Hypertension and the Risk of Mild Cognitive Impairment

Christiane Reitz, MD, PhD; Ming-Xin Tang, PhD; Jennifer Manly, PhD; Richard Mayeux, MD, MSc; José A. Luchsinger, MD, MPH

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, 1.40; 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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Author Affiliations:
The Gertrude H. Sergievsky Center (Drs Reitz, Tang, Manly, Mayeux, and Luchsinger), the Taub Institute for Research on Alzheimer’s Disease and the Aging Brain (Drs Manly, Mayeux, and Luchsinger), Departments of Neurology and Psychiatry (Dr Mayeux) and Medicine (Dr Luchsinger), Columbia University College of Physicians and Surgeons, and Departments of Biostatistics (Dr Tang) and Epidemiology (Dr Mayeux), Mailman School of Public Health, Columbia University, New York, New York.

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.1 Studies using the criteria of Petersen et al2,3 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 dementia4 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.5 There are inconclusive data relating hypertension, a modifiable vascular risk factor, to cognitive impairment and dementia.6-7 While most longitudinal studies6,7 reported an increased blood pressure before the onset of AD or vascular dementia, most cross-sectional studies8,9 or studies with a shorter follow-up10 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.11,12

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.13,14 More direct links between blood pressure and AD are suggested by autopsy studies15,16 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.

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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 follow-up at all 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 [6.8] 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 similarities 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.

METHODS

SUBJECTS AND SETTING

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 principal component analysis with varimax rotation and Kaiser normalization. This analysis yielded 3 factors: (1) a memory factor, for which the 7 subtests of the Selective Reminding Test were the main contributors; (2) a visuospatial reasoning/cognitive factor (executive factor), for which visuospatial tests of reasoning were the main contributors (including the Rosen Drawing Test, and the identities and oddities subtests of the Mattis Dementia Rating Scale); and (3) a language factor, for which language measures were the main contributors (Boston Naming Test, Controlled Oral Word Association Test, and Wechsler Adult Intelligence Scale–Revised similarities subtest). 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 at 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. 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 affirmed, 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, with slight modification. We classified persons as homozygous or heterozygous for the APOE4 allele or as not having any APOE4 allele.
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 1). These associations remained stable in models additionally adjusting for years of education, ethnic group, and APOE4 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 APOE4 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 APOE4 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.

COMMENT

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 AMCI subtype by APOE4 genotype or use of antihypertensive medication. We also found that executive abilities increased over time, which we think was because of practice effects, but this increase was lower in persons with hypertension, consistent with the notion that hypertension increases the risk of impairment in executive abilities. Hypertension was not related to the change over time in memory and language abilities.

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 ε4 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>Modelb</th>
<th>Modelc</th>
<th>Modeld</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>All-cause MCI</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>
</tr>
<tr>
<td>Group with hypertension</td>
<td>258 (41.2)</td>
<td>1</td>
<td>1.20 (0.81-1.69)</td>
<td></td>
</tr>
<tr>
<td>Amnestic MCI</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>
</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>
</tr>
<tr>
<td>Nonamnestic MCI</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>
</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>
</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.

Data are given as hazards ratio (95% confidence interval). Model 1 was adjusted for sex and age; model 2, adjusted for age, sex, years of education, ethnic group, and APOE genotype; and model 3, adjusted for age, sex, ethnic group, years of education, APOE genotype, stroke, diabetes mellitus, heart disease, current smoking, and low-density lipoprotein cholesterol level. In all models, the group without hypertension was the reference group.

### 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>−9.5 ± 2.9</td>
<td>.001</td>
<td>−4.1 ± 2.9</td>
</tr>
<tr>
<td>Time</td>
<td>−4.2 ± 0.8</td>
<td>&lt;.001</td>
<td>−4.2 ± 0.7</td>
</tr>
<tr>
<td>Hypertension × time interaction</td>
<td>0.7 ± 1.1</td>
<td>.46</td>
<td>0.3 ± 0.9</td>
</tr>
<tr>
<td>Executive Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.9 ± 1.7</td>
<td>.59</td>
<td>2.5 ± 1.6</td>
</tr>
<tr>
<td>Time</td>
<td>3.9 ± 0.4</td>
<td>&lt;.001</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Hypertension × time interaction</td>
<td>−1.0 ± 0.5</td>
<td>.03</td>
<td>−1.2 ± 0.5</td>
</tr>
<tr>
<td>Language Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>−0.3 ± 0.3</td>
<td>.33</td>
<td>−0.0 ± 0.3</td>
</tr>
<tr>
<td>Time</td>
<td>−0.2 ± 0.04</td>
<td>&lt;.001</td>
<td>−0.1 ± 0.06</td>
</tr>
<tr>
<td>Hypertension × time interaction</td>
<td>0.05 ± 0.04</td>
<td>.28</td>
<td>0.1 ± 0.1</td>
</tr>
</tbody>
</table>

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.\(^{50}\) The association between hypertension and AD is unclear. A 15-year longitudinal study\(^{51}\) 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 AD\(^{8}\) or did not find an association between hypertension and cognitive impairment.\(^{52}\)

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.\(^{53}\) 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.\(^{54}\) 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 underestimated 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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**Correspondence:** José A. Luchsinger, MD, MPH, Division of General Medicine, Columbia University Medical Center, Presbyterian Hospital, 9 East-105, 630 W 168th St, New York, NY 10706 (jal94@columbia.edu).

**Author Contributions:** Study concept and design: Reitz, Mayeux, and Luchsinger. Acquisition of data: Manly, Mayeux, and Luchsinger. Analysis and interpretation of data: Reitz, Tang, Manly, Mayeux, and Luchsinger. Drafting of the manuscript: Reitz, Mayeux, and Luchsinger. Critical revision of the manuscript for important intellectual content: Tang, Manly, Mayeux, and Luchsinger. Statistical analysis: Reitz and Tang. Obtained funding: Manly, Mayeux, and Luchsinger. Administrative, technical, and material support: Manly and Mayeux. Study supervision: Manly and Luchsinger.
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