ARIC Manuscript Proposal #2351

PC Reviewed: 4/8/14 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI

b. Abbreviated Title (Length 26 characters): Hypertension and MRI

2. Writing Group: Alvaro Alonso, Laura Coker, Rebecca Gottesman (senior), Michael Griswold, Cliff Jack, David Knopman, Tom Mosley, Melinda Power (first), Andrea L.C. Schneider, Lisa Wruck

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MP_ **[please confirm with your initials electronically or in writing]**

F**irst author**: **Melinda Power**
Address: Phipps 446D
600 North Wolfe Street
Baltimore, MD 21287
Phone: 617.721.9984 Fax: 410-955-0672
E-mail: melindacpower@gmail.com

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **Rebecca Gottesman**
Address: Phipps 446D
600 North Wolfe Street
Baltimore, MD

Phone: 410-614-2381 Fax: 410-955-0672
E-mail: rgottesm@jhmi.edu

3. Timeline:

The visit 5 brain MRI data and an initial set of derived variables are now available; we plan to submit for publication within 6 months.

4. Rationale:

The relation between blood pressure and cognition is complex, and appears to be dependent on the time at which blood pressure is measured. Studies of midlife blood pressure and late life cognition typically report adverse associations, with stronger support for an effect of elevated midlife blood pressure on increased cognitive decline or risk of total dementia, but weaker support for an association specifically with Alzheimer's disease, the most common type of dementia.[1,2] Published studies of late life blood pressure and cognition typically report positive associations, such that those with elevated blood pressure may actually be less likely to become demented or experience accelerated cognitive decline, and those with hypotension may experience adverse cognitive consequences.[1,2] Potential explanations for this pattern of findings range from common bias across studies of older adults to true differences in the effect of hypertension on dementia-related brain pathology depending on the timing, duration, and intensity of hyper- or hypotension.[3] Consideration of the relation between blood pressure and brain pathology, particularly neurodegenerative and cerebrovascular pathology, may help to clarify our understanding of how blood pressure is related to cognition in older adults. Both hyper- and hypotension may be related to ischemic and degenerative pathways, and these relations may be modified by age or other age-related factors. Neuroimaging allows evaluation of some of these ischemic and neurodegenerative pathways, with visualization of ischemic changes seen as cortical infarcts, lacunes, white matter hyperintensities (WMH or leukoaraiosis), or cerebral microbleeds, while neurodegeneration is more typically observed on brain magnetic resonance imaging (MRI) as atrophy.

In cross-sectional analyses, elevated blood pressure is unequivocally associated with the presence or severity of WMH,[4-13] and elevated blood pressure also appears to be linked to WMH progression.[14-22] While most studies of blood pressure and WMH consider only concurrent or baseline blood pressure, a handful of studies consider associations with blood pressures earlier in life. For example, in the Rotterdam Scan Study, elevated blood pressure both 20 and 5 years prior to the MRI was associated with increased risk of white matter lesions.[23] Similarly, both midlife and late life blood pressure were associated with increased risk of WMHs in the Cardiovascular Risk Factors, Aging and Incidence of Dementia Study,[24] and elevated midlife blood pressure was related to late-life WMH volume in participants from the National Heart Lung, and Blood Institute Twin Study.[25] In the Atherosclerosis Risk in Communities Study (ARIC), elevated blood pressures at the time of the brain MRI and approximately 6 years prior to brain MRI were associated with greater white matter hyperintensity severity,[7,26] and cumulative systolic blood pressure (SBP) over approximately 17 years of follow-up is a strong predictor of WMH progression over the later 11 years of follow-up among blacks and whites.[15] In the Framingham Offspring Study, hypertension in midlife was related to extensive annual change in WMH volume, but not with linear change in WMH volume.[14]

There is some evidence that the association between blood pressure and WMHs may vary by age or race/ethnicity. Interestingly, several studies of blood pressure and WMHs find strong associations among younger participants, but null associations among older participants.[19,23] In the Washington Heights-Inwood Columbia Aging Project (WHICAP) analyses of WMH volume suggested differences by race/ethnicity,[27] but the association between blood pressure and WMH progression did not differ across race/ethnicity.[21] However, there were subtle differences by race in ARIC, as elevated midlife SBP was only associated with increased risk of WMH progression among blacks.[15]

Similarly, hypertension is an established risk factor for stroke[28] and stroke-related mortality,[29] and is also consistently associated with presence of clinically silent lacunar infarcts seen on brain MRI.[11,30-32] A small number of cross-sectional studies have also reported associations with enlarged perivascular spaces (also referred to as enlarged Virchow-Robin spaces or subcortical lacunes <3mm diameter, and which are likely on the same spectrum as lacunes) and blood pressure.[30,33] Specifically in ARIC, hypertension was previously strongly associated with presence of subcortical lacunes of all sizes, including ≤3mm (sometimes called enlarged perivascular spaces, but probably on the same spectrum as lacunes), 3-7mm, and 8-20mm in cross-sectional analyses. Emerging evidence also supports an association between blood pressure and incident lacunes[16], while studies of blood pressure and incident infarcts are mixed.[19,34,35]

Elevated blood pressure also appears to be significantly or marginally associated with cerebral microbleeds (also known as microhemorrhages) in many,[36-41] but not all[42] cross-sectional studies. Microbleeds are evaluated using T2* gradient echo (T2* GRE) imaging sequences, which shows old and new blood products – because iron and its metabolites are highly paramagnetic, even a very small area of hemorrhage (including many without any associated symptoms) will leave a signal and a hypointense lesion will be seen on the GRE sequence. As expected, given hypertension is associated with clinical intracerebral macro-hemorrhage in the subcortical or deep brain regions, hypertension is also typically associated with microbleeds in this area. In contrast, cerebral amyloid angiopathy is the putative cause of most cortical hemorrhages and cortical microbleeds seen on GRE.[43,44]

Reported cross-sectional associations between blood pressure and MRI markers of neurodegenerative pathology, particularly measures of atrophy, are mixed, with studies reporting both positive,[26,45,46] and null associations.[47,48] In ARIC, although blood pressure was cross-sectionally associated with ventricular and sulcal size, markers of atrophy, associations elevated systolic blood pressure 6 years prior and ventricular size were only marginally significant and there was no association between prior blood pressure and sulcal size. [26] Nevertheless, higher baseline systolic blood pressure was subsequently associated with progression of qualitative ratings of ventricular and sulcal size over approximately 11 years of follow-up.[34] In men from the Honolulu Asia Aging Study, untreated elevated midlife blood pressure was associated with increased hippocampal atrophy,[49] and among persons without antihypertensive medication use, both high and low diastolic blood pressure was associated with faster decline in hippocampal volume in the Rotterdam Scan Study. Similarly, high and low diastolic blood pressure were variably associated with cortical and medial temporal lobe volumes, as well as hippocampal volume change depending on timing of blood pressure assessment and anti-hypertensive medication use status in the Rotterdam Scan Study. [50-52] Interestingly, lower DBP was also associated with greater atrophy in a study of patients with arterial disease.[53] However, in the Framingham Offspring Cohort Study, midlife hypertension was not associated with late life change in total brain volume or temporal horn volume (a surrogate for hippocampal volume).[14]

Prior studies are limited by several factors. First, interpretation and synthesis of prior research using brain MRI has been hampered by use of inconsistent definitions and nomenclature for brain MRI findings.[54] Second, few studies have taken an inclusive approach, considering blood pressure measures at multiple time points and multiple neurodegenerative brain pathologies. While aggregating studies with a more narrow focus does allow insight into the overall pattern, firm conclusions are difficult to draw, as between-study characteristics may artificially induce patterns of findings that differ from the within-study findings considering the same range and timing of blood pressure measures and brain MRI markers. Third, the vast majority of studies have considered primarily, or exclusively, white populations; as relatively few have explicitly considered associations separately by race, and those that do suggest that the association may vary by race,[15,21,27] it is unclear for whether the pattern of association previously observed for most brain MRI markers in typically white samples holds in non-white samples.

As such, we propose to describe the relationship between blood pressure, from midlife to latelife, and a variety of brain MRI markers of neurodegenerative or cerebrovascular disease) assessed at Visit 5. Specifically, we will assess whether elevated blood pressure predicts cortical or lacunar infarcts, greater presence and frequency of microbleeds, greater white matter hyperintensity volume (markers of microvascular changes in the brain), and/or reduced area/region/total brain volume (as markers of neurodegeneration) and whether the associations differ by black versus white race. To promote greater comparability and ease of interpretation, we will adopt use of definitions and nomenclature from the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) guidelines[54] in place of or in addition to those previously used in ARIC MRI studies wherever possible.

5. Main Hypothesis/Study Questions:

We hypothesize that elevated blood pressure will be strongly associated with presence and severity of MRI markers of neurodegeneration and cerebrovascular disease in a dose-dependent manner, and that this relationship will be (1) stronger in black participants than in white participants, (2) stronger for mid-life measures of blood pressure than for late life measures.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Prospective cohort study of blood pressure, measured between 1987 and 2013 and presence and severity of MRI markers of neurodegeneration and cerebrovascular disease in 2011-2013.

Exclusions: No MRI of sufficient quality at visit 5. Presence of tumor, surgery or radiation to the head/brain, or multiple sclerosis. Clinically confirmed stroke prior to MRI in 2011-2013. (Note: Those who completed a brain MRI at visit 5 were selected from the broader set of ARIC participants; sampling strategy and inclusion criteria for Brain MRI at Visit 5 are available in the *ARIC Neurocognitive Exam (Stages 2 and 3) Manual 17*.) Not black or white. No blood pressure data.

Independent variables:
At each visit (1, 2, 3, 4 and 5):
1. Measured systolic blood pressure (continuous)
2. Measured diastolic blood pressure (continuous)
3. Categorical hypertension[55,56]: hypertension (SBP≥140, DBP≥90, or antihypertensive use) pre-hypertension (SBP 120-139 or DBP 80-90 and not classified as hypertensive), or normal (SBP<120 and DBP<80, no anti-hypertensive medications)
4. Categorical "treatment recommended" (Y/N) according to the Joint National Committee (JNC) 8 hypertension guidelines.[57] "Treatment not indicated" was defined as participants without diabetes and without chronic kidney disease (CKD; defined as eGFR calculated using the CKD-EPI equation[58] < 60 mL/min/1.73 m^2) aged 60 and older, with SBP<150 *and* DBP<90; or aged<60 with SBP<140 *and* DBP<90, and not on antihypertensive medications. "Indication for treatment" was defined as all participants 60 years and older with SBP ≥150 *or* DBP ≥90; or age <60 years, SBP ≥140 *or* DBP ≥90; or on any antihypertensive medications; or either diabetes or CKD at any age with SBP ≥140 *or* DBP ≥90.

Dependent variables: Microhemorrhages (number; number by location (deep/ subcortical versus lobar/ cortical); white matter hyperintensities (volume, volume by location); cortical infarcts (number, number by size - <10mm, ≥10mm); lacunar infarcts (number, number by location); and volume (hippocampal, Alzheimer's disease (AD) signature region[59], regional, total).

Covariates: All analyses will be adjusted for a set of variables, determined a priori: total intracranial volume, age, education, race/center, gender, BMI, diabetes, and smoking status. We will explore impact of further adjustment for hyperlipidemia, and other indications of socioeconomic status in sensitivity analyses. Appropriate functional form of continuous covariates will be assessed using penalized splines. We will update time-varying covariates to match the exposure of interest, allowing for appropriate control for confounding.

Effect modifiers: Gender, race, age, antihypertensive medication use.

Statistical Analyses: We propose to use linear regression (white matter hyperintensity volume, brain volume), and poisson or negative binomial regression (cortical infarcts, lacunar infarcts and microbleeds) to assess the association between our

blood pressure variables and MRI markers. We may also use logistic regression in place of methods for count data if it appears appropriate to categorize MRI markers as present/absent, particularly for microbleeds, cortical infarcts, and lacunar infarcts. Outcome data may be transformed for linear regression analyses if the distribution of residuals appears non-normal. We will use multiplicative interaction terms, likelihood ratio tests, and stratified analyses to assess effect modification. All analyses will be weighted using coordinating-center derived weights to account for the sampling strategy for stage 3 MRI and refusals.

Sensitivity Analyses:

- Inverse probability weights for attrition may also be applied to account for attrition prior to Visit 5.
- We may consider cumulative measures of blood pressure (cumulative average systolic or diastolic blood pressure) or hypertension (years since diagnosis), employing appropriate methods to account for time-dependent confounding if necessary.
- We may consider alternate characterizations of hypertension status incorporating self-report or medication use.
- We may include persons with confirmed stroke, to inform on the impact of blood pressure on total infarct.

Limitations/Challenges: Our analysis has several limitations. First, we will not consider within-individual change. Prior scans differed from current scans in terms of pulse sequences, field strength, and image processing and we currently do not understand whether differences detected across scans with different protocols reflect true biological change or artifact of different scanning and processing protocols. While we will adjust for a prior-specified confounders and weight analyses according to IPW sampling and attrition weights, the potential for bias due to confounding or selection remains. Some misclassification of blood pressure and MRI markers is expected; however, as blood pressure was assessed prospectively and MRI measures were derived without reference to hypertension status we expect misclassification to be non-differential and for any resulting bias to be towards the null. We are limited by lack of blood pressure assessment between visits 4 and 5 for the majority of participants, disallowing full characterization of the relationship between hypertension timing and MRI markers; however, we have good characterization of blood pressure from early follow-up and expect measures closer to midlife to be most relevant. Finally, while we will consider anti-hypertensive medication use in stratified or sensitivity analyses, we defer more extensive consideration of the impact of anti-hypertensive medication use to future manuscripts.

7.a. Will the data be used for non-CVD analysis in this manuscript? _Yes _ x_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
____ Yes ___ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ___ Yes _x_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
___ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#2315 Association of Diabetes with Brain Magnetic Resonance Imaging (Schneider)

#2288: Associations of Brain Imaging with Cognitive Change over 20 Years (Knopman)

#2266 Associations Between Brain Vascular Imaging Features and Regional Volumetrics (Graff-Radford/Knopman)

#2175; Midlife blood pressure And 20-year cognitive change: The ARIC-Neurocognitive Study (Gottesman)

#1902: The Metabolic Syndrome, MRI Volumetrics and Cognitive Outcomes: Brain Structure and Function in the ARIC Cohort (Dearborn)

#1553: Associations Between Vascular Risk Factors and Longitudinal Changes in Ventricular Size: a 14-Year Longitudinal Study (Knopman)

#1771: Cognitive, Vascular Risk Factors, and APOE Genotype Predictors of Hippocampal Volume (Knopman)

#1387 Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI Study (Gottesman) -- Gottesman, R. F., et al. (2010). "Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort: Atherosclerosis Risk in Communities (ARIC) Study." Stroke **41**(1): 3-8.

#1121: Cognitive change over 12 years and its relationship to cardiovascular risk factors ARIC MRI Study (Knopman et al.) -- Knopman, D. S., et al. (2011). "Vascular risk factors and longitudinal changes on brain MRI: the ARIC study." Neurology **76**(22): 1879-1885.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

_x_ Yes ____ No

11.b. If yes, is the proposal

_x_ A. primarily the result of an ancillary study
(list number: ARIC NCS: 2008.06)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References

1. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* Aug 2005;4(8):487-499.
2. Power MC, Weuve J, Gagne JJ, McQueen M, Viswanathan A, Blacker D. The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology.* Sep 2011;22(5):646-659.
3. Power MC, Tchetgen EJ, Sparrow D, Schwartz J, Weisskopf MG. Blood pressure and cognition: factors that may account for their inconsistent association. *Epidemiology.* Nov 2013;24(6):886-893.
4. Breteler MM, van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. *Neurology.* Jul 1994;44(7):1246-1252.
5. Choi HS, Cho YM, Kang JH, Shin CS, Park KS, Lee HK. Cerebral white matter hyperintensity is mainly associated with hypertension among the components of metabolic syndrome in Koreans. *Clin Endocrinol (Oxf).* Aug 2009;71(2):184-188.
6. Goldstein IB, Bartzokis G, Hance DB, Shapiro D. Relationship between blood pressure and subcortical lesions in healthy elderly people. *Stroke.* Apr 1998;29(4):765-772.
7. Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. *Neuroepidemiology.* 1997;16(3):149-162.
8. Longstreth WT, Jr., Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke.* Aug 1996;27(8):1274-1282.
9. Mineura K, Sasajima H, Kikuchi K, et al. White matter hyperintensity in neurologically asymptomatic subjects. *Acta Neurol Scand.* Aug 1995;92(2):151-156.
10. Park MK, Jo I, Park MH, Kim TK, Jo SA, Shin C. Cerebral white matter lesions and hypertension status in the elderly Korean: the Ansan Study. *Arch Gerontol Geriatr.* May-Jun 2005;40(3):265-273.
11. Bokura H, Yamaguchi S, Iijima K, Nagai A, Oguro H. Metabolic syndrome is associated with silent ischemic brain lesions. *Stroke.* May 2008;39(5):1607-1609.
12. Shrestha I, Takahashi T, Nomura E, et al. Association between central systolic blood pressure, white matter lesions in cerebral MRI and carotid atherosclerosis. *Hypertens Res.* Oct 2009;32(10):869-874.
13. van Dijk EJ, Breteler MM, Schmidt R, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension.* Nov 2004;44(5):625-630.
14. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology.* Aug 2 2011;77(5):461-468.
15. Gottesman RF, Coresh J, Catellier DJ, et al. Blood Pressure and White-Matter Disease Progression in a Biethnic Cohort: Atherosclerosis Risk in Communities (ARIC) Study. *Stroke.* January 1, 2010 2010;41(1):3-8.
16. Gouw AA, van der Flier WM, Fazekas F, et al. Progression of white matter hyperintensities and incidence of new lacunes over a 3-year period: the Leukoaraiosis and Disability study. *Stroke.* May 2008;39(5):1414-1420.
17. Longstreth WT, Jr., Arnold AM, Beauchamp NJ, Jr., et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Jan 2005;36(1):56-61.
18. Schmidt R, Fazekas F, Kapeller P, Schmidt H, Hartung HP. MRI white matter hyperintensities: three-year follow-up of the Austrian Stroke Prevention Study. *Neurology.* Jul 13 1999;53(1):132-139.
19. van Dijk EJ, Prins ND, Vrooman HA, Hofman A, Koudstaal PJ, Breteler MM. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan study. *Stroke.* Oct 2008;39(10):2712-2719.
20. Verhaaren BF, Vernooij MW, de Boer R, et al. High blood pressure and cerebral white matter lesion progression in the general population. *Hypertension.* Jun 2013;61(6):1354-1359.
21. Brickman AM, Reitz C, Luchsinger JA, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol.* May 2010;67(5):564-569.
22. Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon Magnetic Resonance Imaging Study. *Circulation.* Jan 25 2011;123(3):266-273.

23. de Leeuw FE, de Groot JC, Oudkerk M, et al. A follow-up study of blood pressure and cerebral white matter lesions. *Ann Neurol.* Dec 1999;46(6):827-833.
24. Vuorinen M, Solomon A, Rovio S, et al. Changes in vascular risk factors from midlife to late life and white matter lesions: a 20-year follow-up study. *Dement Geriatr Cogn Disord.* 2011;31(2):119-125.
25. Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology.* Oct 1998;51(4):986-993.
26. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology.* Sep 27 2005;65(6):876-881.
27. Marcus J, Gardener H, Rundek T, et al. Baseline and longitudinal increases in diastolic blood pressure are associated with greater white matter hyperintensity volume: the northern Manhattan study. *Stroke.* Sep 2011;42(9):2639-2641.
28. MacMahon S. Blood pressure and the prevention of stroke. *J Hypertens Suppl.* Dec 1996;14(6):S39-46.
29. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* Dec 14 2002;360(9349):1903-1913.
30. Bezerra DC, Sharrett AR, Matsushita K, et al. Risk factors for lacune subtypes in the Atherosclerosis Risk in Communities (ARIC) Study. *Neurology.* Jan 10 2012;78(2):102-108.
31. Shintani S, Shiigai T, Arinami T. Silent lacunar infarction on magnetic resonance imaging (MRI): risk factors. *J Neurol Sci.* Sep 18 1998;160(1):82-86.
32. Chen X, Wen W, Anstey KJ, Sachdev PS. Prevalence, incidence, and risk factors of lacunar infarcts in a community sample. *Neurology.* Jul 28 2009;73(4):266-272.
33. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study. *Stroke.* Nov 2010;41(11):2483-2490.
34. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology.* May 31 2011;76(22):1879-1885.
35. Longstreth WT, Jr., Dulberg C, Manolio TA, et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke.* Oct 2002;33(10):2376-2382.
36. Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke.* Oct 2010;41(10 Suppl):S103-106.
37. Liu PF, Cui YZ, Na J, Gao PY. Cerebral microbleeds - prevalence, distribution and risk factors in northeast population without preceding large-area stroke. *Chinese medical journal.* Feb 5 2010;123(3):286-290.
38. van Es AC, van der Grond J, de Craen AJ, Admiraal-Behloul F, Blauw GJ, van Buchem MA. Risk factors for cerebral microbleeds in the elderly. *Cerebrovasc Dis.* 2008;26(4):397-403.
39. Tsushima Y, Tanizaki Y, Aoki J, Endo K. MR detection of microhemorrhages in neurologically healthy adults. *Neuroradiology.* Jan 2002;44(1):31-36.
40. Roob G, Schmidt R, Kapeller P, Lechner A, Hartung HP, Fazekas F. MRI evidence of past cerebral microbleeds in a healthy elderly population. *Neurology.* Mar 23 1999;52(5):991-994.
41. Sveinbjornsdottir S, Sigurdsson S, Aspelund T, et al. Cerebral microbleeds in the population based AGES-Reykjavik study: prevalence and location. *J Neurol Neurosurg Psychiatry.* Sep 2008;79(9):1002-1006.
42. Jeerakathil T, Wolf PA, Beiser A, et al. Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. *Stroke.* Aug 2004;35(8):1831-1835.
43. Smith EE, Nandigam KR, Chen YW, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. *Stroke.* Sep 2010;41(9):1933-1938.
44. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology.* Apr 1 2008;70(14):1208-1214.
45. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. *J Hypertens.* Aug 2008;26(8):1636-1641.
46. Salerno JA, Murphy DG, Horwitz B, et al. Brain atrophy in hypertension. A volumetric magnetic resonance imaging study. *Hypertension.* Sep 1992;20(3):340-348.
47. Hajjar I, Zhao P, Alsop D, et al. Association of blood pressure elevation and nocturnal dipping with brain atrophy, perfusion and functional measures in stroke and nonstroke individuals. *Am J Hypertens.* Jan 2010;23(1):17-23.
48. Muller M, van der Graaf Y, Visseren FL, Vlek AL, Mali WP, Geerlings MI. Blood pressure, cerebral blood flow, and brain volumes. The SMART-MR study. *J Hypertens.* Jul 2010;28(7):1498-1505.
49. Korf ES, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study. *Hypertension.* Jul 2004;44(1):29-34.
50. 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.* Sep 2012;8(5):417-425.

51. den Heijer T, Launer LJ, Prins ND, et al. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology*. Jan 25 2005;64(2):263-267.
52. Heijer T, Skoog I, Oudkerk M, et al. Association between blood pressure levels over time and brain atrophy in the elderly. *Neurobiol Aging.* Mar-Apr 2003;24(2):307-313.
53. Jochemsen HM, Muller M, Visseren FL, et al. Blood pressure and progression of brain atrophy: the SMART-MR Study. *JAMA neurology.* Aug 2013;70(8):1046-1053.
54. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology.* Aug 2013
2013-09-20 2013;12(8):822-838.
55. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* May 21 2003;289(19):2560-2572.
56. Wei GS, Coady SA, Goff DC, Jr., et al. Blood pressure and the risk of developing diabetes in african americans and whites: ARIC, CARDIA, and the framingham heart study. *Diabetes Care.* Apr 2011;34(4):873-879.
57. James PA, Oparil S, Carter BL, 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.* Feb 5 2014;311(5):507-520.
58. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* Jul 5 2012;367(1):20-29.
59. Jack C, Wiste HJ, Knopman D, et al. Rates of β-Amyloid Accumulation are Independent of Hippocampal Neurodegeneration. *Neurology.* In Press.