Title

Interarm differences in systolic blood pressure and the risk of dementia and subclinical brain injury

Journal

Alzheimer's & Dementia, 12(4)

ISSN

1552-5260

Authors

Pase, Matthew P
Beiser, Alexa
Aparicio, Hugo
et al.

Publication Date

2016-04-01

DOI

10.1016/j.jalz.2015.09.006

Peer reviewed

HHS Public Access

Author manuscript

Alzheimers Dement. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Alzheimers Dement. 2016 April ; 12(4): 438–445. doi:10.1016/j.jalz.2015.09.006.

Interarm differences in systolic blood pressure and the risk of dementia and subclinical brain injury

Matthew P. Pase[a,b], **Alexa Beiser**[a,c], **Hugo Aparicio**[a], **Charles DeCarli**[d], **Vasan Ramachandran**[a], **Joanne Murabito**[a], and **Sudha Seshadri**[a]

[a]Boston University School of Medicine & Framingham Heart Study, Boston, MA

[b]Centre for Human Psychopharmacology, Swinburne University of Technology, Hawthorn, Australia

[c]Boston University School of Public Health, Boston, MA

[d]Department of Neurology, School of Medicine & Imaging of Dementia and Aging Laboratory, Center for Neuroscience, University of California Davis, Sacramento CA

Abstract

INTRODUCTION—This study examined whether inter-arm differences in systolic blood pressure (IDSBP) ≥10mmHg were associated with the risk of incident dementia and subclinical brain injury.

METHODS—Between 1992 and 1998, 2063 participants of the Framingham Heart Study underwent assessment of IDSBP with results related to the 10 year risk of incident dementia including clinically characterized Alzheimer's disease. Secondary outcomes included markers of subclinical brain injury on MRI.

RESULTS—High IDSBP were associated with a greater risk of incident dementia (HR 1.92; 95% CI: 1.09, 3.40) and Alzheimer's disease (HR 2.32; 95% CI: 1.29, 4.18), but only in those who carried an APOE ε4 allele. IDSBP also predicted lower total brain volumes and more prevalent silent brain infarcts in those who were APOE ε4 positive.

DISCUSSION—High IDSBP were associated with an increased risk of dementia, including clinical Alzheimer's disease, and subclinical brain injury in those who were APOE ε4 positive.

Keywords

Dementia; Alzheimer's disease; blood pressure; interarm differences in systolic blood pressure; cerebrovascular disease; atherosclerosis; peripheral vascular disease; ankle-brachial index; ABI; Magnetic Resonance Imaging; Framingham Heart Study

[*]**Corresponding Author** Dr Matthew P Pase, Boston University School of Medicine & Framingham Heart Study, B603, 72 East Concord St. Boston, 02118, MA, USA.

Conflicts of interest: None.

1. Background

Dementia is a devastating illness associated with the progressive deterioration of brain volume and cognitive ability, eventually leading to a complete loss of independence and mortality. Exposure to vascular risk factors increases to the risk of stroke, white matter lesions, silent brain infarcts and cortical atrophy [1-5], thereby increasing the likelihood of dementia, including its most common form, Alzheimer's disease [6-8]. While considerable interest surrounds the role of vascular risk in the development of cerebrovascular disease [7, 9], numerous vascular risk factors are yet to be examined with respect to dementia or markers of brain aging on Magnetic Resonance Imaging (MRI), such as brain volume and white matter integrity.

Approximately 20% of adults have a difference in systolic blood pressure (BP) between the arms of at least 10mmHg [10]; a sign of possible vascular pathology [11]. Large interarm differences in systolic BP (IDSBP) may suggest peripheral vascular disease, including upper limb ischemia associated with atherosclerosis and subclavian artery stenosis [11]. IDSBP may thus be associated with poorer blood flow and perfusion to the upper extremities, including the brain [12]. In support of this assertion, IDSBP of 15mmHg or more are associated with pre-existing cerebrovascular disease [11]. In patients with acute ischemic stroke, those with an IDSBP of 10mmHg or more have an increased risk of all-cause and cardiovascular mortality [13]. However, to our knowledge, the association of IDSBP with incident dementia has not been investigated prospectively. As IDSBP can be easily measured in primary care, it may be a useful tool to identify those at an increased risk of dementia.

Recently, the Framingham Heart Study showed that IDSBP ≥ 10mmHg were associated with an increased risk of cardiovascular events over 13.3 years of surveillance [14]. Given that cardiovascular disease is often associated with cerebrovascular disease and cerebrovascular disease is known to increase risk for dementia, the aim of this study was to determine the association between IDSBP and the risk of incident dementia and markers of brain injury on MRI among participants of the Framingham Heart Study. IDSBP were calculated at baseline and related to the 10 year risks of incident dementia and clinically apparent Alzheimer's disease. We also examined the association between IDSBP and total brain volume (TBV), white matter hyperintensity volume (WMHV) and silent cerebral infarcts, biological markers of subclinical brain vascular injury also associated with an increased risk of dementia [8].

2. Methods

2.1 Study Population

The sample included participants of the Framingham Heart Study Original [15] and Offspring study [16] cohorts. The Original cohort was established in 1948, with follow-up examination cycles occurring approximately every 2 years. In 1971, offspring of the Original cohort and their spouses were invited to the study and the Offspring cohort was formed. Follow-up examinations have occurred approximately every 4-6 years for the Offspring cohort.

Participants included in this study had a valid IDSBP measurement, which was completed during examination 23 (1991-1994) for the Original cohort and examination 6 (1995-1998) for the Offspring cohort. IDSBP measurements were related to the 10-year risk of incident dementia and to MRI outcomes measured at examination cycle 25 (1997-1999) for the Original Cohort and 7 (1998-2001) for the Offspring cohort, an average of 3.8 years after IDSBP were measured. The selection of study participants, including numbers available for analysis, can be seen in Figure 1. For the sample with available MRI, we only included participants that were free from stroke and dementia at the time IDSBP were measured. For the sample that were followed for incident dementia, we only examined participants who were both aged 60 years or over and free from prevalent dementia at the time IDSBP were measured. The study was approved by the Institutional Review Board at Boston University Medical Centre and written informed consent was obtained from all participants.

2.2 Assessment of IDSBP and the Ankle-Brachial Index

For the original purpose of calculating the ankle-brachial index (ABI), brachial systolic BPs were taken from each arm and ankle by trained technicians following a standardized protocol. Prior to BP measurements, participants lay supine for 5 or more minutes. The sequence of measurement was right arm, left arm, right ankle then left ankle. Participants were classified as having an IDSBP < 10 mmHg or ≥ 10mmHg, a categorization used in previous publications [14, 17]. For the purpose of comparison, we also calculated the ABI, which is a marker of peripheral artery disease calculated as the ratio between the BP in ankle relative to the arm. The arm with the highest systolic BP was used to calculate the ABI separately for the left and right ankles. A low ABI was defined as <0.9 in either leg [18].

2.3 Assessment of Incident Dementia

We calculated the 10 year risk of incident dementia beginning from the time IDSBP measurements were assessed. Dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [19]. Alzheimer's disease was diagnosed based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for definite, probable, or possible Alzheimer's disease [20].

Participants underwent cognitive screening (using the Mini Mental State Examination; MMSE [21]) at each examination cycle and comprehensive neuropsychological testing at selected exam cycles. To complement routine cognitive assessment, screening for dementia also occurred in response to referrals from the participant, their family, primary care provider or other health care professionals. Participants referred for suspected cognitive impairment, based on concern from their family, primary care provider, or MMSE scores, underwent neuropsychological testing. If flagged for suspected dementia by a neuropsychologist, the participant was seen by a neurologist who referred suspected cases to the dementia review committee. Dementia was diagnosed by a committee comprising at least one neurologist and neuropsychologist. For each diagnosis, both type of dementia and date of diagnosis were determined and recorded. The committee made an informed diagnostic decision after reviewing neurologic and neuropsychological assessments, medical

records, brain imaging, autopsy data (if available) and, when indicated, a telephone interview with the family.

2.4 Assessment of brain integrity with MRI

MRI was used to compute TBV, WMHV and silent cerebral infarcts. TBV was calculated as the percentage of total brain parenchymal volume relative to total cranial volume, thus correcting for differences in head size. WMHV was expressed as a percentage of total cranial volume, before undergoing a log transformation. The presence of silent cerebral infarcts was determined according to STRIVE criteria [22]. Full details of the MRI procedures in the Framingham Heart Study have been published elsewhere [23]. Briefly, scanning was undertaken using a Siemens 1T or 1.5T field strength MRI machine using a T2-weighted double spin-echo coronal imaging sequence in contiguous slices of 4mm. Acquisition parameters were as follows; repetition time of 2420 ms; echo time of 1 = 20ms/ echo time 2 = 90ms; echo train length of 8 ms; field of view was 22cm; acquisition matrix of 182 × 256 interpolated to a 256 × 256 with one excitation. The computation of all volumetric MRI parameters was completed blind to subject identifying information.

2.5 Assessment of Apolipoprotein E Genotypes

Participants were classed as Apolipoprotein E (APOE) ε4 positive if they carried at least one ε4 allele or ε4 negative if they did not carry any ε4 alleles. APOE alleles were determined through restriction isotyping of APOE by gene amplification [24]. We examined for interactions with the APOE genotype given that the APOE ε4 allele is associated with the risk of dementia [25, 26], and others have shown interactions between atherosclerosis and APOE ε4 in predicting Alzheimer's disease [27].

2.6 Assessment of Dementia Screening Indicator

The Dementia Screening Indicator is a validated tool designed to identify patients who are 65 years or older at a high risk of dementia, who may benefit from further screening [28]. The indicator is simple to compute making it ideally suited for use in primary care. The indicator score involves the completion of a rapid 7-item checklist involving: (1) Patient age; (2) years of education; (3) body mass index; (4) history of type 2 diabetes; (5) history of stroke; (6) does the patient need help from others to manage money or medications?; and (7) does the patient currently take anti-depressant medications or report that 'everything was an effort' at least 3 days a week over the past week? Each response is assigned a weighted score such that total scores ≥ 22 indicate a patient at high risk [28]. We classified participants as high or low risk based on this cut-off, in order to investigate whether IDSBP could predict incident dementia over and above this dementia screening indicator.

2.7 Statistical Analysis

Statistical analyses were performed using SAS software (SAS Institute, Cary, N.C.). The distribution of IDSBP was positively skewed and treated as a binary variable in our primary analysis, with values ≥ 10mmHg defined as high [14, 17]. Cox proportional-hazard regression models were used to examine the association between IDSBP and dementia incidence, including Alzheimer's disease. Linear or logistic regression was used to examine

the associations between IDSBP and the MRI outcomes. For the analysis of incident dementia, Model 1 included adjustment for age, sex, education and systolic blood pressure from the left arm. Model 1 for the MRI outcomes included adjustment for age, sex, age squared and the elapsed time in years from IDSBP measurement to MRI scans. Model 2 included adjustment for the stroke risk factors included in the Framingham Stroke Risk Profile [5]. Model 3 was computed only for the incident dementia analyses, and included adjustment for the Dementia Screening Indicator modelled as a binary outcome according to the cut-off [28]. We also examined for interactions with the APOE ε4 positive genotypes. Although IDSBP ≥ 10mmHg was our primary exposure, we explored whether IDSBP were associated with our outcome measures when modelled as a continuous variable (using a log transformation) or according to tertiles. Lastly, we also examined the association of the ABI with incident dementia and the MRI markers. The purpose of this analysis was to allow comparison between IDSBP and the ABI, given that the ABI is a popular measure of peripheral artery disease. For analysis involving the prediction of dementia, Hazard Ratios (HR) are presented along with 95% CIs. Results were considered statistically significant at $p < 0.05$.

3. Results

3.1 Baseline sample characteristics

Sample demographics are displayed in Table 1. The mean ± SD IDSBP was 5 ± 4mmHg, with values ranging from 0 to 56 mmHg. Among all persons included in the incident dementia and MRI study samples, 421 (20%) and 322 (15%) individuals respectively, were classified as having a high IDSBP. Those in the incident dementia sample had a higher mean systolic blood pressures and a higher prevalence of cardiovascular disease; most likely because the incident dementia sample were older, given that we restricted this cohort to participants over the age of 60 at the time of IDSBP measurement. Those with and without a significant IDSBP had a similar prevalence of clinical cardiovascular disease, yet those without an IDSBP tended to have fewer vascular risk factors (Table 1).

3.2 IDSBP and Incident dementia

Over 10 years of follow-up, there were 226 new cases of dementia with 184 cases clinically consistent with Alzheimer's disease. Across the entire cohort, there were no associations between IDSBP and dementia or Alzheimer's disease (Table 2).

3.3 IDSBP and MRI outcomes

Across the whole sample, persons with a high IDSBP had a lower TBV at follow-up (Table 3). Those with a high versus normal IDSBP had a 0.5% lower adjusted TBV, which was equivalent to approximately two years of brain aging. There were no associations between IDSBP and WMHV or silent cerebral infarcts.

3.4 Interactions with APOE

There were 59 cases (14%) of dementia in persons who were APOE ε4 positive and 162 cases (10%) in those who were APOE ε4 negative. With respect to Alzheimer's disease,

there were 52 cases (12%) in those who were APOE ε4 positive versus 129 cases (8%) in those who were APOE ε4 negative.

Among those who carried an APOE ε4 allele, higher IDSBP were associated with a near 2-fold higher risk of dementia (HR: 1.92; 95% CI: 1.09, 3.40) and a 2.3 fold higher risk of clinically determined Alzheimer's disease (95% CI: 1.29, 4.18), over and above the effects of age, sex, education and left arm systolic BP (Table 2). These results remained significant after including the Dementia Screening Indicator score in the model (Table 2). In those who were APOE ε4 carriers, adjusting for stroke risk factors attenuated the association between the IDSBP and all-cause dementia whilst the association with Alzheimer's disease remained similar to that of the basic model. Also among APOE ε4 carriers, high IDSBP were associated with lower TBVs and a greater number of silent cerebral infarcts. (Table 3). These associations remained significant when adjusting for the stroke risk factors. IDSBP was not associated with any outcome measures in those who did not carry an APOE ε4 allele.

3.5 IDSBP as a continuous variable and according to tertiles

When modelling IDSBP, the cut-off of 10mmHg proved to be the most useful, in terms of predicting the most outcomes (see Supplemental Tables A2-A4 for analyses modelling IDSBP as a continuous variable and according to tertiles). Briefly, when modelled as a continuous variable, higher IDSBP were associated with lower TBVs ($\beta \pm SE = -0.19 \pm 0.09$, $p = 0.04$ for model 2) and more prevalent silent cerebral infarcts (OR= 1.31, 95% CI: 1.02, 1.68 for model 2) in APOE ε4 carriers. The lowest as compared to the highest IDSBP tertile was associated with a lower risk of Alzheimer's disease in APOE ε4 carriers after adjustment for the Dementia Screening Indicator (HR: 0.47, 95% CI: 0.23, 0.97). The middle as compared to the upper IDSBP tertile was associated with larger TBVs in both the whole sample ($\beta \pm SE = 0.48 \pm 0.15$, $p = 0.002$ for model 2) and APOE ε4 carriers ($\beta \pm SE = 1.12 \pm 0.33$, $p = 0.0008$ for model 2).

3.6 Comparisons with the ABI

A low ABI was associated with lower TBVs ($\beta \pm SE = 0.31 \pm 0.15$, $p = 0.04$) although this association was not statistically significant when adjusting for stroke risk factors ($\beta \pm SE = 0.16 \pm 0.15$, $p = 0.26$). The ABI was not associated with the risk of incident dementia, Alzheimer's disease or any other MRI outcomes (see Supplemental Tables A5-A6).

4. Discussion

The present study examined whether IDSBP could predict the risk of dementia and MRI markers of brain aging in a large community-based prospective cohort study. We found that high IDSBP were associated with lower TBVs across the whole sample. In APOE ε4 carriers, high IDSBP were associated with an increased risk of incident dementia, including clinically characterized Alzheimer's disease, lower TBVs and a higher prevalence of silent cerebral infarcts. The present study thus identifies a relatively select subsample at an increased risk of subclinical brain injury and dementia.

The interactions between APOE ε4 and IDSBP were not surprising given that the APOE ε4 allele is associated with both dementia [25, 26] and atherosclerosis [29]. The Rotterdam study showed that associations between atherosclerosis and dementia, including Alzheimer's disease, were particularly strong in those who carried an APOE ε4 allele [27]. The Framingham Heart Study previously demonstrated that midlife vascular risk burden increased the likelihood of cognitive decline in APOE e4 carriers but not non-carriers [30]. APOE is linked with numerous mechanisms that may contribute to dementia, including cerebrovascular function and integrity as well as Alzheimer's disease type pathology, such as the aggregation of amyloid-β. In knock-out mice models, the absence of APOE was associated with lower blood brain barrier integrity [31]. In humans, the APOE ε4 allele is associated with worse endothelial function [32], lower middle cerebral artery vasoreactivity to inhaled carbon dioxide [33], evidence of cerebrovascular disease on MRI [34] and greater decline in regional cerebral blood flow [35]. Most notably, the APOE ε4 allele is a susceptibility gene for Alzheimer's disease [25, 26] and its presence increases the likelihood of cortical amyloid-β deposition in non-demented individuals [36]. The current results may thus reflect interactions between any number of different mechanisms, with IDSBP more likely to be associated with dementia when concomitant with cerebrovascular or Alzheimer's type pathologies.

In APOE ε4 carriers, IDSBP were associated with TBV and silent cerebral infarcts, but not WMHVs. While a burden of WMHs is typically associated with a vascular pattern of brain injury, WMHV is not always sensitive to the presence of vascular risk factors in young to middle-aged cohorts. Consistent with the present findings, previous studies involving the Framingham Offspring Study cohort have shown that some vascular risk factors, such as plasma homocysteine and visceral fat, are associated with smaller brain volumes [37, 38] and silent cerebral infarcts [37], even in the absence of WMHs. Moreover, others have shown that combined vascular risk factors only account for 2% of the variance in WMHV [39]. These results suggest that WMHs are a common, but not universal or exclusive, feature of vascular disease.

The present results further point towards the important role of vascular health in the aetiology of Alzheimer's disease. Meta-analysis suggests that large IDSBP are indicative of peripheral vascular disease and subclavian artery stenosis [11]. This atherosclerosis of large arteries may concomitantly cause insufficiencies in the cerebral blood supply, leading to periods of ischemia. It has been argued that chronic cerebral hypoperfusion [40] and microvascular abnormalities [41] precede the neurodegenerative hallmarks of Alzheimer's disease, and this may explain why IDSBP were associated with Alzheimer's disease in the present study. In support of this hypothesis, the severity of atherosclerosis has been shown to correlate with the presence of neuritic plaques, tau neurofibrillary tangles and cerebral amyloid angiopathy [42]. An alternative explanation is that IDSBP and Alzheimer's disease are linked by virtue of a shared common mechanism, such as chronic inflammation, hyperlipidaemia or other exposures that remain elusive. Understanding why IDSBP are associated with a higher risk of dementia and Alzheimer's disease will ultimately require a better understanding of how IDSBP affect brain structure and function. To shed light on this issue, future studies could combine IDSBP with measures of cerebral perfusion and in vivo

markers of Alzheimer's disease type pathology, such as amyloid-β load on positron emission tomography (PET).

There are numerous non-invasive methods available to examine underlying peripheral vascular disease and atherosclerosis. Whereas measures derived from ultrasound, such as intima-media thickness, provide information on a specific arterial segment (i.e. internal carotid) and are predictive of worse cognitive function and dementia [27], BP based techniques have the advantage of being faster to administer. The ABI is used commonly to examine for peripheral artery disease yet few large prospective studies have examined the association between the ABI and the risk of dementia. Both the Cardiovascular Health Study [43] and the Honolulu-Asia study [44] reported that a low ABI was associated with an increased risk of dementia, although the Rotterdam Study did not find such an association [45]. In our sample, IDSBP better predicted the risk of dementia and clinically apparent Alzheimer's disease in APOE ε4 carriers, as compared to the ABI. IDSBP also have the advantage over the ABI in that only half the number of cuff inflations are required and a simple subtraction is all that is needed to compute scores. Whereas other easily obtained hemodynamic measures, such as pulse pressure, have been associated with dementia [46] and the progression of atherosclerosis [47], unlike IDSBP, pulse pressure increases as a function of usual aging - due to stiffening of the aorta – and does not necessarily reflect peripheral vascular disease. As testing for genetic polymorphisms becomes ever cheaper and more accessibly, IDSBP may be a useful biomarker to identify individuals at further risk of dementia and Alzheimer's disease.

Strengths of our study include the prospective surveillance for incident dementia, including Alzheimer's disease, the large community-based sample and the measurement of APOE genotyping. Limitations of the present study include the fact that our cohort was overwhelmingly white, limiting the generalizability of our findings to other ethnicities. A further limitation is that BP was measured sequentially from the left and right arm, rather than simultaneously. Simultaneous measurement of left and right arm BP may further reduce error variability, potentially improving risk prediction. Lastly, although we investigated TBV on MRI, we were unable to separate out region specific and grey and white matter volumes given that this information was not available at the chosen cohort exams.

This is the first study to show that high IDSBP are associated with an increased risk of dementia, Alzheimer's disease and subclinical brain injury in those who are APOE ε4 positive. This further underscores the importance of vascular health in the aetiology of clinically characterized Alzheimer's disease as well as the convergence of different pathology in the development of dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Framingham Heart Study participants for generously donating their time to our research.

Funding Support: Dr Pase is funded by an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship (APP1089698). The Framingham Heart Study is supported by the National Heart, Lung and Blood Institute (NHLBI) Framingham Heart Study (contracts N01-HC-25195 and HHSN268201500001I) and grants from the National Institute of Neurological Disorders and Stroke (NS17950) and the National Institute of Aging (AG008122, AG033193, AG0049607).

Abbreviations

APOE	Apolipoprotein
ABI	ankle-brachial index
BP	blood pressure
IDSBP	interarm differences in systolic blood pressure
MRI	magnetic resonance imaging
MMSE	Mini Mental State Examination
PET	positron emission tomography
TBV	total brain volume
WMHV	white matter hyperintensity volume

References

[1]. Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, et al. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. The Lancet Neurology. 11:1039–47. [PubMed: 23122892]

[2]. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, DeCarli C, Au R, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology. 2013; 81:984–91. [PubMed: 23935179]

[3]. Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology. 2011; 77:461–8. [PubMed: 21810696]

[4]. Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S. Subcortical silent brain infarction as a risk factor for clinical stroke. Stroke. 1997; 28:1932–9. [PubMed: 9341698]

[5]. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991; 22:312–8. [PubMed: 2003301]

[6]. Decarli C. Cerebrovascular disease: Assessing the brain as an end-organ of vascular disease. Nature Reviews Cardiology. 2012; 9:435–6.

[7]. Kling MA, Trojanowski JQ, Wolk DA, Lee VMY, Arnold SE. Vascular disease and dementias: Paradigm shifts to drive research in new directions. Alzheimer's and Dementia. 2013; 9:76–92.

[8]. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke. 2010; 41:600–6. [PubMed: 20167919]

[9]. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42:2672–713. [PubMed: 21778438]

[10]. Clark CE, Campbell JL, Evans PH, Millward A. Prevalence and clinical implications of the inter-arm blood pressure difference: A systematic review. Journal of Human Hypertension. 2006; 20:923–31. [PubMed: 17036043]

[11]. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: A systematic review and meta-analysis. The Lancet. 2012; 379:905–14.

[12]. Ochoa VM, Yeghiazarians Y. Subclavian artery stenosis: A review for the vascular medicine practitioner. Vascular Medicine. 2011; 16:29–34. [PubMed: 21078767]

[13]. Kim J, Song TJ, Song D, Lee HS, Nam CM, Nam HS, et al. Interarm blood pressure difference and mortality in patients with acute ischemic stroke. Neurology. 2013; 80:1457–64. [PubMed: 23516316]

[14]. Weinberg I, Gona P, O'Donnell CJ, Jaff MR, Murabito JM. The systolic blood pressure difference between arms and cardiovascular disease in the Framingham Heart Study. American Journal of Medicine. 2014; 127:209–15. [PubMed: 24287007]

[15]. Dawber TR, Meadors GF, Moore FE. Epidemiological Approaches to Heart Disease: The Framingham Study. American Journal of Public Health and the Nations Health. 1951; 41:279–86.

[16]. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The framingham offspring study. Design and preliminary data. Preventive Medicine. 1975; 4:518–25. [PubMed: 1208363]

[17]. Clark CE, Taylor RS, Shore AC, Campbell JL. The difference in blood pressure readings between arms and survival: primary care cohort study2012.

[18]. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PF. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: The framingham study. Archives of Internal Medicine. 2003; 163:1939–42. [PubMed: 12963567]

[19]. American-Psychatric-Association. Diagnostic and Statistical Manual of Mental Disorders 4th ed. 4th. Arlington: Text RevisionVA2000

[20]. McKhann G, Drachman D, Folstein M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology. 1984; 34:939–44. [PubMed: 6610841]

[21]. 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; 12:189–98. [PubMed: 1202204]

[22]. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013; 12:822–38. [PubMed: 23867200]

[23]. DeCarli C, Massaro J, Harvey D, Hald J, Tullberg M, Au R, et al. Measures of brain morphology and infarction in the framingham heart study: establishing what is normal Neurobiology of Aging. 2005; 26:491–510. [PubMed: 15653178]

[24]. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res. 1990; 31:545–8. [PubMed: 2341813]

[25]. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921–3. [PubMed: 8346443]

[26]. Myers RH, Schaefer EJ, Wilson PW, D'Agostino R, Ordovas JM, Espino A, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study. Neurology. 1996; 46:673–7. [PubMed: 8618665]

[27]. Hofman A, Ott A, Breteler MMB, Bots ML, Slooter AJC, Van Harskamp F, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet. 1997; 349:151–4. [PubMed: 9111537]

[28]. Barnes DE, Beiser AS, Lee A, Langa KM, Koyama A, Preis SR, et al. Development and validation of a brief dementia screening indicator for primary care. Alzheimers Dement. 2014; 10:656–65. e1. [PubMed: 24491321]

[29]. Elosua R, Ordovas JM, Cupples LA, Fox CS, Polak JF, Wolf PA, et al. Association of APOE genotype with carotid atherosclerosis in men and women: the Framingham Heart Study. J Lipid Res. 2004; 45:1868–75. [PubMed: 15258198]

[30]. Bangen KJ, Beiser A, Delano-Wood L, Nation DA, Lamar M, Libon DJ, et al. APOE genotype modifies the relationship between midlife vascular risk factors and later cognitive decline. J Stroke Cerebrovasc Dis. 2013; 22:1361–9. [PubMed: 23601373]

[31]. Hafezi-Moghadam A, Thomas KL, Wagner DD. ApoE deficiency leads to a progressive age-dependent blood-brain barrier leakage. Am J Physiol Cell Physiol. 2007; 292:C1256–62. [PubMed: 16870825]

[32]. Guangda X, Linshuang Z, Jie H, Ling Y, Huijuan X. Apo e4 allele is associated with endothelium-dependent arterial dilation in women with type 2 diabetes. Diabetes Res Clin Pract. 2006; 72:155–61. [PubMed: 16337304]

[33]. Hajjar I, Sorond F, Lipsitz LA. Apolipoprotein E, carbon dioxide vasoreactivity, and cognition in older adults: Effect of hypertension. Journal of the American Geriatrics Society. 2015; 63:276–81. [PubMed: 25688603]

[34]. Schilling S, DeStefano AL, Sachdev PS, Choi SH, Mather KA, DeCarli CD, et al. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. Neurology. 2013; 81:292–300. [PubMed: 23858411]

[35]. Thambisetty M, Beason-Held L, An Y, Kraut MA, Resnick SM. APoe ε4 genotype and longitudinal changes in cerebral blood flow in normal aging. Archives of Neurology. 2010; 67:93–8. [PubMed: 20065135]

[36]. Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, et al. Apolipoprotein E, dementia, and cortical deposition of β-amyloid protein. New England Journal of Medicine. 1995; 333:1242–7. [PubMed: 7566000]

[37]. Seshadri S, Wolf PA, Beiser AS, Selhub J, Au R, Jacques PF, et al. Association of plasma total homocysteine levels with subclinical brain injury: cerebral volumes, white matter hyperintensity, and silent brain infarcts at volumetric magnetic resonance imaging in the Framingham Offspring Study. Arch Neurol. 2008; 65:642–9. [PubMed: 18474741]

[38]. Debette S, Beiser A, Hoffmann U, Decarli C, O'Donnell CJ, Massaro JM, et al. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Ann Neurol. 2010; 68:136–44. [PubMed: 20695006]

[39]. Wardlaw JM, Allerhand M, Doubal FN, Valdes Hernandez M, Morris Z, Gow AJ, et al. Vascular risk factors, large-artery atheroma, and brain white matter hyperintensities. Neurology. 2014; 82:1331–8. [PubMed: 24623838]

[40]. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol. 2012; 2012:367516. [PubMed: 23243502]

[41]. Drachman DA. The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer's disease. Alzheimer's & Dementia. 2014; 10:372–80.

[42]. Yarchoan M, Xie SX, Kling MA, Toledo JB, Wolk DA, Lee EB, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. Brain. 2012; 135:3749–56. [PubMed: 23204143]

[43]. Newman AB, Fitzpatrick AL, Lopez O, Jackson S, Lyketsos C, Jagust W, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. J Am Geriatr Soc. 2005; 53:1101–7. [PubMed: 16108925]

[44]. Laurin D, Masaki KH, White LR, Launer LJ. Ankle-to-brachial index and dementia: the Honolulu-Asia Aging Study. Circulation. 2007; 116:2269–74. [PubMed: 17967779]

[45]. van Oijen M, de Jong FJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Atherosclerosis and risk for dementia. Ann Neurol. 2007; 61:403–10. [PubMed: 17328068]

[46]. Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. Stroke. 2003; 34:594–9. [PubMed: 12624277]

[47]. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, et al. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol. 2002; 155:38–47. [PubMed: 11772783]

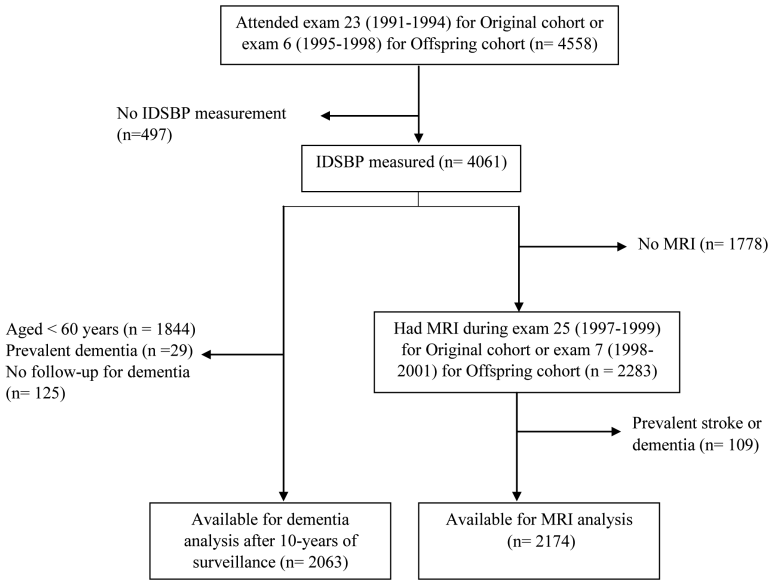

Figure 1.

Selection of study participants. IDSBP = Interarm differences in systolic blood pressure; MRI = Magnetic resonance imaging. Note: MRI was performed an average of 3.8 years after IDSBP were measured. The risk of incident dementia was calculated as the 10-year risk, starting from the time of IDSBP measurement.

Table 1

Sample characteristics stratified by interarm differences in systolic blood pressure

	Incident dementia sample		MRI sample	
IDSBP	**< 10 mmHg**	**≥ 10 mmHg**	**< 10 mmHg**	**≥ 10 mmHg**
N	1642	421	1842	332
Age, y	71.5 (7.6)	72.5 (7.3)*	59.3 (10.7)	62.9 (10.2)*
Male, %	46	43	46	46
Education, %				*
No HS degree	14	18	4	6
HS degree	38	35	28	35
Some college	24	24	30	27
College graduate	25	23	38	32
Body mass index, kg/m^2	27.2 (4.5)	28.1 (5.2)*	27.4 (4.8)	28.9 (5.9)*
Left arm SBP, mmHg	137 (20)	141 (21)*	127 (19)	134 (19)*
Left arm DBP, mmHg	73 (10)	74 (11)	75 (9)	76 (10)*
HTN, %	59	71*	36	54*
HTN treatment, %	41	49*	24	35*
Total cholesterol, mg/dL	206.5 (37.6)	208.3 (40.0)	204.9 (36.1)	206.1 (38.2)
HDL cholesterol, mg/dL	50.3 (16.5)	50.1 (15.8)	51.5 (16.4)	50.7 (15.8)
Diabetes mellitus, %	13	18*	9	14*
Prevalent CVD, %	23	26	10	12
Current smoker, %	10	10	14	11
Apolipoprotein ε4 +, %	21	19	22	21
Incident dementia, n (%)	178 (11)	48 (11)	-	-
Time to MRI, y	-	-	3.8 (1.3)	3.9 (1.2)
Incident AD, n (%)	145 (9)	39 (9)	-	-
TBV, %	-	-	79.1 (3.8)	77.8 (3.9)*
WMHV†, %	-	-	−2.9 (1.2)	−2.7 (1.2)*
Silent infarcts, n %	-	-	11	16*

AD = Alzheimer's disease, CVD = cardiovascular disease, DBP = diastolic blood pressure; HDL = high density lipoprotein, HS = high school, HTN = hypertension, TBV= total brain volume, IDSBP = interarm difference in systolic blood pressure, MRI = magnetic resonance imaging; SBP = systolic blood pressure; WMHV = white matter hyperintensity volume. Means and standard deviations are reported, unless stated otherwise.

† indicates that values have been log transformed,

* indicates a significant difference between the IDSBP groups at $p < 0.05$.

Table 2

Multivariate cox proportional-hazards regression models examining the relation between interarm differences in systolic blood pressure ≥ 10mmHg and the risk of dementia, across the entire sample and stratified by Apolipoprotein ε4 status.

		Whole sample			Apoe ε4−			Apoe ε4+		
Outcome	**Model**	**n cases / subjects**	**HR (95% CI)**	**P**	**n cases / subjects**	**HR (95% CI)**	**P**	**n cases / subjects**	**HR (95% CI)**	**P**
Any dementia										
	1	224/2018	1.05 (0.76, 1.45)	0.78	162/1579	0.83 (0.55, 1.24)	0.35	59/416	1.92 (1.09, 3.40)	0.02
	2	218/1979	1.00 (0.72, 1.40)	0.99	158/1554	0.80 (0.53, 1.21)	0.29	58/404	1.81 (1.00, 3.28)	0.05
	3	217/1926	0.97 (0.70, 1.35)	0.86	157/1510	0.75 (0.50, 1.12)	0.16	58/396	1.97 (1.12, 3.47)	0.02
Alzheimer's disease										
	1	184/2018	1.07 (0.75, 1.52)	0.72	129/1579	0.75 (0.47, 1.19)	0.22	52/416	2.32 (1.29, 4.18)	0.005
	2	179/1979	1.02 (0.71, 1.47)	0.92	125/1554	0.72 (0.44, 1.16)	0.18	52/404	2.28 (1.24, 4.20)	0.008
	3	178/1926	0.97 (0.68, 1.39)	0.87	124/1510	0.66 (0.41, 1.06)	0.09	52/396	2.30 (1.29, 4.11)	0.005

Model 1 adjusts for age, sex, education and systolic blood pressure in the left arm; model 2 adjusts for the stroke risk factors outlined in the Framingham Stroke Risk Profile [5]; model 3 adjusts for a positive Dementia Screening Indicator score (score ≥ 22). APOE = Apolipoprotein ε4 status.

Table 3

Regression models examining the relation between interarm differences in systolic blood pressure ≥ 10mmHg and brain injury on magnetic resonance imaging, across the entire sample and stratified by Apolipoprotein ε4 status.

		Whole sample			Apoe ε4−			Apoe ε4+		
Outcome	**Model**	**n**	**β ± SE***	**P**	**n**	**β ± SE***	**P**	**n**	**β ± SE***	**P**
TBV										
	1	2174	−0.46 (0.17)	0.006	1665	−0.23 (0.19)	0.22	470	−1.30 (0.38)	0.0006
	2	2147	−0.43 (0.17)	0.01	1646	−0.21 (0.19)	0.26	463	−1.26 (0.38)	0.0009
WMHV										
	1	2174	−0.04 (0.05)	0.46	1665	−0.02 (0.06)	0.70	470	−0.14 (0.11)	0.23
	2	2147	−0.04 (0.05)	0.43	1646	−0.01 (0.06)	0.80	463	−0.15 (0.11)	0.20
Silent cerebral infarcts										
	1	2174	1.21 (0.86, 1.70)	0.27	1665	0.99 (0.66, 1.48)	0.95	470	2.06 (1.07, 3.99)	0.03
	2	2147	1.21 (0.86, 1.71)	0.27	1646	0.98 (0.65, 1.47)	0.91	463	2.14 (1.10, 4.19)	0.03

Model 1 adjusts for age, sex, systolic blood pressure in the left arm, age squared and time to MRI; model 2 additionally adjusts for the stroke risk factors outlined in the Framingham Stroke Risk Profile [5]. APOE = Apolipoprotein ε4 status, TBV = total brain volume, WMHV = white matter hyperintensity volume.

*Odds ratio and 95% CI reported for silent cerebral infarcts.