



Universiteit
Leiden
The Netherlands

Blood pressure in old age : exploring the relation with the structure, function and hemodynamics of the brain

Foster-Dingley, J.C.

Citation

Foster-Dingley, J. C. (2016, September 6). *Blood pressure in old age : exploring the relation with the structure, function and hemodynamics of the brain*. Retrieved from <https://hdl.handle.net/1887/42751>

Version: Not Applicable (or Unknown)

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/42751>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/42751> holds various files of this Leiden University dissertation

Author: Foster-Dingley, J.C.

Title: Blood pressure in old age : exploring the relation with the structure, function and hemodynamics of the brain

Issue Date: 2016-09-06

Chapter 2

Lower blood pressure is associated with smaller subcortical brain volume in older persons

Foster-Dingley JC, van der Grond J, Moonen JEF, van den Berg-Huijsmans AA, de Ruijter W, van Buchem MA, de Craen AJM, van der Mast RC

Am J Hypertens. Sep 2015; 28(9):1127-1133

Abstract

Background

Both high and low blood pressure (BP) have been positively as well as negatively associated with brain volumes in a variety of populations. The objective of this study was to investigate whether BP is associated with cortical and subcortical brain volumes in older old persons with mild cognitive deficits.

Methods

Within the Discontinuation of Antihypertensive Treatment in the Elderly trial, the cross-sectional relation of BP parameters with both cortical and subcortical brain volumes was investigated in 220 older old persons with mild cognitive deficits (43% men, mean age=80.7 (SD=4.1), median Mini-Mental State Examination score=26 (interquartile range: 25–27)), using linear regression analysis. All analyses were adjusted for age, gender, volume of white matter hyperintensities, and duration of antihypertensive treatment. Brain volumes were determined on 3DT1-weighted brain magnetic resonance imaging scans.

Results

Lower systolic BP, diastolic BP, and mean arterial pressure (MAP) were significantly associated with lower volumes of thalamus and putamen (all $P \leq 0.01$). In addition, lower MAP was also associated with reduced hippocampal volume ($P=0.035$). There were no associations between any of the BP parameters with cortical grey matter or white matter volume.

Conclusion

In an older population using antihypertensive medication with mild cognitive deficits, a lower BP, rather than a high BP is associated with reduced volumes of thalamus, putamen, and hippocampus.

Introduction

The relation between high blood pressure (BP) and brain atrophy is well known. In 1984, Hatazawa *et al.*¹ showed that in persons with hypertension aged 20–79 years, brain volume was significantly reduced. Subsequently, many cross-sectional,^{2–6} and longitudinal studies have confirmed this finding.^{7–11} An association of high BP with brain atrophy was not only found in persons with established hypertension, but also in persons without hypertension.²

In contrast to these findings several studies in older persons have reported that low BP, rather than high BP, is related to brain atrophy. In a population of non-demented older persons aged between 60 and 90 years, both high and low BP were associated with increased cerebral atrophy.¹² Additionally, a steep decline in BP over 20 years was associated with increased levels of cortical atrophy.¹² In another study, in the same study population, it was shown that among older hypertensive persons a low BP was associated with more extensive brain atrophy than in those without hypertension.¹³

In addition to brain atrophy, various studies have also revealed the paradoxical relationship in older persons between low BP and adverse medical outcomes, including Alzheimer's disease and dementia,¹⁴ cognitive function,¹⁵ and mortality.^{16,17} Recent reports have even suggested that in persons aged 75 years and above, a high BP might not be as harmful as it is in younger persons, suggesting a possible favourable effect of a high BP.^{16,18}

Thus, it is well accepted that in middle-aged and in young old persons high BP is associated with increased brain atrophy in later life. However, in the old to very old persons, this association is less clear and may even be reversed. The aim of the present study was to investigate whether BP is associated with cortical and subcortical brain volumes in an older population with mild cognitive deficits.

Methods

Study participants

The present study included participants from the Discontinuation of Antihypertensive Treatment in the Elderly (DANTE) trial, a randomised controlled trial assessing whether temporary discontinuation of antihypertensive therapy in older participants with mild cognitive deficits improves cognitive, psychological and general daily functioning. Participants were recruited from 128 general practices in Leiden and surroundings (the Netherlands). Based on inclusion and exclusion criteria potential participants were selected from the general practitioner's information system with a search query. The Mini-Mental State Examination (MMSE) was used for cognitive screening and to include persons with mild cognitive deficits according to an MMSE score 21-27.¹⁹ A score of 21 or less is considered to indicate impaired cognition.²⁰ Inclusion criteria were: (i) age ≥ 75 years, (ii) currently using antihypertensive treatment, (iii) current systolic BP (SBP) ≤ 160 mm Hg for persons without a history of cardiovascular disease (defined as myocardial infarction, coronary reperfusion procedures, peripheral artery vascular disease) and for persons without diabetes; or current SBP ≤ 140 mm Hg for persons with a cardiovascular event (defined as myocardial infarction, coronary reperfusion procedures, peripheral artery vascular disease) or diabetes. The current BP was based on the last BP measurement obtained from the general practitioner's information system. Exclusion criteria were: (i) a history of stroke or transient ischemic attack, (ii) a recent (≤ 3 years) myocardial infarction or coronary reperfusion procedure, (iii) current angina pectoris, (iv) cardiac arrhythmias, (v) heart failure, (vi) use of antihypertensive medication other than for hypertension, (vii) a clinical diagnosis of dementia, or (viii) a limited life expectancy.

The current analysis used baseline data of the magnetic resonance imaging (MRI) sub-study. A total of 236 participants underwent a MRI scan of the brain of which 16 participants were excluded from the study due to incidental MRI findings, resulting in a total of 220 participants for analysis. The Medical Ethical Committee of the Leiden University Medical Center approved the study, and written informed consent was obtained from all participants.

Blood pressure

SBP (mm Hg) and diastolic BP (DBP, mm Hg) were measured by trained research personnel during home visits. Two measurements, one after 5 and one after 7 minutes of rest were conducted in a seated position with the arm at heart level fully supported on a flat surface, using a fully automated electronic sphygmomanometer (Omron M6 comfort). All participants were asked to refrain from smoking or drinking beverages containing caffeine and not to perform vigorous physical activity 2 hours prior to BP measurements. In the analyses we used the average of the 2 BP measurements. Mean arterial pressure ($MAP = 1/3 (SBP) + 2/3 (DBP)$) and pulse pressure ($PP = (SBP) - (DBP)$) were calculated using the mean BPs.

Imaging data acquisition and analysis

MRI scans were acquired on a Philips 3T MRI system (3T Achieva; Philips Healthcare, Best, The Netherlands), equipped with a 32-channel head coil. For each subject, a gradient echo 3DT1 image was acquired with repetition time/echo time=9.7/4.6ms, flip angle=8°, field of view=224×177×168mm, matrix=192×152, 120 slices, nominal voxel size=1.17×1.17×1.4mm, and a fluid-attenuated inversion recovery image with repetition time/echo time=11,000/125ms, flip angle=90°, field of view=220×176×137 mm, matrix=320×240, 25 slices.

All images were analyzed using the FMRIB Software Library (FSL).²¹ Grey and white matter volumes, were calculated based on the 3DT1-weighted scans using the SIENAX (Structural image Evaluation, using Normalization, of Atrophy) tool.^{22;23} Briefly, first all images were skull stripped,²³ and registered to MNI152 standard space.²⁴ The original unstripped brain images were used to determine the volumetric scaling factor to normalize brain volumes for head size.²⁵

To bilaterally determine the volumes of the thalamus, putamen, caudate nucleus, nucleus accumbens, pallidum, hippocampus, and, amygdala, the FMRIB's Integrated Image Registration and Segmentation Tool was used.²⁶ All segmented subcortical brain structures were visually checked for errors in registration and segmentation.

For the automated measurement of white matter hyperintensity volumes, 3DT1 and fluid-attenuated inversion recovery images were skull stripped and affine-

registered.^{24,27} Thereafter the brain-extracted fluid-attenuated inversion recovery image was affine-registered to MNI152. White matter hyperintensities were extracted from fluid-attenuated inversion recovery with a conservative MNI152 white matter mask and a threshold was set to identify which white matter voxels were hyperintense, followed by manually checking and editing for quality control.

To assess focal differences in cortical thickness voxel-based morphometric (VBM) analyses were performed.²⁸ After brain extraction, the grey matter of all individual images was segmented.²⁵ A study specific template of the grey matter partial volume images was calculated in MNI152 using affine registration.²⁷ Subsequently, all the native grey matter images were nonlinearly reregistered to this template. To correct for local expansion or contraction, the registered partial volume images were modulated by multiplying by the Jacobian of the warp field, and smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, a voxel-wise general linear model was applied using permutation-based nonparametric testing, correcting for multiple comparisons across space. The association between SBP, DBP, MAP, and PP with cortical grey matter was analyzed by voxel-based morphometry adjusting for age and gender.

Cognitive and psychological functioning

Cognitive and psychological functioning was assessed by trained research personnel. Executive function was assessed with the difference between the time to complete the trail making test part A and B (TMT delta),²⁹ and the interference score of the abbreviated Stroop Color-Word Test.³⁰ The immediate (3 trials) and delayed recall on the 15-Word Verbal Learning Test were used to measure memory. Psychomotor speed was evaluated with the Letter Digit Substitution Test,³¹ using the number of correctly digits coded after 90 seconds for analyses. Symptoms of depression and apathy were measured with the Geriatric Depression Scale-15 (range 0–15 points),³² and the Apathy Scale (range 0–42 points).³³

Sociodemographic and clinical variables

Sociodemographic characteristics were determined by means of standardized interviews. The MMSE score at inclusion was used as a measure of global cognitive functioning. Information about medical history including use of antihypertensive medications, history of cardiovascular disease, and the presence of diabetes type II, was obtained from their general practitioner using structured questionnaires.

Statistical analysis

For statistical analyses, SPSS software for windows (version 20.0.0.1; SPSS, Chicago, IL) was used. Data are reported as mean (SD), median (interquartile range), or number (percentage) when appropriate.

SBP and DBP were grouped into 3 clinically relevant subcategories; SBP into the categories <140 , $140\text{--}159$, and ≥ 160 mm Hg, and DBP into the categories <80 , $80\text{--}89$, and ≥ 90 mm Hg. Since no clinically relevant groups for MAP and PP are known, we divided persons in 3 equally sized tertiles of MAP and PP. For analysis per subcortical brain structure the sum of bilateral volumes was calculated. Linear regression models were used to investigate the association between BP parameters and grey, white matter, and subcortical brain volumes, with the clinically relevant groups of SBP and DBP and tertiles of PP and MAP as independent variables and measures of brain volumes as continuous outcome measures. Adjustments were made for age, gender, white matter hyperintensity volume, and duration of antihypertensive treatment. As diabetes has been known to be related to reduced brain volumes,³⁴ we further explored whether the association of BP with grey, white matter, and subcortical brain volumes changed according to diabetes type II by adding this as a covariate.

For the volumes that were significantly associated with lower BP, we also assessed whether there was an association of reduced brain volume with cognitive and psychological functioning. Linear regression analyses were used with brain volumes as independent variables and cognition, Geriatric Depression Scale-15, and Apathy Scale scores as outcome measures, adjusting for age and gender.

To test whether type or number of antihypertensive medications was associated with brain volume, global cognition, symptoms of depression or apathy, linear regression analysis was used. Type or number of antihypertensive medication was entered as independent variable with brain volumes, MMSE, Geriatric Depression Scale-15, or the Apathy Scale score as outcome measure (adjusted for age, gender, cardio-vascular disease, diabetes type II, smoking status, alcohol use, body mass index, and BP).

A p-value <0.05 was considered statistically significant. We used a mainly descriptive and exploratory approach, thus correction for multiple statistical comparisons was not implemented.

Results

Table 1 summarizes the demographic and clinical characteristics of the 220 older persons in our study. Of them, 56.8% were female and the mean age was 80.7 (SD=4.1) years. Mean SBP was 146 (SD=21) mm Hg and mean DBP was 76 (SD=11) mmHg. The median MMSE score was 26, reflecting mild cognitive deficits. All participants were using antihypertensive medications, including (either one or a combination of the following types): beta blockers (37%), diuretics (52%), angiotensin-converting enzyme inhibitor (32%), angiotensin receptor blocker (36%), and calcium antagonists (59%).

Table 2 shows the associations between SBP and DBP with total grey, total white matter, and subcortical brain volumes. There were no significant associations of SBP and DBP with total grey or white matter volumes. However, participants with a lower SBP had a significantly lower thalamus volume ($B=0.25$, $P=0.013$), whereas participants with a lower DBP had significantly lower volumes of both thalamus ($B=0.28$, $P=0.008$) and putamen ($B=0.37$, $P=0.002$).

The associations of MAP and PP with total grey, total white matter and subcortical brain volume are presented in Table 3. No significant associations of MAP and PP with grey or white matter volumes were found. Yet, participants with a lower MAP had a significantly lower thalamus volume ($B=0.30$, $P=0.002$), putamen volume ($B=0.26$, $P=0.021$), and hippocampal volume ($B=0.14$, $P=0.035$). PP was not associated with any of the subcortical brain volumes.

Table 1. Characteristics of study population

Characteristics	(n=220)
Demographics	
Female	125 (56.8)
Age in years	80.7 (4.1)
Education in years	9 (6-10)
Clinical characteristics	
Current smoking	17 (7.7)
Alcohol >14 units/week	24 (10.9)
Cardiovascular disease ^a	20 (9.1)
MMSE score	26 (25-27)
Hypertension	220 (100)
Duration of antihypertensive treatment ^b , y	
<1 year	5 (2.3)
1-5 years	57 (25.9)
>5 years	149 (67.7)
Blood pressure (mm Hg)	
Systolic blood pressure	146 (21)
Diastolic blood pressure	76 (11)
Mean arterial pressure	102 (13)
Pulse pressure	65 (15)
MRI characteristics	
Volume white matter hyperintensities (ml)	22 (9-56)

Data are presented as mean (SD), median (interquartile range) or number (percentage) when appropriate. Abbreviations: MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

^aCardiovascular disease include myocardial infarction or percutaneous coronary intervention or coronary artery bypass graft.

^bInformation about the duration of antihypertensive treatment was available for n=211.

To further explore our results, we performed additional analyses to assess whether adjusting for diabetes type II affected the observed associations. We found that the associations did not essentially change. Lower SBP was still significantly associated with lower thalamus volume ($B=0.23$, $P=0.021$). Lower DBP remained significantly associated with lower volumes of both thalamus ($B=0.26$, $P=0.015$) and putamen ($B=0.34$, $P=0.004$), as was lower MAP with lower thalamus and putamen volume ($B=0.13$, $P=0.034$ and $B=0.15$, $P=0.024$, respectively). Only the association of lower MAP with lower hippocampal volume disappeared after adjusting for diabetes type II ($B=0.08$, $P=0.269$).

In voxel-based morphometric analyses, no significant relation of any of the BP parameters with cortical grey matter areas was found.

The associations of thalamus, putamen, and hippocampal volumes with cognitive and psychological functioning are shown in Table 4. Lower thalamus volume was associated with lower executive function, including TMT delta ($B=-11.80$, $P=0.003$) and Stroop interference ($B=-5.42$, $P=0.006$), and with lower psychomotor speed ($B=1.28$, $P<0.001$). Lower putamen volume was associated with lower psychomotor speed ($B=0.78$, $P=0.018$). Lower hippocampal volume was associated with lower executive function (TMT delta, $B=-13.24$, $P=0.023$), lower memory (immediate $B=1.34$, $P=0.005$, and delayed recall $B=0.80$, $P<0.001$), and lower psychomotor speed ($B=1.19$, $P=0.029$). For all associations a lower volume indicated worse test scores. There were no associations of thalamus, putamen, and hippocampal volume with symptoms of depression or apathy.

Additionally, no significant associations were found between type or number of antihypertensive medications and brain volumes or cognitive and psychological functioning.

Table 4. Association of thalamus, putamen and hippocampal volume with cognitive and psychological functioning

	Thalamus (ml) B (95% CI)	P value	Putamen (ml) B (95% CI)	P value	Hippocampus (ml) B (95% CI)	P value
Executive function						
TMT delta ^a (seconds)	-11.80 (-19.49, -4.10)	0.003	-3.18 (10.17, 3.81)	0.371	-13.24 (-24.67, -1.81)	0.023
Stroop interference ^a (seconds)	-5.42 (-9.29, -1.56)	0.006	0.93 (-2.56, 4.42)	0.601	-5.22 (-10.99, 0.55)	0.076
Memory 15-WVLT (words remembered)						
Immediate recall	0.51 (-0.13, 1.15)	0.120	0.38 (-0.19, 0.95)	0.195	1.34 (0.41, 2.28)	0.005
Delayed recall	0.22 (-0.09, 0.52)	0.159	-0.05 (-0.32, 0.22)	0.734	0.80 (0.36, 1.23)	<0.001
Psychomotor function						
LDST (digits coded)	1.28 (0.57, 1.99)	<0.001	0.78 (0.14, 1.42)	0.018	1.19 (0.12, 2.25)	0.029
GDS-15 ^a (points)	-0.02 (-0.27, 0.24)	0.893	-0.04 (-0.27, 0.18)	0.709	-0.13 (-0.50, 0.25)	0.511
Apathy scale ^a (points)	-0.12 (-0.65, 0.42)	0.668	0.29 (-0.19, 0.77)	0.230	-0.32 (-1.10, 0.47)	0.431

Data are presented as unstandardized beta with 95% CI. Linear regression analysis was used to examine the effect per ml increase in volume of the thalamus, putamen, or hippocampus as independent variable on cognitive function, symptoms of depression, and apathy as dependent variable. All analyses were adjusted for age, gender, and volume of white matter hyperintensities. Abbreviations: 15-WVLT, 15-word verbal learning test; CI, confidence interval; GDS-15, Geriatric Depression Scale-15; LDST, Letter Digit Substitution Test; TMT, trail making test.

^a Higher scores indicate worse functioning.

Discussion

The main finding of our study is that, lower SBP, DBP, and MAP are associated with lower volumes of thalamus and putamen in older old persons with mild cognitive deficits using antihypertensive medication. Furthermore, lower MAP was also associated with lower hippocampal volume, which disappeared after adjusting for diabetes. No associations were found between any of the BP parameters and volume of total, cortical grey, or white matter.

A recent study showed that in older persons with manifest arterial disease, low DBP and MAP were associated with higher volumes of the ventricular system, suggesting atrophy of the subcortical structures.⁹ Our results in a much older population partly confirm these findings, since we found lower SBP, lower DBP, and lower MAP all to be associated with lower volumes of thalamus and putamen. In contrast, previous studies have reported associations between hypertension and lower thalamus volume,^{8,35} or no association of BP with thalamus volume.⁵ In the latter studies persons were younger and relatively healthy, hampering comparison with our study. Hence, in younger healthier persons high BP might be a risk factor promoting subcortical atrophy, when persons have vascular disease or are older this relation may be reversed.¹⁵

Furthermore, our results suggesting lower MAP is associated with lower hippocampal volumes, is supported by the finding that in older persons, low DBP has been related to smaller hippocampal volumes,¹³ and low DBP was associated with a faster decline in hippocampal volume.³⁶ Furthermore, in persons with diabetes, especially midlife onset diabetes has been related to hippocampal atrophy.³⁴ We observed that after adjustment for diabetes type II the estimates of the relation between low MAP and hippocampal atrophy changed. Thus, it remains unclear whether a lower BP is related to hippocampal atrophy independent of diabetes type II.

In our study, that included persons with mild cognitive deficits, lower BP measures were associated with lower volumes of the thalamus, putamen, and hippocampus. The finding of these reduced subcortical volumes is of clinical significance since an association with decreased cognitive, but not psychological functioning, was found. Furthermore, it is of interest that persons with Alzheimer's disease showed

lower brain volumes in the same subcortical structures.³⁷ Increasing evidence suggests that particularly older persons with hypertension and cerebrovascular disease are at increased risk of cognitive decline when exposed to lower BP.¹⁸ It might be that in older persons a neurodegenerative process could partly be driven by vascular factors such as low BP.

Contrasting other studies, we did not find an association between BP parameters and total, cortical grey or white matter atrophy. Another study in older persons with cardiovascular risk factors also showed no such associations,¹⁰ whereas a study in a relatively healthy older population showed an association between low SBP and grey matter atrophy.³ In younger persons, high BP was associated with more cortical grey matter atrophy.² Thus, it seems reasonable to assume that the mixed findings of associations between BP and cortical atrophy may be strongly influenced by age of the persons studied.

Different explanations can be proposed for the observed relation between low BP and atrophy of subcortical brain structures. One could speculate on a mechanism whereby low BP could lead to hypoperfusion and subsequent brain damage. In the brain, neurovascular autoregulation maintains constant perfusion over a wide range of BP levels. Once arterioles are damaged, for example by atherosclerosis, lower perfusion pressure cannot be compensated for resulting in hypoperfusion followed by ischemia and tissue damage.³⁸ Long-standing hypertension damages cerebral vessels through hemodynamic stress and increases the risk for cerebrovascular pathologies.³⁹ Perhaps, higher BP is necessary to ensure adequate perfusion in older, but not younger, persons with hypertension. However, another plausible explanation for our results may be that a low BP is a consequence of atrophy of subcortical brain structures in our population of persons with mild cognitive deficits, since it has been shown that BP declines in the years preceding dementia onset.⁴⁰ In this way, neurodegeneration in subcortical brain areas (the regulating center of the brain) may be the cause rather than the consequence of dysregulation of BP and cerebrovascular homeostasis.⁴⁰

Several limitations need to be considered when interpreting the results of our study. Due to our strict exclusion criteria our findings cannot be generalized to the entire older population, but only to persons with mild cognitive deficits, with a similar age, and without a history of serious cardiovascular disease. In addition,

our relatively small sample size may have limited our results due to a type II error. Accordingly, there is a possibility that subtle associations of BP with grey or white matter brain volumes or nonlinear associations with a small effect size could have been missed. Also, our BP measurements performed on a single day at the participants' home might be influenced by a white-coat effect, which may have led to an underestimation of the associations found. Furthermore, we must emphasize that because of the cross-sectional design of this study the direction of causality is unclear, meaning that it is not certain whether BP precedes changes in brain volume or *vice versa*.

In conclusion, in an older old population using antihypertensive medication with mild cognitive deficits a lower BP is associated with smaller volumes of thalamus, putamen, and hippocampus, which in turn is related to lower cognitive functioning, suggesting that the target BP should not be too low in older persons with hypertension.

References

1. Hatazawa J, Yamaguchi T, Ito M, Yamaura H, Matsuzawa T. Association of hypertension with increased atrophy of brain matter in the elderly. *J Am Geriatr Soc.* 1984;32(5):370-374.
2. Celle S, Annweiler C, Pichot V et al. Association between ambulatory 24-hour blood pressure levels and brain volume reduction: a cross-sectional elderly population-based study. *Hypertension.* 2012;60(5):1324-1331.
3. Gianaros PJ, Greer PJ, Ryan CM, Jennings JR. Higher blood pressure predicts lower regional grey matter volume: Consequences on short-term information processing. *Neuroimage.* 2006;31(2):754-765.
4. Ikram MA, Vrooman HA, Vernooij MW et al. Brain tissue volumes in the general elderly population. The Rotterdam Scan Study. *Neurobiol Aging.* 2008;29(6):882-890.
5. Salerno JA, Murphy DG, Horwitz B et al. Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension.* 1992;20(3):340-348.
6. Wiseman RM, Saxby BK, Burton EJ, Barber R, Ford GA, O'Brien JT. Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. *Neurology.* 2004;63(10):1892-1897.
7. Fribank MJ, Wiseman RM, Burton EJ, Saxby BK, O'Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. *J Neurol.* 2007;254(6):713-721.
8. Jennings JR, Mendelson DN, Muldoon MF et al. Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure. *J Hum Hypertens.* 2012;26(5):295-305.
9. Jochemsen HM, Muller M, Visseren FL et al. Blood pressure and progression of brain atrophy: the SMART-MR Study. *JAMA Neurol.* 2013;70(8):1046-1053.
10. Manolio TA, Kronmal RA, Burke GL et al. Magnetic resonance abnormalities and cardiovascular disease in older adults. The Cardiovascular Health Study. *Stroke.* 1994;25(2):318-327.
11. Vlek AL, Visseren FL, Kappelle LJ et al. Blood pressure and progression of cerebral atrophy in patients with vascular disease. *Am J Hypertens.* 2009;22(11):1183-1189.
12. den Heijer T, Skoog I, Oudkerk M et al. Association between blood pressure levels over time and brain atrophy in the elderly. *Neurobiol Aging.* 2003;24(2):307-313.
13. den Heijer T, Launer LJ, Prins ND et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology.* 2005;64(2):263-267.
14. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* 2005;4(8):487-499.
15. Euser SM, van BT, Schram MT et al. The effect of age on the association between blood pressure and cognitive function later in life. *J Am Geriatr Soc.* 2009;57(7):1232-1237.
16. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM et al. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *J Hypertens.* 2010;28(7):1366-1372.
17. Molander L, Lovheim H, Norman T, Nordstrom P, Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. *J Am Geriatr Soc.* 2008;56(10):1853-1859.
18. Birns J, Markus H, Kalra L. Blood pressure reduction for vascular risk - Is there a price to be paid? *Stroke.* 2005;36(6):1308-1313.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
20. MacKenzie DM, Copp P, Shaw RJ, Goodwin GM. Brief cognitive screening of the elderly: a comparison of the Mini-Mental State Examination (MMSE), Abbreviated Mental Test (AMT) and Mental Status Questionnaire (MSQ). *Psychol Med.* 1996;26(2):427-430.
21. Smith SM, Jenkinson M, Woolrich MW et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage.* 2004;23 Suppl 1:S208-S219.
22. Smith SM, De Stefano N, Jenkinson M, Matthews PM. Normalized accurate measurement of longitudinal brain change. *J Comput Assist Tomogr.* 2001;25(3):466-475.

23. Smith SM, Zhang Y, Jenkinson M et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage*. 2002;17(1):479-489.
24. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001;5(2):143-156.
25. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging*. 2001;20(1):45-57.
26. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage*. 2011;56(3):907-922.
27. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002;17(2):825-841.
28. Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage*. 2001;14(3):685-700.
29. Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol*. 2000;22(4):518-528.
30. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. *Exp Aging Res*. 1993;19(3):209-224.
31. Van der Elst W, van Boxtel MP, Van Breukelen GJ, Jolles J. The Concept Shifting Test: adult normative data. *Psychol Assess*. 2006;18(4):424-432.
32. Sheikh JJ, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. 1986;5(1/2):165-173.
33. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4(2):134-139.
34. Roberts RO, Knopman DS, Przybelski SA et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology*. 2014;82(13):1132-1141.
35. Strassburger TL, Lee HC, Daly EM et al. Interactive effects of age and hypertension on volumes of brain structures. *Stroke*. 1997;28(7):1410-1417.
36. den Heijer T, van der Lijn F, Ikram A et al. Vascular risk factors, apolipoprotein E, and hippocampal decline on magnetic resonance imaging over a 10-year follow-up. *Alzheimers Dement*. 2012;8(5):417-425.
37. de Jong LW, van der Hiele K, Veer IM et al. Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study. *Brain*. 2008;131(Pt 12):3277-3285.
38. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. *Cell Metab*. 2008;7(6):476-484.
39. Lammie GA. Hypertensive cerebral small vessel disease and stroke. *Brain Pathol*. 2002;12(3):358-370.
40. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurol Res*. 2006;28(6):605-611.

