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Risk Factors for Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study: Part 2

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ORIGINAL CONTRIBUTION

Risk Factors for Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study

Part 2

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Objective: To examine the risk factors for mild cognitive impairment (MCI) in a longitudinal population study—the Cardiovascular Health Study Cognition Study.

Design: We examined the factors that in the period 1991 through 1994 predicted the development of MCI in all participants of the Cardiovascular Health Study Cognition Study. Further examination was conducted in the Pittsburgh, Pa, cohort (n=927), where participants with MCI were classified as having either the MCI amnestic-type or the MCI multiple cognitive deficits–type.

Setting: Multicenter population study.

Patients: This study includes all participants of the Cardiovascular Health Study Cognition Study (n=3608) who had a magnetic resonance imaging (MRI) scan of the brain between 1991 and 1994, and detailed neuropsychological, neurological, and medical evaluations to identify the presence of MCI or dementia in the period 1998 to 1999. The mean time between the closest clinical examination to the MRI and the diagnostic evaluation for cognitive disorders was 5.8 years for the Cardiovascular Health Study Cognition Study cohort and 6.0 years for the Pittsburgh cohort.

Main Outcome Measures: Risk factors for MCI at the time of the MRI were identified using logistic regression, controlling for age, race, educational level, baseline Modified Mini-Mental State Examination and Digit Symbol Test scores, measurements of depression, MRI findings (atrophy, ventricular volume, white matter lesions, and infarcts), the presence of the apolipoprotein E (*APOE*) ε4 allele, hypertension, diabetes mellitus, and heart disease.

Results: Mild cognitive impairment (n=577) was associated with race (African American), low educational level, low Modified Mini-Mental State Examination and Digit Symbol Test scores, cortical atrophy, MRI-identified infarcts, and measurements of depression. The MCI amnestic-type was associated with MRI-identified infarcts, the presence of the *APOE* ε*4* allele, and low Modified Mini-Mental State Examination scores. The MCI multiple cognitive deficits–type was associated with low Modified Mini-Mental State Examination and Digit Symbol Test scores.

Conclusions: The development of MCI is associated with measurements of cognition and depression, racial and constitutional factors, and cerebrovascular disease. Early cognitive deficits seem to be a common denominator for the 2 forms of MCI; the presence of cerebrovascular disease and the *APOE* ε*4* allele is associated with the amnestic type of MCI.

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OLDER PARTICIPANTS with mild cognitive impairment (MCI) have an increased risk of developing dementia, especially Alzheimer disease.[1] Therefore, the proper identification of these individuals is important because they constitute a clinical

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entity that is suitable for therapeutic interventions. However, one of the problems in identifying risk factors for MCI is that there are several neurological, systemic, and psychiatric syndromes that can cause cognitive impairment. Elderly subjects who have cerebrovascular disease,[2] white matter lesions (WMLs),[3] diabetes mellitus,[4] and hypertension and heart disease,[5] or depression[6] can present with mild cognitive deficits. Furthermore, studies that focused only on risk factors for MCI have found that hypertension diagnosed in midlife[7] and a history of coronary artery bypass grafting[8] increased the risk of developing MCI. In this study, we examined the risk factors for MCI in the context of a longitudinal population study, the Cardiovascular Health Study (CHS) Cognition Study. These factors were first examined for the whole CHS cohort, and fur-

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ther analysis was conducted in the Pitts burgh, Pa, sample, where we examined the association between risk factors and MCI subgroups.

METHODS

Details of the CHS annual evaluations as well as the methods of the CHS Cognition Study are described in the companion article in this issue.[9]

MAGNETIC RESONANCE IMAGING (MRI) RATING SCALE

The sulcal prominence (or cortical atrophy), ventricular grade, and white matter signal-intensity changes were assessed on a semiquantitative 10-point scale (grades 0-9) by using predefined visual standard atlases. Details of the CHS MRI examination have been published previously.[10] For this study the MRI measurements were dichotomized as follows: ventricular size grade higher than 4, cortical atrophy grade higher than 4, and WMLs grade higher than 2.

CHS COGNITIVE STUDY MCI CRITERIA

Details of the CHS MCI criteria, as well as the criteria for probable and possible MCI are given in the companion article in the "CHS Cognitive Study MCI Criteria" subsection of the "Methods" section.[9]

STATISTICAL ANALYSIS

Logistic regression models for the risk of MCI compared with healthy participants included age, educational level, the Center for Epidemiologic Studies–Depression (CES-D) Scale, Modified Mini-Mental State Examination (3MSE) and Digit Symbol Test (DST)[9] scores closest to the MRI, MRI findings, and the presence of the apolipoprotein E ϵ4 (*APOE ϵ4*) allele, diabetes mellitus, hypertension, and/or ischemic heart disease. The analyses were conducted to determine the factors associated with the presence of MCI in all available participants with MCI and in healthy participants.

RESULTS

CHS COGNITIVE STUDY COHORT

Demographic and Neuropsychiatric Characteristics

Participants with MCI were significantly older than the healthy participants. There were more African American participants in the MCI group than among the healthy participants. The participants with MCI had lower levels of education (ie, high school or less) and more of them carried the *APOE ϵ4* allele. Participants with MCI had lower 3MSE and DST scores than did the healthy participants (**Table 1**).

Table 1. Demographic, Genetic, and Cognitive Characteristics of All Participants in the Cardiovascular Health Study Cognition Study*

	Healthy Participants (n = 2318)	Participants With MCI (n = 577)	*t* Test or χ^2 Test
Age at MRI scan, mean (SD), y	74.0 (4.4)	75.4 (5.0)	26.2
Age in 1997-1998, mean (SD), y	78.4 (4.2)	79.7 (4.9)	30.4†
Educational level, high school or less	1123 (49)	374 (65)	48.9‡
Male sex	951 (41)	236 (41)	.003
White participants	2102 (91)	364 (63)	278.7†
3MSE score, mean (SD)			
Closest to MRI	93.9 (5.0)	88.9 (7.2)	19.2†
Last available score	94.2 (6.1)	86.8 (7.8)	26.7†
DST score, mean (SD)			
Closest to MRI	43.7 (11.9)	34.2 (12.4)	16.5†
Last available score	40.6 (12.4)	30.5 (11.7)	18.6†
APOE ϵ4 allele	465 (22)	136 (26)	4.4‡
Deceased in 1998-1999	313 (13.5)	112 (19)	12.8†

Abbreviations: *APOE ϵ4*, apolipoprotein ϵ4; DST, Digit Symbol Test; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; 3MSE, Modified Mini-Mental State Examination.

*Data are given as the number (percentage) of participants unless otherwise indicated.

†$P<.001$.

‡$P<.05$.

Systemic, Neurological, Mood-Related Disorders, and MRI Findings

Significantly greater proportions of participants with MCI had diabetes mellitus, heart disease (including myocardial infarction, congestive heart failure, or angina), hypertension, and a CES-D score exceeding 7 than the healthy participants. There was a greater proportion of participants with MCI who had a white matter lesion grade higher than 2, ventricular volume higher than 4, cortical atrophy higher than 4, and MRI-identified infarcts than the healthy participants (**Table 2**).

Logistic Regression Analysis

Mild cognitive impairment was associated with race (being African American), educational level, MRI-identified infarcts, a cortical atrophy grade higher than 4, low 3MSE and DST scores, and a CES-D score exceeding 7 (**Table 3**).

PITTSBURGH COHORT

Demographic and Neuropsychiatric Characteristics

Distribution of risk factors for MCI in the Pittsburgh sample were similar to the results for the 4 centers (Sacramento, Calif; Winston-Salem, NC; Hagerstown, Md; and Pittsburgh) combined (**Table 4**). Participants with MCI amnestic-type (AT) and MCI multiple cognitive deficits–type (MCDT) were significantly different from healthy participants for lower 3MSE and DST scores. The MCI-MCDT group was older, less educated, and had higher percentages of African American participants. The 2 MCI types differed significantly from one another for educational level and 3MSE and DST scores. Participants with MCI-MCDT were less educated and had lower cognitive test scores than participants with MCI-AT (Table 4).

Table 2. Prevalence of Selected Disorders and Neuroradiological Findings at the Time of the MRI Among All Participants in the Cardiovascular Health Study Cognition Study*

Variable	Healthy Participants	Participants With MCI	χ^2 Test
Systemic disorders			
Diabetes mellitus (by ADA)	278 (12)	111 (19)	21.3†
Hypertension	983 (42)	279 (48)	5.6‡
Heart disease§	455 (20)	141 (24)	6.5‡
Coronary artery bypass grafting	110 (5)	20 (3.5)	1.8
Coronary artery angioplasty	51 (2)	10 (2)	0.5
Cerebrovascular disease			
Clinical stroke	86 (4)	26 (4.5)	0.8
Depression			
CES-D Scale score >7 closest to MRI	443 (19)	184 (40)	44.6†
Neuroradiological findings			
White matter lesion grade >2	647 (28)	217 (40)	20.8‖
Ventricular volume grade >4	331 (14)	125 (22)	19.2‖
Cortical atrophy grade >4	348 (15)	128 (22)	17.4‖
MRI-identified infarcts	593 (26)	206 (36)	23.6†

Abbreviations: ADA, American Diabetes Association; CES-D, Center for Epidemiologic Studies–Depression; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

*Data are given as the number (percentage) of participants.

†$P<.01$.

‡$P<.05$.

§Heart disease includes myocardial infarction and congestive heart failure or angina.

‖$P<.001$.

Table 3. Risk Factors for MCI in All Cardiovascular Health Study Cognition Study Participants*

Risk Factor at the Time of MRI	OR	95% CI for Lower-Upper Values	*P* Value
African American	4.4	3.22-5.71	<.001
Educational level of high school or less	0.8	0.61-0.99	.04
MRI-identified infarcts	1.4	1.12-1.82	.004
Cortical atrophy grade >4	1.5	1.11-1.97	.007
DST score closest to MRI	1.0	0.97-0.99	<.001
3MSE score closest to MRI	0.9	0.91-0.95	<.001
CES-D Scale score >7 closest to MRI	1.5	1.21-1.98	.001

Abbreviations: CES-D, Center for Epidemiologic Studies–Depression; CI, confidence interval; DST, Digit Symbol Test; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; 3MSE, Modified Mini-Mental State Examination; OR, odds ratio.

*Regression model included age; sex; race; educational level; the presence of the apolipoprotein E ϵ4 allele; the presence of diabetes mellitus, hypertension, and heart disease; 3MSE and DST scores; and neuroradiological findings.

Systemic, Neurological, Mood-Related Disorders, and MRI Findings

Significantly higher percentages of the participants with MCI had hypertension, diabetes mellitus, depression, and poor neuroradiological findings. Participants with MCI-AT had poor neuroradiological findings on all 4 measurements, while participants with MCI-MCDT had significantly higher percentages of diabetes mellitus, a WML grade higher than 2, and a ventricular volume higher than 4 (**Table 5**).

Logistic Regression Analysis

Mild cognitive impairment in the Pittsburgh subsample was associated with the presence of the *APOE* ϵ*4* allele, MRI-identified infarcts, and low baseline 3MSE and DST scores. Mild cognitive impairment amnestic-type was associated with the same risk factors except for low DST scores; MCI-MCDT was significantly associated with 3MSE and DST scores (**Table 6**).

PROBABLE AND POSSIBLE MCI

Further exploratory analysis revealed interesting associations that require further studies in larger cohorts. For example, probable MCI-AT (n=10) was associated with the presence of the *APOE* ϵ*4* allele (odds ratio [OR], 5.6; 95% confidence interval [CI], 1.35-23.4) and low 3MSE scores (OR, 0.8; 95% CI, 0.72-.94). Possible MCI-AT (n=23) was associated with MRI-identified infarcts (OR, 4.3; 95% CI, 1.69-10.7) and WMLs (OR, 3.25; 95% CI, 1.37-8.77). Probable MCI-MCDT (n=26) was associated with low DST scores (OR, 0.9; 95% CI, 0.88-0.99) and the presence of the *APOE* ϵ*4* allele (OR, 3.3; 95% CI, 1.16-9.44). Possible MCI-MCDT (n=79) was associated with MRI-identified infarcts (OR, 2.0; 95% CI, 1.10-3.80) and low 3MSE scores (OR, 0.8; 95% CI, 0.80-0.90).

COMMENT

Mild cognitive impairment was associated with measurements of cognition and depression, racial and constitutional factors, and the presence of cerebrovascular disease. Low scores on neuropsychological measurements were the common predictor for the 2 types of MCI, and they may have reflected the early effect of several disease processes (eg, heart disease, hypertension, diabetes mellitus, and cerebrovascular disease), an incipient neurodegenerative process, or both. To some extent, neuropsychological test results must be interpreted cautiously as they also formed the basis of our diagnosis.

The increased frequency of cerebrovascular risk factors and the presence of the *APOE* ϵ*4* allele among African American participants may explain why elderly African Americans had a greater risk of developing MCI.[11] However, in this study, we found an association between being African American and having MCI independent of the presence of cerebrovascular risk factors and the presence of the *APOE* ϵ*4* allele.

Several genetic studies have shown that participants who do not have dementia but are carrying the *APOE* ϵ*4* allele had lower global cognitive performance than those without the allele, and participants with focal memory deficits who are carrying the *APOE* ϵ*4* allele have the highest risk of subsequent development of dementia.[1] However, we found that the presence of the *APOE* ϵ*4* allele was associated with MCI-AT, and

Table 4. Demographic, Genetic, and Cognitive Characteristics of the Pittsburgh, Pa, Cohort*

Variable	All Participants With MCI vs Healthy Participants			Participants With MCI Subtypes vs Healthy Participants		
	Healthy Participants (n = 552)	Participants With MCI (n = 159)	*t* Test or χ^2 Test	Participants With MCI-AT (n = 40)	Participants With MCI-MCDT (n = 119)	*t* Test or χ^2 Test
Age at the MRI, mean (SD), y	73.5 (4.0)	75.4 (5.0)	4.8†	75.2 (4.9)	75.5 (5.0)	11.6‡§
Age in 1998-1999, mean (SD)	78.2 (3.8)	79.6 (4.7)	3.5†	79.4 (4.8)	79.7 (4.8)	6.2‡§
Educational level, high school or less	226 (41)	97 (61)	20.0†	16 (40)	81 (68)	29.6†§‖
Male sex	227 (41)	75 (48)	2.2	16 (40)	60 (50)	3.6
White participants	459 (83)	98 (62)	33.7†	30 (75)	68 (57)	39.3†§
3MSE score, mean (SD)						
Closest to MRI	94.4 (4.6)	88.9 (6.2)	12.1†	91.8 (5.0)	87.9 (6.2)	83.8†§‖¶
Last available score	95.1 (4.4)	87.0 (6.0)	18.5†	89.2 (5.8)	86.3 (5.9)	179.2†§‖¶
DST score, mean (SD)						
Closest to MRI	46.3 (12.1)	35.2 (12.3)	10.2†	42.2 (12.0)	32.8 (11.6)	62.0†§‖
Last available score	44.2 (12.1)	30.6 (11.3)	12.4†	35.3 (12.4)	29.0 (10.5)	81.9†§‖¶
APOE ϵ4 allele	101 (20)	40 (28)	4.2‡	12 (33)	28 (27)	4.9

Abbreviations: *APOE ϵ4*, apolipoprotein E ϵ4; AT, amnestic type; DST, Digit Symbol Test; MCDT, multiple cognitive deficits–type; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; 3MSE, Modified Mini-Mental State Examination.

*Data are given as the number (percentage) of participants unless otherwise indicated.

†$P<.001$.

‡$P<.05$.

§Participants with MCI-MCDT are different from healthy participants in Bonferroni post hoc comparisons ($P<.02$).

‖Participants with MCI-AT are different from participants with MCI-MCDT in Bonferroni post hoc comparisons ($P<.02$).

¶Participants with MCI-AT are different from healthy participants in Bonferroni post hoc comparisons ($P<.02$).

Table 5. Prevalence of Selected Disorders and Neuroradiological Findings Among Healthy Participants and Pittsburgh, Pa, Cohort With MCI*

Variable	All Participants With MCI vs Healthy Participants			Participants With MCI Subtypes vs Healthy Participants		
	Healthy Participants	Participants With MCI	χ^2 Test	Participants With MCI-AT	Participants With MCI-MCDT	χ^2 Test
Systemic disorders						
Diabetes mellitus (by ADA)	66 (12)	37 (23)	13.0†	7 (17.5)	30 (25)	14.5‡§
Hypertension	194 (35)	74 (46.5)	6.8‖	19 (47.5)	55 (46)	6.8§¶
Heart disease#	115 (21)	43 (27)	2.8	10 (25)	33 (28)	2.9
Coronary artery bypass grafting	24 (4)	9 (6)	0.5	3 (7.5)	6 (5)	0.9
Coronary artery angioplasty	14 (2.5)	7 (4)	1.5	3 (7.5)	4 (3)	3.3
Cererbrovascular disease						
Clinical stroke	16 (3)	8 (5)	1.7	3 (7.5)	5 (4)	2.7
Depression measure						
CES-D Scale score >7 closest to MRI	140 (25)	57 (36)	6.8‖	14 (35)	43 (36)	6.8§‖
Neuroradiological findings						
White matter lesion grade >2	92 (17)	50 (32)	16.9‡	16 (41)	34 (29)	19.8§¶
Ventricular volume grade >4	75 (14)	38 (24)	10.2‡	11 (28)	27 (23)	10.8‡§¶
Cortical atrophy grade >4	118 (21.5)	43 (27)	2.4	12 (31)	31 (26)	2.8
MRI-identified infarcts	153 (28)	60 (38)	5.9‖	21 (52.5)	39 (33)	11.5‖¶

Abbreviations: ADA, American Diabetes Association; AT, amnestic type; CES-D, Center for Epidemiologic Studies–Depression; MCDT, multiple cognitive deficits–type; MCI, mild cognitive impairment; MRI, magnetic resonance imaging.

*Data are given as the number (percentage) of participants.

†$P<.001$.

‡$P<.01$.

§Participants with MCI-MCDT are different from healthy participants in Bonferroni post hoc comparisons ($P<.02$).

‖$P<.05$.

¶Participants with MCI-AT are different from healthy participants in Bonferroni post hoc comparisons ($P<.02$).

#Heart disease includes myocardial infarction, congestive heart failure, and/or angina.

especially, with the "pure" (probable) forms of MCI. Further studies are necessary to determine the relationship between the *APOE ϵ4* allele and the specific types of MCI and dementia.

Magnetic resonance imaging–identified infarcts were important predictors of MCI, especially of the possible MCI-AT and MCI-MCDT subtypes. This finding converges with the notion that the presence of cerebrovas-

Table 6. Risk Factors for MCI From Logistic Regression Models Based on the Pittsburgh, Pa, Cohort With the Diagnosis of MCI-AT and MCI-MCDT*

	All Participants vs Healthy Participants			Participants With MCI-AT vs Healthy Participants			Participants With MCI-MCDT vs Healthy Participants		
Risk Factor at Time of MRI	OR	95% CI for Lower-Upper	*P* Value	OR	95% CI for Lower-Upper	*P* Value	OR	95% CI for Lower-Upper	*P* Value
APOE ϵ4 allele	1.9	1.14-3.31	.01	2.5	1.13-5.69	.02	NA	NA	NA
MRI-identified infarcts	1.7	1.03-2.77	.007	2.3	1.07-5.02	.03	NA	NA	NA
3MSE score closest to MRI	0.9	0.83-0.91	<.001	0.9	0.82-0.96	.01	0.9	0.82-0.91	<.001
DST score closest to MRI	1.0	0.95-1.00	.02	NA	NA	NA	1.0	0.93-0.99	.003

Abbreviations: *APOE ϵ4*, apolipoprotein E ϵ4; AT, amnestic type; CI, confidence interval; DST, Digit Symbol Test; MCDT, multiple cognitive deficits–type; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; 3MSE, Modified Mini-Mental State Examination; NA, not applicable; OR, odds ratio.

*Regression model included age; sex; race; educational level; *APOE ϵ4* allele; the presence of diabetes mellitus, hypertension, or heart disease; 3MSE and DST scores; and neuroradiological findings.

cular risk factors (hypertension, diabetes mellitus, and heart disease) is associated with MCI.[12] However, in this study, the effect of cerebrovascular risk factors on the clinical expression of MCI was attenuated when neuroradiological findings were entered into the multivariate analysis. Furthermore, although participants with MCI had more WMLs than healthy participants, this association was not significant in the multiple logistic analysis. It is possible that the presence of other MRI findings and cardiovascular factors attenuated the effect of WMLs on the development of MCI. Importantly, the possible MCI-AT group was associated with both MRI-identified infarcts and WMLs, suggesting a greater cerebrovascular process in this subgroup. Clinical studies have shown that the presence of WMLs was closely related to MRI-identified infarcts and cerebrovascular risk factors.[10] Therefore, additional studies are necessary to investigate the role that the association (and interaction) between cerebrovascular risk factors and the severity of cerebrovascular disease have in the development of specific MCI subtypes.

There are several issues that make depression an important factor in the study of the natural history of MCI and Alzheimer disease. (1) Idiopathic depression can cause cognitive deficits in elderly persons.[6] (2) Elderly persons who do not have dementia but do have cardiovascular disease, strokes, and WMLs[13] have more depression than those without ischemic lesions. (3) Cardiovascular disease increases the risk of depression in elderly persons.[14] (4) Elderly persons who do not have dementia but are depressed have smaller hippocampal volumes than those who are not depressed.[15]

One limitation of our study is that we did not have detailed annual neuropsychological assessments, which would have allowed us to determine the exact time of onset of MCI. Longitudinal studies are necessary to determine how MCI subgroups evolve to dementia and especially to identify those participants with MCI whose conditions do not progress to dementia.

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