

Association between Blood Pressure and Cognition among Old Age PeoplePranay Jadav¹, Neha Bavarva²¹ Assistant Professor, ² Tutor, Department of Community Medicine, GMERS Medical College, Gandhinagar, Gujarat**Correspondence** : Dr. Neha Bavarva, E mail: nehabavarva@gmail.com**Abstract :**

Introduction : High Blood pressure may lead to memory impairment in old age. Present study had been conducted to know relation between cognition and blood pressure in geriatric people. **Method :** A cross sectional study was conducted among 600 study participants aged of 60 years or more in villages of Vadodara district. Blood pressure was measured by sphygmomanometer and cognition was screened through Mini Mental State Examination (MMSE). **Results:** The overall prevalence of high blood pressure among study participants was 42.7%. Cognitive impairment (MMSE score < 22) was prevalent in 23.5% of study participants. High SBP was significantly associated with low MMSE score even after adjusting potential confounders in multiple linear regression models. **Conclusion:-** SBP is related to poorer performance on Mini-Mental State Exam in the geriatric population aged 60 years and above in absence of any apparent neurological deficit. Diastolic blood pressure does not find any significant relation between MMSE score.

Keywords : Association, Blood Pressure, Cognition, Memory**Introduction :**

No man on earth can escape of growing old. Aging is certain and all you can do is protect it, promote it and extend it. Aging is an integral part of the growth and development which is terminated by death. Old age persons are a valuable asset for any country and community as they are rich in their experience and wisdom. They can guide youth what are dos and don'ts of life. Nowadays there are improvements in health care services which increases life expectancy. The ratio of older persons has changed dramatically from approximately one in fourteen in the fifties as in past to about one in four at present.^[1-3]

Epidemiological studies have indeed demonstrated that mean blood pressure increases with age^[4-9], not only in old age but also in young adults.^[10] Other underlying mechanisms for the increase in blood pressure with age include age-related reductions in blood volume and cardiac output, alterations in the function of and response to the sympathetic nervous system and reduced baroreceptor sensitivity, the latter leading to increased blood pressure variability.^[11-12]

Cardiovascular risk factors like diabetes, hypertension, hyperlipidemia and smoking are modifiable risk factors and highly prevalent, leading to mortality and disability. These risk factors are associated with increased risk of cognitive decline and dementia. There is increasing evidence from India and other countries that cerebrovascular risk factors are associated with an increased risk of cognitive decline and dementia. Hypertension is one of the risk factors that can cause cognitive decline even in the absence of the stroke.^[13]

The relationship between blood pressure (BP) and cognitive outcomes in the elderly has gained attention because of its implications for global healthcare. There is a deficit of regular screening and unawareness about complications of long-term high blood pressure in old age, in rural area. Cognitive decline is one of the major complications of the long standing hypertension.^[13-16] So the purpose of this study was to find the prevalence of hypertension and cognitive decline and the association of cognitive impairment and hypertension in elderly people.

Method:**Study setting, Study type, and study participants:**

-After getting approval from the Institutional Ethical Committee, study was started. A Cross-sectional study was done in the villages of Vadodara district from October 2010 to July 2012. The study included the Geriatric population: person having age \geq 60 years.

Sample size and sampling : A sample size of 600 was obtained using the formula $Z_{\alpha}PQ/l^2$: Where $Z = 95\%$ confidence intervals (1.96 table value), the prevalence of cognitive decline in geriatric population in a rural area India is (p) 14.89 from the previous study^[17] (so $q=1-p$) and $L= 3\%$ margin of error. The calculated minimum sample had been inflated by 10% to account for anticipated subject non-response. Six Talukas were selected by simple random sampling from the 12 Talukas of the Vadodara district. From each of these selected 6 talukas, 4 villages were selected by simple random technique. From each of the selected village, 25 study participants were selected conveniently by the house to house survey. The survey was started on the right-hand side of the Village Panchayat Office. The village next to that in the random list was selected to fulfill the study subjects if study participants were not enough in a selected village.

Measurement tools:

Measurement of blood pressure: Blood pressure was measured by Random Zero mercury sphygmomanometer and stethoscope in sitting position in right brachial artery after 5-minute of rest. Korotkoff sound 1 and 5 were considered as systolic and diastolic blood pressure respectively. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Mean arterial blood pressure was calculated by using following formula: $DBP+1/3$ Pulse pressure. Measurement of blood pressure of all participants was done by a single investigator.

Assessment of cognitive status : The Folstein Mini-Mental State Exam (MMSE) is a widely used and well-

validated tool for the evaluation of cognitive impairment. It briefly measures orientation to time and place, registration, immediate recall, short-term verbal memory, calculation, language and constructs ability.^[15] The MMSE includes following items: the maximum score is 30 points (10 points for orientation, 3 for registration, 5 for attention and calculation, 3 for recall, 4 for naming the objects, 1 for repetition, 1 for following the command, 1 for reading ability, 1 for writing ability and 1 for visuospatial construction). Scores of > 27 are generally considered normal, 22-26 as mild cognitive impairment and those less than 22 as possible dementia. Hindi 16 and Gujarati 17 version of MMSE were used.

Data Collection: House to house survey was done to find the study subjects from the selected villages. After acquiring the study subject the details regarding the study viz. purpose of the study, method of the study was explained in the vernacular language to each participant and head of the family. Written consent was taken from the each subject with assuring that their name was not be disclosed other than the person's concern with the study. The questionnaire was filled by personal interview. Questionnaires were of two parts. The first part included socio-demographic details regarding age, sex, religion, marital status, education, occupation, income, addiction (tobacco and alcohol) and drug using for any chronic illness etc. The second part of the questionnaire was of Gujarati version of minimal state examination for cognitive assessment. Blood pressure was measured at the start of the study after 5-minute rest and again after in between socio-demographic and MMSE interview. The mean of two reading was taken into account.

Statistical analysis : Data were cleaned, validated and analyzed with Epi-info 7. For continuous variables range, mean and standard deviation were calculated and for categorical variables proportion and percentage were obtained. To know the association between two variable, tests of significance were applied. Chi-square test was applied for proportions and t- test was applied for

Table 1: Prevalence of Hypertension and cognitive impairment (MMSE score < 22) among study participants (n=600)

	Hypertension	Impaired Cognition (MMSE <22)
Age group		
60-69 years	198 (46.8%)	93 (22%)
70-79 years	28 (21.9%)	18 (14.1%)
≥ 80 years	30 (61.2%)	30 (61.2%)
Sex		
Male	142 (38.90%)	56 (15.3%)
Female	114 (48.51%)	85 (36.2%)
Total prevalence	256 (42.7%)	141 (23.5%)

Table 2 : Factors affecting impaired cognition among study participants (n=600)

Variables	Cognition in form of MMSE score		p-value
	Impaired cognition (MMSE<22) n=141	Normal cognition (MMSE≥ 22) n=459	
Age			
60-69 years	93 (22%)	330 (78%)	p < 0.001
70-79 years	18 (14.1%)	110 (85.9%)	
≥ 80	30 (61.2%)	19 (38.8%)	
Sex			
Male	56 (15.3%)	309 (84.7%)	p < 0.001
Female	85 (36.2%)	150 (63.8%)	
Marital status			
Unmarried	9 (50%)	9 (50%)	p < 0.0037
Married	94 (21.3%)	347 (78.7%)	
Separated/divorced	0 (0)	10 (100%)	
Widow/widower	38 (29%)	93 (71%)	
Living arrangement			
Living alone	28 (43.1%)	37 (56.9%)	p < 0.001
Living with spouse	38 (39%)	93 (71%)	
Living with children	9 (9.6%)	85 (90.4%)	
Living with both spouse and children	66 (21.3%)	244 (78.7%)	
Education			
Illiterate/ Just literate	102 (47.3%)	111 (52.1%)	p < 0.001
Primary	39 (18.1%)	176 (81.9%)	

Secondary/Higher secondary	0 (0)	37 (100%)	
Graduate/post graduate	0 (0)	135 (100%)	
Occupation			
Working	27 (17%)	132 (83%)	p = 0.024
Not working	114 (25.9%)	327 (74.1%)	
Smoking habit			
Never used	141 (30.5%)	321 (69.5%)	p < 0.02
Ever used	28(20.28%)	110(79.72%)	
Smokeless tobacco use			
Never used	121 (26.4%)	375 (75.6%)	p = 0.26
Ever used	20 (23.5%)	84(76.5%)	
Alcohol consumption			
Never consume	141 (26.3%)	375 (73.7%)	p = 0.01
Ever consume	8(12.5%)	56(87.5%)	
Poly-pharmacy			
No	102(24.3%)	318(75.7%)	p = 0.488
Yes	39(21.7%)	141(78.3%)	
Depression			
Yes	123 (37.8%)	202(62.2%)	p <0.001
No	18 (6.5%)	257 (93.5%)	
Systolic blood pressure			
Normal (<120mm Hg)	9(31%)	20(59%)	p < 0.001
Pre-Hypertension (120-139 mm Hg)	46 (14.2%)	279 (85.8%)	
Hypertension stage 1 (140-159 mm Hg)	77 (43%)	102 (57%)	
Hypertension stage 2 (\geq 160 mm Hg)	9 (13.4%)	58 (86.6%)	
Diastolic blood pressure			
Normal (<80 mm Hg)	27 (41.5%)	38 (58.5%)	p < 0.001
Pre-Hypertension (80-89 mm Hg)	75 (18.3%)	335 (81.7%)	
Hypertension stage 1 (90 -99 mm Hg)	39 (40.6%)	57 (59.4%)	
Hypertension stage 2 (\geq 100 mm Hg)	0 (0)	29 (100%)	

Overall blood pressure			
Normal (<120 and < 90 mm Hg)	9(31%)	20(59%)	p < 0.001
Pre-Hypertension (120-139 mm Hg and/or 80-89 mm Hg)	46 (14.6%)	269 (85.4%)	
Hypertension stage 1 (140 -159mm Hg and or 90-99 mm Hg)	77 (40.7%)	112 (59.3%)	
Hypertension stage 2 (\geq 160 mm Hg and/or \geq 100 mm Hg)	9 (13.4%)	58 (86.6%)	

Table 3: Simple Linear relation between blood pressure and MMSE score among study participants (n=600)

Variables	Correlation coefficient (r)	R²	Constant (Intercept on y axis)	Regression coefficient	p-value
Systolic BP	-0.239	0.0565	37.34	- 0.081	< 0.005
Diastolic BP	0.022	0.0005	25.13	0.014	0.587
Pulse pressure	-0.317	0.0992	33.44	-0.135	< 0.005
Mean arterial blood pressure	-0.284	0.0131	32.65	-0.063	< 0.005

continuous variables. First simple linear regression was done between blood pressure variables and MMSE score. Multiple linear regressions was done for adjustment of age, sex, education, use of anti-hypertensive medications and depression. A p-value < 0.05 was considered as statistically significant.

Results :

The overall prevalence of high blood pressure among study participants was 42.7%. As shown in Table 1 high blood pressure is more prevalent in advanced age and female sex. Cognitive impairment (MMSE score < 22) was prevalent in 23.5% of among study participants. Prevalence was as higher as 61.2% in age group of more than 80 years of the population as compared to other age groups and also high (36.2%) in female sex (Table 1).

While calculating simple linear regression between MMSE score and blood pressure variables, it has been observed that systolic blood pressure, Pulse pressure and mean arterial blood pressure were negatively correlated with an MMSE score which was statistically significant. Diastolic blood pressure has a positive correlation with the MMSE score and it was statistically insignificant (Table 3).

To counter the effect of confounding variables, blood pressure was adjusted for age, sex, education, use of anti-hypertensive medication and depression. In these models, age and depression were inserted as continuous variables while sex, education and anti-hypertensive medication were inserted as dummy variables. From table 4 it has been revealed that systolic blood pressure remains negatively correlated even after adjusting for major

Table 4: Multiple linear regression models of systolic blood pressure as a predictor of the MMSE score after adjusting for major confounding variables.

Variables	Regression coefficient	p value	R2	Constant
Model 1				
SBP	-0.078	<0.001	0.08	44.85
Age	-0.118	<0.001		
Model 2				
SBP	-0.069	<0.001	0.21	46.30
Age	-0.139	<0.001		
Sex	-3.368	<0.001		
Model 3				
SBP	-0.067	<0.001	0.31	45.63
Age	-0.177	<0.001		
Sex	-1.955	<0.001		
Education	3.612	<0.001		
Model 4				
SBP	-0.069	<0.001	0.32	45.41
Age	-0.169	<0.001		
Sex	-2.022	<0.001		
Education	3.383	<0.001		
Anti-HT medication	0.729	0.04		
Model 5				
SBP	-0.036	0.001	0.477	36.80
Age	-0.038	0.112		
Sex	-0.402	0.232		
Education	2.604	<0.001		
Anti-HT medication	0.376	0.248		
Depression	-1.014	<0.001		

confounding factors. Model 5 has R2 of 0.477 means 47.7% change in MMSE score can be explained by this model and it is statistically significant ($p < 0.005$)

Discussion

The present cross-sectional study was conducted to know the association between blood pressure and cognition changes among old age population (≥ 60 years). Hypertension is an important cause of

morbidity and mortality in the elderly population and is a risk factor for many other diseases. The present study reports a prevalence rate of hypertension as 42.7% which compares well with other studies carried out by Kokiwaret al^[18] at rural community of central India (38.1%) and Agrawal et al^[13] from Rajasthan (42.1%). While a higher prevalence of 69% was reported among the elderly population aged sixty and above (Bulletin of WHO

2011)^[19] and 54% among persons aged ≥ 40 from Chennai.^[20] Prevalence of hypertension in the present study was as high as 48.5% in females compared to males 38.9%. Similar findings were reported by Hazarika N C et al^[21] and Malhotra P et al^[22] while Gupta R et al^[23] and Guang Hui Dong et al^[24] found it was more in males. A study done in Surat city of Gujarat by Power AB et al reported Prevalence of hypertension among elderly women was 33.3%.

The overall prevalence of cognitive decline was 23.5% (Table 1) in the study population. Prevalence of cognitive decline among male study participants was 15.3%. Prevalence of cognitive decline among female study participants was 36.2%. A hospital based study done by Begda AA^[25] in the same city found the overall prevalence of cognitive impairment 39.2% which was 31.7% in male subjects and 47.9% in female subjects. This may be due to sampling variability. In a rural community-based study from Ballabhdgarh^[26] among non-demented people aged 55 years and above, cognitive impairment was reported to be present in 10.2%. In two communities based study in rural areas, from Spain^[27] and Japan^[28] cognitive impairment was reported to be 7.1% and 8.6% respectively, which was lower than the present study.

It has also been found in present study that the prevalence of cognitive impairment was significantly associated especially with advancing age. The similar association found in a hospital based study done in 2006 in the same city^[25] and also found in other study.^[29] The economic dependence and loneliness are two important factors which are associated with old age and also believed to have an influence on cognitive changes.

This cross-sectional study showed a linear relationship between higher SBP and impaired cognitive levels in individuals without prior history of any neurological damage. This relationship persisted even after adjustment for age, sex, education, use of anti-hypertensive medication and depression, which is consistent with the result from most of the previous studies.^[30-34] Previous studies

have reported mixed results regarding the relationship of cognitive impairment and BP. Cross-sectionally, Scherr et al^[35] found no association between either SBP or DBP and cognitive performance; Wallace et al^[36] and the Tsivgoulisge^[37] at al found that only elevated DBP was associated with poor memory performance, and Budge et al^[38] reported that higher MMSE scores were significantly associated with lower SBP. A prospective study^[39] by found that elevated midlife SBP was a significant predictor of poor cognitive functioning in later life. In a large community-based elderly Swedish cohort, Guo ET al^[38] found that those with lower baseline SBP had an almost 2-fold elevated risk of low MMSE scores at 3-year follow-up. In another cohort study, Glynn et al^[40] showed that those with lower SBP were more likely to have an incident cognitive impairment. In Farmer et al^[41] a found that participants 75 years and older with isolated systolic hypertension had better cognitive performance than those without systolic hypertension, but not after adjusting for confounding variables. In contrast, our findings were significant even after adjusting the confounding variables. In Indo-US cross-national epidemiologic study^[26], every 10 mm HG difference in DBP or SBP was related to more than 10% decrement in cognitive impairment.

Diastolic blood pressure in the present study was not independently associated with cognition while Schmidt R et al^[42] and Deleev F E et al^[43] found that higher DBP (not SBP or PP) was an independent predictor of white matter hyperintensity progression in elderly individuals, both without neuropsychiatric disease and Alzheimer's disease.

The exact mechanism of how hypertension leads to impaired cognition is still unclear but Biologically plausible explanations are: hypertension-induced proliferation of smooth muscle cells, basal lamina alterations, luminal narrowing, endothelial-hyalinosis, and ultimately fibrosis; hypertension-related microvascular degeneration and cerebral amyloid angiopathy can cause alteration in the cerebral endothelium and become an important dementia precursor; hypertension-induced

endothelial dysfunction in the small cerebral vessels may also cause chronic cerebral oxygen deprivation and greater susceptibility to hypoxia^[44-47].

Conclusions :

In conclusion, the findings from the present study provide evidence that increased resting SBP is related to poorer performance on Mini-Mental State Exam in the geriatric population aged 60 years and above in absence of any apparent neurological deficit. Diastolic blood pressure does not find any significant relation between MMSE score.

Declaration:

Funding: Nil

Conflict of Interest: Nil

References :

- Prakash R, Chaudhry S, Singh U. A study of morbidity pattern among geriatric population in the urban area of Udaipur Rajasthan. *IJCM* 2004; 29(1): 35-40.
- Singh C, Mathur JS, Mishra VN, Singh JB, Garg BS, Kumar A. *IJCM* 1995; 20(1-4):24-27
- Purty A, Bazroy J, Kar M, Vasudevan K, Velialth A, Panda P. Morbidity pattern among the elderly population in the rural area of Tamilnadu, India *TURK J MED SCIENCE* 2005;36:45-50.
- Franklin SS, Gustin Wt, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96: 308-315
- Kotchen JM, McKean HE, Kotchen TA. Blood pressure trends with aging. *Hypertension*. 1982;4: III128-134.
- Landahl S, Bengtsson C, Sigurdsson JA, Svanborg A, Svardsudd K. Age-related changes in blood pressure. *Hypertension*. 1986;8: 1044-1049.
- Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA*. 2003;289: 2363-2369.
- Tell GS, Rutan GH, Kronmal RA, et al., for the Cardiovascular Health Study (CHS) Collaborative Research Group. Correlates of blood pressure in community-dwelling older adults. The Cardiovascular Health Study. *Hypertension*. 1994;23: 59-67.
- Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995;25: 305-313.
- Oberman A, Lane NE, Harlan WR, Graybiel A, Mitchell RE. Trends in systolic blood pressure in the thousand aviator cohort over a twenty-four-year period. *Circulation*. 1967;36: 812-822.
- Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003; 107: 139-146.
- Shuaib A. Alteration of blood pressure regulation and cerebrovascular disorders in the elderly. *Cerebrovasc Brain Metab Rev*. 1992;4: 329-345.
- Agrawal H, Baweja S, Haldiya K, Mathur A. Prevalence of hypertension in an elderly population of the desert region of Rajasthan. *Journal of the Indian Academy of Geriatrics*, 2005; 1:14-17.
- Das SK, Bose P, Biswas A, Dutt A, Banerjee TK, Hazra A, Raut DK, Chaudhuri A, Roy T. An epidemiologic study of mild cognitive impairment in Kolkata, India. *Neurology*. 2007 Jun 5;68(23):2019-26.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 1975 Nov 1;12(3):189-98.
- Ganguli M, Ratclif G, Chandra V, Sharma S, Pandav R. A Hindi version of MMSE: The development of a cognitive screening instrument for a largely illiterate rural elderly population in India. *International of Geriatric Psychiatry* 1995;10:367-77.
- Lindsay J, Jagger C, Mlynik-Szamid A, Sinorwala A, Peet S, Moledina F. The Mini-Mental State Examination (MMSE) in elderly immigrant Gujarati population in the United Kingdom. *International Journal of Geriatric Psychiatry* 1997;12(12): 1155-67.
- Kokiwar PR, Gupta SS, and Dudge PN. Prevalence of Hypertension in Rural Community of Central India. *JAPI* 2012; 60;26-2
- Hypertension Study Group. Prevalence, awareness, treatment, and control of hypertension among elderly in Bangladesh and India: a multicentric study. *Bulletin of the WHO* 2001; 79(6): 490-500. 10.
- Ramachandran A, Snehalatha C, Vijay V, King H. Impact of poverty on the prevalence of diabetes and its complications in urban southern India. *Diabet Med*. 2002; 19(2): 130-5.
- Hazarika NC, Narain K, Biswas D, Kalita HC, Mahanta J. Hypertension in the native rural population of Assam. *Natl Med J India* 2004; 17 (6) :300-304.
- Malhotra P, Kumari S, Kumar R, Jain S, Sharma BK. Prevalence and determinants of hypertension in an un-industrialised rural population of North India. *J Hum Hypertens*. 1999; 13 (7) : 467-72.
- Gupta R, Prakash H, Gupta VP, Gupta KD. Prevalence and determinants of coronary heart disease in a rural population of India. *J Clin Epidemiol* 1997; 50 (2) : 203-209.
- Guang Hui Dong, Zhao Qing Sun, Xin Zhong Zhang, Jia Jin Li, Li Qiang Zheng, Jue Li, et al. Prevalence, awareness, treatment and control of hypertension in a rural Liaoning Province, China. *Indian J Med Res* 2008; 128: 122-127.
- Begda A and Kantharia SL. Screening of Cognitive Impairment and Depression in Elderly Patients. *Indian Journal of Gerontology* 2006;20(4):347-58.
- Pandav R, Dodge HH, DeKosky ST, Ganguli M. Blood pressure and cognitive impairment in India and the United States: a

- crossnational epidemiological study. *Arch Neurol* 2003;60:1123-1128.
27. Coria F, Gomez de Caso JA, Minguez L, et al. Prevalence of age-associated memory impairment and dementia in a rural community. *J Neurol Neurosurg Psychiatry* 1993;56:973-976.
28. Liang J, Borowski-Clark E, Liu X, et al. Transitions in cognitive status among the aged in Japan. *Soc Sci Med* 1996;43:325-337.
29. Swarnalatha N. Cognitive Status Among Rural Elderly Women. *Journal of The Indian Academy of Geriatrics*, 2007; 3:15-19.
30. Seux ML, Thijs L, Forette F, Staessen JA, Birkenhager WH, Bulpitt CJ, Girerd X, Jaaskivi M, Vanhanen H, Kivinen P, Yodfat Y, Vanska O, Antikainen R, Laks T, Webster JR, Hakamaki T, Lehtomaki E, Lilov E, Grigorov M, Janculova K, Halonen K, Kohonen-Jalonen P, Kermowa R, Nachev C, Tuomilehto J. Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. *J Hypertens* 1998;16:963-9.
31. 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.
32. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology* 1998;51:986-93.
33. Starr JM, Whalley LJ. Senile hypertension and cognitive impairment: an overview. *J Hypertens Suppl* 1992;10(Suppl):31-42.
34. Zelinski EM, Crimmins E, Reynolds S, Seeman T. Do medical conditions affect cognition in older adults? *Health Psychol* 1998;17:504-12.
35. Scherr PA, Hebert LE, Smith LA, Evans DA. Relation of blood pressure to cognitive function in the elderly. *Am J Epidemiol*. 1991;134:1303-1315.
36. Wallace RB, Lemke JH, Morris MC, Goodenberger M, Kohout F, Hinrichs JV. Relationship of free-recall memory to hypertension in the elderly: the Iowa 65+ Rural Health Study. *J Chronic Dis*. 1985;38:475-481.
37. Tsivgoulis G, Alexandrov AV, Wadley VG, Unverzagt FW, Go RCP, Moy CS. Association of higher diastolic blood pressure levels with cognitive impairment. *Neurology* 2009;73:589-595.
38. Budge MM, De Jager C, Hogervorst E, Smith AD, for the Oxford Project to Investigate Memory. Total plasma homocysteine, age, systolic blood pressure, and cognitive performance in older people. *J Am Geriatr Soc*. 2002;50:2014-2018.
39. 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;274:1846-1851
40. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA*. 1999;281:438-445.
41. Farmer ME, White LR, Abbott RD, et al. Blood pressure and cognitive performance: the Framingham Study. *Am J Epidemiol*. 1987;126:1103-1114.
42. Schmidt R, Schmidt H, Kapeller P, Lechner A, Fazekas F. Evolution of white matter lesions. *Cerebrovascular Disease* 2002;13 Suppl 2:16-20.
43. de Leeuw FE, Barkhof F, Scheltens P. Progression of cerebral white matter lesions in Alzheimer's disease: a new window for therapy? *J Neurol Neurosurg Psychiatry* 2005;76:1286-1288.
44. Perlmutter LS, Barron E, Saperia D, et al. Association between vascular basement membrane components and the lesions of Alzheimer's disease. *J Neurosci Res* 1991;30:673-681.
45. Hardy JA, Mann DM, Wester P, et al. An integrative hypothesis concerning the pathogenesis and progression of Alzheimer's disease. *Neurobiol Aging* 1986;7:489-502.
46. Lukiw WJ, Bazan NG. Cyclooxygenase 2 RNA message abundance, stability, and hypervariability in sporadic Alzheimer neocortex. *J Neurosci Res* 1997;50:937-94.
47. Perkins DJ, Kniss DA. Tumor necrosis factor-alpha promotes sustained cyclooxygenase-2 expression: Attenuation by dexamethasone and NSAIDs. *Prostaglandins* 1997;54:727-743.