Association of Incident Alzheimer Disease and Blood Pressure Measured From 13 Years Before to 2 Years After Diagnosis in a Large Community Study

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Background: It is uncertain whether high blood pressure increases the risk of developing Alzheimer disease (AD).

Objective: To examine the association between incident AD and blood pressure measured up to 13 years before diagnosis.

Design: Longitudinal cohort study conducted from 1982 to 1988, with blood pressure measured every 3 years in home interviews, and in 1973 for a portion (60%) of the sample.

Setting: Community of East Boston, Mass.

Participants: Six hundred thirty-four subjects 65 years or older and without AD were selected as a stratified random sample of participants of the East Boston Established Populations for Epidemiologic Studies of the Elderly.

Main Outcome Measure: Alzheimer disease was diagnosed by a neurologist using a structured clinical evaluation.

Results: High blood pressure was not associated with an increased risk of AD in logistic regression models adjusted for age, sex, and level of education. There was no association with systolic pressure measured 13 years before diagnosis (odds ratio = 1.03/10 mm Hg; 95% confidence interval, 0.80-1.32) and an inverse association with systolic pressure measured 4 years before diagnosis (odds ratio = 0.82/10 mm Hg; 95% confidence interval, 0.72-0.95). Associations for diastolic pressure were in the same direction as those for systolic pressure except with wider confidence intervals. The odds ratios were not materially different with further adjustment for cardiovascular risk factors and diseases.

Conclusion: In this large community study, high blood pressure was not associated with an increased risk of AD.

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PARTICIPANTS AND METHODS

STUDY POPULATION

The study of risk factors for AD was conducted in a sample of participants from the East Boston Established Populations for Epidemiologic Studies of the Elderly (EPESE). Between 1982 and 1983, as part of the EPESE study, all persons 65 years and older residing in East Boston, Mass, were contacted for a home interview. A total of 3809 (85%) age-eligible residents participated, and all survivors were recontacted for home follow-up interviews approximately 3 and 6 years later.

At baseline, 2313 persons were determined to be free of AD either by direct clinical examination (n=177) or by good memory performance at the initial interview (n=2136). In a clinically evaluated sample of the population, 97% of the good memory performers were found to be unaffected with AD.

From 1985 to 1986, participants were reinterviewed in their homes, and a random sample of 642 persons from the disease-free cohort (stratified by age, sex, and change in cognitive performance) was clinically evaluated for incident AD (Figure 1).

BLOOD PRESSURE MEASUREMENT

Blood pressure was measured at 4 different time points: a mean of 13.6 years before evaluation for incident AD, 4.5 years before evaluation, 1.5 years before evaluation, and 2 years after diagnosis. The latter 3 measurement periods were part of the EPESE population interviews. The first set of measurements were obtained in 1973 for 378 persons as part of a community blood pressure screening for the Hypertension Detection and Follow-Up Program (HDFP). Among sample participants younger than 80 years, 72% underwent HDFP blood pressure screening (participants 80 years and older were not eligible for the HDFP). Measurements were available for 634 sample participants at baseline, 612 participants at the 3-year follow-up, and 426 participants (67%) at the 6-year follow-up (Table 1).

All blood pressure measurements were obtained in participants’ homes according to the HDFP protocol. On each occasion, blood pressure was measured 3 consecutive times with 30 seconds between measurements using mercury sphygmomanometers on seated subjects with the arm resting at heart level. For analyses of each time point, the average of the 3 blood pressure measurements was used. A more detailed description of the blood pressure procedures has been published previously. All interviewers passed a written test, a videotaped test of blood pressure readings, and live practice tests with a supervisor using a split stethoscope. The overall mean of blood pressure readings by trainees had to be within ±1.96 mm Hg of the standard mean on the videotaped test. Data from the HDFP on blinded duplicate blood pressure readings demonstrated good reproducibility of trainee readings.

DIAGNOSIS OF AD

The clinical evaluations included a neurological examination, neuropsychological performance testing, a medical history, and a brief psychiatric evaluation. The definition of probable AD was based on criteria consistent with the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association. We modified the definition to include

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Table 1. Blood Pressure Measurements Among 642 Persons Evaluated for Incident AD

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>HDFP</td>
<td>EPESE</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Blood pressure measurement</td>
<td>378</td>
<td>634</td>
<td>612</td>
<td>426</td>
</tr>
<tr>
<td>AD</td>
<td>41</td>
<td>99</td>
<td>94</td>
<td>39</td>
</tr>
<tr>
<td>Deceased</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>No blood pressure measurement</td>
<td>264‡</td>
<td>8</td>
<td>12</td>
<td>111‡</td>
</tr>
</tbody>
</table>

*Data are presented as number of subjects. AD indicates Alzheimer disease; HDFP, Hypertension Detection and Follow-up Program; EPESE, Established Populations for Epidemiologic Studies of the Elderly.

†Not eligible (primarily because of age) for HDFP screening.

‡Most missing blood pressure measurements were due to telephone interviews.

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BLOOD PRESSURE MEASURED

4 YEARS BEFORE DIAGNOSIS

Systolic and diastolic blood pressures measured 4 years previously for 634 persons were inversely associated with incident AD in logistic models adjusted for age, sex, educational level, and interval to diagnosis. The

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persons who met the criteria for probable AD and who had a coexisting dementing condition to prevent the possibility of a protective association due to the classification system (for example, if high blood pressure levels were associated with an increased risk of vascular dementia). A more complete description of sampling for incident AD and of the clinical evaluation was published previously.31,37

COVARIATES

All covariates except for clinical stroke and antihypertensive medication use at HDFP were based on data from the EPESE baseline interview. History of hypertension was self-reported. Heart disease was defined as a self-reported history of myocardial infarction, the use of digitalis or loop diuretics, or evidence of angina pectoris based on participant responses to the London School of Hygiene Cardiovascular Questionnaire.38 Diabetes was defined as the use of antidiabetic medication or a participant report of clinically diagnosed "diabetes, sugar in the urine, or high blood sugar." Body mass index was computed as weight in kilograms divided by height in meters squared using self-reported height and weight. The use of digitalis, antihypertensives, and diabetic medications was determined by interviewer inspection of all medications taken within the previous 2 weeks. Clinical stroke was based on medical history and examination by a neurologist at the clinical evaluation. The presence of the apolipoprotein E4 allele (APOE*E4) was based on the genotyping of blood obtained at the clinical evaluation. DNA was extracted from blood specimens stored at −70°C for periods ranging from 7 to 12 years, and genotyping was carried out according to the method described by Hixson and Vernier.39 Indicator variables at the HDFP for current and past use of antihypertensive medications were based on participant self-report.

Table 2. Baseline Characteristics by Level of Baseline Blood Pressure of 634 Participants Who Were Clinically Evaluated for Incident Alzheimer Disease, East Boston, Mass, 1982-1985

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Systolic Blood Pressure, mm Hg</th>
<th>Diastolic Blood Pressure, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;130</td>
<td>130-139</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>147</td>
<td>145</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>70.8</td>
<td>71.5</td>
</tr>
<tr>
<td>Women, %</td>
<td>64.8</td>
<td>65.7</td>
</tr>
<tr>
<td>Mean level of education, y</td>
<td>8.5</td>
<td>9.0</td>
</tr>
<tr>
<td>APOE*E4, %</td>
<td>17.4</td>
<td>18.9</td>
</tr>
<tr>
<td>Hypertension history, %</td>
<td>27.9</td>
<td>27.0</td>
</tr>
<tr>
<td>Clinical stroke, %</td>
<td>1.6</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart disease, %</td>
<td>20.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Antihypertensive use, %</td>
<td>33.7</td>
<td>31.0</td>
</tr>
<tr>
<td>Use of diuretics, %</td>
<td>25.1</td>
<td>23.7</td>
</tr>
<tr>
<td>Thiazides</td>
<td>11.5</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*Percentages are weighted to reflect the distribution of the population.
†APOE* E4 indicates apolipoprotein E4 allele.

association with systolic pressure was linear and statistically significant (odds ratio [OR] = 0.82/10 mm Hg increase; 95% confidence interval [CI], 0.72-0.95) (Table 3). In categorical analyses, compared with the reference level of 130 to 139 mm Hg, the risk of incident AD was lower in the group with a systolic pressure reading of 160 mm Hg or greater (OR = 0.29; 95% CI, 0.10-0.86) and nearly equivalent for subjects with a systolic pressure reading less than 130 mm Hg (OR = 0.87; 95% CI, 0.37-2.06). The association with diastolic pres-
Pulse pressure measured 4 years prior to the clinical evaluation had a marginally significant inverse association with the risk of AD (OR = 0.74/10 mm Hg increase; 95% CI, 0.53-1.01). The risk of AD was not significantly different from the reference level of 80 to 89 mm Hg for diastolic pressure readings of 90 mm Hg or greater (OR = 0.74; 95% CI, 0.23-2.40) or for those less than 70 mm Hg (OR = 1.81; 95% CI, 0.77-4.29).

The ORs did not change materially with further adjustment for other covariates including APOE*E4, body mass index, or history of hypertension, heart disease, clinical stroke, or diabetes (Table 3); there was also no evidence of effect modification by these covariates. A self-reported history of hypertension was not associated with incident AD in the basic-adjusted model (OR = 1.13; 95% CI, 0.60-2.13).

**Antihypertensive Medication Use**

We considered that the inverse association between blood pressure and AD could be due to treatment with antihypertensive medications. In the basic-adjusted model, incident AD was not associated with the use of these medications or with any specific type of antihypertensive medication (Table 4). There was no evidence of interactive effects of these medications with blood pressure on the risk of AD.

**Pulse Pressure**

Pulse pressure measured 4 years prior to the clinical evaluation had a marginally significant inverse association with the risk of AD (OR = 0.85/10 mm Hg increase in pulse pressure; 95% CI, 0.70-1.02). Compared with the reference pulse pressure of 60 to 69 mm Hg, the ORs for incident AD were as follows: 0.97 for subjects with a pulse pressure reading less than 50 mm Hg, 2.1 for those with a reading between 50 and 59 mm Hg, 0.77 for a level between 70 and 79 mm Hg, and 0.66 for 80 mm Hg or higher.

**Blood Pressure Measured 13 Years Before Diagnosis**

Blood pressure measured 13 years before diagnosis had no association with incident AD. The 378 subjects in this analysis were as young as 54 years at the time of blood pressure measurement and between the ages of 69 and 80 years at the clinical evaluation for incident AD (41 were diagnosed with incident AD). In basic-adjusted models, the ORs for AD were 1.03/10 mm Hg increase in systolic pressure (95% CI, 0.80-1.32) and 1.16/10 mm Hg increase in diastolic pressure (95% CI, 0.75-1.81) (Table 5). There was no increased risk of AD for persons with blood pressures in the hypertensive range. Compared with lower levels, the OR for subjects with a systolic pressure reading of 160 mm Hg or greater was 1.13 (95% CI, 0.24-5.37) and for those with a diastolic pressure reading of 90 mm Hg or higher, 1.56 (95% CI, 0.46-5.32) (Table 5). Further adjustment for current use of antihypertensive medications or any other covariates from the baseline interview did not materially change the results.

**Hypertensive Levels at Both Measurement Points**

Of the 378 persons who had their blood pressure measured at both 13 and 4 years before the clinical evaluation for incident AD, 44 had blood pressure levels consistently in the hypertensive range of 160 mm Hg or greater for systolic pressure or 90 mm Hg or higher for diastolic pressure. Of the remainder, 98 subjects had consistently normal blood pressure readings (<140/85 mm Hg), and 236 persons had mixed (≥160 mm Hg or ≥90 mm Hg at 1 time point only) or high-normal (systolic, 140-159 mm Hg; diastolic, 85-89 mm Hg) blood pressure readings at the 2 time points. In basic-adjusted models, relative to the normotensive subjects (<140/85 mm Hg), the risk of incident AD was not significantly differ-
In our study, there was little association between blood pressure levels during 15 years of observation and risk of AD. There was no evidence of increased risk of AD among persons with high blood pressure 13 years before disease onset, an inverse association for blood pressure measured 4 years before diagnosis, and no effect of AD on blood pressure measured 2 years after the diagnosis. The inverse association between blood pressure measured 4 years previously and risk of AD is puzzling. The pathogenic mechanism for any protective effect is unclear, and we had no prior hypothesis of an inverse association. Together with the lack of association between disease risk and blood pressure measurements at other times, these data suggest that this inverse association at 1 time point may be due to chance.

The estimated ORs were adjusted for important confounders that were previously associated with incident AD in the East Boston population, including age, level of education, and APOE*E4. Longitudinal follow-up of a community population, as was done in the East Boston study, offers several advantages in the evaluation of high blood pressure as a risk factor for AD. Cases of AD are identified by structured, uniform clinical evaluation of a random sample of the population at risk, reducing persons with blood pressure measurements at all 4 time points.

Figure 2. Mean blood pressure levels, adjusted for age and sex, from 13 years before clinical evaluation to 2 years after for persons affected (solid line) and unaffected (dotted line) with incident Alzheimer disease.

Table 4. ORs and 95% CIs for 4-Year Risk of Incident AD by Antihypertensive Medication Use and Level of Systolic Pressure Based on Logistic Regression Models Adjusted for Age, Sex, and Level of Education, East Boston Study (East Boston, Mass), 1982-1988

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any antihypertensive medication</td>
<td>0.66 (0.68-2.61)</td>
</tr>
<tr>
<td>Systolic pressure (per 10 mm Hg)</td>
<td>0.82 (0.71-0.94)</td>
</tr>
<tr>
<td>2. Thiazide diuretic (n = 168)</td>
<td>1.33 (0.68-2.61)</td>
</tr>
<tr>
<td>Systolic pressure (per 10 mm Hg)</td>
<td>0.83 (0.72-0.96)</td>
</tr>
<tr>
<td>3. Potassium-sparing diuretic (n = 50)</td>
<td>0.63 (0.26-1.54)</td>
</tr>
<tr>
<td>Systolic pressure (per 10 mm Hg)</td>
<td>0.82 (0.71-0.95)</td>
</tr>
<tr>
<td>4. β-Blockers (n = 65)</td>
<td>0.91 (0.26-3.17)</td>
</tr>
<tr>
<td>Systolic pressure (per 10 mm Hg)</td>
<td>0.83 (0.72-0.95)</td>
</tr>
<tr>
<td>5. Loop diuretics (n = 29)</td>
<td>1.06 (0.37-3.06)</td>
</tr>
<tr>
<td>Systolic pressure (per 10 mm Hg)</td>
<td>0.83 (0.72-0.95)</td>
</tr>
</tbody>
</table>

*Models are also adjusted for interval to disease diagnosis and stratified sampling. OR indicates odds ratio; CI, confidence interval; and AD, Alzheimer disease.

Table 5. ORs and 95% CIs of Incident AD by Level of Systolic and Diastolic Blood Pressure Measured 13 Years Earlier Among 378 Participants in the East Boston Study (East Boston, Mass), 1973-1988

<table>
<thead>
<tr>
<th>Systolic Pressure 13 Years Before Diagnosis</th>
<th>Diastolic Pressure 13 Years Before Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous (per 10-mm Hg increase)</td>
<td>Continuous (per 10-mm Hg increase)</td>
</tr>
<tr>
<td>No.</td>
<td>AD, %‡</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Continuous (per 10-mm Hg increase)</td>
<td>Continuous (per 10-mm Hg increase)</td>
</tr>
<tr>
<td>&lt;160 mm Hg</td>
<td>324</td>
</tr>
<tr>
<td>160 mm Hg</td>
<td>54</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; and AD, Alzheimer disease.
†Based on logistic regression models adjusted for age (years), sex, education (years), interval to disease diagnosis, and stratified sampling.
‡Weighted percentages of sample with incident AD over 4.5 years based on stratified random sampling.
the potential for biased results. Blood pressure measurement 4 to 13 years before diagnosis more clearly establishes blood pressure as a cause rather than an effect of the disease, and using the mean of multiple blood pressure measurements at each time point increases the likelihood of capturing the true underlying blood pressure. The large number of AD cases allowed for a more accurate estimation of the 4-year risk of disease. One limitation of the study was the small number of participants with very high blood pressure. Another limitation was the unavailability of blood pressure measurements for about a third of participants, both 13 years before diagnosis and 2 years after diagnosis. The fewer cases of AD at these time points resulted in wide 95% CIs that included small to moderate ORs reported in a previous study. Analysis of the data suggests that the estimated ORs for the earlier blood pressure levels are not likely to be biased. Adjusting for age, sex, and educational level, the risk of AD was not significantly different for persons who did and did not have HDFP blood pressure measurements, and the associations between AD and baseline blood pressures were the same for the 2 groups. Participants without blood pressure measurements at the sixth follow-up interview (of whom 50% had died) were more likely to have been diagnosed with AD than those analyzed, and had higher mean levels of systolic pressure at baseline (148 vs 144 mm Hg, respectively). The unavailability of blood pressure measurements for some of the survivors may have biased the observed associations with subsequent blood pressures.

Few prospective studies have examined whether high blood pressure increases the risk of developing AD. One longitudinal study showed higher initial blood pressure levels among 10 persons who developed AD compared with those who remained unaffected during 15 years of follow-up. Another found a greater risk of dementia and AD with a high diastolic pressure in middle age, but only among men who had never been treated. Although one study found no association between high blood pressure and a 7-year incidence of AD, it did observe a statistically significant increased risk of vascular dementia as the level of systolic pressure increased (OR = 1.98/1-SD increase in systolic mm Hg).

There are many studies on the association between high blood pressure and the risk of dementia or cognitive decline, and 2 clinical trials on blood pressure treatment and cognitive change. With few exceptions, the reported associations between high blood pressure and dementia have been restricted to levels greater than either 160 mm Hg for systolic pressure or 95 mm Hg for diastolic pressure. Participants in both clinical trials had blood pressures in this range, but only one trial found a reduced risk of dementia in the treated group. In our study, chronically high blood pressure (>160/90 mm Hg) during a 9-year period did not increase the risk of AD, nor was there evidence of an association with high pulse pressure. Few participants in the East Boston study had chronically high blood pressure levels, and there were few cases of vascular dementia (3 of 99 subjects with AD had evidence of vascular dementia).

The results of our study do not support the hypothesis that high blood pressure increases the risk of AD. The study could not address whether high blood pressure increases the risk of vascular dementia because there were few such cases in the East Boston population. Evidence suggests that cerebrovascular disease may alter the clinical expression of AD, and various associations observed between blood pressure and AD may be due to population differences in the prevalence of cerebrovascular disease. These relationships can be understood only by conducting longitudinal studies of large representative populations with a wide range of blood pressure levels and by using neuroimaging techniques for the diagnosis of cerebrovascular disease.

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REFERENCES


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