Ankle-to-Brachial Index and Dementia
The Honolulu-Asia Aging Study

Danielle Laurin, PhD; Kamal H. Masaki, MD; Lon R. White, MD, MPH; Lenore J. Launer, PhD

Background—Measurement of the ankle-to-brachial index (ABI) is a noninvasive test to assess peripheral arterial disease. A low ABI is a strong correlate of cardiovascular disease and subsequent mortality. Evidence indicates the existence of vascular components in the pathogenesis of dementia. Here, we examine the association of ABI with dementia and subtypes.

Methods and Results—Data are from the Honolulu-Asia Aging Study (HAAS), a prospective community-based study of 3734 Japanese American men 71 to 93 years of age at baseline in 1991 to 1993. The analysis included 2588 men who were free of dementia at the first assessment, had an ABI measure, and were examined up to 2 more times for dementia between 1994 and 1999. The sample included 240 incident cases of dementia (144 of Alzheimer’s disease, 46 of vascular dementia, and 50 of dementia of other causes). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from Cox proportional-hazards models with age as the time scale after adjustment for education, year of birth, high blood pressure, body mass index, diabetes mellitus, cholesterol concentration, smoking status, alcohol consumption, and apolipoprotein E ε4 allele. A low ABI was associated with an increased risk of dementia and vascular dementia (HR, 1.66; 95% CI, 1.16 to 2.37; and HR, 2.25; 95% CI, 1.07 to 4.73, respectively). ABI was weakly associated with Alzheimer’s disease (HR, 1.57; 95% CI, 0.98 to 2.53), particularly in the apolipoprotein E ε4 carriers (HR, 1.43; 95% CI, 1.02 to 1.96).

Conclusions—These results suggest that ABI, a measure of atherosclerosis, is associated with the incidence of total dementia, vascular dementia, and Alzheimer’s disease in carriers of the apolipoprotein E ε4 allele. (Circulation. 2007; 116:2269-2274.)

Key Words: aging ■ apolipoproteins ■ epidemiology ■ peripheral vascular disease ■ population ■ risk factors

Peripheral artery disease (PAD) is a common disorder in aging populations that could benefit from a number of preventive interventions. PAD, which results from the accumulation of atherosclerosis in the lower limbs, affects up to 30% of North Americans and Europeans >55 years of age, half of whom are asymptomatic. The ankle-to-brachial index (ABI) has proved to be the most effective and accurate noninvasive test to assess PAD. Modifiable risk factors associated with PAD include heavy smoking, hypertension, and diabetes mellitus. A low ABI has been reported to be a strong independent correlate of cardiovascular disease and subsequent mortality in older persons.

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Although the influence of cerebrovascular disease on cognition is well established, the evidence that PAD may lead to cognitive loss or impairment is less well studied. In clinical settings, poorer performance on several neuropsychological tests, including measures of attention, psychomotor speed, and visuospatial and executive function, has been documented among amputees or other highly selected patients with PAD compared with control subjects, although inconsistently.

Few epidemiological studies have examined the association of cognitive function and PAD in the general population. A PAD link to poorer performance of cognition has been reported in cross-sectional analyses that measured cognition with the Mini-Mental State Examination; again, these results have not consistently been replicated. Two studies reported that subjects with a low ABI and an apolipoprotein (Apo) E ε4 allele had the greatest cognitive decline compared with those with 1 or 0 of those risk factors. The ApoE ε4 allele has been reported to modify the association of other cerebrovascular disease risk factors to cognitive function and Alzheimer’s disease.

It is not known whether PAD is associated with clinical dementia. Vascular risk factors, including atherogenic and stroke-related damage, are known to play a predominant role...
in vascular dementia (VaD), but there also is significant evidence of their involvement in AD.\textsuperscript{17} Therefore, we hypothesized that the ABI is associated with the risk of all dementia, VaD, and AD. In addition, we evaluated the potential effect modification of risk associated with ApoE $e4$.\textsuperscript{16}

**Methods**

**Study Population**

Data are from the Honolulu-Asia Aging Study (HAAS), which is a longitudinal community-based study derived from the Honolulu Heart Program (HHP), a study of cardiovascular disease in men of Japanese ancestry born between 1900 and 1919 who were living on the island of Oahu, Hawaii, at the time of the first examination.\textsuperscript{18} This examination was carried out from 1965 through 1968; subjects were reevaluated in 1968 to 1970 (examination 2) and in 1971 to 1974 (examination 3). A standardized clinical evaluation of several physical and laboratory functions was performed at all examinations; data on sociodemographic characteristics and medical history were collected by structured interview. The HAAS was initiated in 1991 to 1993 to coincide with the fourth examination of the HHP.\textsuperscript{19} Of the HHP cohort, 3734 subjects (80\% of survivors) between 71 and 93 years of age agreed to participate in the HAAS when the first evaluation for dementia was performed. Subjects were evaluated for dementia on 2 other occasions in 1994 to 1996 (examination 5) and 1997 to 1999 (examination 6). The Kuakini Medical Center Institutional Review Board approved the study, and all subjects, or their caretakers when subjects were demented, provided written informed consent.

**Dementia Case Findings**

At HAAS baseline (examination 4) and subsequent examinations, subjects were first screened for dementia with the 100-point Cognitive Abilities Screening Instrument,\textsuperscript{20} a combination of the Hasegawa Dementia Screening Scale, the Folstein Mini-Mental State Examination, and the Modified Mini-Mental State Test. Case finding was conducted according to a multistep procedure previously described,\textsuperscript{19} with the Cognitive Abilities Screening Instrument score used to determine subgroups for evaluation. The dementia evaluation included a neurological examination, neuropsychological testing, and an informant interview about changes in cognitive function and behavior. In subjects suspected to have dementia, a brain image was made and routine blood tests were conducted. On the basis of these data, a consensus diagnosis for dementia was given by the study neurologist and 2 physicians with expertise in dementia, according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* criteria.\textsuperscript{21} Of the 3734 subjects evaluated at examination 4, 1095 subjects were positive for dementia; 20.1\% of them were diagnosed as prevalent cases of dementia. Of the 2693 subjects evaluated at examination 5, 751 were screened positive; 19.6\% of them were diagnosed as incident cases of dementia. Finally, of the 1982 subjects evaluated at examination 6, 307 were screened positive; 35\% of them were diagnosed as incident cases of dementia. Definite AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria.\textsuperscript{22} Mixed dementia involving AD as the primary cause was defined as possible AD. Definite AD can be diagnosed only with neuropathological data. The sensitivity of the clinical diagnosis of AD compared with autopsied brains has been previously examined in a subset of the HAAS sample; 65\% of clinical AD cases had sufficient neuritic plaques to meet neuropathologically definite or probable AD criteria.\textsuperscript{23} VaD was diagnosed with the criteria of the California Alzheimer’s Disease Diagnostic and Treatment Centers.\textsuperscript{24} Other dementias included those caused by alcohol, brain tumor, subdural hematoma, Parkinson’s disease, Lewy body disease, Pick’s disease, trauma, vitamin $B_{12}$ deficiency, hypothyroidism, progressive supranuclear palsy, and unknown cause.

**ABI Measurement**

The ABI was measured at HAAS baseline (1991 to 1993) according to a standard protocol.\textsuperscript{25,26} The brachial pressure was measured twice in the right arm, and the ankle (posterior tibial) pressure was measured twice in each ankle with subjects in the supine position by use of a handheld Doppler device (Huntleigh D500 Mini Dopplex Luton, Bedfordshire, Great Britain) attached to a standard sphygmomanometer. The means of the 2 measurements in the arm and each ankle were taken to calculate the ABI for both the left and right sides, and the lowest value of the ABI was chosen. A ratio $<0.9$ results from a relatively low ankle pressure, which may indicate subclinical atherosclerosis in lower extremity arteries. The validity criteria of the ABI as a screening tool for coronary heart disease have been measured; the sensitivity and specificity of an ABI $<1$ for coronary heart disease were 41\% and 73\%, respectively.\textsuperscript{27}

**Covariates and Potential Confounders**

Covariates and potential confounders taken into consideration were measured at HAAS baseline. Cigarette smoking status was coded as never smoker, past smoker, and current smoker. Alcohol consumption was categorized into no alcohol, $<15$ g/d ($<1$ drink per day), 15 to 30 g/d (1 to 2 drinks per day), and $>30$ g/d ($>3$ drinks per day). Systolic and diastolic blood pressure values corresponded to the mean of 3 measurements made on the left arm with subjects in the seated position. High blood pressure was defined as systolic blood pressure $\geq 160$ mm Hg, diastolic blood pressure $\geq 95$ mm Hg, or the use of medications for hypertension. Total cholesterol, triglycerides, glucose, insulin, and a standard 2-hour oral glucose tolerance test were measured in specimens collected from subjects in a fasting state. Impaired glucose regulation, including impaired fasting glucose or impaired glucose tolerance, was defined as fasting blood glucose between 5.6 and 7.0 mmol/L (100 to 126 mg/dL) or 2-hour postload glucose between 7.8 and 11.1 mmol/L (140 to 200 mg/dL). Diabetes mellitus was defined as fasting blood glucose $\geq 7.0$ mmol/L (126 mg/dL), 2-hour postload glucose $\geq 11.1$ mmol/L (200 mg/dL), or the use of medications.\textsuperscript{28} Body mass index was calculated as the weight (kg) divided by the height (m) squared. ApoE genotyping was obtained by standard DNA amplification and restriction isotyping.\textsuperscript{29} All carriers of ApoE $e4$ were combined and coded as a binary variable, the presence/absence of ApoE $e4$. A variable for the history of cardiovascular disease relative to HAAS baseline was created using the information from the continuous surveillance of hospital discharge and death records on Oahu. A positive history referred to either a stroke or a coronary heart disease event before examination 4. Confounders with $<5\%$ missing data were imputed; missing-value dummy variables when variables were discrete or were given the mean value of the distribution of the study population when continuous.

**Statistical Analyses**

Characteristics of incident dementia cases and the cases negative for dementia were compared by use of the Kruskal-Wallis tests for continuous variables and $\chi^2$ tests for categorical variables after adjustment for age and education. ABI was studied 2 ways. First, we divided the variable into 3 categories: $<0.90$, the grouping that reflects PAD; 0.90 to 1.20, the referent group; and $\geq 1.20$. This second cutoff was defined to take into account subjects having stiffened noncompressible peripheral vessels, like diabetics, which may show falsely elevated ABI values.\textsuperscript{30} To examine the linear relationship of ABI to dementia, we also converted ABI, which was relatively normally distributed, into a $z$ score, with a mean of 0 and SD of 1 (range, $-4.1$ to 6.3). We tested for a nonlinear relationship by adding the ABI as its quadratic term to the model. The association between ABI and VaD was linear; the associations between ABI and all dementia and AD were nonlinear and treated accordingly.

The Cox proportional-hazards regression model with delayed entry and age as the time scale was used to identify and adjust for confounding variables.\textsuperscript{31} The age of onset was assigned at the mid point of the interval between the last examination without dementia and the first follow-up with dementia. Subjects who died or did not...
participate in subsequent follow-up examinations were censored as of the time of their last evaluation. Covariates included year of birth and education (model 1). In addition to model 1 variables, we included high blood pressure, diabetes mellitus, smoking status, alcohol consumption, cholesterol (coded in quintiles), body mass index, and ApoE e4 status in model 2, plus history of cardiovascular disease in model 3.

The proportional-hazards assumptions were tested graphically and by including the interaction of time with each covariate. The effect of year of birth did not follow the proportional-hazards model assumption, so it was entered as a 3-category stratum variable in all analyses; thus, all analyses are stratified by category of birth year, and the final model results are summarized over these categories. Cutoffs of strata were picked to achieve a balanced distribution of cases and noncases. We further tested the effect modification by ApoE e4 status of dementia risk by stratifying the analysis according to ApoE e4 status (carrier versus noncarrier) and by formally testing the interaction term (ABI × ApoE e4 status). Analyses were performed with the Statistical Analysis System version 9.1 software (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Of the 3734 HAAS subjects, 226 were prevalent cases of dementia and were excluded. Of the remaining eligible subjects, 920 could not be included because of death (n=418), refusal of another case-finding examination (n=462), or missing data for ABI (n=40), leaving 2588 subjects for final analyses. Compared with those from the analytical sample, subjects with missing ABI or who refused were on average older (78.6 versus 76.9 years; P<0.001) and less educated (9.5 versus 10.8 years; P<0.001) at baseline.

The mean±SD age of subjects at baseline was 76.9±4.1 years. PAD, defined by an ABI <0.90, affected 271 subjects (10.5%) of the study sample. Over the 5.1 years of follow-up (range, 1.1 to 7.8 years), 2348 subjects remained nondemented, and 240 developed dementia; this included 144 cases of AD (103 probable AD and 41 possible AD with contributing cerebrovascular disease), 46 cases of VaD, and 50 cases resulting from other causes. The mean age at baseline was 79.6 years (SD, 4.8 years) for the AD group and 78.6 years (SD, 5.2 years) for the VaD group; this difference was not statistically different (P=0.24). Men who screened as demented at follow-up were significantly older at baseline (79.3 versus 76.6 years; higher proportion of men born between 1900 and 1912: 46.3% versus 23.4%), had fewer years of education (10.2 versus 10.9 years), showed a higher proportion of ApoE e4 (22.5% versus 18.0%), and had lower mean values of cholesterol, triglycerides, and body mass index (Table 1).

After adjustment for education and year of birth, ABI was significantly associated with the risk for total dementia and VaD (Table 2, model 1). After additional adjustment (Table 2, model 2), however, the risk for dementia was no longer significant. The risk of VaD increased significantly with each 1-SD unit reduction in ABI (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.07 to 2.00). Additional adjustment by history of cardiovascular disease (model 3) reduced the risk estimate by 13% (HR, 1.28; 95% CI, 0.93 to 1.75). Similar results on total dementia and VaD were observed when the distribution of ABI was divided into 3 categories.

### Table 1. Baseline Characteristics of Nondemented Subjects and Subjects With Incident Dementia: The HAAS, 1991 to 1999

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nondemented Subjects (n=2348)</th>
<th>Subjects With Incident Dementia (n=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>76.6±3.9</td>
<td>79.3±4.8</td>
</tr>
<tr>
<td>Year of birth*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1900 to 1912</td>
<td>23.4</td>
<td>46.3</td>
</tr>
<tr>
<td>1913 to 1916</td>
<td>34.8</td>
<td>33.3</td>
</tr>
<tr>
<td>1917 to 1919</td>
<td>41.7</td>
<td>20.4</td>
</tr>
<tr>
<td>Education, y†</td>
<td>10.9±3.1</td>
<td>10.2±3.3</td>
</tr>
<tr>
<td>ABI</td>
<td>1.05±0.14</td>
<td>1.03±0.19</td>
</tr>
<tr>
<td>Smoking, %‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>37.5</td>
<td>41.8</td>
</tr>
<tr>
<td>Past</td>
<td>56.3</td>
<td>50.4</td>
</tr>
<tr>
<td>Current</td>
<td>6.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Alcohol intake, g/d‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>42.0</td>
<td>42.1</td>
</tr>
<tr>
<td>0 to 15</td>
<td>29.1</td>
<td>28.1</td>
</tr>
<tr>
<td>15 to 30</td>
<td>11.1</td>
<td>14.0</td>
</tr>
<tr>
<td>&gt;30</td>
<td>17.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>149.4±21.9</td>
<td>150.8±23.0</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80.7±10.7</td>
<td>80.1±10.8</td>
</tr>
<tr>
<td>Diabetes mellitus, ‰‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>20.4</td>
<td>24.9</td>
</tr>
<tr>
<td>IFG/IGT</td>
<td>53.6</td>
<td>46.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>26.0</td>
<td>28.3</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L‡</td>
<td>113±121</td>
<td>122±182</td>
</tr>
<tr>
<td>Cholesterol, mmol/L†‡</td>
<td>4.98±0.83</td>
<td>4.84±0.81</td>
</tr>
<tr>
<td>Triglycerides, mmol/L†‡</td>
<td>1.73±1.10</td>
<td>1.56±0.92</td>
</tr>
<tr>
<td>Body mass index, kg/m²†‡</td>
<td>23.8±3.0</td>
<td>23.0±3.1</td>
</tr>
<tr>
<td>ApoE e4 allele (yes), ‰‡</td>
<td>18.0</td>
<td>22.5</td>
</tr>
</tbody>
</table>

IFG/IGT indicates impaired fasting glucose/impaired glucose tolerance. Values are mean±SD when appropriate.

*P<0.001; †P<0.05; ‡Means and proportions are calculated without missing values.

After full multivariate adjustment (model 2), subjects with PAD showed a 66% increase in risk of dementia and a >2-fold increase in risk of VaD (HR, 2.25; 95% CI, 1.07 to 4.73) compared with the referent group. This increased risk remained significant in model 3 for total dementia (HR, 1.62; 95% CI, 1.13 to 2.32). PAD was associated with the risk of AD in the simplest model (HR, 1.60; 95% CI, 1.01 to 2.53). The presence of stiffened vessels (ABI ≥1.20) was not associated with the risk of total dementia and subtypes.

Effect modification was tested in total dementia and AD with the simplest model (model 1) and with ABI as a continuous variable (Table 3). Given the small number of incident cases with ApoE e4 (n=7), effect modification was not tested in VaD. Among ApoE e4 carriers, the risk of AD increased significantly with each 1-SD unit reduction in ABI (HR, 1.43; 95% CI, 1.02 to 1.96). The risk of AD was not related to ABI in noncarriers of ApoE e4. No interaction was observed between ABI and ApoE e4 in total dementia.
The present study suggests that a low ABI was related to an increased risk of total dementia and VaD. In addition, a low ABI was associated with an increased risk of AD if subjects were carriers of ApoE4. These results are based on a large community-based study of Japanese American men followed up extensively for 30 years for vascular risk factors and for 10 years for dementia.

Limitations of this study need to be discussed when the data are interpreted. Of eligible subjects, 25.1% could not be included because they died (11.9%) or refused a follow-up examination (13.2%). Subjects excluded were, at baseline, slightly older and less educated, both risk factors for dementia, but also showed a 1.9% lower ABI mean value. Excluding decedents and nonresponders may have therefore underestimated the risks. Furthermore, subjects in this cohort were very old at baseline. Survival bias may have distorted results and further underestimated the risks because patients with more severe cases of PAD may have died of coronary heart disease before developing dementia. Second, given that the ABI is a noninvasive tool, it has been demonstrated that various factors may produce significant interobserver and intraobserver error in the measure. In the present study, the ABI was measured according to a protocol with trained technicians using a standardized methodology to reduce the error. These results could be limited because they were observed in a cohort consisting exclusively of men. Symptomatic PAD, defined as intermittent claudication, has been reported to be more common in men than women. However, the prevalence of PAD, defined by an ABI ≤0.90, has been shown to be higher in older women than men or not to vary by gender. No gender differences in the consequences of PAD have been reported. Third, results were not adjusted for the carotid intima-media thickness, which has been correlated to cognitive function and reported to be a definite risk factor for myocardial infarction and stroke in older people. On the other hand, one may argue that because carotid intima-media thickness is, like ABI, a marker of atherosclerosis, adjusting for it would have been more appropriate.

### Table 2. Relative Risk* (HR, 95% CI) of Total Dementia and Subtypes Associated With ABI: The HAAS, 1991 to 1999

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Total dementia</th>
<th>AD</th>
<th>VaD</th>
<th>Other Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standardized ABI (per 1-SD unit decrease)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.14 (1.01–1.27)</td>
<td>1.05 (0.90–1.23)</td>
<td>1.61 (1.22–2.17)</td>
<td>1.16 (0.85–1.59)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.10 (0.97–1.25)</td>
<td>1.04 (0.82–1.13)</td>
<td>1.47 (1.07–2.00)</td>
<td>1.22 (0.89–1.69)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.09 (0.95–1.23)</td>
<td>1.04 (0.89–1.23)</td>
<td>1.28 (0.93–1.75)</td>
<td>1.23 (0.89–1.69)</td>
</tr>
</tbody>
</table>

*HR was adjusted for education and year of birth in model 1; additionally adjusted for high blood pressure, body mass index, diabetes mellitus, cholesterol concentration, smoking status, alcohol consumption, and ApoE4 in model 2; and additionally adjusted for history of cardiovascular disease in model 3.

### Table 3. Relative Risk* (HR, 95% CI) of Total Dementia and AD Associated With ABI by ApoE4: The HAAS, 1991 to 1999

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Dementia</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Events</td>
<td>Standardized ABI per 1-SD Unit Decrease</td>
</tr>
<tr>
<td>ApoE4 carrier</td>
<td>473</td>
<td>54</td>
</tr>
<tr>
<td>ApoE4 noncarrier</td>
<td>2095</td>
<td>186</td>
</tr>
</tbody>
</table>

*HR was adjusted for education and year of birth. *P for interaction=0.65 and 0.13 for total dementia and AD, respectively.
for this variable could create a problem of collinearity. Finally, analyses were restricted to small subsets of subjects, in particular when testing for effect modification; this may have biased the results toward the null hypothesis. Moreover, results on VaD and other dementia were based on small numbers of events and should be interpreted with caution.

These findings contribute uniquely to the growing body of evidence on vascular risk factors and dementia. Previous investigations\(^4\)–\(^11\) of the relationship between PAD and cognitive function were based on cross-sectional designs, volunteers, or severe cases of PAD. Cognitive function was assessed with the Mini-Mental State Examination\(^7\)–\(^13\) and/or neuropsychological tests.\(^4\)–\(^7\),\(^10\),\(^12\),\(^39\) In relatively young cohorts, the prevalence\(^10\) and occurrence\(^39\) of intermittent claudication were associated with poor cognitive function. A cross-sectional association of PAD with cognition also was observed in population-based studies in older persons, including the Rotterdam Study\(^8\),\(^13\) and the Cardiovascular Health Study.\(^12\) Here, we show that PAD, as measured by ABI, is associated with an increased risk for dementia.

Reduced ABI was significantly associated with an increased risk of VaD. Potential mechanisms that might underlie this association include the progressive occlusion of arteries and vascular disease that leads to occlusion of the cerebral arteries, cerebral tissue loss, and cognitive decline. There also is evidence of a strong positive association between PAD and inflammation, which has been inferred in the pathogenesis of atherosclerosis\(^46\) and linked to the onset of dementia and AD.\(^41\) Although we expected an association of ABI with AD, it was weak in this analysis. It is possible that atherosclerosis per se is not as an essential vascular risk factor for cerebral disease found in AD compared with VaD cases. When results were further adjusted for stroke or coronary heart disease (model 3), these events had a major impact on VaD but almost none on AD. However, subjects with ApoE\(^4\) and a low ABI were at a higher risk of AD compared with those with a higher ABI. Similar findings on the modification effect of ApoE\(^4\) on the relationship of ABI to cognitive function have been reported in 2 other studies.\(^12\),\(^13\)

Because there still is no cure for dementia, modifiable risk factors must be identified to delay its onset or progression. The ABI is an invaluable tool, showing high validity for the prediction of coronary heart disease and stroke. The present study found that a low ABI value was associated with the risk of VaD and total dementia. Preventive strategies during midlife, including reducing smoking, controlling diabetes mellitus, and normalizing blood pressure, could help to reduce the risk of VaD.

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### Disclosures

None.

### References


**CLINICAL PERSPECTIVE**

Long-term epidemiological population-based studies provide unique opportunities to investigate hypotheses assessing risk factors, especially in diseases with long latency periods. The Honolulu Heart Program was initiated in 1965 as a prospective study of biological and behavioral risk factors for cardiovascular disease among 8006 Japanese American men living in Oahu, Hawaii. Since 1991, as a part of the Honolulu-Asia Aging Study (HAAS), the men (n = 3734) have been followed up for diseases of old age, including dementia. The ankle-to-brachial index (ABI) is a reliable measure, frequently obtained in vascular clinics, to determine the presence of peripheral arterial disease. In this prospective analysis that included 2588 nondemented subjects at HAAS baseline examination, a low ABI was significantly associated with an increased risk of dementia, including vascular dementia, which may be expected, and Alzheimer’s disease, which typically has not been considered a part of a vascular disease processes. In particular, persons with a low ABI who carried an apolipoprotein E ε4 allele, a marker of genetic susceptibility for Alzheimer’s disease, were at significantly higher risk for Alzheimer’s disease. These findings suggest that atherosclerosis may play a role in the initiation or progression of the pathology resulting in dementia, of which vascular dementia and Alzheimer’s disease are the most common. The ABI is a simple, useful, and relatively inexpensive test that can be performed in any physician’s office or vascular laboratory. Various preventive strategies could be recommended to patients with a critically low ABI value to delay the development of not only peripheral arterial disease but possibly dementia as well.
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