Published in final edited form as:

Int J Geriatr Psychiatry. 2015 October ; 30(10): 999–1007. doi:10.1002/gps.4253.

Ankle-brachial index and inter-artery blood pressure differences as predictors of cognitive function in overweight and obese older adults with diabetes: Results from the Action for Health in Diabetes Movement and Memory Study

Mark A Espeland¹, Kristen M Beavers¹, Bethany Barone Gibbs², Karen C Johnson³, Timothy M Hughes¹, Laura D Baker¹, John Jakicic², Mary Korytkowski², Marsha Miller⁴, and George A Bray⁵ for the Look AHEAD Research Group

¹Wake Forest School of Medicine, Winston-Salem, NC

²University of Pittsburgh, Pittsburgh, PA

³University of Tennessee Health Science Center, Memphis, TN

⁴University of Colorado Health Science Center, Aurora, CO

⁵Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA

Abstract

Objective—Ankle-brachial index (ABI) and inter-artery systolic blood pressure differences, as markers of vascular disease, are plausible risk factors for deficits in cognitive function among overweight and obese adults with type 2 diabetes.

Methods—ABI and maximum inter-artery differences (MIAD) in systolic blood pressures were assessed annually for five years among 479 participants assigned to the control condition in a randomized clinical trial of a behavioral weight loss intervention. A battery of standardized cognitive function tests was administered four to five years later. Analyses of covariance were used to assess relationships that ABI, MIAD, and progression of ABI and MIAD had with cognitive function.

Results—There was a curvilinear relationship between ABI and a composite index of cognitive function ($p=0.03$), with lower ABI being associated with poorer function. In graded fashions, both greater MIAD and increases in MIAD over time also had modest relationships with poorer verbal memory (both $p \leq 0.05$), processing speed (both $p \leq 0.05$), and composite cognitive function (both $p \leq 0.04$). These relationships were independent of each other and remained evident after extensive covariate adjustment.

Correspondence: Dr. Mark A. Espeland, Department of Biostatistical Sciences, Wake Forest School of Medicine, One Medical Center Blvd, Winston-Salem, NC, USA 27157.

Trial Registration: clinicaltrials.gov Identifier: NCT00017953

All other Look AHEAD staffs are listed alphabetically by site.

Conclusions—In overweight and obese adults with type 2 diabetes, lower ABI and larger inter-artery systolic blood pressure differences have modest, independent, graded relationships with poorer cognitive function 4–5 year later.

Keywords

Cognitive function; Arterial disease; Diabetes; Obesity

INTRODUCTION

Low (<0.90) ankle-brachial index (ABI) values are markers of peripheral artery disease and systemic cardiovascular disease (Murabito *et al.*, 2003; Resnick *et al.*, 2004; Lee *et al.*, 2004; McDermott *et al.* 2005). Several recent reports suggest that low ABI is a risk factor for cognitive deficits and cognitive impairment, independent of systolic blood pressure and hypertension (Rafnsson *et al.*, 2009; Guerchet *et al.*, 2001). Of particular relevance to the current paper is a report from the Freemantle Diabetes Study, a large cohort of older individuals with diabetes (99% type 2 diabetes), that a history of low ABI was an independent predictor of prevalent and incident cognitive impairment (Bruce *et al.*, 2008).

This paper is organized with two principal goals. Using ABI measures across five annual visits, we characterize their relationship with cognitive function measures collected four to five years subsequently in a large cohort of overweight and obese individuals with type 2 diabetes who were, on average, both younger and heavier than the Freemantle Diabetes Study. This establishes whether the relationship between ABI and cognitive function is evident among younger individuals with type 2 diabetes and whether greater obesity, a risk factor for cognitive deficits that is independent of diabetes (Kloppenborg *et al.*, 2008), obscures these relationships. It is also the first opportunity in the literature to examine whether changes in ABI from annual measures across five years is associated with poorer cognitive function four to five years later. These changes, while gradual in most individuals (Kennedy, *et al.*, 2005), are thought to identify those with increasing systemic vascular disease. If such an association is evident, it may signal that approaches to slowing or preventing declines in ABI may be promising strategies for preserving cognitive function. Secondly, there is growing evidence that other differences in systolic pressures among arterial sites, beyond what is captured by ABI, may also be markers of atherosclerosis (Kimura *et al.*, 2004; Clark *et al.*, 2007; Verberk *et al.*, 2011; Espeland *et al.*, 2014a). ABI evaluations include systolic blood pressure measurements taken from four ankle arterial sites (right and left dorsal pedis and posterior tibial arteries): we are the first to explore whether differences among these measures, and changes in such differences over four years, also serve as independent risk factors for cognitive deficits.

METHODS

The Action for Health in Diabetes (Look AHEAD) is a multi-center randomized clinical trial that enrolled 5,145 overweight or obese volunteers with type 2 diabetes between June 2001 and March 2004 (Look AHEAD 2003). Its primary goal was to assess the long-term effects on cardiovascular events of an intensive lifestyle intervention program designed to achieve

and maintain weight loss by decreased caloric intake and increased physical activity. Participants were randomly assigned to intensive lifestyle intervention or the control condition of diabetes support and education (Look AHEAD 2011). We limit our analyses to participants assigned to this control condition to avoid any confounding associated with the intensive intervention.

At enrollment, Look AHEAD participants ranged in age from 45–76 years and had a body mass index ≥ 25 kg/m², or ≥ 27 kg/m² if taking insulin. They were required to have at least moderately well controlled blood pressure ($<160/100$ mmHg, treated or untreated), HbA1c $<11\%$, plasma triglycerides <8.0 mmol/L (600 mg/dl), and willingness to accept random assignment. Potential volunteers were excluded if they were judged to be unlikely to be able to carry out components of the intensive lifestyle intervention or did not pass a graded exercise test.

The Look AHEAD Movement and Memory ancillary study (Look AHEAD M&M) enrolled Look AHEAD participants at four clinical centers (Baton Rouge, Denver, Memphis, and Pittsburgh) to participate in an ancillary study to assess cognitive and physical function at either 8 or 9 years after randomization. Only those who were currently active (i.e. had not been lost to follow-up or refused further Look AHEAD involvement) and who provided separate informed consent were eligible for enrollment. The Look AHEAD M&M protocol and consent forms were approved by local Institutional Review Boards prior to use.

Baseline correlates and potential confounders

Standardized interviewer-administered questionnaires were used to obtain data on demography and medical history (Look AHEAD 2003). History of cardiovascular disease was defined by self-report of prior myocardial infarction, stroke, coronary or lower extremity revascularization, carotid endarterectomy, or coronary bypass surgery. For calculating body mass index (ratio of weight to height squared), weight was measured in duplicate on a digital scale and standing height was determined in duplicate with a standard stadiometer. Seated blood pressure was measured twice with a Dinamap Monitor Pro 100 automated device using a common protocol and certified staff. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of anti-hypertensive medications.

Cognitive function

The Look AHEAD M&M study assessed several key cognitive functions that have previously been demonstrated to be related to obesity, either during a clinic examination or by telephone at the 8th or 9th year of Look AHEAD follow-up (Espeland *et al.*, 2014b). For consistency, this manuscript is limited to analyses of the battery of measures collected during clinic visits (a limited alternative battery was used for telephone assessments): these were collected on 90% of the Look AHEAD M&M enrollees. Tests included Trail Making Test-Parts A and B for attention and executive function (Reitan 1958), the modified Stroop Color and Word Test for executive function (Stroop 1935; Houx *et al.*, 1993), the Digit Symbol-Coding Test for processing speed (Wechsler 1981), the Rey Auditory Verbal Learning Test for learning and verbal memory (Lesak 1995), and the four-legged animals

item from Modified Mini-Mental State Exam for verbal fluency (Teng and Chui, 1987). Each neurocognitive test in this battery has been validated previously. Tests were administered by centrally trained and certified examiners.

Ankle-brachial blood pressures and inter-site blood pressure differences

Systolic blood pressures were measured at baseline and during each of four annual examinations at the right arm, left arm, right dorsalis pedis, right posterior tibial, left dorsal pedis, and left posterior tibial by trained and certified study personnel using a continuous wave Doppler with a 5–8 mHz probe for ankle pressures and a standard mercury sphygmomanometer for brachial pressures. During enrollment, Look AHEAD transitioned through three measurement protocols in an effort to streamline ABI data collection while maintaining the validity of the data (Espeland *et al.*, 2008). These involved obtaining from one to three measurements at each arterial site: we use the average of all available measures from each site. While the three measurement protocols used during baseline exams may not yield identical ABI values, the expected differences are minor (<0.03) and were ignored in our analyses (Espeland *et al.*, 2008). A single protocol was used during follow-up, which involved single measurement at each of the six sites and a replicate measure at the arm with the highest initial systolic blood pressure (7 total measurements).

Leg-specific ABI was calculated according to the American Heart Association algorithm (Hirsch *et al.*, 2006), for which the ABI for each leg equals the ratio of the higher of the two ankle systolic blood pressure measurements (posterior tibial versus dorsal pedis) divided by either the average of the right and left brachial artery pressures, or if there is a discrepancy ≥ 10 mmHg in systolic blood pressure values between the two brachial values, the higher of the two brachial values. The individual's ABI is then the minimum of the two leg-specific ABI. The cutpoint 0.90 was used to define low ABI (Hirsch *et al.*, 2006).

As a measure of differences in systolic blood pressure measures among arteries, we calculated the maximum inter-artery differences in systolic blood pressure among the four ankle arterial sites (Espeland *et al.*, 2014a), which we will refer to as MIAD.

Statistical analysis

The prevalence of low ABI was calculated at each year and ABI values across the five annual exams were averaged. We also examined changes in ABI levels over time with adjustment for baseline level. MIAD at each year and its mean and least squares regression slopes over time for each participant were calculated. For analyses of progression, we divided the cohort according to quartile of these slopes in MIAD over time using the cutpoints of -2.8 mmHg/yr (25th percentile), -0.2 mmHg/yr (50th percentile), and 2.6 mmHg/yr (75th percentile). This was done to reduce the influence of the skewed distribution on analyses.

Verbal fluency was based on the 4-legged animals item of the Modified Mini-Mental State Exam (Teng and Chui, 1987). Immediate and delayed verbal memory scores were calculated from the Rey Auditory Verbal Learning Test (Lesak 1995) and averaged. Attention was based on Trail Making Test-Part A times (Reitan 1958). Executive function was based on averages from the Trail Making Test-Part B times and the modified Stroop

Color and Word Test scores (Stroop 1935; Houx *et al.*, 1993). Processing speed was based on the Digit Symbol-Coding Test (Wechsler 1981). Each cognitive test subscale was first converted to z-scores by dividing its difference from the mean by the cohort's standard deviation and ordered so that positive scores reflected better performance. A 5% winsorization was first applied to limit the effect of extremes on means and inferences and to provide more robust characterizations of relationships across the principal range of cognitive function: scores <5th percentile or >95th percentile were replaced with the 5th and 95th percentiles of the distribution. Composite cognitive function was formed by averaging standardized scores for each tests and re-normalizing this average to have unit standard deviation.

Weighted analyses of covariance were used to assess relationships that composite cognitive function had with mean ABI and MIAD, with weights corresponding to the number of years these measures were collected. All models included age, education, race/ethnicity, gender, and clinic site as covariates. The effect of adding additional correlates and potential confounders for relationships with cognitive deficits as covariates was also assessed.

RESULTS

Our analyses were limited to the 479 Look AHEAD M&M participants who had been assigned to the control condition and had clinic-based assessments of cognitive function and at least one ABI measure (91% of the control group). Table 1 describes baseline characteristics of the study sample: 57% were female; 45% were over age 60 years; 86% were obese (body mass index ≥ 30 kg/m²), 12% were currently prescribed insulin, and 52% had diabetes for five or more years. MIAD averaged 22.8 mmHg and was strongly associated with ABI in a convex relationship ($p < 0.001$): among the 21 individuals with ABI < 0.90, the mean (standard error) was 25.6 (2.8) mmHg, among the 432 individuals with ABI between 0.90 and 1.30 the mean was 22.4 (0.7) mmHg, and among the 26 individuals with ABI > 1.30 the mean was 26.7 (3.2) mmHg.

The prevalence of low ABI was 4.4% at baseline, 2.3% at year 1, 3.6% at year 2, 4.4% at year 3, and 4.9% at year 4, with no significant trend over time ($p = 0.19$). The prevalence of high ABI tended to increase over time: 5.4% at baseline, 10.0% at year 1, 11.9% at year 2, 14.0% at year 3, and 11.3% at year 4 ($p = 0.01$). The mean MIAD (SE) at 22.8 (0.3) mmHg at baseline, 22.8 (0.6) mmHg at year 1, 23.2 (0.6) mmHg at year 2, 22.2 (0.6) mmHg at year 3, and 22.6 (0.6) mmHg at year 4, also with no overall significant trend over time ($p = 0.59$).

Mean scores for the individual tests of cognitive function are presented in Table 2. These were aggregated to produce a composite cognitive function score with mean 0 and standard deviation 1.

With a two degree of freedom quadratic function to capture curvature and with covariate adjustment for age, gender, education, race/ethnicity, and clinic site, mean ABI over time was significantly related to composite cognitive function ($p = 0.03$). It had a borderline relationship with processing speed ($p = 0.06$) and weaker associations with other cognitive functions (all $p > 0.10$). As seen for composite cognitive function in Figure 1a, individuals

with lower ABI tended to have lower cognitive function scores. For ABI values exceeding 1.0, there was little association with cognitive function. There are two outlying high mean ABI values in the figure: eliminating them did not materially influence the shape of the portrayed curve and the quadratic relationship remained of borderline statistical significance ($p=0.08$), suggesting that much of the support for curvature is derived from the flattening of the relationship with lower ABI. Changes in ABI category over follow-up, after controlling for baseline status, were not associated with any of the cognitive functions ($p>0.10$).

Mean MIAD was inversely related to verbal memory ($p=0.004$), processing speed ($p=0.02$), and composite cognitive function ($p=0.04$): see Table 3. These relationships tended to have less curvature than for ABI, as seen for composite cognitive function in Figure 1b. For participants grouped according to quartile of change in MIAD over the five measures (Table 3), greater increases in MIAD were marginally associated with lower verbal memory ($p=0.05$) and processing speed ($p=0.05$), and lower composite cognitive function ($p=0.03$). These relationships were largely independent of ABI. For example, including quadratic terms for ABI as covariates did not materially alter the relationships that mean MIAD ($p=0.08$) and quartile of MIAD progression ($p=0.03$) had with composite cognitive function. Similarly, the curvilinear relationship that composite cognitive function had with ABI was not attenuated with the addition of mean MIAD and progression of MIAD as covariates ($p=0.006$).

We repeated the analyses with covariate adjustment for all factors in Table 1. This adjustment did not materially change findings. For example, composite cognitive function continued to have relationships with ABI ($p=0.02$), mean MIAD ($p=0.05$), and changes in MIAD quartile ($p=0.02$).

We examined whether use of statins, antihypertensive medications, or insulin may have influenced our findings. Among individuals included in our analyses, 77% were using statins sometime during the first four years of follow-up, 85% were using antihypertensive medications, and 25% were using insulin. Compared to non-users in analyses controlling for age, education, gender, race/ethnicity, and clinic, use of statins ($p=0.21$) and of antihypertensive medications ($p=0.11$) were not significantly associated with lower mean composite cognitive function. Insulin users had lower mean (SE) composite cognitive function scores: -0.25 (0.08) among users versus 0.06 (0.04) among non-users ($p=0.0006$). None of the classes of drugs significantly altered the relationships that ABI and MIAD had with composite cognitive function (all interactions $p>0.10$). Two participants had a stroke and 22 others had a carotid endarterectomy during follow-up. Eliminating these individuals from analyses produced no material changes in our findings.

DISCUSSION

In the Look AHEAD cohort, ABI and inter-artery differences in systolic blood pressure had significant independent relationships with cognitive functioning among overweight and obese adults with type 2 diabetes. In addition, changes in inter-artery differences across five annual assessments were also related to cognitive functions. Covariate adjustment for a battery of risk factors for cognitive impairment did not materially alter these relationships,

which were also independent of each other. Relationships were also unaffected by the use of statins and antihypertensive medications. Additional adjustment for baseline levels of fasting glucose, LDL-cholesterol, and HDL-cholesterol also did not affect relationships.

Cognitive function and ABI

Our findings, in an overweight or obese cohort of adults with type 2 diabetes, confirm relationships that have been described in other cohorts, that low ABI is related to poorer cognitive functions (Rafnsson, *et al.*, 2009; Guerchet *et al.*, 2001). These relationships appear to affect many functions, consistent with our findings of the strongest relationships for measures of global and composite cognitive function. These relationships were not materially altered by covariate adjustment for other cardiovascular risk factors and potential confounders (including age, hypertension, blood pressure, smoking, diabetes duration, history of cardiovascular disease, body mass index, and HbA1c), which is consistent with other reports (Rafnsson *et al.*, 2009; Sugawara *et al.*, 2010).

Individuals with peripheral vascular disease are at increased risk for microvascular disease, and the expectation that vascular disease is the principal link between lower ABI and cognition is consistent with associations that low ABI has with other manifestations of systemic vascular disease exacerbated by diabetes, such as chronic kidney disease and retinopathy (Liew *et al.*, 2008; Kim *et al.*, 2013; Lacroix *et al.*, 2013). Peripheral artery disease has been found to be related to markers of cerebrovascular disease with brain MRI (Bots *et al.*, 1993; Geerlings *et al.*, 2010; Hughes *et al.*, 2013; Hilal *et al.*, 2014). The co-occurrence of peripheral artery disease may accentuate the adverse impact of microvascular disease in other vascular beds on cognition (Vupputuri *et al.*, 2008). These findings have led to calls for ABI to be a clinical tool for identifying older individuals at greater risk for cognitive decline (Rafnsson *et al.*, 2009). In the Look AHEAD cohort, while independent of other risk factors such as hypertension, the relationships were modest (but stronger in this cohort for composite cognitive function than hypertension ($p=0.51$), smoking ($p=0.62$), or history of cardiovascular disease ($p=0.74$)). It may be that the low prevalence of abnormal ABI in this cohort attenuated this relationship. Alternatively, the requirement for Look AHEAD participants to successfully complete a maximum graded exercise test may have culled many potential participants with low ABI (Curtis *et al.*, 2010).

Inter-artery differences in systolic blood pressure

Inter-artery systolic blood pressure differences were modestly elevated among participants with low ABI, and more so among those with high ABI. We are the first to report that larger differences in inter-artery systolic blood pressures and increases in these differences over time are risk factors for poorer cognition, independent of ABI. Thus these differences, a by-product of ABI measurement, provide additional clinical information that is independent of traditional risk factors.

Differences in systolic blood pressures between arms have been linked to peripheral vascular disease, unilateral neurological abnormalities, subclinical atherosclerosis, and increased risk of stroke and cardiovascular disease (Verberk *et al.*, 2011; Perloff *et al.*, 1993; Tanaka *et al.*, 2014). Differences in blood pressures between adjacent sites on a peripheral artery that

exceed 20 mmHg signal the presence of a clinically important focal stenosis (Hirsch *et al.*, 2006). While we have focused on differences among ankle sites, the mechanism linking these to poorer cognitive function are likely to be similar to those of other markers of vascular disease.

Limitations

The Look AHEAD M&M cohort, as eligible volunteers for a randomized clinical trial may not resemble other cohorts. In particular, the requirement that they successfully pass a graded exercise test excluded many potential volunteers with some level of peripheral vascular disease (Curtis *et al.*, 2010). The cognitive assessments were collected 4–5 years after ABI was measured, so that differential behavior or medical care in this intervening time and the development of comorbidities such as depression may have influenced findings (Brown *et al.*, 2014). The relatively low prevalence of abnormal ABI and the lack of overall increase over time in its prevalence and in MIAD limited the statistical power available to describe relationships.

CONCLUSIONS

Within a well-characterized cohort of overweight and obese adults with type 2 diabetes, low ABI and greater inter-artery systolic blood pressure differences were associated with poorer cognitive function.

Acknowledgments

Funding and Support:

This work was supported by the National Institute on Aging, National Institutes of Health, Department of Health and Human Services, R-01AG033087-01 and R-01AG033087-04S1. The Action for Health in Diabetes is supported through the following cooperative agreements from the National Institutes of Health: DK57136, DK57149, DK56990, DK57177, DK57171, DK57151, DK57182, DK57131, DK57002, DK57078, DK57154, DK57178, DK57219, DK57008, DK57135, and DK56992. The following federal agencies have contributed support: National Institute of Diabetes and Digestive and Kidney Diseases; National Heart, Lung, and Blood Institute; National Institute of Nursing Research; National Center on Minority Health and Health Disparities; Office of Research on Women's Health; the Centers for Disease Control and Prevention; and the Department of Veterans Affairs. This research was supported in part by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. The Indian Health Service (I.H.S.) provided personnel, medical oversight, and use of facilities. The opinions expressed in this paper are those of the authors and do not necessarily reflect the views of the I.H.S. or other funding sources.

Additional support was received from the University of Colorado Health Sciences Center General Clinical Research Center (M01RR00051) and Clinical Nutrition Research Unit (P30 DK48520); the University of Tennessee at Memphis General Clinical Research Center (M01RR0021140); and the University of Pittsburgh General Clinical Research Center (GCRC) (M01RR000056), the Clinical Translational Research Center (CTRC) funded by the Clinical & Translational Science Award (UL1 RR 024153) and NIH grant (DK 046204); and the Frederic C. Bartter General Clinical Research Center (M01RR01346)

The following organizations have committed to make major contributions to Look AHEAD: FedEx Corporation; Health Management Resources; LifeScan, Inc., a Johnson & Johnson Company; OPTIFAST® of Nestle HealthCare Nutrition, Inc.; Hoffmann-La Roche Inc.; Abbott Nutrition; and Slim-Fast Brand of Unilever North America.

References

Bots ML, van Swieten JC, Breteler MM, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam study. *Lancet*. 1993; 341:1232–1237. [PubMed: 8098390]

- Brown PJ, Sneed JR, Rutherford BR, Devanand DP, Roose SP. The nuances of cognition and depression in older adults: the need for a comprehensive assessment. *Int J Geriatr Psych*. 2014; 19:506–514.
- Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia*. 2008; 51:241–248. [PubMed: 18060658]
- Clark CE, Campbell JL, Powell R, Thompson JF. The inter-arm blood pressure difference and peripheral vascular disease: cross-sectional study. *Fam Practice*. 2007; 24:420–6.
- Curtis JM, Horton ES, Bahnson JB, et al. Prevalence and predictors of abnormal cardiovascular responses to exercise testing among individuals with type 2 diabetes. *Diabetes Care*. 2010; 33:901–907. [PubMed: 20056948]
- Espeland MA, Lewis CB, Bahnson J, et al. Impact of intensive lifestyle intervention on ankle-brachial index and inter-artery systolic blood pressures in a cohort of overweight and obese individuals with diabetes: results from the Action for Health in Diabetes (Look AHEAD) Clinical Trial. *Obesity*. 2014a; 22:1032–1041. [PubMed: 24174392]
- Espeland MA, Rapp SR, Bray GA, et al. Long-term impact of behavioral weight loss intervention on cognitive function. *J Gerontol Med Sci*. 2014b; 69:1101–1108.
- Espeland MA, Regensteiner JG, Jaramillo SA, et al. Measurement characteristics of the ankle-brachial index: Results from the Action for Health in Diabetes Study. *Vasc Med*. 2008; 13:225–233. [PubMed: 18687759]
- Geerlings MI, Appleman APA, Vincken KL, et al. Brain volumes and cerebrovascular lesions in MRI patients with atherosclerotic disease, The SMARTA-MR study. *Atherosclerosis*. 2010; 210:130–136. [PubMed: 19945704]
- Guerchet M, Aboyans V, Nubukpo P, Lacoix P, Clements J-P, Preux M-P. Ankle-brachial index as a marker of cognitive impairment and dementia in general population. A systematic review. *Atherosclerosis*. 2001; 216:251–257. [PubMed: 21497350]
- Hilal S, Saini M, Tan CS, et al. Ankle-brachial index, cognitive impairment, and cerebrovascular disease in a Chinese population. *Neuroepidemiology*. 2014; 42:131–138. [PubMed: 24481144]
- Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA 2005 Practice guidelines for the management of patients with peripheral arterial disease (Lower extremity, renal, mesenteric, and abdominal aortic). *Circulation*. 2006; 113:e463–654. [PubMed: 16549646]
- Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. *Exp Aging Res*. 1993; 19:209–24. [PubMed: 8223823]
- Hughes TM, Kuller LH, Barinas-Mitchell EF, et al. Pulse wave velocity is associated with B-amyloid deposition in the brains of very elderly adults. *Neurol*. 2013; 81:1711–1718.
- Kennedy M, Solomon C, Manolio T, et al. Risk factors for declining brachial-index in men and women 65 years or older. *JAMA Intern Med*. 2005; 165:1896–1902.
- Kim WJ, Park S-Y, Park SE, et al. The association between regional arterial stiffness and diabetic retinopathy in type 2 diabetes. *Atherosclerosis*. 2013; 225:237–241. [PubMed: 23017354]
- Kimura A, Hashimoto J, Watabe D, et al. Patient characteristics and factors associated with inter-arm difference of blood pressure measurements in a general population in Ohasama, Japan. *J Hypertens*. 2004; 22:2277–2283. [PubMed: 15614021]
- Kloppenborg RP, van den Berg E, Kappelle LJ, et al. Diabetes and other vascular risk factors for dementia: Which matters most? A systematic review. *Eur J Pharmacol*. 2008; 585:97–108. [PubMed: 18395201]
- Lacroix P, Aboyans V, Desormais I, et al. Chronic kidney disease and the short-term risk of mortality and amputation in patients hospitalized for peripheral artery disease. *J Vasc Surgery*. 2013; 58:966–971.
- Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MCW, Fowkes FGR. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors. The Edinburgh Artery Study. *Circulation*. 2004; 110:3075–3080. [PubMed: 15477416]
- Lesak, MD. *Neuropsychological Assessment*. Oxford University Press; New York: 1995.
- Liew YP, Bartholomew JR, Demirjian S, Michaels J, Schreiber MJ. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high risk population. *Clin J Am Soc Nephrol*. 2008; 3:1084–1089. [PubMed: 18337552]

- McDermott MM, Liu K, Criqui MH, et al. Ankle-brachial index and subclinical cardiac and carotid disease. The Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2005; 162:33–41. [PubMed: 15961584]
- Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PWF. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death. The Framingham Study. *Arch Intern Med*. 2003; 163:1939–1942. [PubMed: 12963567]
- Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. *Circulation*. 1993; 88:2460–2470. [PubMed: 8222141]
- Rafnsson SB, Deary IJ, Fowkes FGR. Peripheral arterial disease and cognitive function. *Vasc Med*. 2009; 14:51–61. [PubMed: 19144780]
- Reitan RM. The validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*. 1958; 8:271–6.
- Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation*. 2004; 109:733–739. [PubMed: 14970108]
- Stroop JR. Studies of interference in serial verbal reactions. *Exp Psychol*. 1935; 18:643–62.
- Sugawara N, Yaui-Furukori N, Umeda T, et al. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of cognitive function in a community dwelling population. *BMC Psychiatry*. 2010; 10:46. [PubMed: 20537134]
- Tanaka Y, Fukui M, Tanaka M, et al. The inter-arm difference in systolic blood pressure is a novel risk marker for subclinical atherosclerosis in patients with type 2 diabetes. *Hypertens Res*. 2014; 37:548–552. [PubMed: 24599017]
- Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987; 48:314–8. [PubMed: 3611032]
- The Look AHEAD Research Group. Look AHEAD: Action for Health in Diabetes. Design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Controlled Clin Trials*. 2003; 24:610–28. [PubMed: 14500058]
- The Look AHEAD Research Group. The development and description of the diabetes support and education (comparison group) intervention for the Action for Health in Diabetes (Look AHEAD) Trial. *Clin Trials*. 2011; 8:320–9. [PubMed: 21730080]
- Verberk WJ, Kessels AGH, Thien T. Blood pressure measurement method and inter-arm differences: a meta-analysis. *Am J Hypertens*. 2011; 24:1201–1208. [PubMed: 21776035]
- Vupputuri S, Shoham DE, Hogan SL, Kshirsagar AV. Microalbuminuria, peripheral vascular disease, and cognitive function. *Inter Soc Nephrol*. 2008; 73:316–346.
- Wechsler, D. WAIS-R Manual. New York: Psychological Corporation, New York; 1981.

Clinical Sites

Pennington Biomedical Research Center

George A. Bray, MD¹; Kristi Rau²; Allison Strate, RN²; Frank L. Greenway, MD³; Donna H. Ryan, MD³; Donald Williamson, PhD³; Brandi Armand, LPN; Jennifer Arceneaux; Amy Bachand, MA; Michelle Begnaud, LDN, RD, CDE; Betsy Berhard; Elizabeth Caderette; Barbara Cerniauskas, LDN, RD, CDE; David Creel, MA; Diane Crow; Crystal Duncan; Helen Guay, LDN, LPC, RD; Carolyn Johnson, Lisa Jones; Nancy Kora; Kelly LaFleur; Kim Landry; Missy Lingle; Jennifer Perault; Cindy Puckett; Mandy Shipp, RD; Marisa Smith; Elizabeth Tucker

¹Principal Investigator

²Program Coordinator

³Co-Investigator

University of Colorado Health Sciences Center

James O. Hill, PhD¹; Marsha Miller, MS, RD²; Brent Van Dorsten, PhD³; Judith Regensteiner, PhD³; Ligia Coelho, BS; Paulette Cohrs, RN, BSN; Susan Green; April Hamilton, BS, CCRC; Jere Hamilton, BA; Eugene Leshchinskiy; Lindsey Munkwitz, BS; Loretta Rome, TRS; Terra Worley, BA; Kirstie Craul, RD,CDE; Sheila Smith, BS

The University of Tennessee Health Science Center

University of Tennessee East

Karen C. Johnson, MD, MPH¹; Carolyn Gresham, RN²; Stephanie Connelly, MD, MPH³; Amy Brewer, RD, MS; Mace Coday, PhD; Lisa Jones, RN; Lynne Lichtermann, RN, BSN; Shirley Vosburg, RD, MPH; and J. Lee Taylor, MEd, MBA. *University of Tennessee Downtown.* Abbas E. Kitabchi, PhD, MD¹; Ebenezer Nyenwe, MD³; Helen Lambeth, RN, BSN²; Amy Brewer, MS, RD,LDN; Debra Clark, LPN; Andrea Crisler, MT; Debra Force, MS, RD, LDN; Donna Green, RN; Robert Kores, PhD

University of Pittsburgh

John M. Jakicic, PhD¹, David E. Kelley, MD¹; Jacqueline Wesche-Thobaben, RN, BSN, CDE²; Lewis H. Kuller, MD, DrPH³; Andrea Kriska, PhD³; Amy D. Otto, PhD, RD, LDN³, Lin Ewing, PhD, RN³, Mary Korytkowski, MD³, Daniel Edmundowicz, MD³; Monica E. Yamamoto, DrPH, RD, FADA³; Rebecca Danchenko, BS; Barbara Elnyczky; David O. Garcia, MS; George A. Grove, MS; Patricia H. Harper, MS, RD, LDN; Susan Harrier, BS; Nicole L. Helbling, MS, RN; Diane Ives, MPH; Juliet Mancino, MS, RD, CDE, LDN; Anne Mathews, PhD, RD, LDN; Tracey Y. Murray, BS; Joan R. Ritchea; Susan Urda, BS, CTR; Donna L. Wolf, PhD

Coordinating Center

Wake Forest School of Medicine

Stephen B. Kritchevsky, PhD¹; Denise K. Houston, PhD³; Jeff D. Williamson, MD³; Stephen R. Rapp, PhD³; Mark A. Espeland, PhD³; Xiaoyina (Iris) Leng, MD, PhD³; Gary Miller, PhD³; Amelia Hodges, BS, CCRP²; Michelle Gordon, MS; Jennifer Walker; Tara Beckner; Jason Griffin, BS; Lea Harvin, BS; Kathy Lane, BS; Rebecca H. Neiberg, MS;

Key points

- 1.** In a cohort of overweight and obese individuals with type 2 diabetes, lower ankle-brachial index, an established marker for peripheral vascular disease, is independently associated with poorer cognitive function four to five years later.
- 2.** A novel marker of vascular disease, the maximum difference in systolic blood pressure among four ankle sites, is also independently related to cognitive function. In a graded fashion, individuals with greater inter-artery differences in systolic blood pressure tended to have lower cognitive function.
- 3.** Over four years, increases in the maximum inter-artery difference in systolic blood pressure, were also independently associated with poorer cognitive function. This is the first report of this risk factor relationship.
- 4.** Further work is required to determine whether interventions targeting the prevention or treatment of peripheral vascular disease may also prevent cognitive decline.

Figures 1ab.

Relationships that average ABI and maximum inter-artery systolic blood pressure differences across follow-up have with composite cognitive function. Portrayed regression curve was fitted with cubic splines. P-values were derived from a two degree of freedom quadratic function. Covariate adjustment was made for age, education, race/ethnicity, gender, and clinic.

Table 1

Baseline correlates and potential confounders for relationships that ABI values and inter-artery systolic blood pressure differences have with cognitive function on 479 Look AHEAD M&M control participants.

Cardiovascular Disease Risk Factor	N (Percent) or Mean (SD)
Sex	
Female	272 (56.8)
Male	207 (43.2)
Age, yrs	
45–59	262 (54.7)
60–76	217 (45.3)
Education, years [Missing=15]	
High school or less	71 (15.5)
Post high school	205 (44.8)
College graduate	188 (40.3)
Race/Ethnicity	
African-American	96 (20.0)
White	343 (71.6)
Multiple/Other	40 (8.4)
Hypertension	
Yes	391 (81.6)
No	88 (18.4)
Blood pressure, mmHg	
Systolic	129.1 (16.3)
Diastolic	70.6 (9.6)
Cigarette smoking	
Never	258 (53.9)
Former	200 (41.8)
Current	21 (4.4)
Years with Type 2 diabetes [Missing=6]	
<5 years	226 (47.8)
5 years	247 (52.2)
Cardiovascular disease history	
Yes	64 (13.4)
No	415 (86.6)
Body mass index, kg/m ²	
25–29	69 (14.4)
30–39	310 (64.7)

Cardiovascular Disease Risk Factor	N (Percent) or Mean (SD)
40	100 (20.9)
Insulin use, [Missing=15]	
Yes	58 (12.5)
No	406 (87.5)
Statin Use [Missing=10]	
Yes	226 (48.2)
No	243 (51.8)
HbA1c	
< 7.0%	231 (48.2)
7.0–8.9%	203 (42.4)
9.0–10.9%	45 (9.4)
ABI	
<0.90	21 (4.4)
0.90–1.30	432 (90.2)
>1.30 ^I	26 (5.4)
Maximum ankle inter-artery SBP difference, mmHg	24.0 (17.4)

^IThe cutpoint of >1.30 is commonly used to denote abnormally high ABI (e.g. [22]).

Table 2

Mean winsorized scores from individual tests.

Cognitive Test Score	Mean (SD)
Trail Making Test	
Psychomotor speed: Part A (sec)	36.3 (12.4)
Tracking speed: Part B (sec)	102.8 (57.9)
Stroop Test	
Interference (time + errors)	37.3 (13.7)
Digit Symbol	
Processing speed (sec)	41.0 (10.8)
Rey Auditory Verbal Learning Test	
Total adjusted raw learning	41.6 (9.1)
Short delay recall	7.7 (3.0)
Short term retention (%)	72.8 (20.5)
Long delay recall	7.3 (3.2)
Long term retention (%)	67.7 (23.4)
Modified Mini-Mental State Exam	
Verbal fluency	9.2 (1.4)

Table 3

Relationships that maximum inter-artery systolic blood pressure differences (MIAD) have with standardized cognitive function scores, with covariate adjustment with covariate adjustment for age, gender, education, race/ethnicity, and clinic.

Cognitive Function	Relationship with Mean MIAD Over Follow-up: Regression Slope (SE) (p-value)	Relationship with Quartile of Change ^I in MIAD Over Follow-up: Regression Slope (SE) (p-value)
Verbal Fluency	−0.003 (0.006) P=0.57	−0.029 (0.039) P=0.46
Verbal Memory	−0.015 (0.005) P=0.004	−0.069 (0.035) P=0.05
Attention	−0.004 (0.005) P=0.42	−0.033 (0.036) P=0.33
Executive Function	−0.006 (0.005) P=0.24	−0.027 (0.036) P=0.45
Processing Speed	−0.012 (0.005) P=0.02	−0.069 (0.035) P=0.05
Composite	−0.010 (0.005) P=0.04	−0.071 (0.033) P=0.03

^IQuartiles groupings are based on linear regression slopes for each participant's MIAD measures across the five annual examinations.