Hypertension, Executive Dysfunction, and Progression to Dementia

The Canadian Study of Health and Aging

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Background: Midlife hypertension has long been established as a risk factor for dementia, but the role of late-life hypertension remains unclear.

Objective: To investigate the role of hypertension in cognitive deterioration among older subjects with cognitive impairment, no dementia.


Setting: Community-based cohort study.

Patients: We studied 990 subjects with a mean (SD) age of 83.06 (6.97) years having cognitive impairment, no dementia who were followed up for 5 years in the Canadian Study of Health and Aging.

Main Outcome Measures: Determination of cognitive dysfunction and association between hypertension and cognitive deterioration.

Results: No difference in the rate of progression to dementia based on the presence of hypertension was found between subjects with memory dysfunction alone or in combination with executive dysfunction. However, among subjects with executive dysfunction alone, 57.7% having hypertension progressed to dementia compared with 28.0% having normotension (P = .02).

Conclusions: Hypertension predicts progression to dementia in older subjects with executive dysfunction but not memory dysfunction. Control of hypertension could prevent progression to dementia in one-third of the subjects with cognitive impairment, no dementia.

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One in 3 subjects reaching the age of 60 years will experience stroke, dementia, or both unless prevention intervenes. The worldwide prevalence of dementia is 24.3 million, with the addition of 1 new case every 7 seconds.

Although midlife hypertension has been confirmed as a risk factor for the development of dementia in late life, there have been conflicting findings about the role of late-life hypertension. Some longitudinal investigations have found an association between late-life hypertension and the development of dementia, while others have not. Such inconsistency exists even between clinical trials that evaluated antihypertensive treatment in older subjects.

The term mild cognitive impairment (MCI) was introduced to describe the state between cognitive changes of aging and fully developed dementia. The rationale to study MCI is derived from the assumption that earlier intervention in a neurodegenerative process may prevent damage to the central nervous system. If hypertension has a deleterious effect on cognition, the use of antihypertensive drugs at the MCI stage will have a profound effect in the prevention of dementia among community dwellers.

Subjects with vascular cognitive impairment usually have deficits in executive function. Subjects with MCI who have deficits only in memory function (called single-domain amnestic MCI) are more prone to develop Alzheimer disease.

Because hypertension is a major risk factor for vascular brain diseases and vascular cognitive impairment, we postulated that the cognitive domain of dysfunction may be the crucial factor that determines the association between hypertension and cognitive deterioration. To our knowledge, this has not been addressed in previous studies. Our study was designed to investigate this association and its interaction with the cognitive domain of dysfunction using data from a large...
population-based longitudinal study (the Canadian Study of Health and Aging [CSHA]).

### METHODS

#### STUDY POPULATION

The CSHA was a community-based cohort study of Canadians dwelling in community and institutional settings sampled from 36 urban and surrounding rural areas in 10 Canadian provinces. The first wave of the study, CSHA-1, started in 1991 and sampled about 9000 and 1300 older (≥65 years) Canadians from community and institutional settings, respectively. Community dwellers were screened for cognitive impairment; if found, subjects were fully evaluated by physicians and neuropsychologists to determine their cognitive status. All subjects dwelling in institutional settings were fully evaluated by physicians and neuropsychologists because of their high likelihood of having cognitive impairment. In addition, a random sample of community dwellers who showed no cognitive impairment on screening were fully evaluated. Based on this process, community dwellers whose cognition was screened as normal in CSHA-1 and followed the same protocols as CSHA-1. A random sample of community dwellers whose cognition was screened as normal in CSHA-1 and all who were evaluated by physicians and neuropsychologists in CSHA-1 were examined, and their cognitive status was determined. The same diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders [Third Edition Revised]) were used, and subjects’ cognitive status was also determined using the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).

The third wave of the study, CSHA-3, started in 2001 to 2002 and followed the same protocols except that the cutoff point was changed at which subjects screened positive for cognitive impairment. In CSHA-1 and CSHA-2, subjects whose scores on the screening test (Modified Mini-Mental State Examination) were less than 78 were invited for more clinical and neuropsychological examinations, while in CSHA-3 this cut point was raised to 90 to include more subjects in the examinations. The Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria were used for the diagnoses in CSHA-3.

Between waves of the CSHA, some subjects died, and their antemortem cognitive status was estimated with a predictive algorithm using death certificate information and interviews with spouses or close relatives of the decedent. These sources led to an overall estimation of the probability of antemortem dementia. The details of the sampling method, screening, and diagnostic criteria used by the CSHA have been published elsewhere.

The present study included subjects who were diagnosed as having CIND in CSHA-1 or CSHA-2 and whose cognitive impairment was not caused by neurologic or psychiatric diseases such as multiple sclerosis, epilepsy, or depression (Table 1). There were 578 such subjects in CSHA-1 and 474 in CSHA-2. Sixty-two CSHA-1 subjects who were also in CSHA-2 were excluded from the CSHA-1 sample and were included only in the CSHA-2 sample. The cognitive status of CSHA-1 subjects, CSHA-1 and CSHA-2 subjects was determined at the 5-year follow-up in CSHA-2 and CSHA-3, respectively. For subjects who died before their follow-up examination, diagnoses were coded as demented and nondemented if the probabilities of dementia were at least 0.90 and less than 0.25, respectively. Follow-up cognitive status of 384 subjects (38.8%) was indeterminable because of uncertainty about the diagnosis, their refusal to participate further in the study, death with an antemortem probability of dementia between 0.25 and 0.90, or lack of documentation to verify cognitive status before death. Compared with subjects having CIND and known follow-up cognitive status, these 384 subjects were similar in age, education, and prevalence of hypertension but included more male participants. The study was approved by the research ethics committee of the University of Western Ontario.

#### STATISTICAL ANALYSIS

The following steps comprised the statistical methods: selection of neuropsychological tests, use of correspondence analysis to derive cognitive domains, and determination of cognitive dysfunction domains.

### Selection of Neuropsychological Tests

These tests were selected from the following neuropsychological test battery that was administered in CSHA-1 and CSHA-2: Wechsler Memory Scale (information subtest), Buschke Cued Recall Procedure (first, third, and delayed free and total recall), Wechsler Adult Intelligence Scale–Revised (WAIS-R) block design, WAIS-R similarities, Token Test (color naming and 11 item), Digit Span Test, WAIS-R comprehension, Rey Auditory Verbal Learning Test (first, fifth, and sixth trials; new list trial; and true positive and true negative recognition trial), Verbal Fluency (the FAS Test), Benton Visual Retention Test, Verbal Fluency Animal Naming, and WAIS-R digit symbol subtest. In CSHA-1, these tests were administered to 1791 subjects; 591 had 1 or more missing tests; in CSHA-2, these tests were administered to 1466 subjects; 369 had 1 or more missing tests. Missing tests were because of physical disability in 37.2%, other missing factors in 33.3%, unwillingness to perform a test in 26.8%, and misunderstanding about a test in 2.6%. Compared with subjects who did not miss any tests, subjects with missing tests were significantly more cognitively impaired.
Use of Correspondence Analysis to Derive Cognitive Domains

Correspondence analysis was applied to the neuropsychological test results to derive cognitive domains. Correspondence analysis is a more powerful generalization of principal component analysis\(^2\) that can be used with continuous, categorical, and count variables and explains maximum amount of variance that can be derived by any linear method. As in principal component analysis, correspondence analysis results in factors, each of which explains a domain of variance among the data. The first derived factor explains most of the variance, the second derived factor explains most of the remaining variance, and so forth until all variances are extracted into different factors or domains. Usually the first 2 to 3 dimensions denote meaningful factors. To assess what is measured by each dimension, correlations between derived dimensions and neuropsychological test results were calculated. Spearman rank correlation coefficient was used for this purpose.

Correspondence analysis was performed separately on CSHA-1 and CSHA-2 neuropsychological test results. Each data set included test results of subjects with normal cognition and subjects with dementia.

**Determination of Cognitive Dysfunction Domains**

The mean (SD) of each correspondence analysis–derived cognitive domain was computed by selecting subjects with normal cognition and was performed separately in CSHA-1 and CSHA-2. A subject was considered to have dysfunction in a cognitive domain if his or her score was more than 1 SD below the mean of the domain.

Hypertension was defined as a diastolic blood pressure (supine or sitting) of at least 90 mm Hg or a systolic blood pressure (supine or sitting) of at least 140 mm Hg. A subject’s history of stroke was obtained by the physicians.

Pearson product moment correlation \(\chi^2\) with Yates continuity correction was used to test the association between hypertension and dementia. Logistic regression analysis was used to control for the effect of age and apolipoprotein E \(\varepsilon\) 4 allele status.

The analysis was performed using commercially available statistical software (SPSS, version 15; SPSS Inc, Chicago, Illinois). \(P < .05\) was considered statistically significant.

### RESULTS

#### DETERMINATION OF COGNITIVE DYSFUNCTION DOMAINS

Correspondence analysis was performed separately on CSHA-1 and CSHA-2 neuropsychological test results. In CSHA-1, the first to fifth derived dimensions explained about 30%, 16%, 10%, 7%, and 5% of the variance; in CSHA-2, these percentages were about 32%, 14%, 11%, 7%, and 6%. The first 3 (of 24 derived dimensions) could explain more than half of the variance and were selected for further analysis.

Correlations of the first 3 derived dimensions (Table 2) were analyzed to determine sets of tests that were highly correlated with each dimension. A test was selected to be highly correlated with a dimension if its correlation coefficient with the dimension had high absolute value and large difference relative to the value of correlations with other dimensions. (For example, WAIS-R comprehension was highly correlated with dimension 1 because it had correlation coefficients of 0.57, 0.04, and 0.04 relative to dimensions 1, 2, and 3, respectively, in CSHA-1.) The sets of tests derived by correlation analysis were almost the same in CSHA-1 and CSHA-2. Dimension 1 was considered the executive function domain because of high correlations with WAIS-R comprehension, WAIS-R similarities, Verbal Fluency, and WAIS-R digit symbol subtest (these tests had their highest correlations with dimension 1). Dimension 2 was considered the memory function domain because of high correlations with Buschke Cued Recall Procedure (first, third, and delayed free recall trials) (these tests had their highest correlations with dimension 2). Dimension 3 did not have high correlations with the tests and was removed from further analysis.

The mean (SD) of executive function and memory function domains was determined among subjects with normal cognition separately in CSHA-1 and CSHA-2. The mean (SD) values for the executive function domain were 0.29 (0.82) in CSHA-1 and 0.26 (0.86) in CSHA-2; the values for the memory function domain were 0.30 (0.73) in CSHA-1 and 0.40 (0.68) in CSHA-2.

#### ASSOCIATION BETWEEN HYPERTENSION AND COGNITIVE DETERIORATION

Descriptive statistics of the analyzed cohort with CIND are given in Table 3. About three-fourths of subjects had dysfunction in 1 of 2 cognitive domains.

The presence of hypertension did not result in cognitive deterioration across the cohort: 59.5% of subjects with hypertension vs 64.2% of subjects with normotension had developed dementia after 5 years of follow-up \(P = .32\). However, there was a significant difference among the following 3 patterns of cognitive impairment: in subgroup 1 with cognitive impairment and executive dysfunction alone, the presence of hypertension resulted in cognitive deterioration (57.7% having hypertension progressed to dementia vs 28.0% having normotension, \(P = .02\)), while it did not in subgroup 2 (cognitive impairment and memory dysfunction alone) or subgroup 3 (cognitive impairment and both executive and memory dysfunction) (Figure).

Logistic regression analysis was performed using dementia development as the dependent variable and using hypertension, patterns of cognitive impairment (executive dysfunction alone, memory dysfunction alone, or both executive and memory dysfunction), and their interaction as independent variables. The interaction term (but not hypertension) and the patterns of cognitive impairment remained significant in the model. The analysis was repeated, and age, sex, and apolipoprotein E allele status (\(\varepsilon\) 4, \(\varepsilon\) 2, or \(\varepsilon\) 3) were added to the independent variables; there was no change in the results.

To remove a possible mediating role of stroke in the effect of hypertension on cognitive deterioration among subgroup 1, the rates of progression to dementia were compared between subjects without a history of stroke having hypertension vs normotension in subgroup 1. The
The presence of hypertension did not result in cognitive deterioration across the cohort. However, there was increased progression to dementia among subjects with hypertension whose cognitive impairment was associated with executive dysfunction but not memory dysfunction.

Among 4 longitudinal studies reviewed by Qiu et al,3 only 1 found hypertension to be a risk factor for the development of dementia among older subjects. According to Skoog et al,4 subjects who developed dementia later in life had significantly higher systolic and diastolic blood pressures about 10 to 15 years before cognitive assessment than subjects who did not subsequently develop dementia. In contrast, Pettiti et al6 reported no significant difference in blood pressure levels 9 years before cognitive assessment between subjects who developed dementia and subjects who did not develop dementia. Although the 2 studies were of dissimilar design, their contradictory results preclude conclusions about the role of hypertension in the development of dementia among older subjects.

In this study, we excluded subjects with CIND whose cognitive impairment was due to neurologic or psychiatric illness or chronic alcohol or substance abuse, which may cause static encephalopathies but do not result in progression to dementia. By this definition, our analysis is comparable to investigations that have evaluated subjects with MCI.8 Furthermore, the rate of progression to dementia was almost 12% a year among the present cohort, the same as that reported for subjects with MCI.7

Few studies have evaluated the role of hypertension in progression of MCI to dementia. In a clinic-based setting, Ravaglia et al28 followed up 165 outpatients with MCI for 3 years. The presence of hypertension had no

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Abbreviation: WAIS-R, Wechsler Adult Intelligence Scale–Revised.

a Significant at $P \leq .05$. The coefficients are absolute values.

b Test 1 is Wechsler Memory Scale (information subtest). Test 2 is Buschke Cued Recall Procedure (visual identification task). Test 3 is Buschke Cued Recall Procedure (object naming). Test 4 is Buschke Cued Recall Procedure (free recall trial 1). Test 5 is Buschke Cued Recall Procedure (free recall trial 3). Test 6 is Buschke Cued Recall Procedure (total recall trial 1). Test 7 is Buschke Cued Recall Procedure (total recall trial 3). Test 8 is WAIS-R block design. Test 9 is Buschke Cued Recall Procedure (free recall delayed trial). Test 10 is Buschke Cued Recall Procedure (total recall delayed trial). Test 11 is WAIS-R similarities. Test 12 is Token Test (color naming). Test 13 is Token Test (11 item). Test 14 is Digit Span Test. Test 15 is WAIS-R comprehension. Test 16 is Rey Auditory Verbal Learning Test (first trial). Test 17 is Rey Auditory Verbal Learning Test (fifth trial). Test 18 is Rey Auditory Verbal Learning Test (new list trial). Test 19 is Rey Auditory Verbal Learning Test (sixth trial). Test 20 is Rey Auditory Verbal Learning Test (true positive recognition trial). Test 21 is Rey Auditory Verbal Learning Test (true negative recognition trial). Test 22 is Verbal Fluency (the FAS Test). Test 23 is Benton Visual Retention Test. Test 24 is Verbal Fluency Animal Naming. Test 25 is WAIS-R digit symbol subtest.

c Correspondence analysis–derived dimensions.

d Significant at $P \leq .01$.
effect on progression of MCI to dementia. Similarly, hypertension was not a risk factor for the development of dementia among subjects in our study. However, Ravaglia et al did not include an interaction term between MCI subtypes and hypertension in their multivariate model of MCI conversion to dementia.

Sollfrizzi et al\(^a\) evaluated Italian patients with MCI in a community-based study and followed them up for 3½ years. Although the presence of hypertension did not seem to have a detrimental effect on cognitive function, the investigators included only patients with amnestic MCI in their study. Similarly, hypertension did not accelerate cognitive deterioration among subjects in our study with memory dysfunction.

Recently, Knopman et al\(^b\) reported a stronger association of stroke with nonamnestic MCI than with amnestic MCI in a cross-sectional study derived from a population-based cohort. It seemed plausible that the association between hypertension and executive dysfunction in our study might be mediated by stroke in these subjects. However, after exclusion of subgroup 1 subjects with a history of stroke from the analysis, hypertension did not have a detrimental effect on cognitive function, the investigators included only patients with amnestic MCI in their study. Similarly, hypertension did not accelerate cognitive deterioration among subjects in our study with memory dysfunction.

This study has some limitations. Our study is a secondary analysis and has the limitations of a post hoc analysis. About 10% of the cohort refused further clinical examinations, and their cognitive status was indeterminable. About 30% of subjects died, and their antemortem cognitive status was estimated with a predictive algorithm using death certificate information and interviews with spouses or close relatives of the decedent. This study may have profound implications for community dwellers with CIND. Worldwide, neurologic disorders are the most frequent cause of disability-adjusted life-years; among these, cerebrovascular disease is the most common risk factor, and dementia is the second most common.\(^c\) There is no preventive or therapeutic intervention to mitigate this public health burden. It is assumed that cognitive decline progresses to CIND before the development of dementia. We show herein that the presence of hypertension predicts progression to dementia in a subgroup of about one-third of subjects with CIND. Control of hypertension in this population could decrease by one-half the projected 50% 5-year rate of progression to dementia.\(^d\)

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Author Contributions: Dr Hachinski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Oveisgharan. Acquisition of data: Hachinski and Oveisgharan. Analysis and interpretation of data: Oveisgharan and Hachinski. Drafting of the manuscript: Oveisgharan and Hachinski. Statistical analysis: Oveisgharan. Obtained funding: Hachinski and Oveisgharan. Study supervision: Hachinski.

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