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Hypertension and the Risk of Mild Cognitive Impairment

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Abstract

Background and Objective—There are conflicting data relating hypertension to the risk of Alzheime's disease (AD). We sought to explore whether hypertension is associated with the risk of mild cognitive impairment (MCI), an intermediate stage to dementia.

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Design and Setting—Prospective community-based cohort study conducted in northern Manhattan.

Methods—Multivariate proportional hazards regression analyses, relating hypertension to incident all-cause MCI, amnestic MCI, and non-amnestic MCI in 918 persons without prevalent MCI at baseline followed for a mean of 4.7 years.

Results—There were 334 cases of incident MCI, 160 cases of amnestic MCI and 174 cases of non-amnestic MCI during 4337 person years of follow-up. Hypertension was associated with an increased risk of all-cause MCI (HR 1.4, 95% CI 1.06-1.77, p=0.02) and non-amnestic MCI (HR 1.7, 95% CI 1.13-2.42, p=0.009) after adjusting for age and gender. 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 (HR 1.1, 95% CI 0.79-1.63, p=0.49). Consistent with this association, hypertension was related with the slope of change in an executive ability score, but not with memory or language scores. There was no effect modification of the association between hypertension and MCI by APOEε4 genotype or use of antihypertensive medication.

Conclusion—A history of hypertension is related to a higher risk of MCI. The association seems to be stronger with the non-amnestic than the amnestic component of MCI. These findings suggest that prevention and treatment of hypertension may have an important impact in lowering the risk of cognitive impairment.

Keywords

blood pressure; hypertension; mild cognitive impairment

INTRODUCTION

Mild cognitive impairment (MCI) has attracted increasing interest over the past years, particularly as a means of identifying early stages of Alzheime's 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 by Petersen et al. for diagnosing MCI in clinical and epidemiological settings,[2, 3] report an incidence rate of 9.9/1,000 person-years for MCI among nondemented elderly,[4] and an annual conversion rate of 10% to 12% to AD in subjects with MCI, particularly amnestic MCI, in contrast to a conversion rate of 1% to 2% in the normal elderly population.[5]

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 (VaD),[6, 7] most cross-sectional studies[8, 9] or studies with shorter follow up[10] observed associations between low blood pressure and dementia, or no association between hypertension and cognitive impairment. We previously reported relations between hypertension and VaD 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 (WMH) on MRI 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 studies reporting an increased frequency of neurofibrillary tangles and brain atrophy in hypertensive persons.[15, 16]

Our objective in the present longitudinal study was to determine whether or not 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, Inwood). The sampling procedures have been described elsewhere.[17] Each participant underwent an in-person interview of general health and function at the time of study entry followed by a standard assessment, including medical history, physical and neurological examination as well as a neuropsychological battery.[18] 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 due to refusal, relocation or death. About one half of participants were evaluated at the third follow-up visit. This study was approved by the institutional review board of the Columbia-Presbyterian Medical Center.

The sample for this study comprised those participants who were without MCI or dementia at baseline, who had at least one follow-up interval, and who had complete information to ascertain MCI following the Petersen criteria.[2, 5] Of the 1,772 participants in whom a full neuropsychological exam was attempted, 339 (19.7%) were excluded due to prevalent dementia, 304 (17.7%) were excluded due to prevalent MCI, and 211 (12.3%) were excluded due to loss to follow-up. Thus, the final analytic sample included 918 individuals.

Compared to the original 1,772 participants, the final sample without prevalent MCI and dementia and with prospective data was younger 76.3 ± 6.1vs. 77.3 ± 6.8 years; $p < 0.0001$), and had a similar distribution of women (69.4 vs. 69.4%), African-Americans (33.6 vs. 32.6.3%), a lower proportion of Hispanics (43.9 vs. 47.0%; $p < 0.0001$), a higher proportion of Non-Hispanic Whites (22.6 vs. 20.4%; $p = 0.008$).

Clinical assessments

Data were available from medical, neurological, and neuropsychological evaluations.[18, 19] All participants underwent a standardized neuropsychological test battery that examined multiple domains in either English or Spanish.[18] Orientation was evaluated using parts of the modified Mini-Mental State Examination.[20] Language was assessed using the Boston Naming Test,[21] the Controlled Word Association Test,[22] category naming, and the Complex Ideational Material and Phrase Repetition subtests from the Boston Diagnostic Aphasia Evaluation.[23] Abstract Reasoning was evaluated using WAIS-R Similarities subtest,[24] and the non-verbal Identities and Oddities subtest of the Mattis Dementia Rating Scale.[25] Visuospatial ability was examined using the Rosen Drawing Test,[26] and a matching version of the Benton Visual Retention Test.[27] Memory was evaluated using the multiple choice version of the Benton Visual Retention Test[27] and the seven subtests of the Selective Reminding Test:[28] 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[29, 30] and the Blessed Functional Activities Scale.[31] In addition, participants were asked if they had difficulties in general, as well as specific areas such as names of persons or things. Participants were considered to have memory complaints if they indicated problems on one or more of these items. This neuropsychological test battery has established norms for the same community.[32]

Diagnosis of Dementia

Diagnosis of dementia and assignment of specific cause was made by consensus of neurologists, psychiatrists, and neuropsychologists based on baseline and follow-up

information. The diagnosis of dementia was based on DSM-IV criteria[33] and required evidence of cognitive deficits on the neuropsychological test battery as well as evidence of impairment in social or occupational function (Clinical Dementia Rating of 1 or more).[34] Diagnosis of AD was based on the NINCDS-ADRDA criteria.[35]

Definition of MCI

MCI criteria were retrospectively applied among nondemented individuals after the consensus conference. Persons considered for MCI were required to have: 1) a memory complaint, assessed as described above 2) objective impairment in at least one 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 (defined above), and 4) no diagnosis of dementia at the consensus conference.

In order 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 Petersen criteria,[2] which focus on memory impairment, were expanded to include mutually exclusive subtypes based on cognitive features. The first subtype, MCI-Amnestic (MCI-A), corresponds most closely to the original definition used by Petersen and colleagues. Memory impairment was defined as a score < 1.5 SD below demographically corrected mean on an average composite measure comprising the following learning and memory measures: 1) total recall from the SRT 2) delayed free recall from the SRT, and 3) recognition from the BVRT. Performance on composite scores from all other cognitive domains (i.e., executive, language, and visuospatial) was required to be within normal limits (score must be greater than or equal to 1.5 SD below the demographically corrected mean). Other MCI subtypes were classified that allowed for impairment in a single non-memory domain if performance on composite scores from all other cognitive domains was within normal limits. MCI-Executive Function (MCI-E) was assigned if impairment was demonstrated on an average composite measure comprising the following measures: 1) Letter Fluency; 2) Category Fluency, and 3) the WAIS-R Similarities subtest. MCI-Language (MCI-L) was defined as isolated impairment on an average composite measure comprising: 1) Boston Naming Test; 2) BDAE Repetition, and the 3) BDAE Comprehension test. MCI-Visuospatial (MCI-V) was assigned if impairment was demonstrated on an average composite score comprising: 1) Rosen Drawing and 2) BVRT matching. Finally, we allowed for impairment in multiple cognitive domains in the absence of dementia. MCI-Multiple Cognitive Domains with memory impairment (MCI-MCDM) was diagnosed if there was objective impairment on the memory domain composite score and if there was impairment on at least one other cognitive domain. MCI-Multiple Cognitive Domains without memory impairment (MCI-MCDN) was assigned if there was impairment in two or more of the three non-memory domains, and if the memory domain composite score was within normal limits. Again, classification into the six subtypes was mutually exclusive. We used three outcomes for these analyses: 1) all-cause MCI; 2) amnestic MCI, which included MCI-A and MCI-MCDM; and 3) non-amnestic MCI. The rationale for this classification is that MCI-A and MCI-MCDM equally predict the development of AD, and MCI-MCDM is thought to be a more advanced form of MCI-A 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 three factors: (1) a memory factor, where the seven subtests of the Selective Reminding Test were the main contributors;[28] (2) a visuospatial reasoning/cognitive factor (executive factor), in which visuospatial tests of reasoning were the main contributors. These included the Rosen Drawing Test,[26] matching

and recognition components of the Benton Visual Retention Test[27] and the Identities and Oddities of the Mattis Dementia Rating Scale;[25] (3) a language factor, where language measures were the main contributors: The Boston Naming Test,[21] the Controlled Oral Word Association test[22] and the WAIS-R Similarities.[24] 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 or not they had a history of hypertension any time during their life. If affirmative, they were asked whether or not they were under treatment and the specific type of treatment. Blood pressure was also recorded at each visit using the Dinamap Pro 100 (Critikon Co., Tampa, FL). 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 above 140 mm Hg (systolic) and 90 mm Hg (diastolic) were used as criteria for hypertension.

Stroke was defined according to the WHO 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 was confirmed by direct examination. Diabetes mellitus was defined as a history at any time during life. At baseline, all participants were asked whether or not they had a history of diabetes. If affirmed, they were asked whether or not they were under treatment and the specific type of medication. Heart disease was defined as a history of atrial fibrillation and other arrythmias, 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.[38] We classified persons as homozygeous or heterozygeous for the APOEε4 allele or not having any ε4 allele.

Statistical Methods

Information on demographic characteristics and other potentially relevant factors were compared among individuals with and without a history of hypertension. χ^2 tests were used for categorical data and analysis of variance for continuous variables. Multivariate Cox proportional hazard models were used to estimate the association of hypertension to incident all-cause MCI, amnestic MCI and non-amnestic MCI. Since 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 time of 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 the time of 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, education and APOEε4 genotype in a second model. In a third model we adjusted for sex, age, ethnic group, education, APOEε4 genotype, stroke, diabetes mellitus, heart disease, and plasma low-density lipoprotein (LDL)-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 measures of blood pressure as the independent variable. We estimated the risk of conversion to dementia among persons with MCI using logistic regression. Generalized Estimation Equations (GEE)[39] were used to examine changes in neuropsychological domains, represented by cognitive scores, over time and compare them between persons with and without hypertension. The dependent variables were the cognitive scores, and the independent variables hypertension and time, included as a continuous variable. The GEE 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 two groups at the 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 SPSS version 13.0 software (SPSS Inc, Chicago, Ill) and SAS 9.1 for Windows (Cary, NC).

RESULTS

There were 334 cases of incident MCI, 160 cases of amnestic MCI and 174 cases of non-amnestic MCI during 4337 person years of follow-up (incidence densities = 7.7, 3.7 and 4.0 cases, respectively, per 100 person-years of observation). The mean age of the sample was 76.3 ± 6.1 years, and 69.4% were women, 22.6% were white, 33.6% black and 43.9% were hispanic. The mean of years of education was 8.7± 4.6, and 62.8% had hypertension, 21.3% diabetes, and 30.4% heart disease. 25.0% of the sample were homo- or heterozygeous for the APOEε4 allele, and use of antihypertensive medication was reported by 394 subjects (42.9%). Persons with hypertension were more often women, less educated, and had more often a history of stroke, diabetes or heart disease than persons without hypertension (table 1). Compared to persons without MCI, persons with amnestic MCI were 6 times more likely (OR = 6.0, 95% CI: 4.0,8.9) to convert to dementia after adjustment for age, gender, education, ethnic group and APOE-ε4. The OR for persons with non-amnestic MCI was not statistically significant (OR = 1.4; 95% CI: 0.9, 2.3).

Risk of incident MCI

The mean 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 (HR 1.4, 95% CI 1.06-1.77, p=0.02) and non-amnestic MCI (HR 1.7, 95% CI 1.13-2.42, p=0.009) after adjusting for age and gender (table 2). These associations remained stable in models additionally adjusting for education, ethnic group and APOEε4 genotype, and were slightly attenuated in models additionally adjusting for stroke and other vascular risk factors such as diabetes, LDL-Cholesterol, 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 amnestic MCI (HR 1.1, 95% CI 0.79-1.63, p=0.49) 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 longer follow-up time (observation time ≥ the median follow-up time of 3.9 years) did not change the observed associations.

Hypertension and change in cognitive scores over time

We conducted GEE analyses comparing slopes of cognitive score change between persons with and without hypertension (Table 3). All subjects had repeat cognitive data in at least two intervals, 79% had at least 3 intervals, and 59% had 4 or more intervals. For the memory score we found after adjustment for age, gender, education, ethnic group, and APOE-ε4 (model 2) that it was not related to differences in hypertension status at baseline, declined with time, but 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, increased over time (indicated by a positive coefficient for time), but 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.

DISCUSSION

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 non-amnestic MCI after adjusting for age and gender. There was no relation between hypertension history and the risk of incident amnestic MCI and there was no effect modification of the association between hypertension and any MCI subtype by APOEε4 genotype or use of antihypertensive medication. We also found that executive abilities increased over time, which we think was due to 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 of memory and language abilities.

The mechanisms by which blood pressure affects the risk of cognitive impairment or dementia remain unclear. It has been proposed that hypertension may cause cognitive impairment through cerebrovascular disease. Hypertension is a risk factor for subcortical white matter lesions (WMLs) found commonly in AD.[40] Hypertension may also contribute to a blood-brain barrier dysfunction, which has been suggested to be involved in the aetiology of AD.[40] Other possible explanations for the association are shared risk factors, such as the formation of free oxygen radicals.[40,41] 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,[42] but no distinction was made between persons with amnestic and non-amnestic MCI. White matter disease on MRI, 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 related to diabetes that was close to statistical significance,[43] but no distinction was made between amnestic and non-amnestic MCI. A study in Finland also found that hypertension was related to a higher risk of MCI,[44] 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 non-amnestic MCI. MCI has been described as an intermediate stage between normal cognition and dementia.[2,45] There is evidence that non-amnestic MCI is related in particular to cerebrovascular disease and vascular cognitive impairment (VCI). Since hypertension is associated with a higher risk of cerebrovascular disease and vascular dementia,[46, 47] it seems reasonable that it is related with the risk of non-amnestic MCI in our study. Also, the relation of hypertension to non-

amnestic MCI remained stable after adjusting for education, ethnic group and APOEε4 genotype and was attenuated after adjustment for stroke and vascular risk factors, indirectly suggesting that cerebrovascular disease may be mediating the relation between hypertension and non-amnestic MCI. These results suggest that hypertension is mainly related to an increased risk of non-amnestic forms of cognitive impairment,[48] such as frontal-executive cognitive impairment.

There was no relation between hypertension and the risk of incident amnestic MCI. Episodic memory deficits have been found to be a strong predictor of conversion to dementia, in particular AD.[49] Consequently, the term amnestic MCI represents a subgroup with a high probability of conversion to dementia caused by AD.[49] The association between hypertension and AD is unclear. A 15-year longitudinal study reported increased blood pressure 10-15 years before the onset of both AD and vascular dementia.[50] Others found it to be lower in old individuals with AD,[8] or did not find an association between hypertension and cognitive impairment.[51]

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 both the definition of the disorder and the underlying pathophysiology. Thus, it is possible that 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 pre-clinical syndrome of non-amnestic MCI, or that persons with pre-clinical non-amnestic MCI reported hypertension while subjects that 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 longer follow-up time. Another potential explanation for our findings is chance due to multiple comparisons. However, the results are in line with the *a priori* hypothesis of an association of hypertension with non-amnestic MCI rather than amnestic MCI when using the present MCI definition, and are mechanistically plausible. These facts make chance due to multiple comparisons an unlikely explanation for our findings.[52] Another potential explanation is confounding. For example, if lower education is related to hypertension, and persons with lower education are more likely to be diagnosed with MCI, then it is possible that the relation between hypertension and all-cause or non-amnestic MCI could be due to 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 EKG 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.[53] 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 amnestic MCI. It is possible that studies in younger age groups with measures of hypertension burden in mid-life could find stronger associations with risk of MCI than we report, including an association with amnestic MCI. Also, it is important to point out that 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, at baseline older, 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 prior to 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 that permitted the ascertainment of different types of incident MCI.

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

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Table 1

Comparison of characteristics among persons with and without hypertension in 918 subjects followed prospectively

	No hypertension (n=292)	Hypertension (n=626)
Women, n (%)	178 (61.0)	461 (73.6)*
Age, mean (SD), year	76.9 (6.6)	75.6 (5.7)
Education, mean (SD), year	9.8 (4.5)	8.4 (4.5)*
Ethnic group, n (%) †		
White/Non-Hispanic	84 (28.8)	116 (18.5)
Black/Non-Hispanic	101 (34.6)	207 (33.1)
Hispanic	105 (36.0)	298 (47.6)
APOE genotype 4/- or 4/4, n (%)	76 (27.9)	264 (26.5)
Stroke, n (%)	24 (8.2)	114 (18.2)*
Diabetes, n (%)	35 (12.0)	184 (29.4)*
Heart disease, n (%)	55 (18.8)	256 (40.9)*
Current Smoking, n (%)	33 (11.3)	62 (9.9)
LDL (mg/dl), mean (SD)	121.1 (36.3)	120.1 (36.9)
MCI, n (%)	76 (26.0%)	251 (41.2)*

Some percentages are based on an incomplete sample due to small amounts of missing data.

MCI = mild cognitive impairment

LDL = low-density lipoprotein (LDL) Cholesterol

† Classified by self-report using the format of the 1990 US census.[54]

* significant at a 0.05 level vs. group without hypertension

Table 2

Hazard ratios and 95% confidence intervals, relating hypertension and the risk of incident MCI

MCI subtype	No. (%) of Incident MCI	Model 1 HR (95% CI)	Model 2 HR (5% CI)	Model 3 HR (95% CI)
All-cause MCI				
No hypertension	76 (26.0)	1.0	1.0	1.0
Hypertension	258 (41.2)	1.4 (1.06-1.77)*	1.3 (1.02-1.73)*	1.2 (0.81-1.69)
Amnestic MCI				
No hypertension	42 (14.4)	1.0	1.0	1.0
Hypertension	118 (18.8)	1.1 (0.79-1.63)	1.1 (0.80-1.67)	0.9 (0.54-1.47)
Non-amnestic MCI				
No hypertension	34 (11.6)	1.0	1.0	1.0
Hypertension	140 (22.4)	1.7 (1.13-2.42)*	1.6 (1.06-2.29)*	1.6 (0.93-2.85)

Cox proportional hazards model, with age-at-onset as time variable, as described in the text. Some percentages are based on an incomplete sample due to small amounts of missing data. HR=hazard ratio, 95% CI= 95 percent confidence interval

Model 1: adjusted for gender and age

Model 2: adjusted for age, gender, education, ethnic group and APOE

Model 3: adjusted for gender, age, ethnic group, education, APOE, stroke, diabetes, heart disease, current smoking and LDL-cholesterol

Table 3

Coefficients, standand deviations (SD) and p values from general estimating equations relating hypertension to change in cognitive scores with time. A statistically significant result for the hypertension term indicates as 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.

	Model 1		Model 2		Model 3	
	Coefficient ± SD	**p**	**Coefficient ± SD**	**p**	**Coefficient ± SD**	**p**
			Memory score			
Hypertension	-9.5±2.9	0.001	-4.1 ± 2.9	0.15	-1.8±2.9	0.54
Time	-4.2±0.8	<0.0001	-4.2 ±0.7	<0.0001	-4.1±0.7	<0.0001
Hypertension*time	0.7±1.1	0.46	0.3 ± 0.86	0.72	0.3±0.9	0.69
			Executive score			
Hypertension	-0.9±1.7	0.59	2.5±1.6	0.13	1.1±1.6	0.5
Time	3.9±0.4	<0.0001	3.9±0.4	<0.0001	3.2±0.4	<0.0001
Hypertension*time	-1.0±0.5	0.03	-1.2±0.5	0.01	-0.7±0.4	0.09
			Language score			
Hypertension	-0.3±0.3	0.33	-0.0±0.27	0.87	-0.1±0.3	0.74
Time	-0.2±0.04	0.0002	-0.1±0.06	0.06	-0.2±0.0	<0.0001
Hypertension*time	0.05±0.04	0.28	0.1±0.1	0.44	0.1±0.0	0.20