutive blank spaces point to the end of the test. Paired symbols after two or more blank spaces are not considered in total score. DSST has no cutting points, score constitutes a continuous variable and has no individual value; it takes utility at population level when different groups are compared and is also useful when applied in the same individual overtime. Score reflects the speed of information processing as an executive function, and in comparison with other cognitive tests, DSST performance is strongly correlated with the volume of the prefrontal cortex[16].
2. Mini-mental state examination (MMSE): this is widely validated tool, values in < 10 min cognitive state examining functions such as the ability to record, attention, calculus, memory, language, ability to follow simple instructions, and guidance. MMSE is used primarily to detect patients with mild cognitive impairment and other more severe forms of cognitive deterioration. Cutting point < 25 was an elimination criterion[17].
3. Beck-II depression inventory (BDI-II): BDI-II requires 5-10 min to be completed and it explores data of major depression in the past 2 weeks, consistent with DSM-5 criteria. Depression has significant repercussions on global cognitive function and can affect test results such as DSST, so score > 19 (of a maximum of 63) was an elimination criterion[18].

The procedures were the same for the control group (not hypertensive), only the interrogation on arterial hypertension was excluded from the study.

Ethical considerations

The study was carried out in accordance with the provisions of the General Law on Health in the field of research, Mexican Secretariat of Health 1987. Ethical principles of the Helsinki World Medical Assembly and The International Code of Medical Ethics, as well as the provisions and Guidelines of the National Bioethics Commission (Conbioetica) 2016, were attended too. The project was evaluated and approved by the Ethics and Research Committee of the UUIS of the Autonomous University of Yucatán.

Statistical analysis

It was carried out with the statistical program GraphPad Prism 7®. The normality of the data was determined with the Shapiro-Wilk test. We compared the values of the scores of DSST with values of BP, age, duration of hypertension, using Student's t-test for unrelated samples. For variables: sex, therapeutic status, and Chi-square test were used. Linear correlation was performed with hypertension length, age, SBP, and diastolic blood pressure (DBP) related to the DSST score. The statistical significance was 95%, $p < 0.05$.

Results

The results presented below correspond to 85 adults. Table 1 describes its main characteristics, grouped as a control group (not hypertensive) and hypertension group.

We found similar distribution of sex, age and BMI in both groups.

There were no differences in BP between men and women, neither in the hypertension group nor in the control group. DSST values in the hypertension group were lower than the control group. Hypertensive men performed less than women did ($p = 0.007$). In the control group, there was no sex difference ($p = 0.15$).

Diagnostic average duration in the hypertension group was 11.9 ± 5 years, on men was 11.31 ± 5.5 years and woman 12.28 ± 4.7 ($p = 0.55$). Most hypertensive patients (82.9%) were receiving some form of pharmacological treatment, 17% of patients had abandoned

Table 1. Characteristics and ejective function of adults with and without hypertension

Characteristic	Group		p
	Control (n = 44)	Hypertension (n = 41)	
Sex Female Male	 61% 39%	 59% 41%	 0.99*
Age (years)	50.70 ± 6.70	52.50 ± 5.30	0.17
BMI (kg/m^2)	26.38 ± 1.98	27.07 ± 2.16	0.12
BP (mmHg) Systolic Diastolic	 115 ± 9.76 74.32 ± 6.85	 137.70 ± 16 86.44 ± 10.71	 < 0.001 0.002
DSST Total group Female Male	 40.84 ± 11.66 42.96 ± 11.95 37.78 ± 11.99	 22.95 ± 12.16 26.88 ± 12.04 16.81 ± 9.82	 < 0.001 < 0.001 < 0.001

*Chi-square.
Continuous variables represent the average ± the standard deviation. Categorical data are expressed as a percentage. The blood pressure (BP) value represents the average of three monthly measurements of each participant. Student's t-test statistical analysis for independent samples. BMI: body mass index; DSST: digit symbol substitution test.

Table 2. Comparison of controlled and uncontrolled hypertensive patients

Characteristic	Subgroup		p
	Controlled (41.4%)	Uncontrolled (58.6%)	
Sex Female Male	 47.4% 50%	 58.6% 50%	 0.87*
BP (mmHg) Systolic Diastolic	 116.50 ± 10.57 75.88 ± 7.12	 144.20 ± 9.60 83.75 ± 11.73	 < 0.001 0.018
Pharmacotherapy	100%	70.17%	0.02†
DSST Total group	 27.12 ± 12.23	 20 ± 11.32	 0.06

*Chi-square.
DSST: digit symbol substitution test. Student's t-test statistical analysis for independent samples. Continuous variables represent the average ± the standard deviation. Categorical data are expressed as a percentage. The blood pressure (BP) value represents the average of three monthly measurements of each participant.

treatment or had never consumed drugs for it. About 97% of patients with treatment were taking one drug, 3% taken two or more. About 76% consuming angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 11.7% were taking beta-blockers, and 12% receiving calcium antagonist or diuretics. Table 2 shows the results of controlled and uncontrolled hypertensive patients.

In the hypertension group, there was a negative correlation between the DSST score with age ($y = -1.139*x + 82.76$, $R^2 = 0.24$, $p = 0.001$), with SBP ($y = -0.292*x + 61.75$, $R^2 = 0.16$, $p = 0.008$), and DBP ($y = -0.357*x + 51.69$, $R^2 = 0.09$, $p = 0.045$). No correlation was found between the DSST score and the duration of hypertension. The control group showed no correlation (data not shown).

Discussion

This study showed that hypertension in middle-aged Mexican adults is associated with lower scores in the DSST, a validated test with a high sensitivity to detect variations in executive function[16,19]. Hypertension is a well-known risk factor for numerous adverse cardiovascular outcomes[2]. Given their impact in brain vessels vasodilatory capacity, it could decrease biological efficacy to execute some cognitive functions[3]. Although there is a normal increase in the BP while aging due to calcification and atherosclerosis, hypertension in younger subjects suggests a possible genetic predisposition negatively modulated by environmental and lifestyle factors such as obesity and elevated salt intake and others[20].

Mean duration of hypertension in participants in our study was higher than that reported by the National Health Survey, which states that most hypertensive individuals in Mexico had 4-10 years with the diagnosis[1]. This could be explained by our selection criteria only allowed people with at least 5 years with hypertension. About 83% of hypertensive participants in our study had pharmacological treatment, similar with 79.3% reported in other studies for Mexican hypertensive patients[1]. There is evidence that lack of pharmacological treatment in hypertensive people increases their risk of ischemic heart disease, heart failure, stroke, and kidney diseases[21].

Although the treatment of hypertension is cheap and simple compared to other chronic diseases, their asymptomatic nature can cause patients to refuse to undergo lifelong treatment or reduce their adherence. Remarkably, only 50% of patients with treatment had achieved therapeutic goals. Mexican National Health Survey reported a hypertensive control proportion of 45.6%[1]. Most hypertensive patients in our study consume antihypertensive drugs in monotherapy, and though this approach facilitates compliance, it is well documented that few patients achieve adequate

hypertensive control without two or more drugs[22,23]. We observed an important number of patients receiving beta-blockers, which, according to recent guidelines should not be used as first choice antihypertensive drugs because they promote the development of dyslipidemias, impair glucose tolerance and hinder weight reduction[23,24]. It is important to analyze individual patient conditions to offer the best treatment in each case and achieve therapeutic goals.

Our findings show that hypertensive patients have a worse performance in the DSST compared with normotensive people. Cognitive impairment is a gradual process and having hypertension could accelerate this process. Controversial results of the effect of hypertension on cognitive function have been found[24,25]. In our study, SBP was responsible for 16% of the variance in DSST scores in the hypertensive patients.

Some studies have found a better executive performance in men[26]; however, we found that men hypertensive obtained lower scores in DSST compared with woman hypertensive or normotensive people. There is evidence that in women, prenatal exposition to different hormonal concentrations promotes the overdevelopment of specific neuronal pathways and the neurotrophic effects of estrogens are well described[27]. The patients in this study were around 50 years old, so the women were in the menopausal period; consequently, it is likely that they maintained some degree of neurotrophic estrogenic stimulation and better cerebral blood flow compared to man[28].

The mechanisms that regulate arterial BP are similar in men and women; however, there are physiological differences at the molecular, cellular, and tissue levels between the sexes that contribute to differences in disease onset, susceptibility, prevalence, and treatment responses. The sympathetic nervous system, the renin-angiotensin-aldosterone system, and the immune system are differentially activated in males and females. Sex hormones such as estrogens or testosterone as well as sex chromosome complement likely contribute to sex differences in BP and cardiovascular disease. At the cellular level, differences in cell senescence pathways may contribute to increased longevity in women and may limit brain damage caused by hypertension[29]. Therefore, this may be an explanation because the women in our study were less affected in their executive function. In addition, many lifestyles and environmental factors such as smoking, alcohol consumption, and diet, they are usually different in men and women, as well as their possible effect on BP and brain function, were not evaluated in the present study.

SBP and DBP were higher than those reported in the previous studies in Mexico[1], and higher BP readings were correlated with lower DSST scores. Uncontrolled hypertension increases vascular stiffness which rises pulse pressure. Increased BP is a risk factor for white matter lesions and subclinical hemorrhages that can cause cognitive alterations[30]. In concordance with other authors[31], we could not find differences in executive function between controlled or uncontrolled hypertensive patients, maybe due to the small sample size. Several studies have reported that an elevated BP during middle age predicts cognitive impairment 20-30 years later[32,33] and SBP control since middle age reduces this risk[27,34].

Many studies have reported intense prefrontal activation during DSST resolution using functional MRI and electroencephalography[35,36], these areas are particularly vulnerable to subclinical ischemia because they depend on distal blood supply. Vasomotor dysfunction characteristic of hypertension impairs their capacity for compensatory redistribution of blood flow in response to cognitive challenge[9]. DSST is a powerful tool to explore the executive cognitive domain associated with brain regions most affected by hypertensive vasculopathy. On the hypertensive group, we found an inverse correlation between age and DSST performance, which is consistent with the previous reports[21,37]. Motor dexterity decline through aging may contribute to this consistent finding and hypertension could accelerate this process. Although we guarantee a minimum level of education in our inclusion criteria, we did not specifically explore the influence of the educational level on DSST performance. However, the previous reports state that there is no relationship between education and DSST performance probably due to their iconographic nature, making it useful in poor educated populations like ours[8]. As opposed to most studies revised, we could not observe a significant correlation between DSST scores and duration of disease. The duration of hypertension is relevant because there is evidence that their neurodegenerative effects are accumulative[38].

Effective hypertension management requires a substantial amount of self-planning and adherence to pharmacological and non-pharmacological treatment. Thus, we propose that executive dysfunction may worsen self-care on hypertensive patients. Assessing executive function since middle age with easy administrated tests

like the DSST in primary health-care settings could promote early interventions that preserve the functional independence of hypertensive patients.

Conclusion

In conclusion, mature adults with hypertension had less efficiency in the executive function test. Men showed worse test performance compared to women. In this population the control of hypertension and the duration of the disease did not affect the performance of the executive function.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Campos-Nonato I, Hernández-Barrera L, Pedroza-Tobías A, Medina C, Barquera S. Hipertensión arterial en adultos mexicanos: prevalencia, diagnóstico y tipo de tratamiento. Ensanut MC 2016. Salud Pública Méx. 2018;60:233-43.
2. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. Lancet. 2012;380:2224-60.
3. Ibrahim MM, Damasceno A. Hypertension in developing countries. Lancet. 2012;380:611-9.
4. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nat Rev Cardiol. 2010;7:686-98.
5. Vicario A, Martinez CD, Baretto D, Diaz Casale A, Nicolosi L. Hypertension and cognitive decline: impact on executive function. J Clin Hypertens (Greenwich). 2005;7:598-604.
6. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of hypertension on cognitive function: a scientific statement from the American heart association. Hypertension. 2016;68:e67-e94.
7. Royall DR, Lauterbach EC, Cummings JL, Reeve A, Rummans TA, Kaufer DI, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the committee on research of the American neuropsychiatric association. J Neuropsychiatry Clin Neurosci. 2002;14:377-405.
8. Abell JG, Kivimäki M, Dugravot A, Tabak AG, Fayosse A, Shipley M, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. Eur Heart J. 2018;39:3119-25.
9. Raz N, Rodrigue KM, Acker JD. Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. Behav Neurosci. 2003;117:1169-80.
10. Iyer AS, Ahmed MI, Filippatos GS, Ekundayo OJ, Aban IB, Love TE, et al. Uncontrolled hypertension and increased risk for incident heart failure in older adults with hypertension: findings from a propensity-matched prospective population study. J Am Soc Hypertens. 2010;4:22-31.
11. Gaertner B, Wagner M, Luck T, Buttery AK, Fuchs J, Busch MA. Normative data for the digit symbol substitution test in a population-based sample aged 65-79 years: results from the German health interview and examination survey for adults (DEGS1). Clin Neuropsychol. 2018; 32:114-32.
12. Secretaría de Salud. Para la Prevención, Detección, Diagnóstico, Tratamiento y Control de la Hipertensión Arterial Sistémica. NOM-030-SSA2-2017. Mexico: Diario Oficial de la Federación; 2017.
13. Vanotti S, Smerbeck A, Benedict RH, Caceres F. A new assessment tool for patients with multiple sclerosis from Spanish-speaking countries: validation of the brief international cognitive assessment for MS (BICAMS) in Argentina. Clin Neuropsychol. 2016;30:1023-31.
14. Díaz-López LF, Haro-García LC, Juárez-Pérez CA, Aguilar-Madrid G. Alteraciones neuropsicológicas por exposición crónica a concentraciones bajas de monóxido de carbono en trabajadores de autopista de peaje de México. Salud Ment. 2015;38:353-9.
15. Tarraf W, Rodríguez CJ, Daviglus ML, Lamar M, Schneiderman N, Gallo L, et al. Blood pressure and hispanic/latino cognitive function: hispanic community health study/study of latinos results. J Alzheimers Dis. 2017;59:31-42.
16. Rosano C, Studenski SA, Aizenstein HJ, Boudreau RM, Longstreth WT Jr., Newman AB. Slower gait, slower information processing and smaller prefrontal area in older adults. Age Ageing. 2012;41:58-64.
17. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. JAMA. 1993;269:2386-91.
18. Aranda BD, Álvarez CD, Hernández RL, Ramírez MT. Propiedades psicométricas del modelo bifactorial del BDI-II (versión española) en muestras mexicanas de población general y estudiantes universitarios. Univ Psychol. 2015;14:15-26.
19. Lafont S, Marin-Lamellet C, Paire-Ficout L, Thomas-Anterion C, Laurent B, Fabrigoule C. The wechsler digit symbol substitution test as the best indicator of the risk of impaired driving in Alzheimer disease and normal aging. Dement Geriatr Cogn Disord. 2010;29:154-63.
20. Pinto E. Blood pressure and ageing. Postgrad Med J. 2007;83:109-14.
21. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth joint national committee (JNC 8). JAMA. 2014;311:507-20.
22. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Hypertension. 2018;71:1269-324.
23. Owen JG, Reisin E. Anti-hypertensive drug treatment of patients with and the metabolic syndrome and obesity: a review of evidence, meta-analysis, post hoc and guidelines publications. Curr Hypertens Rep. 2015;17:558.
24. Vasilopoulos T, Kremen WS, Kim K, Panizzon MS, Stein PK, Xian H, et al. Untreated hypertension decreases heritability of cognition in late middle age. Behav Genet. 2012;42:107-20.
25. Knecht S, Wersching H, Lohmann H, Berger K, Ringelstein EB. How much does hypertension affect cognition? Explained variance in cross-sectional analysis of non-demented community-dwelling individuals in the SEARCH study. J Neurol Sci. 2009;283:149-52.
26. Singh-Manoux A, Marmot M. High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. J Clin Epidemiol. 2005;58:1308-15.
27. Sherwin BB, Henry JF. Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. Front Neuroendocrinol. 2008;29:88-113.

28. Memon A, McCullough L. Cerebral circulation in men and women. In: Kerkhof PL, Miller VM, editors. Sex-specific Analysis of Cardiovascular Function. Switzerland: Springer International Publishing AG, part of Springer Nature; 2018. p. 279-91.
29. Colafella KMM, Denton KM. Sex-specific differences in hypertension and associated cardiovascular disease. Nat Rev Nephrol. 2018; 14:185-201.
30. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985). 2008;105:1652-60.
31. Wei J, Yin X, Liu Q, Tan L, Jia C. Association between hypertension and cognitive function: a cross-sectional study in people over 45 years old in China. J Clin Hypertens (Greenwich). 2018;20:1575-83.
32. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. Hypertension. 1998;31:780-6.
33. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia aging study. JAMA. 1995;274:1846-51.
34. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurol. 2014;71:1218-27.
35. Usui N, Haji T, Maruyama M, Katsuyama N, Uchida S, Hozawa A, et al. Cortical areas related to performance of WAIS digit symbol test: a functional imaging study. Neurosci Lett. 2009;463:1-5.
36. Thornton KE, Carmody DP. Symbol digit and the quantitative EEG. Neurotherapy. 2012;16:210–222.
37. Smith EE, O'Donnell M, Dagenais G, Lear SA, Wielgosz A, Sharma M, et al. Early cerebral small vessel disease and brain volume, cognition, and gait. Ann Neurol. 2015;77:251-61.
38. Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. Curr Hypertens Rep. 2017;19:24.