Hypertension and the Risk of Mild Cognitive Impairment

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Objective: To explore whether hypertension is associated with the risk of mild cognitive impairment (MCI), an intermediate stage of dementia, because there are conflicting data relating hypertension to the risk of Alzheimer disease.

Design and Setting: Prospective community-based cohort study conducted in northern Manhattan. Multivariate proportional hazards regression analyses were used, relating hypertension to incident all-cause MCI, amnestic MCI, and nonamnestic MCI in 918 persons without prevalent MCI at baseline followed up for a mean of 4.7 years.

Results: There were 334 cases of incident MCI, 160 cases of amnestic MCI, and 174 cases of nonamnestic MCI during 4337 person-years of follow-up. Hypertension was associated with an increased risk of all-cause MCI (hazard ratio, 1.46; 95% confidence interval, 1.06-1.77) and nonamnestic MCI (hazard ratio, 1.70; 95% confidence interval, 1.13-2.42; P=.009) after adjusting for age and sex. Both associations were slightly attenuated in models additionally adjusting for stroke and other vascular risk factors. There was no association between hypertension and the risk of amnestic MCI (hazard ratio, 1.10; 95% confidence interval, 0.79-1.63; P=.49). Consistent with this association, hypertension was related with the slope of change in an executive ability score, but not with memory or language score. There was no effect modification of the association between hypertension and MCI by APOEε4 genotype or use of antihypertensive medication.

Conclusions: A history of hypertension is related to a higher risk of MCI. The association seems to be stronger with the nonamnestic than the amnestic type of MCI in the elderly. These findings suggest that prevention and treatment of hypertension may have an important impact in lowering the risk of cognitive impairment.

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Mild Cognitive Impairment (MCI) has attracted increasing interest during the past years, particularly as a means of identifying the early stages of Alzheimer disease (AD) as a target for treatment and prevention. Existing prevalence and incidence data are inconsistent because of different operational criteria, sampling, and assessment procedures. Studies using the criteria of Petersen et al. for diagnosing MCI in clinical and epidemiological settings report an incidence rate of 9.9 per 1000 person-years for MCI among elderly persons without dementia and an annual conversion rate of 10% to 12% to AD in subjects with MCI, particularly amnestic MCI (AMCI), in contrast to a conversion rate of 1% to 2% in the healthy elderly population.

There are inconclusive data relating hypertension, a modifiable vascular risk factor, to cognitive impairment and dementia. While most longitudinal studies reported an increased blood pressure before the onset of AD or vascular dementia, most cross-sectional studies or studies with a shorter follow-up observed associations between low blood pressure and dementia or no association between hypertension and cognitive impairment. We previously reported relationships between hypertension and vascular dementia but not AD. There are also conflicting data on the effect of antihypertensive treatment on cognition.

The mechanisms underlying the associations between blood pressure and cognitive impairment or dementia remain unclear. High blood pressure levels may lead to white matter hyperintensities on magnetic resonance imaging or lacunar brain infarcts, which in turn may lead to cognitive impairment or dementia. More direct links between blood pressure and AD are suggested by autopsy studies reporting an increased frequency of neurofibrillary tangles and brain atrophy in hypertensive persons.

Our objective in the present longitudinal study was to determine whether hypertension is associated with the risk of incident MCI.
METHODS

SUBJECTS AND SETTING

Participants were enrolled in a longitudinal cohort study by a random sampling of Medicare recipients 65 years or older residing in northern Manhattan (Washington Heights, Hamilton Heights, and Inwood). The sampling procedures have been described elsewhere. Each participant underwent an interview of general health and function at study enrollment, followed by a standard assessment, including medical history, physical and neurological examination, and neuropsychological battery. Baseline data were collected from 1992 through 1994. Follow-up data were collected during evaluations at sequential intervals of approximately 18 months, performed from 1994 to 1996, 1996 to 1997, and 1997 to 1999. In this elderly population, some participants did not complete all evaluations at intervals because of refusal, relocation, or death. About half of participants were evaluated at the third follow-up visit. This study was approved by the institutional review board of Columbia-Presbyterian Medical Center.

The sample for this study comprised those participants who were without MCI or dementia at baseline, who had at least 1 follow-up interval, and who had complete information to ascertain MCI following the criteria of Petersen et al. Of the 1772 participants in whom a full neuropsychological examination was attempted, 339 (19.1%) were excluded because of prevalent dementia, 304 (17.2%) were excluded because of prevalent MCI, and 211 (11.9%) were excluded because of unavailability for follow-up. Thus, the final analytic sample included 918 individuals.

Compared with the original 1772 participants, the final sample without prevalent MCI and dementia and with prospective data was younger (mean [SD] age, 76.3 [6.1] vs 77.3 [5.0] years; P < .001) and had a similar distribution of women (69.4% for both) and African Americans (33.6% vs 32.6%), fewer Hispanics (43.9% vs 47.0%; P < .001), and more non-Hispanic whites (22.6% vs 20.4%; P = .008).

CLINICAL ASSESSMENTS

Data were available from medical, neurological, and neuropsychological evaluations. All participants underwent a standardized neuropsychological test battery that examined multiple domains in either English or Spanish. Orientation was evaluated using parts of the modified Mini-Mental State Examination. Language was assessed using the Boston Naming Test, the Controlled Word Association Test, category naming, and the complex ideational material and phrase repetition subtests from the Boston Diagnostic Aphasia Evaluation. Abstract reasoning was evaluated using the Wechsler Adult Intelligence Scale–Revised similarities subtest and the nonverbal identities and oddities subtest of the Mattis Dementia Rating Scale. Visuospatial ability was examined using the Rosen Drawing Test and a matching version of the Benton Visual Retention Test. Memory was evaluated using the multiple choice version of the Benton Visual Retention Test and the 7 subtests of the Selective Reminding Test, total recall, long-term recall, long-term storage, continuous long-term storage, words recalled on last trial, delayed recall, and delayed recognition. Memory complaints were assessed using 11 items from the Disability and Functional Limitations Scale and the Blessed Functional Activities Scale. In addition, participants were asked if they had difficulties in general and in specific areas, such as names of persons or things. Participants were considered to have memory complaints if they indicated problems on 1 or more of these items. This neuropsychological test battery has established norms for the same community.

DIAGNOSIS OF DEMENTIA

Diagnosis of dementia and assignment of specific cause were done by consensus of neurologists, psychiatrists, and neuropsychologists based on baseline and follow-up information. The diagnosis of dementia was based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria and required evidence of cognitive deficits on the neuropsychological test battery and evidence of impairment in social or occupational function (Clinical Dementia Rating of ≥1). Diagnosis of AD was based on the National Institute of Neurological and Communication Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria.

DEFINITION OF MCI

The MCI criteria were retrospectively applied among individuals without dementia after the consensus conference. Persons considered for MCI were required to have the following: (1) a memory complaint, assessed as previously described; (2) objective impairment in at least 1 cognitive domain based on the average of the scores on the neuropsychological measures within that domain and a 1.5-SD cutoff using normative corrections for age, years of education, ethnicity, and sex; (3) essentially preserved activities of daily living (previously defined); and (4) no diagnosis of dementia at the consensus conference.

To cast the widest net to determine the prevalence of MCI and to determine which individuals were more likely to progress to dementia, the original criteria of Petersen et al., which focus on memory impairment, were expanded to include mutually exclusive subtypes based on cognitive features. The first subtype, AMCI without involvement of other cognitive domains, corresponds most closely to the original definition used by Petersen and colleagues. Memory impairment was defined as a score of less than 1.5 SDs below the demographically corrected mean on an average composite measure comprising the following learning and memory measures: (1) total recall from the Selective Reminding Test, (2) delayed free recall from the Selective Reminding Test, and (3) recognition from the Benton Visual Retention Test. Performance on composite scores from all other cognitive domains (executive, language, and visuospatial) was required to be within normal limits (score must be ≥1.5 SDs below the demographically corrected mean). Other MCI subtypes were classified that allowed for impairment in a single nonmemory domain if performance on composite scores from all other cognitive domains was within normal limits. Executive function MCI was assigned if impairment was demonstrated on an average composite measure comprising the following measures: (1) letter fluency, (2) category fluency, and (3) the Wechsler Adult Intelligence Scale–Revised similarities subtest. Language MCI was defined as isolated impairment on an average composite measure comprising (1) the Boston Naming Test, (2) the Boston Diagnostic Aphasia Examination repetition test subtest, and (3) the Boston Diagnostic Aphasia Examination comprehension subtest. Visuospatial MCI was assigned if impairment was demonstrated on an average composite score comprising (1) the Rosen Drawing Test and (2) the Benton Visual Retention Test matching subtest. Finally, we allowed for impairment in multiple cognitive domains in the absence of dementia. Multiple-cognitive-domains-with-memory-impairment MCI (MCI-MCDM) was diagnosed if there was objective impairment on the memory domain composite score and if there was impairment on at least 1 other cognitive domain. Multiple-cognitive-domains-without-memory-impairment MCI was assigned if there was impairment in 2 or more of the 3 nonmemory domains and if the memory domain composite score was within normal limits. Again, classification into the 6 subtypes was mutually exclusive. We used 3 out-
comes for these analyses: (1) all-cause MCI; (2) AMCI (including AMCI without involvement of other cognitive domains and MCI-MCDM); and (3) nonamnestic MCI (NAMCI). The rationale for this classification is that AMCI without involvement of other cognitive domains and MCI-MCDM equally predict the development of AD, and MCI-MCDM is thought to be a more advanced form of AMCI involving other cognitive domains.

COGNITIVE SCORES

A factor analysis was performed using data from the baseline assessment of the entire cohort with the 15 neuropsychological measures using a principal component analysis with varimax rotation and Kaiser normalization.36 This analysis yielded 3 factors: (1) a memory factor, for which the 7 subtests of the Selective Reminding Test were the main contributors28; (2) a visuospatial reasoning/cognitive factor (executive factor), for which visuospatial tests of reasoning were the main contributors (including the Rosen Drawing Test,29 matching and recognition components of the Benton Visual Retention Test,27 and the identities and oddities subtests of the Mattis Dementia Rating Scale30); and (3) a language factor, for which language measures were the main contributors (including the Boston Naming Test,31 Controlled Oral Word Association Test,32 and Wechsler Adult Intelligence Scale—Revised similarities subtest).33 Component scores for each subject at each visit were calculated by adding the loading weighted scores of the measures that contributed to each factor. We used the factor weights of the baseline factor scores and normalizing equations to calculate factor scores for the follow-up assessments.

DEFINITION OF HYPERTENSION AND OTHER COVARIATES

At baseline, all participants were asked whether they had a history of hypertension any time during their life. If affirmative, they were asked whether they were under treatment and the specific type of treatment. Blood pressure was also recorded at each visit using a monitor (Dinamap Pro 100; Critikon Co, Tampa, Florida). The blood pressure cuff was placed on the right arm while the individual was seated, and a recording was obtained every 3 minutes over 9 minutes. The third measurement was recorded in the database. Values higher than 140 mm Hg (systolic) and 90 mm Hg (diastolic) were used as criteria for hypertension. Stroke was defined according to the World Health Organization criteria.37 The presence of stroke was ascertained from an interview with participants and their informants. Persons with stroke were confirmed through their medical records, 85% of which included results of brain imaging. The remainder were confirmed by direct examination. Diabetes mellitus was defined as a history at any time during life. At baseline, all participants were asked whether they had a history of diabetes. If affirmative, they were asked whether they were under treatment and the specific type of medication. Heart disease was defined as a history of atrial fibrillation and other arrhythmias, myocardial infarction, congestive heart failure, or angina pectoris at any time during life. Assessment of all covariates was independent of cognitive assessment and diagnosis of cognitive impairment or dementia.

APOE GENOTYPING

APOE genotypes were determined as described by Hixson and Vernier,38 with slight modification. We classified persons as homozygous or heterozygous for the APOEε4 allele or as not having any APOEε4 allele.

STATISTICAL ANALYSES

Information on demographic characteristics and other potentially relevant factors was compared among individuals with and without a history of hypertension. χ² Tests were used for categorical data, and analysis of variance was used for continuous variables. Multivariate Cox proportional hazards models were used to estimate the association of hypertension to incident all-cause MCI, AMCI, and NAMCI. Because the period between the follow-up assessments in this cohort is relatively short, the time-to-event variable was age at onset of MCI (ie, the age at the assessment at which the research diagnosis was made). Among individuals who did not develop MCI, those who developed dementia were censored at the dementia diagnosis and those who did not develop dementia, who died, or who were lost to follow-up owing to relocation before development of MCI were censored at their last evaluation. Information on covariates was obtained at baseline. We initially adjusted for sex and age, then we adjusted for sex, age, ethnic group, years of education, and APOEε4 genotype in a second model. In a third model, we adjusted for sex, age, ethnic group, years of education, APOEε4 genotype, stroke, diabetes, heart disease, and plasma low-density lipoprotein cholesterol level. The additional covariates in the third model are theoretically in the pathways linking hypertension and MCI. Thus, any attenuation of hazard ratios observed in this model should be interpreted as evidence of mediation and not of confounding. We checked the proportional hazards assumption that the effect of variables of interest is constant in time, by creating time-dependent variables that we then added to the model. When the variable tested added significant information (eg, proportional hazard assumption not satisfied), the model was adjusted for this variable. To explore the association between blood pressure levels and risk of MCI, we finally repeated all analyses using the continuous measure of blood pressure as the independent variable. We estimated the risk of conversion to dementia among persons with MCI using logistic regression. Generalized estimating equations49 were used to examine changes in neuropsychological domains over time, represented by cognitive scores, and compare them between persons with and without hypertension. The dependent variables were the cognitive scores, and the independent variables were hypertension and time (included as a continuous variable). Generalized estimating equation analyses yield coefficient values that represent associations between factor scores and variables included in the model. A significant coefficient for hypertension indicates a difference between 2 groups at baseline or at any subsequent interval. A positive value for the coefficient indicates that the group with a specific variable performed better than the group without that variable. A significant time coefficient would indicate a significant change in a score over the total duration of follow-up. A significant interaction term would indicate a difference in the rate of change in cognitive score between persons with and without hypertension. Data analysis was performed using 2 commercially available software programs (SPSS, version 13.0 [SPSS Inc, Chicago, Illinois], and SAS statistical software, version 9.1 for Windows [SAS Institute Inc, Cary, North Carolina]).

RESULTS

There were 334 cases of incident MCI, 160 cases of AMCI, and 174 cases of NAMCI during 4337 person-years of follow-up (incidence densities, 7.7, 3.7, and 4.0 cases,
respectively, per 1000 person-years of observation). The mean ± SD age of the sample was 76.3 ± 6.1 years, and 69.4% were women; 22.6% were white, 33.6% were black, and 43.9% were Hispanic (percentages do not total 100 because of rounding). The mean (SD) years of education were 8.7 (± 6.6); 62.8% had hypertension, 21.3% had diabetes, and 30.4% had heart disease. Of the sample, 25.0% were homozygous or heterozygous for the APOEε4 allele, and use of antihypertensive medication was reported by 394 subjects (42.9%). Persons with hypertension were more often women, were less educated, and more often had a history of stroke, diabetes, or heart disease than were persons without hypertension (Table 1). Compared with persons without MCI, persons with AMCI were 6 times more likely (odds ratio, 6.0; 95% confidence interval, 4.0-8.9) to convert to dementia after adjustment for age, sex, years of education, ethnic group, and APOEε4 genotype. The odds ratio for persons with NAMCI was not statistically significant (odds ratio, 1.4; 95% confidence interval, 0.9-2.3).

**RISK OF INCIDENT MCI**

The mean (SD) age at onset of MCI was 80.7 (5.9) years. In multivariate analyses, hypertension was associated with an increased risk of all-cause MCI (P = .02) and NAMCI (P = .009) after adjusting for age and sex (Table 2). These associations remained stable in models additionally adjusting for years of education, ethnic group, and APOEε4 genotype, and were slightly attenuated in models additionally adjusting for stroke and other vascular risk factors, such as diabetes, low-density lipoprotein cholesterol level, smoking, or heart disease. The results did not change after adjusting for blood pressure measurements or use of antihypertensive medication. There was no relation between hypertension and the risk of AMCI (P = .49) in either model. There was no effect modification of the association between hypertension and MCI by APOEε4 genotype. Using blood pressure measurements instead of diagnosis of hypertension as the independent variable or restricting the analyses to persons with a longer follow-up (observation time is equal to the median follow-up of 3.9 years or longer) did not change the observed associations.

**HYPERTENSION AND CHANGE IN COGNITIVE SCORES OVER TIME**

We conducted generalized estimating equation analyses comparing slopes of cognitive score change between persons with and without hypertension (Table 3). All subjects had successive cognitive data in at least 2 intervals, 79% had at least 3 intervals, and 59% had 4 or more intervals. For the memory score, we found—after adjustment for age, sex, years of education, ethnic group, and APOEε4 genotype (model 2)—that it was not related to differences in hypertension status at baseline and declined with time. However, this decline was not different by hypertension status, indicated by the lack of significance of the interaction term. For the executive score, we found that it was not related to baseline hypertension and increased over time (indicated by a positive coefficient for time). However, this increase over time was lower for persons with hypertension, indicated by the significant negative interaction term for hypertension and time. We also found after adjustment for other vascular risk factors and stroke that the statistical significance for the interaction term was attenuated, which we interpret as evidence of mediation of vascular disease and stroke in the relation between hypertension and executive impairment. There was no relation between hypertension and changes in the language score.

**Table 1. Comparison of Characteristics Among Persons With and Without Hypertension in 918 Subjects Followed Up Prospectively**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group Without Hypertension (n = 292)</th>
<th>Group With Hypertension (n = 626)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>178 (61.0)</td>
<td>461 (73.6)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>76.9 (6.0)</td>
<td>75.6 (5.7)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>9.8 (4.5)</td>
<td>8.4 (4.5)</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>84 (28.8)</td>
<td>118 (18.5)</td>
</tr>
<tr>
<td>Black</td>
<td>101 (34.6)</td>
<td>207 (33.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>105 (36.0)</td>
<td>298 (47.6)</td>
</tr>
<tr>
<td>APOE genotype 4/− or 4/4</td>
<td>76 (26.0)</td>
<td>264 (42.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>24 (8.2)</td>
<td>114 (18.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (12.0)</td>
<td>184 (29.4)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>55 (18.8)</td>
<td>256 (40.9)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>33 (11.3)</td>
<td>62 (9.9)</td>
</tr>
<tr>
<td>LDL cholesterol level, mean (SD), mg/dL</td>
<td>121.1 (36.3)</td>
<td>120.1 (36.9)</td>
</tr>
<tr>
<td>MCI</td>
<td>76 (26.0)</td>
<td>251 (40.1)</td>
</tr>
</tbody>
</table>

Abbreviations: LDL, low-density lipoprotein; MCI, mild cognitive impairment.  
SI conversion factor: To convert LDL cholesterol to millimoles per liter, multiply by 0.0259.  
*a* Data are given as number (percentage) of each group unless otherwise indicated. Some percentages are based on an incomplete sample because of missing data.  
b Significant (P < .05) vs the group without hypertension.  
c Classified by self-report using the format of the 1991 US census.

In this longitudinal analysis of 918 persons, hypertension was associated with an increased risk of all-cause MCI that was mostly driven by an association with an increased risk of NAMCI after adjusting for age and sex. There was no relation between hypertension history and the risk of incident AMCI and there was no effect modification of the association between hypertension and MCI by APOEε4 genotype. Using blood pressure measurements instead of diagnosis of hypertension as the independent variable or restricting the analyses to persons with a longer follow-up (observation time is equal to the median follow-up of 3.9 years or longer) did not change the observed associations.

The mechanisms by which blood pressure affects the risk of cognitive impairment or dementia remain un-
Hypertension may cause cognitive impairment through cerebrovascular disease. Hypertension is a risk factor for subcortical white matter lesions found commonly in AD. Hypertension may also contribute to a blood-brain barrier dysfunction, which has been suggested to be involved in the cause of AD. Other possible explanations for the association are shared risk factors, such as the formation of free oxygen radicals.

Several studies have previously examined the relation of hypertension with MCI. In the Cardiovascular Health Study, persons with MCI had a higher prevalence of hypertension, but no distinction was made between persons with AMCI and NAMCI. White matter disease on magnetic resonance imaging, which could be considered an intermediary between hypertension and MCI, was also more prevalent in persons with MCI in this study. In the Italian Longitudinal Study of Aging, hypertension was related to a 44% higher risk of MCI that was close to statistical significance, but no distinction was made between AMCI and NAMCI. A study in Finland also found that hypertension was related to a higher risk of MCI, without distinction of MCI subtype. The main contribution of our study is the examination of this association in a multiethnic cohort in New York City, and the distinction between MCI subtypes.

In our study, hypertension was associated with a higher risk of all-cause MCI and NAMCI. Mild cognitive impairment has been described as an intermediate stage between normal cognition and dementia. There is evidence that NAMCI is related in particular to cerebrovascular disease and vascular cognitive impairment. Because hypertension is associated with a higher risk of cerebrovascular disease and vascular dementia, it seems reasonable that it is related to the risk of NAMCI in our study. Also, the relation of hypertension to NAMCI remained stable after adjusting for years of education, ethnic group, and APOE genotype.

### Table 2. Data Relating Hypertension and the Risk of Incident MCI

<table>
<thead>
<tr>
<th>MCI Subtype</th>
<th>Incident MCI, No. (%)</th>
<th>Modela</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>All-cause MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group without hypertension</td>
<td>76 (26.0)</td>
<td>1</td>
<td>1.40 (1.06-1.77)c</td>
<td>1.30 (1.02-1.73)c</td>
<td>1.20 (0.81-1.69)</td>
</tr>
<tr>
<td>Group with hypertension</td>
<td>258 (41.2)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group without hypertension</td>
<td>42 (14.4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group with hypertension</td>
<td>118 (18.8)</td>
<td>1.10 (0.79-1.63)</td>
<td>1.10 (0.80-1.67)</td>
<td>0.90 (0.54-1.47)</td>
<td></td>
</tr>
<tr>
<td>Nonamnestic MCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group without hypertension</td>
<td>34 (11.6)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Group with hypertension</td>
<td>140 (22.4)</td>
<td>1.70 (1.13-2.42)c</td>
<td>1.60 (1.06-2.29)c</td>
<td>1.60 (0.93-2.85)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MCI, mild cognitive impairment.
a Cox proportional hazards model was used, with age at onset as the time variable, as described in the “Statistical Analyses” subsection of the “Methods” section.

### Table 3. Data From General Estimating Equations Relating Hypertension to Change in Cognitive Scores With Time

<table>
<thead>
<tr>
<th>Variablea</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient ± SD</td>
<td>P Value</td>
<td>Coefficient ± SD</td>
</tr>
<tr>
<td>Memory Score</td>
<td>Hypertension</td>
<td>-9.5±2.9</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-4.2±0.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Hypertension × time interaction</td>
<td>0.7±1.1</td>
<td>.46</td>
</tr>
<tr>
<td>Executive Score</td>
<td>Hypertension</td>
<td>-0.9±1.7</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>3.9±0.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Hypertension × time interaction</td>
<td>-1.0±0.5</td>
<td>.03</td>
</tr>
<tr>
<td>Language Score</td>
<td>Hypertension</td>
<td>-0.3±0.3</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-0.2±0.04</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Hypertension × time interaction</td>
<td>0.05±0.04</td>
<td>.28</td>
</tr>
</tbody>
</table>

a A statistically significant result for the hypertension term indicates a difference in score at baseline between persons with and without hypertension. A statistically significant coefficient for time indicates a significant change in the cognitive score with time. A significant interaction term for hypertension × time indicates that the slopes of change in cognitive score between persons with and without hypertension were significant.
type, and was attenuated after adjustment for stroke and vascular risk factors, indirectly suggesting that cerebrovascular disease may be mediating the relation between hypertension and NAMCI. These results suggest that hypertension is mainly related to an increased risk of nonamnestic forms of cognitive impairment,⁴⁹ such as frontal-executive cognitive impairment.

There was no relation between hypertension and the risk of incident AMCI. Episodic memory deficits are a strong predictor of conversion to dementia, in particular AD.⁵⁰ Consequently, the term amnestic MCI represents a subgroup with a high probability of conversion to dementia caused by AD.⁵¹ The association between hypertension and AD is unclear. A 15-year longitudinal study⁵² reported increased blood pressure 10 to 15 years before the onset of AD and vascular dementia. Others found it to be lower in older individuals with AD⁵³ or did not find an association between hypertension and cognitive impairment.⁵⁴

In the interpretation of these findings, it is of major importance to keep in mind that MCI is likely to be a clinically and pathologically heterogeneous syndrome, and that definitions of MCI and MCI subtypes rather represent diagnostic constructs than established diagnostic entities. The frequency of dementia in a group of individuals with cognitive impairment is the result of the definition of the disorder and the underlying pathological features. Thus, it is possible that a different definition of MCI or MCI subtypes would have led to different results.

There are alternative explanations for our observations. One is that hypertension is part of a preclinical syndrome of NAMCI or that persons with preclinical NAMCI reported hypertension while subjects who would not develop MCI did not; we tried to eliminate these possibilities by excluding persons with baseline MCI from the analyses and by repeating the analyses restricted to persons with a longer follow-up. Another potential explanation for our findings is chance because of multiple comparisons. However, the results are in line with the a priori hypothesis of an association of hypertension with NAMCI rather than AMCI when using the present MCI definition, and are mechanistically plausible. These facts make chance because of multiple comparisons an unlikely explanation for our findings.⁵⁵ Another potential explanation is confounding. For example, if less education is related to hypertension, and persons with less education are more likely to be diagnosed as having MCI, then it is possible that the relation between hypertension and all-cause or NAMCI could be because of confounding by socioeconomic factors. We adjusted for years of education and ethnicity as markers of socioeconomic status to account for this possibility. However, it is possible that hypertension is related to other behaviors related to poor health that, in turn, may increase the risk of cognitive decline that we could not adjust for, and we cannot eliminate the possibility of lack of control for unknown confounders as a potential explanation for our findings.

The main limitation of our study is the lack of subclinical markers of hypertension, such as left ventricular hypertrophy by electrocardiogram or echocardiogram, and the use of self-reported history as our main measurement of hypertension. As shown in our sample, most elderly people will develop hypertension in their lifetime.⁵⁶ Therefore, elderly cohorts may be too homogeneous to show differences in outcomes related to a history of hypertension. Our measurement of hypertension did not take into account severity or duration. Thus, it is possible that our results tend to underestimate the association between hypertension and MCI, and could bias our results to the finding of no association with AMCI. It is possible that studies in younger age groups with measures of hypertension burden in midlife could find stronger associations with risk of MCI than we report, including an association with AMCI. Also, this study was conducted in an elderly multiethnic community in an urban setting with a high prevalence of risk factors for morbidity and mortality, such as diabetes and hypertension. Persons who dropped out of the study during follow-up were mainly Hispanic and, at baseline, were older, were less educated, and had a higher prevalence of vascular risk factors than those who remained in the study. This could have resulted in an underestimation of the association between hypertension and MCI compared with the original cohort. Also, hypertension is related to higher cardiovascular mortality, and it is possible that some hypertensive persons would have demonstrated cognitive decline had they not died before inclusion in this cohort. Thus, there are important biases related to the sample of this study that should be taken into account in the interpretation and generalization of these findings. We did not have information on brain magnetic resonance imaging and measures of cerebrovascular disease. Thus, our stroke variable is likely an underestimation of the prevalence of cerebrovascular disease. We expected that the other vascular risk factor variables would be surrogate markers of cerebrovascular disease risk. Our ascertainment of MCI subtypes was based on neuropsychological criteria and would not have been affected by the availability of imaging data.

The main strength of our study is that it is a prospective cohort study designed for the diagnosis of cognitive impairment and dementia with standard criteria, and with complete clinical and neuropsychological evaluation at each interval, which permitted the ascertainment of different types of incident MCI.

Our findings support the hypothesis that hypertension increases the risk of incident MCI, especially NAMCI. Preventing and treating hypertension may have an important impact in lowering the risk of cognitive impairment.

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