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Metabolic Syndrome, Inflammation, and Non-Amnestic Mild Cognitive Impairment in Older Persons: A Population-Based Study

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Abstract

The metabolic syndrome (MetS) is more strongly associated with cognitive impairment in the presence of inflammation. This suggests that the association of MetS with mild cognitive impairment (MCI) may vary with the etiology and the subtype of MCI. This study investigated the association between MetS with or without inflammation and MCI (amnestic [a-MCI] and non-amnestic [na-MCI]). We studied a randomly selected sample of 1969 subjects (ages 70 to 89 years) from Olmsted County, MN, using the Clinical Dementia Rating Scale, a neurological evaluation, and neuropsychological testing. Data for participants were reviewed for a diagnosis of normal cognition, MCI, or dementia. Clinical components of MetS were ascertained by interview and confirmed from the medical records; biochemical measurements were assayed from a blood draw. We compared 88 na-MCI cases and 241 a-MCI cases with 1640 cognitively normal subjects. MetS was not associated with either na-MCI or a-MCI. High C-reactive protein (CRP highest tertile vs lowest tertile) was associated with na-MCI (odds ratio [OR] = 1.85; 95% confidence interval [CI] = 1.05, 3.24) but not with a-MCI, after adjusting for sex, age, and years of education. The combination of MetS and high CRP (compared to no Mets and lowest CRP tertile) was associated with na-MCI (OR = 2.31; 95% CI = 1.07, 5.00), but not with a-MCI (OR = 0.96; 95% CI = 0.59, 1.54). The combined presence of MetS and high levels of inflammation is associated with na-MCI in this elderly cohort, and suggests etiologic differences in MCI subtypes.

Keywords

metabolic syndrome; insulin resistance; mild cognitive impairment; C-reactive protein; inflammation; cross-sectional study

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The metabolic or insulin resistance syndrome is a predictor of cardiovascular events including coronary heart disease and stroke.[1,2] The components of the MetS, impaired fasting blood sugar, hypertension, abdominal obesity, hypertriglyceridemia, and low high density lipoprotein, have all been associated with dementia in several studies.[3-5] The MetS may accelerate cognitive ageing through mechanisms related to micro and macrovascular damage, insulin resistance, inflammation, and adiposity.[6] Consistent with this hypothesis, the MetS has been associated with Alzheimer's disease,[5] vascular dementia,[7] and with cognitive decline.[8,9] However, other investigators have reported no associations of the MetS with cognition.[10,11]

The inconsistency in study findings may relate to differences in assessment of cognitive impairment, criteria used for cognitive impairment, etiologic differences in MCI subtypes, or age at which MetS is assessed. To our knowledge, the association between the MetS and MCI (defined by specified criteria at the time of evaluation) has not been assessed in the population-based setting. Our previous studies have shown associations of vascular risk factors including diabetes,12 coronary heart disease,13 and stroke14 with na-MCI, but not with the amnestic subtype (a-MCI) which has been shown to have a stronger association with the Apolipoprotein ε4 allele, and with degenerative disease. Thus, we hypothesize that the MetS may be associated with the non-amnestic MCI subtype (na-MCI). This association of the MetS with na-MCI may occur through an inflammatory process with associated endothelial dysfunction. Finally, age at assessment of MetS, may influence the associations observed with MCI. In this study, we investigate the association of MetS with MCI overall and with MCI subtypes, and the potential interaction with inflammation in a population-based sample of elderly subjects who have been well characterized for MCI using published criteria at the time of evaluation.

Methods

Identification of Study Participants

The study was conducted as part of a population based study. The details of the study design and participant selection have been previously published.15 Briefly, we used the medical records linkage system[16] to construct a sampling frame of all Olmsted County, Minnesota, residents aged 70 to 89 years old on October 1, 2004. Of the eligible 4392 subjects, 2719 (61.9%) agreed to participate in the study by telephone (n = 669) or in person (n = 2050), and 1673 declined participation. All participants provided informed, written consent prior to participation. Study participants underwent a blood draw; a nurse evaluation that included a risk factor assessment and administration of the Clinical Dementia Rating Scale to the participant and to an informant; a physician evaluation; and a neuropsychological assessment using 9 cognitive tests to assess impairment in 4 cognitive domains: memory, executive function, language, and visuospatial skills.[15]

Criteria for MCI, Dementia, and Normal Cognition

All the data for each participant were reviewed by an expert panel of physicians, neuropsychologists, and nurses who evaluated the subject, for a diagnosis of MCI, normal cognition, or dementia by consensus. A diagnosis of MCI (cases) was made according to published criteria: cognitive concern by physician, nurse, or participant; impairment in one or more of the four cognitive domains; essentially normal functional activities; and absence of dementia.[17] Participants were classified as having amnestic MCI (a-MCI) if the memory domain was impaired or non-amnestic MCI (na-MCI) if there was no impairment in memory. A diagnosis of dementia was made according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.*[18] Subjects who did not receive a diagnosis of MCI or dementia were considered cognitively normal (controls) in accordance with published criteria.[17,19]

Assessment of the Metabolic Syndrome

Self-report of a physician diagnosis of diabetes and hypertension or treatment for these conditions was ascertained by interview. Participants were requested to bring bottles of all their current medications to the evaluation and from this, pharmacologic treatments for diabetes or hypertension were assessed. The diagnoses were also confirmed in the medical records linkage system.[16] Weight was measured using an electronic balance, height was measured using a stadiometer, and blood pressure was measured in duplicate using a sphygmomanometer and averaged. Blood glucose levels at baseline were determined at the time of the blood draw after an overnight fast (for subjects evaluated in the morning) and after a 4-hour fast for subjects seen in the afternoon. Samples were aliquoted and stored at -70°C. Serum triglycerides, high-density lipoprotein, and total cholesterol were measured from thawed frozen plasma or serum samples from the blood draw.[15]

MetS was defined according to criteria proposed by the National Cholesterol Education Program (NCEP) Adult Treatment panel III (ATP III),2 the International Diabetes Federation, 20,21 and the American Heart Association.22 The criteria include presence of 3 or more of the following conditions: 1) use of anti-diabetic agents (oral agents or insulin) or impaired fasting glucose ≥ 110 mg/dl;2,22 2) treatment for hypertension, systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg; 3) serum triglycerides ≥ 150 mg/dl or treatment; 4) serum high density lipoprotein < 40 mg/dl for men or < 50 mg/dl for women; 5) Obesity, defined as a body mass index (BMI; weight in kilograms divided by the height in meters squared) ≥ 30 kg/m^2 based on the criterion used by the World Health Organization.21,23 This measure was a substitute for abdominal adiposity, the criterion used by NCEP ATP III (waist circumference ≥ 50 inches in men and ≥ 40 inches in women)[2] because abdominal adiposity was not measured at baseline. Since subjects evaluated in the afternoon only had a 4-hour fast, a total cholesterol ≥ 200 mg/dl was considered abnormal instead of triglyceride level ≥ 150 mg/dl,22 and a blood glucose level ≥ 140 mg/dl was considered impaired.24

Covariates

Date of birth, sex, educational status, marital status, and current cigarette smoking were assessed by interview.15 A history of coronary heart disease (CHD) and stroke were also assessed by interview and confirmed from the records-linkage system.16 The presence of depressive symptoms was assessed by administration of the Neuropsychiatric Inventory Questionnaire to a spouse or to an informant of the participant.25 C-reactive protein was measured from the thawed frozen samples from the baseline blood draw, and apolipoprotein (Apoe) ε2, ε3, ε4 genotyping was performed using standard methods.26 All study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Statistical Analyses

We compared subjects with and without MCI using the non-parametric Wilcoxon rank sum test for continuous measures and a chi-squared test for categorical variables. We used logistic regression models to estimate associations (odds ratios [OR]; 95% confidence intervals [CI]) between MetS and MCI, adjusting for age in years, sex, and number of years of education. We repeated the analyses for MCI subtypes (na-MCI and a-MCI). In additional multivariable analyses we assessed potential confounding by Apoe genotype, coronary heart disease, depression, and stroke (fully adjusted model). We evaluated effect modification in stratified analyses across strata of age (70 to 79 years vs 80 to 89 years), sex, and years of education (< 12 years vs ≥ 12 years), and by explicitly incorporating interaction terms between MetS and the variable in the logistic regression models. Because of the reported interaction between MetS and inflammation in their association with cognitive decline,8 and the observed associations of vascular risk factors with na-MCI among subjects in the present study, we investigated the potential interaction between inflammation and MetS in their associations with MCI and its

subtypes, with CRP as the measure of inflammation. To further explore this interaction, we categorized subjects into 6 groups based both on presence or absence of MetS and on CRP tertile. We then assessed the OR (95% CI) of MCI for 5 of the categories compared to the reference group which comprised subjects with no MetS and CRP in the lowest tertile. In regard to criteria for MetS, we also defined an impaired fasting glucose as ≥ 100 mg/dl as suggested in more recent literature and repeated the analyses using this cutpoint for impaired fasting glucose. However, the results were essentially the same and only the data using the cutpoint of ≥ 110 mg/dl are reported. We also performed analyses to assess the association of MetS with MCI, adjusting for use of statins (yes or no) to assess confounding, and stratified by use of statins to assess possible interaction (effect modification). This is because subjects with MetS are typically more likely to be receiving treatment with statins, which in turn, may reduce the burden of MetS and the impact of inflammation.27 All analyses were performed using SAS version 8.0 software (SAS Institute, Cary, NC).

Results

Of the 2050 who were evaluated in person, 1969 completed the face-to-face evaluation; 67 subjects who were diagnosed with dementia based on the evaluation and 14 who did not complete the evaluation are not included in the present study. The characteristics of the 1969 participants are described in Table 1; 51% were male, 48% were < 80 years, and 53% had more than 12 years of education. The frequency of the MetS was 48% overall and did not differ between MCI cases and controls: 46% in subjects with any MCI, and 48% in cognitively normal subjects. Age, sex, years of education, history of CHD, stroke, depression, and ApoE ε4 allele status were associated with MCI in unadjusted analyses; there was no difference in the use of statins (Table 1). The frequency of a BMI ≥ 30 kg/m^2 was lower in MCI cases than in controls (P = 0.04; Table 1), but there were no significant differences in regard to the remaining 4 individual components of the MetS.

The frequency of MetS was higher among subjects with na-MCI (51.1%) than among subjects with a-MCI (44.4%), but neither differed significantly from cognitively normal subjects (48.3%; Table 2). Compared to subjects with a-MCI, subjects with na-MCI had a non-significantly higher frequency of an impaired fasting glucose (P = 0.26), elevated blood pressure (P = 0.10), and BMI ≥ 30 kg/m^2 (P = 0.19). Compared to cognitively normal subjects, subjects with na-MCI had a higher frequency of an elevated blood pressure (P = 0.06), whereas subjects with a-MCI had a significantly lower frequency of a BMI ≥ 30 kg/m^2 (P = 0.02). Subjects with na-MCI had higher median CRP levels than subjects with a-MCI (P = 0.02) and cognitively normal subjects (P = 0.003; Table 2).

Subjects with MetS had higher CRP levels than subjects without MetS; this difference was statistically significant among cognitively normal subjects, but not among subjects with either MCI subtype (Figure). CRP levels were highest among subjects with na-MCI; the median CRP (25th, 75th percentile mg/L) was 2.44 (0.9, 5.89 mg/L) in na-MCI subjects with MetS and 1.98 (0.93, 4.48 mg/L) in na-MCI subjects without MetS. In contrast, the median CRP (25th, 75th percentile) levels were lower in both cognitively normal subjects with MetS (1.73 [0.8, 3 3.58] mg/L) and without MetS (1.35 [0.68, 2.93] mg/L).

In multivariable models, MetS was not significantly associated with MCI (combined a-MCI and na-MCI), a-MCI or na-MCI; the point estimates were all close to the null (Table 3). The point estimates and 95% CIs remained essentially the same in the fully-adjusted models. With additional adjustment for use of statins, the ORs were unchanged (Table 3). There were essentially no differences across strata based on statin use for association of MetS with all MCI, a-MCI, and na-MCI (data not reported). However, we did not have sufficient power to detect a significant effect modification for the association of MetS with na-MCI. High C-reactive

protein (CRP highest tertile vs lowest tertile) was associated with na-MCI (OR = 1.85; 95% CI = 1.05, 3.24) but not with a-MCI (OR = 1.07; 95% CI = 0.76, 1.52), after adjusting for sex, age, and years of education. When CRP (tertiles) and MetS were simultaneously assessed in the same model, the highest CRP tertile was significantly associated with na-MCI (OR = 1.84; 95% CI = 1.05, 3.25) but not with a-MCI (OR = 1.09; 95% CI = 0.77, 1.54); MetS was not associated with either na-MCI (OR = 1.03; 95% CI = 0.66, 1.61) or a-MCI (OR = 0.90; 95% CI = 0.68, 1.20). The interactions between MetS and inflammation, as measured by tertiles of CRP were not statistically significant for all MCI ($P = 0.872$), for a-MCI ($P = 0.877$), or na-MCI ($P = 0.435$). When associations of MCI with the combined categories of inflammation (based on CRP tertiles) and MetS were examined, the combination of MetS and high CRP (compared to no MetS and lowest CRP tertile; the reference group) was associated with na-MCI (OR = 2.31; 95% CI = 1.07, 5.00; $P = 0.03$), but not with a-MCI (OR = 0.96; 95% CI = 0.59, 1.54; Table 4). However, given that the interaction between MetS and CRP did not reach significance, we cannot exclude the possibility that this difference predominantly reflects that main effect of CRP that we have observed.

Discussion

In our population-based sample of 70 to 89 year olds, subjects with MetS and high levels of inflammation had a 2.3-fold elevated OR of na-MCI. Given several prior reports of an interaction between levels of inflammatory response markers and MetS, our finding was not completely unexpected.[8,9,28] Although we found no overall association between MetS and MCI, we have previously observed in this cohort, that vascular phenomena such as diabetes,[12] stroke,[14] and CHD[13] are associated with na-MCI rather than with a-MCI, the MCI subtype that is typically associated with AD. Thus, we have extended prior observations by others, in demonstrating that in the presence of inflammation, the MetS may be more likely to be associated with the form of cognitive impairment, na-MCI, that may be more closely linked to cerebrovascular disease.[29]

The observation that the combined presence of MetS and a high level of inflammation is associated with na-MCI but not with a-MCI, is novel. Other investigators have reported associations of MetS with cognitive impairment among subjects with high levels of inflammation.[8,9,28] However, these studies have typically not distinguished between cognitive impairment subtypes. In two prospective cohort studies, subjects with MetS and high levels of inflammation had a greater cognitive decline during follow-up[8] or an increased risk of cognitive impairment[9,28] compared to subjects with low levels of inflammation. Thus, the effects of the MetS on cognition in elderly persons may be mediated directly through inflammation, or indirectly through effects of inflammation on cerebral atherosclerosis and endothelial dysfunction.[6,22] Consistent with the observed modifying role of inflammation, it has been suggested that the effect of including CRP in criteria for MetS in predicting atherosclerotic vascular disease should be investigated.[30]

The lack of an association of MetS with a-MCI is inconsistent with the purported role of a-MCI as a prodromal stage for AD and the positive association of vascular risk factors with AD. This inconsistency may, in part, be due to a certain reasons. The association of Apoe ε4 allele with a-MCI may be stronger and evident earlier in the pathologic disease process than the effect of vascular diseases. This is confirmed by the significant association between a-MCI and presence of an Apoe ε4 allele (OR = 1.68; 95% CI = 1.23, 2.30) in the present study.[14] In addition, Apoe ε4 allele has been associated with lower levels of inflammation.[31,32] These factors may mitigate against observing an association of MetS with a-MCI in the earlier stages of the disease or until there is more severe vascular disease as in AD. Subjects with a-MCI in this study were at the very mild end of the disease spectrum; the mean CDR sum of boxes score was only 0.5. Thus, as with other studies that have not observed a predictive role of MetS for

vascular outcomes in the short term,22,33 a positive association of MetS or vascular risk factors with a-MCI, or a-MCI progression to AD may be observed in the longer term. Thus, although vascular risk factors may be associated with both a-MCI and na-MCI, the association with a-MCI may be observed at a more severe stage of MCI.

We did not observe an association between MetS and MCI overall. This lack of an association when MCI subtype or inflammation is not taken into account may be related to the older age of subjects in the present study, and is consistent with similar studies conducted among older subjects. In the Leiden 85-Plus study (all age 85 years at baseline), there were no differences between subjects with and without the MetS for any of the cognitive tests at baseline;34 however, during follow-up there was a decelerated decline in cognition among subjects with MetS at baseline compared to subjects with no MetS.34 Similarly, among subjects with a mean age of 79 years, subjects with MetS had significantly better cognitive function compared to subjects without MetS (OR = 0.37; 95% CI = 0.15, 0.91).35

Alternately, significant positive associations between MetS and cognitive impairment have been reported in cohorts that were younger than subjects in the present study.8,9,28,36 Typically, these studies also did not distinguish between MCI subtypes or specific cognitive domains. In the Longitudinal Aging Study Amsterdam (65 to 88 year olds), MetS was associated with cognitive impairment cross-sectionally.28 In another prospective cohort (mean age 71 years), subjects with MetS at baseline had a greater cognitive decline than subjects without MetS during follow-up.8 In the Health, Aging and Body Composition Study (mean age 74 years), there were no significant differences in cognitive scores between subjects with and without MetS at baseline, but the MetS was associated with a 20% increased risk of cognitive impairment during follow-up.9 In the Singapore Longitudinal Aging Studies (mean age approximately 55 years), the MetS was significantly associated with a decline in cognition. 37

Together, these studies suggest that the association between the MetS and cognitive function may vary with age at ascertainment of the MetS. Components of the MetS in mid-life are a risk factor for late-life dementia or accelerated cognitive impairment,38,39 yet, when assessed in elderly subjects, these conditions are associated with either a decelerated cognitive decline or have no association with late-life cognitive impairment.10,11,40 The decline in weight prior to dementia onset may represent adverse health conditions that may promote cognitive impairment or dementia.41 In contrast, high BMI in elderly persons may reflect well-being, consistent with the hypothesis that some forms of obesity may not be associated with insulin resistance and therefore, may not increase the risk of cognitive impairment.37 Similarly, elevated blood pressure in older persons may prevent cerebral hypoperfusion and thereby, may protect against cognitive impairment.40 It is also possible that the perceived beneficial effects of MetS or its components on cognition in the elderly may be due to survival bias wherein subjects with MetS or its components who are at greater risk for cognitive impairment have greater mortality, and do not survive to an older age.

There are several strengths of our study. The population-based design reduces the potential for selection bias. The prospective characterization of subjects for MCI using previously published specified criteria reduces the potential for misclassification of the MCI diagnosis, as could occur from retrospective application of MCI criteria to previously collected data on cognition, or from the use of non-established criteria for MCI. The medical records-linkage system allowed us to validate self-report of diabetes and hypertension, thereby minimizing misclassification regarding presence of the MetS. These findings in an older population-based cohort, add to the current literature suggesting that among the elderly, MetS or its components may not necessarily have an adverse impact on cognition. Future follow-up of the cohort will enable us to determine whether the combined presence of inflammation and MetS at baseline

is associated with cognitive decline during follow-up, incident na-MCI, or whether in contrast, MetS without inflammation has no association with cognitive decline or contributes to a decelerated cognitive decline as suggested.[34]

Limitations to our study that should be noted include the cross-sectional assessment of the association of MetS with MCI; this precludes our ability to assess causality. There is potential for non-participation bias if subjects with MetS and cognitive impairment were less likely to participate in the study. To address potential non-participation bias, we used a propensity scores approach and medical record information abstracted from the record linkage system for participants and non-participants, to assess potential non-participation bias. This approach takes into account the characteristics of non-participants[42] and assigns higher weights for participants who have characteristics similar to non-participants in logistic regression models. The propensity-adjusted estimates for this study were the same as the unadjusted estimates, suggesting an absence of non-participation bias on our findings (these results are not reported). Finally, the study was conducted among an older cohort of primarily Caucasian subjects; therefore caution should be exercised in applying the findings to subjects not represented in the study.

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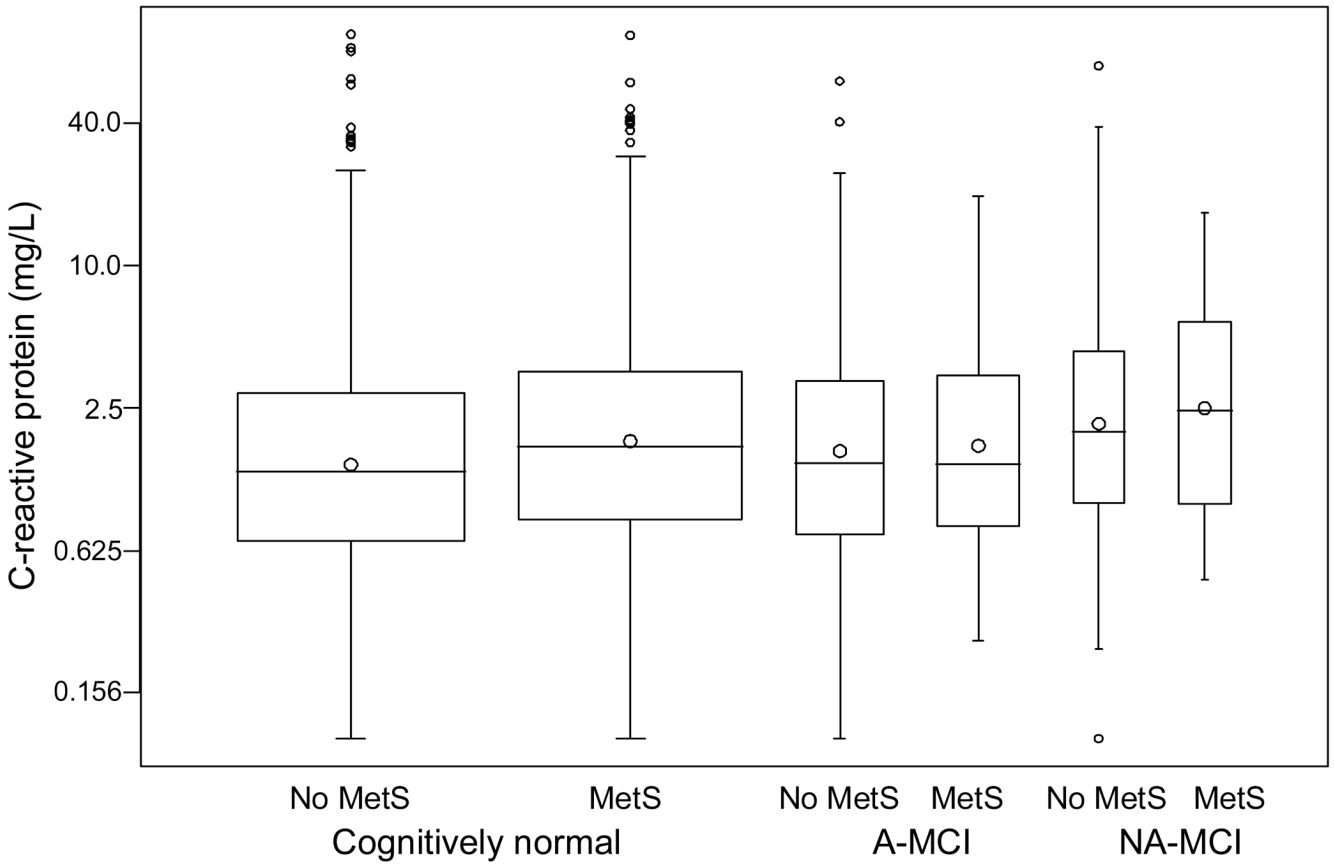

Figure.

Distribution of C-reactive protein levels in subjects with and without the metabolic syndrome (MetS) in cognitively normal subjects, and in subjects with amnestic (a-MCI) and non-amnestic (na-MCI) MCI, with y-axis on a log scale. CRP levels were highest in subjects with na-MCI and metabolic syndrome (MetS). The lower and upper margins of the box represent the 25th and 75th percentiles; the line in the middle represents the median. The round circle in the middle of the box represents the mean, and circles outside of the box represent outliers that are greater than or less than 1.5 times the interquartile range. The short horizontal line connected to the box by a vertical line represents the largest and smallest values that are not considered outliers. The width of each box corresponds to the number of subjects in that group.

Table 1
Characteristics of study subjects at baseline

Variable	All subjects N = 1969 N (%)	All MCI N = 329 N (%)	Cognitively Normal N = 1640 N (%)	P (MCI vs Normal)
Demographic				
Male Sex	1002 (50.9)	192 (58.4)	810 (49.4)	0.003
Age, yr				
< 80	950 (48.2)	103 (31.3)	847 (51.6)	<.0001
≥ 80	1019 (51.8)	226 (68.7)	793 (48.4)	
Education, yr				
< 9	140 (7.1)	48 (14.6)	92 (5.6)	<.0001
9-12	781 (39.7)	141 (42.9)	640 (39.0)	
> 12	1048 (53.2)	140 (42.5)	908 (55.4)	
Clinical Conditions				
CHD				
No	1414 (71.8)	219 (66.6)	1195 (72.9)	0.020
Yes	555 (28.2)	110 (33.4)	445 (27.1)	
Stroke				
No	1743 (88.5)	263 (79.9)	1480 (90.2)	<.0001
Yes	226 (11.5)	66 (20.1)	160 (9.8)	
Depression (NPI criteria)*				
No	1640 (86.0)	233 (73.0)	1407 (88.5)	<.0001
Yes	268 (14.0)	86 (27.0)	182 (11.5)	
Metabolic Syndrome Criteria†				
Number of criteria				
0-1	430 (21.8)	67 (20.4)	363 (22.1)	0.37
2	595 (30.2)	110 (33.4)	485 (29.6)	
≥ 3	944 (47.9)	152 (46.2)	792 (48.3)	
Impaired Fasting Glucose‡				
No	1566 (79.6)	257 (78.1)	1309 (79.9)	0.47
Yes	402 (20.4)	72 (21.9)	330 (20.1)	
Elevated Blood Pressure§				
No	291 (14.8)	43 (13.1)	248 (15.1)	0.34
Yes	1678 (85.2)	286 (86.9)	1392 (84.9)	
Elevated Triglycerides‖				
No	576 (30.2)	97 (30.9)	479 (30.1)	0.77
Yes	1331 (69.8)	217 (69.1)	1114 (69.9)	
Low HDL¶				

	All subjects N = 1969	All MCI N = 329	Cognitively Normal N = 1640	
Variable	**N (%)**	**N (%)**	**N (%)**	**P (MCI vs Normal)**
No	902 (48.7)	141 (46.4)	761 (49.2)	0.37
Yes	949 (51.3)	163 (53.6)	786 (50.8)	
BMI ≥ 30, Kg/m^2**				
No	1407 (73.1)	247 (77.7)	1160 (72.2)	0.04
Yes	518 (26.9)	71 (22.3)	447 (27.8)	
ApoE ε4 allele††				
No ε4	1410 (76.9)	216 (70.8)	1194 (78.1)	0.006
ε4+	423 (23.1)	89 (29.2)	334 (21.9)	

* Information was missing for 10 MCI cases and 51 normals.

† Criteria were based on the NCEP ATP III criteria except that BMI was used instead of waist circumference.

‡ Diabetes mellitus with treatment or fasting blood glucose ≥ 110 mg/dL at baseline, information was missing for 1 cognitively normal subject.

§ Treatment for hypertension or systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg.

// AM Triglycerides ≥ 150 mg/dL, PM cholesterol ≥ 200 mg/dL or treatment for elevated lipids, information was missing for 15 MCI cases and 47 normals.

¶ High density lipoprotein < 40 mg/dL in men, < 50 in women; information was missing for 25 MCI cases and 93 normals.

** Information was missing for 11 MCI cases and 33 normals.

†† Subjects with ApoE ε2ε4 (2.3%) are excluded, and information was missing for 18 MCI cases and 75 normals.

CHD, coronary heart disease; BMI, body mass index; Apoe, apolipoprotein; HDL, high density lipoprotein

Table 2
Frequency of MetS criteria and CRP distribution by mild cognitive impairment subtype

Variable	No MCI (n=1640) N (%)	Amnestic MCI (n=241) N (%)	Non-amnestic MCI (n=88) N (%)
Metabolic Syndrome			
Number of criteria			
0-1	363 (22.1)	50 (20.7)	17 (19.3)
2	485 (29.6)	84 (34.9)	26 (29.5)
≥ 3	792 (48.3)	107 (44.4)	45 (51.1)
Impaired fasting glucose*			
No	1309 (79.9)	192 (79.7)	65 (73.9)
Yes	330 (20.1)	49 (20.3)	23 (26.1)
Elevated blood pressure†			
No	248 (15.1)	36 (14.9)	7 (8.0)
Yes	1392 (84.9)	205 (85.1)	81 (92.0)
Elevated Triglycerides‡			
No	479 (30.1)	68 (30.1)	29 (33.0)
Yes	1114 (69.9)	158 (69.9)	59 (67.0)
Low HDL§			
No	761 (49.2)	101 (46.1)	40 (47.1)
Yes	786 (50.8)	118 (53.9)	45 (52.9)
BMI ≥ 30 Kg/m^2//			
No	1160 (72.2)	186 (79.5)	61 (72.6)
Yes	447 (27.8)	48 (20.5)	23 (27.4)
	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)
C-reactive protein, mg/L¶	1.56 (0.74, 3.20)	1.47 (0.76, 3.41)	2.23 (0.98, 5.28)

*Missing information for 1 subject with normal cognition.

†Treatment for hypertension, SBP ≥130 mm Hg, DBP ≥ 85 mmHg.

‡High triglyceride or treatment; information was missing for 47 cognitively normal and 15 amnestic MCI.

§Information was missing for 93 cognitively normal, 22 amnestic MCI, 3 non-amnestic MCI.

//Information was missing for 33 normal, 7 amnestic MCI, 4 non-amnestic MCI. Amnestic MCI cases were significantly different from cognitively normal (p = 0.019).

¶Information was missing for 71 cognitively normal, 15 amnestic MCI, 1 non-amnestic MCI. Non-amnestic MCI were significantly different from amnestic MC (p=0.016), and from cognitively normal (p=0.003).

DM, diabetes mellitus, CHD, coronary heart disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; TG, triglyceride; FBG, fasting blood glucose; ApoE, apolipoprotein; Q1; 25th percentile; Q3, 75th percentile; % is in non- missing subjects.

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Table 3

Associations of metabolic syndrome with all MCI, amnestic and non-amnestic MCI

Variable	No MCI	All MCI			Amnestic MCI			Non-amnestic MCI		
	N (%)		OR (95%CI)	p	N (%)	OR (95%CI)	p	N (%)	OR (95%CI	p
Adjusted*		N (%)								
A. No of Criteria										
0-2	848 (51.7)	177 (53.8)	1.00 (reference)		134 (55.6)	1.00 (reference)		43 (48.9)	1.00 (reference)	
≥ 3	792 (48.3)	152 (46.2)	0.93 (0.73, 1.19)	0.57	107 (44.4)	0.86 (0.65, 1.14)	0.29	45 (51.1)	1.10 (0.71, 1.71)	0.66
B. Ordinal	1640 (100)	329 (100)	1.00 (0.90, 1.11)	0.96	241 (100)	0.95 (0.85, 1.07)	0.44	88(100)	1.10 (0.92, 1.32)	0.28
Fully Adjusted†										
A. No of criteria										
0-2	848 (51.7)	177 (53.8)	1.00 (reference)		134 (55.6)	1.00 (reference)		43 (48.9)	1.00 (reference)	
≥ 3	792 (48.3)	152 (46.2)	0.95 (0.72, 1.23)	0.68	107 (44.4)	0.91 (0.67, 1.22)	0.52	45 (51.1)	1.01 (0.64, 1.60)	0.96
B. Ordinal	1640 (100)	329 (100)	0.99 (0.89, 1.11)	0.91	241 (100)	0.97 (0.85, 1.10)	0.64	88(100)	1.05 (0.87, 1.27)	0.62

*Adjusted for age and years of education (as continuous variables), and sex.

†Adjusted for age, years of education, sex, coronary heart disease, stroke, depression, and ApoE ε4 (ε3ε4/ε4ε4 vs. ε2ε2, eε2ε3, ε3ε3).

MCI: mild cognitive impairment; OR: odds ratio; CI: confidence interval;

Table 4

Associations of metabolic syndrome and tertiles of C-reactive protein with any MCI, amnestic and non-amnestic MCI

	No MCI (N = 1569)	Any MCI (N = 313)		Amnestic MCI (N = 226)		Non-amnestic MCI (N = 87)	
Variable	**N (%)**	**N (%)**	**OR (95%CI)***	**N (%)**	**OR (95%CI)**	**N (%)**	**OR (95%CI)**
CRP/METS categories							
CRPT1, No MetS	303 (19.3)	54 (17.3)	1.00 (reference)	44 (19.5)	1.00 (reference)	10 (11.5)	1.00 (reference)
CRPT1, MetS	229 (14.6)	43 (13.7)	1.03 (0.66, 1.61)	33 (14.6)	0.97 (0.59, 1.58)	10 (11.5)	1.30 (0.53, 3.21)
CRPT2, No MetS	259 (16.5)	54 (17.3)	1.15 (0.75, 1.75)	37 (16.4)	0.99 (0.62, 1.60)	17 (19.5)	1.95 (0.87, 4.36)
CRPT2, MetS	264 (16.8)	49 (15.7)	1.00 (0.65, 1.55)	36 (15.9)	0.92 (0.57, 1.49)	13 (14.9)	1.35 (0.58, 3.16)
CRPT3, No MetS	235 (15.0)	54 (17.3)	1.29 (0.84, 1.98)	39 (17.3)	1.18 (0.73, 1.89)	15 (17.2)	1.83 (0.80, 4.18)
CRPT3, MetS	279 (17.8)	59 (18.8)	1.22 (0.81, 1.85)	37 (16.4)	0.96 (0.59, 1.54)	22 (25.3)	2.31 (1.07, 5.00)

*Adjusted for age and years of education (as continuous variables), and sex.

MCI: mild cognitive impairment; OR: odds ratio; CI: confidence interval; CRPT1: C reactive protein lowest tertile; T2 = middle tertile; T3 = highest tertile (≥ 2.49 mg/L)