Original Investigation

Metabolic Syndrome and the Risk of Mild Cognitive Impairment and Progression to Dementia

Follow-up of the Singapore Longitudinal Ageing Study Cohort

Tze Pin Ng, MD; Liang Feng, PhD; Ma Shwe Zin Nyunt, PhD; Lei Feng, PhD; Qi Gao, PhD; May Li Lim, BSc; Simon L. Collinson, PhD; Mei Sian Chong, MRCP; Wee Shiong Lim, MRCP; Tih Shih Lee, MD, PhD; Philip Yap, MRCP; Keng Bee Yap, MRCP

IMPORTANCE The association of the metabolic syndrome (MetS) and component cardiovascular risk factors with the risk of developing mild cognitive impairment (MCI) and MCI progression to dementia is not well established.

OBJECTIVE To investigate the association of the MetS and its component cardiovascular risk factors with the incidence of MCI and its progression to dementia.

DESIGN, SETTING, AND PARTICIPANTS Prospective longitudinal study from September 1, 2003, through December 31, 2009, in communities in 5 districts in the South East region of Singapore. Study participants were a population-based sample of 1519 cognitively normal adults 55 years and older.

MAIN OUTCOMES AND MEASURES Prespecified outcomes were incident MCI and MCI progression to dementia.

RESULTS The study cohort comprised 1519 participants. Their mean (SD) age was 64.9 (6.8) years, and 64.8% (n = 984) were female. Baseline characteristics associated with an increased risk of incident MCI were MetS (hazard ratio [HR], 1.46; 95% CI, 1.02-2.09), central obesity (HR, 1.41; 95% CI, 1.01-1.98), diabetes mellitus (HR, 2.84; 95% CI, 1.92-4.19), dyslipidemia (HR, 1.48; 95% CI, 1.01-2.15), and 3 or more component cardiovascular risk factors (HR, 1.58; 95% CI, 1.13-2.33). Baseline characteristics associated with an increased risk of MCI progression to dementia were MetS (HR, 4.25; 95% CI, 1.29-14.00), diabetes mellitus (HR, 2.47; 95% CI, 1.92-4.19), and 3 or more component cardiovascular risk factors (HR, 4.92; 95% CI, 1.39-17.4).

CONCLUSIONS AND RELEVANCE The MetS was associated with an increased incidence of MCI and progression to dementia. Identifying individuals with diabetes mellitus or the MetS with or without MCI is a promising approach in early interventions to prevent or slow progression to dementia.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Tze Pin Ng, MD, Gerontological Research Programme, Department of Psychological Medicine, National University of Singapore, Level 9, National University Hospital System Tower Block, 1E Kent Ridge Rd, Singapore 119228 (pcmngtp@nus.edu.sg).

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The metabolic syndrome (MetS) is a clustering of cardiovascular risk factors (CVRFs) (namely, obesity, diabetes mellitus, hypertension, and dyslipidemia) that is known to predict increased risks of cardiovascular disease and stroke.[1] Among them, diabetes mellitus in midlife and late life is consistently and strongly associated with subsequent dementia (particularly vascular dementia), as well as with mild cognitive impairment (MCI), a predementia syndrome known to confer an increased risk of progressing to dementia.[2] Studies show that hypertension in midlife is strongly associated with incident dementia in later life, particularly vascular dementia,[2] but late-life hypertension is not associated with dementia.[3,4] There are contradictory reports of associations of body and fat mass and total cholesterol level with incident dementia or vascular dementia in the elderly.[5-7]

Evidence for an association between the MetS and the risk of dementia is limited and conflicting. The MetS appears to increase the rate of cognitive decline,[8-11] but no association was found among individuals 85 years and older.[12] Several cross-sectional and case-control studies have found the MetS to be associated with overall dementia among women[9] and with Alzheimer disease (AD).[13,14] Prospective cohort studies have reported positive associations of the MetS with overall dementia[15] and vascular dementia,[16,17] no association between the MetS and incident dementia,[18,19] and association of the MetS with a lower risk of AD after age 75 years.[19]

Few studies[20-23] have investigated the relationship between the MetS and MCI. One population-based cross-sectional study[20] found no association of the MetS with MCI overall, and only the combination of the MetS and high levels of inflammation was significantly associated with nonamnestic MCI (na-MCI). Our group's previous case-control study[21] showed an association between the MetS and amnestic MCI (a-MCI). Among 2 prospective cohort studies, one study[22] found that the MetS, hyperglycemia, and more CVRFs were associated with incident cognitive impairment (including MCI and dementia) but had limited power to determine whether the MetS was associated with incident MCI itself. The more recent Italian cohort study by Solfrizzi et al[23] reported no significant differences in overall risk of developing incident MCI among noncognitively impaired individuals with the MetS compared with those without the MetS over 3½ years of follow-up, but the investigators found that among individuals with MCI those with the MetS were more than 4 times more likely to progress to dementia. In this study, we investigated the association of the MetS and its component CVRFs with the incidence of MCI and its progression to dementia over a median of 3.8 years of follow-up in a large Chinese population-based sample.

Key Points

Question: Are the metabolic syndrome (MetS) and its component cardiovascular risk factors (CVRFs) associated with increased risks of the development of mild cognitive impairment (MCI) and MCI progression to dementia?

Findings: In this prospective cohort study of 1519 cognitively normal older adults, baseline MetS, central obesity, diabetes mellitus, dyslipidemia, and 3 or more component CVRFs were associated with increased risks of incident MCI. The MetS, diabetes mellitus, and 3 or more component CVRFs among those with MCI carried an increased risk of progression to dementia.

Meaning: The MetS and its components represent potential targets for early intervention to prevent or slow MCI progression to dementia.

Methods

Population

The Singapore Longitudinal Ageing Study (SLAS) is a population-based study designed for long-term follow-up of a young aging cohort (≥55 years) that aims to relate cardiovascular and other risk factors measured in midlife and late life to subsequent risks of incident MCI and dementia. Details of the population sampling and study methods of the first-wave recruitment cohort (SLAS-1) among participants 55 years and older have been described previously.[24] Recruitment and baseline assessments for 2804 participants were conducted in 2003-2004, and approximately 3-year follow-ups were conducted in 2005-2007 and 2007-2009. At baseline, each participant underwent detailed structured interviews, clinical evaluation, blood sampling, and performance-based tests for an extensive range of demographic, medical, biological, psychosocial, and neurocognitive characteristics. The study was approved by the National University of Singapore Institutional Review Board, and written informed consent was obtained from all participants.

The study sample was restricted to 2611 Chinese participants, after excluding Malay and Indian participants because of small numbers. After excluding individuals with prevalent MCI (n = 506) and dementia (n = 53) at baseline, a cohort of 2042 (the remainder had missing data) cognitively normal participants with available data on the MetS and CVRFs were followed up from January 1, 2006, to December 31, 2009 (median follow-up, 3.8 years). During this period, 227 participants died, and 296 participants were lost to follow-up. The longitudinal analysis was based on 1519 individuals, with 5146 person-years of follow-up (mean [SD], 3.4 [1.5] person-years) to incident MCI (n = 141). Individuals who were excluded from the analysis owing to death and loss to follow-up were significantly more likely to be older, male, smokers, and less physically and socially active and to have diabetes mellitus.

Among 504 participants with MCI and available MetS data at baseline, longitudinal data were analyzed for 425 persons with 1529 person-years of follow-up to dementia progression (n = 14), after excluding 79 individuals who died (n = 44) or were lost to follow-up (n = 35). The excluded individuals with MCI were significantly more likely to be smokers and less physically and socially active and to have hypertension.

Measurements

Self-reports of a diagnosis of diabetes mellitus, hypertension, heart disease, and stroke, with details of medications, were ascertained by research nurses at the individual's home. The mean of 3 blood pressure readings with the participant

seated was recorded using a standard mercury sphygmomanometer (Dekamet; Accoson). Waist circumference was measured in centimeters at the midpoint between the lowest rib margin and the top of the iliac crest at minimal respiration to the closest 0.1 cm. Overnight fasting serum samples were analyzed for blood glucose and lipid levels using standard laboratory techniques.

The MetS was defined using several International Diabetes Federation criteria.[25] First was central obesity (waist circumference ≥90 cm for men and ≥80 cm for women) plus at least 2 CVRFs, including raised triglyceride levels (≥150 mg/dL) or specific treatment for this lipid abnormality (to convert triglyceride levels to millimoles per liter, multiply by 0.0113). Second was reduced high-density lipoprotein cholesterol level (<40 mg/dL in men and <50 mg/dL in women) or specific treatment for this lipid abnormality (to convert cholesterol level to millimoles per liter, multiply by 0.0259). Third was raised blood pressure (systolic ≥130 mm Hg or diastolic ≥85 mm Hg or treatment of previously diagnosed hypertension) and raised fasting plasma glucose level (≥100 mg/dL or previously diagnosed type 2 diabetes mellitus) (to convert glucose level to millimoles per liter, multiply by 0.0555).

Neuropsychological Evaluation

Screening and assessment of cognitive impairment and decline, as well as diagnosis of MCI and dementia, were performed according to a standard clinical assessment for dementia protocol. The Chinese modified version of the Mini-Mental State Examination (MMSE) with education-stratified norms[26] (previously validated to have high sensitivity and specificity) was used to screen for dementia and MCI.[27] Participants with a MMSE score below 27 or a MMSE score decline of 2 points or at least 1 point per year underwent detailed neuropsychological testing and the Clinical Dementia Rating.

The neuropsychological evaluation with a standardized test battery assessed included the following: (1) memory (Rey Auditory Verbal Learning Test immediate and delayed recall[28] and visual reproduction immediate and delayed recall[29]), (2) executive function (Symbol Digit Modality Test,[30] Design Fluency,[31] and Trail Making Test Part B[32]), (3) language (categorical verbal fluency[31]), (4) visuospatial skills (block design[29]), and (5) attention (digit span forward and backward[33] and spatial span forward and backward[29]). The assessment was administered by trained psychology research assistants in English, Mandarin, or Chinese dialects. Details of the neuropsychological tests and their normative values have been described previously.[34,35]

The Clinical Dementia Rating was conducted and scored by trained research nurses (http://www.biostat.wustl.edu/~adrc/cdrpgm/). Functional ability was assessed by dependency in performing 10 basic activities of daily living, including bowels, bladder, grooming, toilet use, feeding, transferring, mobility, dressing, stairs, and bathing.

Final case ascertainment and diagnosis were performed by a review panel consisting of 2 geriatricians (M.S.C. and W.S.L.) and one psychiatrist (T.S.L.). These assessments were based on all available information from baseline and follow-up assessments, including brain magnetic resonance imaging if available.

Diagnosis of MCI and Dementia

Mild cognitive impairment was defined according to published criteria.[36,37] These variables included the following: (1) self-reported subjective memory and cognitive difficulties and the Informant Questionnaire on Cognitive Decline in the Elderly; (2) cognitive deficits in 1 or more domains, including a modified MMSE score of 24 to 27, decline of 2 or more points from baseline, and a neurocognitive domain (memory, executive function, language, visuospatial skills, or attention) score that was 1 to 2 SDs below the age and education-adjusted means or decline from baseline of 0.5 SD from serial measurements); (3) Clinical Dementia Rating of 0 or 0.5; (4) no functional dependency in performing basic activities of daily living[38]; and (5) no dementia.

Dementia diagnosis was based on the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for dementia syndrome,[39] evidence of cognitive deficit from objective assessment (MMSE score ≤23 or neuropsychological domain scores 2 SDs below the age and education-adjusted means), and evidence of social or occupational function impairment (dependency in ≥1 basic activities of daily living[38] or Clinical Dementia Rating ≥1). Participants who did not meet these criteria for MCI or dementia were classified as cognitively normal.

Covariates

Covariates included age, sex, education (none, 1-5 years, or ≥6 years), *APOE-ε4* (MIM 104310) genotype, smoking (current or past smoking vs never smoking), and level of physical, social, or productive activities. The latter were based on the number and frequencies of usual participation in 18 different categories of physical, social, and productive activities.[24]

Statistical Analysis

The incidence rates of MCI and MCI progression to dementia for groups with the MetS, component CVRFs, and 3 or more component CVRFs were calculated as the number of events per 1000 person-years at risk. Cox proportional hazards models were used to model the time to new events of incident MCI or MCI progression to dementia and to estimate hazard ratios (HRs) and 95% CIs. Covariate adjustments were made for age (in years), sex, education, *APOE* genotype (1-2 *ε4* alleles vs no *ε4* allele), and physical, social, and productive activities score. Covariate adjustment did not include cardiac diseases or stroke because they were considered to be more likely mediators rather than confounders. Individuals who did not develop the outcome of interest, died, or were lost to follow-up were censored at the time of their last evaluation. The Cox proportional hazards assumption was checked using a log vs log minus log plot. Effect modifications were explored in stratified analyses performed for subgroups defined by sex, age, and *APOE-ε4* genotype. Data analysis was performed using statistical software (SPSS, version 21.0; IBM Corporation). Statistical significance was set at $P < .05$.

Table 1. Baseline Characteristics of Cognitively Normal SLAS-1 Participants by the Presence or Absence of the Metabolic Syndrome[a]

Variable	All (N = 1519)	Metabolic Syndrome		P Value
		Yes (n = 340)	No (n = 1179)	
Central obesity, No. (%)[b]	663 (43.6)	340 (100)	323 (27.4)	<.001
Type 2 diabetes mellitus, No. (%)	221 (14.5)	120 (35.3)	101 (8.6)	<.001
Hypertension, No. (%)	824 (54.2)	324 (95.3)	500 (42.4)	<.001
Dyslipidemia, No. (%)	912 (60.0)	310 (91.2)	602 (51.1)	<.001
Female sex, No. (%)	984 (64.8)	228 (67.1)	756 (64.1)	.32
Age, mean (SD), y	64.9 (6.8)	66.2 (6.3)	64.6 (6.9)	<.001
Education <6 y, No. (%)	662 (43.6)	193 (56.8)	469 (39.8)	<.001
APOE-ε4 genotype, No. (%)	267 (17.6)	52 (15.3)	215 (18.2)	.22
Current or past smoker, No. (%)	230 (15.1)	54 (15.9)	176 (14.9)	.66
Physical, social, and productive activities score, mean (SD)	10.0 (4.3)	9.4 (4.3)	10.2 (4.3)	<.001
Self-reported stroke, No. (%)	39 (2.6)	9 (2.6)	30 (2.5)	.91
Self-reported cardiac disease, No. (%)	105 (6.9)	48 (14.1)	57 (4.8)	<.001
On cohort follow-up, No. (%)				
MCI	141 (9.3)	46 (13.5)	95 (8.1)	<.001
Dementia	13 (0.9)	3 (0.9)	10 (0.8)	

Abbreviations: MCI, mild cognitive impairment; SLAS-1, Singapore Longitudinal Ageing Study.

[a] Unless otherwise indicated, all data are presented as number (percentage).

[b] Waist circumference exceeding 90 cm in men and exceeding 80 cm in women.

Results

The demographics, risk factors, and MetS characteristics of the cohort members are summarized in **Table 1**. Those with the MetS compared with their non-MetS counterparts were older and less educated; had lower levels of physical, social, and productive activities; and reported more cardiac diseases but not stroke. There were significantly more cases of incident MCI from follow-up among those with the MetS (13.5% [46 of 340]) than among those without the MetS (8.1% [95 of 1179]) ($P < .001$).

The incidence rates, crude and adjusted HRs (95% CIs) of MCI by the MetS, component CVRFs, and number of CVRFs are summarized in **Table 2**. Significantly (1.5-fold to 3-fold) increased risks of MCI were associated with the MetS, as well as in those with diabetes mellitus, central obesity, dyslipidemia, and 3 or more component CVRFs (but not hypertension) compared with their counterparts. The HR estimates were unchanged or modestly attenuated after adjustment for sex, age, education, *APOE-ε4* genotype, smoking, and physical, social, and productive activities score.

Among cohort members who had MCI at baseline (n = 425), those with the MetS had lower levels of physical, social, and productive activities and reported more cardiac diseases and stroke (**Table 3**). There were significantly more cases of incident dementia among those with the MetS (8 of 103 [7.8%]) than among those without the MetS (6 of 322 [1.9%]) ($P < .003$).

The incidence rates and crude and adjusted HRs (95% CIs) of MCI progression to dementia among those with MCI at baseline by the MetS, component CVRFs, and number of CVRFs are summarized in **Table 4**. Significantly increased risks of progression to dementia were associated with the MetS, 3 or more component CVRFs (>4 fold), and diabetes mellitus (approximately ≥2 fold) compared with their counterparts. The risks were also elevated (almost 2 fold) but with statistical nonsignificance for those with central obesity, dyslipidemia, or hypertension. The HR estimates were unchanged or modestly attenuated after adjustment for confounding risk factors.

We repeated our analyses for stratified groups of participants younger than 75 years vs 75 years and older and found that the MetS and component CVRFs were significantly and positively associated with MCI only among the younger subcohort. No significant positive association was observed among those 75 years and older, with nonsignificance of statistical interactions (eTable 1 in the Supplement). Stratified analyses and tests of statistical interaction also did not reveal significant effect modification by sex or *APOE-ε4* genotype.

Discussion

This longitudinal analysis of a Chinese cohort of cognitively normal older persons 55 years and older in Singapore showed that the MetS, diabetes mellitus, central obesity, dyslipidemia, and the presence of 3 or more component CVRFs were associated with a 1.5 to 2 times higher risk of developing MCI. Among those with MCI at baseline, the risks of progression to dementia were more than 4 times greater among those with the MetS or those with 3 or more component CVRFs and more than 2 times greater among those with diabetes mellitus.

We assessed the MetS in a young aging cohort (mean age, 64.9 years) and observed them for up to 10 years (median, 3.8 years) to incident MCI and MCI progression to dementia. Our finding that the MetS and component CVRFs were significantly associated with MCI only among the younger subcohort, with no significant positive association observed among those 75 years and older, suggests that the MetS-MCI relationship was most evident before age 75 years.

Table 2. Associations of the Metabolic Syndrome and Components With Incident Mild Cognitive Impairment on Cohort Follow-up of 1519 Cognitively Normal Participants[a]

Variable	Person-years at Risk	Incident Mild Cognitive Impairment Cases, No.	Cases per 1000 Person-years	Crude HR (95% CI)	*P* Value	Multivariable-Adjusted HR (95% CI)[b]	*P* Value
Metabolic syndrome							
No	4007	95	23.7	1 [Reference]	NA	1 [Reference]	NA
Yes	1139	46	40.4	1.67 (1.18-2.38)	.004	1.46 (1.02-2.09)	.04
Type 2 diabetes mellitus							
No	4399	100	22.7	1 [Reference]	NA	1 [Reference]	NA
Yes	747	41	54.9	2.44 (1.70-3.52)	<.001	2.84 (1.92-4.19)	.001
Central obesity							
No	2971	69	23.2	1 [Reference]	NA	1 [Reference]	NA
Yes	2174	72	33.1	1.54 (1.10-2.14)	.01	1.41 (1.01-1.98)	.045
Hypertension							
No	2353	56	23.8	1 [Reference]	NA	1 [Reference]	NA
Yes	2793	85	30.4	1.09 (0.78-1.54)	.60	0.90 (0.64-1.27)	.55
Dyslipidemia							
No	1998	37	18.5	1 [Reference]	NA	1 [Reference]	NA
Yes	3148	104	33.0	1.54 (1.06-2.24)	.03	1.48 (1.01-2.15)	.04
Component cardiovascular risk factors							
<3	3804	84	22.1	1 [Reference]	NA	1 [Reference]	NA
≥3	1341	57	42.5	1.77 (1.26-2.48)	.001	1.58 (1.13-2.33)	.008

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] Assuming that 13 cases of incident dementia were undetected mild cognitive impairment cases, HRs were reestimated as follows: metabolic syndrome (HR, 1.42; 95% CI, 1.01-2.01; *P* = .048), type 2 diabetes mellitus (HR, 2.50; 95% CI, 1.75-3.57; *P* < .001), central obesity (HR, 1.43; 95% CI, 1.04-1.98; *P* = .03), hypertension (HR, 0.87; 95% CI, 0.62-1.22; *P* = .42), dyslipidemia (HR, 1.38; 95% CI, 0.97-1.97; *P* = .08), and 3 or more component cardiovascular risk factors (HR, 1.55; 95% CI, 1.12-2.16; *P* = .008).

[b] Adjusted for sex, age, education, *APOE-ε4* genotype, smoking, and physical, social, and productive activities score.

Table 3. Baseline Characteristics of SLAS-1 Participants With Mild Cognitive Impairment by the Presence or Absence of the Metabolic Syndrome[a]

Variable	All (N = 425)	Metabolic Syndrome		*P* Value
		Yes (n = 103)	No (n = 322)	
Central obesity, No. (%)[b]	195 (45.9)	103 (100)	92 (28.6)	<.001
Type 2 diabetes mellitus, No. (%)	95 (22.4)	54 (52.4)	41 (12.7)	<.001
Hypertension, No. (%)	230 (54.1)	95 (92.2)	135 (41.9)	<.001
Dyslipidemia, No. (%)	238 (56.0)	88 (85.4)	150 (46.6)	<.001
Female sex, No. (%)	275 (64.7)	67 (65.0)	208 (64.6)	.93
Age, mean (SD), y	68.3 (7.7)	69.1 (7.8)	68.1 (7.7)	.23
Education <6 y, No. (%)	328 (77.2)	80 (77.7)	248 (77.0)	<.09
APOE-ε4 genotype, No. (%)	79 (18.6)	18 (17.5)	61 (18.9)	.70
Current or past smoker, No. (%)	65 (15.3)	16 (15.5)	49 (15.2)	.94
Physical, social, and productive activities score, mean (SD)	8.5 (4.2)	7.7 (4.1)	8.7 (4.2)	.04
Self-reported stroke, No. (%)	22 (5.2)	11 (10.7)	11 (3.4)	.004
Self-reported cardiac disease, No. (%)	36 (8.5)	15 (14.6)	21 (6.5)	.01
Dementia on cohort follow-up, No. (%)	14 (3.3)	8 (7.8)	6 (1.9)	<.003

Abbreviation: SLAS-1, Singapore Longitudinal Ageing Study.

[a] Unless otherwise indicated, all data are presented as number (percentage).

[b] Waist circumference exceeding 90 cm in men and exceeding 80 cm in women.

Previous studies involving older population cohorts (mean age, >75 years) have variously reported that the MetS was associated with MCI overall,[20] with less cognitive decline,[11] or with better cognitive function among the elderly.[40] On the other hand, significant positive associations between the MetS and cognitive impairment or decline have mostly been more consistently reported in middle-aged and younger population-based cross-sectional or case-control studies[9,21,41] or prospective cohort studies.[8,10,11,42,43]

For the MCI syndrome, only 2 studies using cross-sectional and case-control study designs, respectively, have reported positive associations of the MetS with na-MCI[20] or

Table 4. Associations of the Metabolic Syndrome and Components With Progression to Dementia on Cohort Follow-up of 425 Participants With Mild Cognitive Impairment at Baseline

Variable	Person-years at Risk	Incident Dementia Cases, No.	Cases per 1000 Person-years	Crude HR (95% CI)	*P* Value	Multivariable-Adjusted HR (95% CI)[a]	*P* Value
Metabolic syndrome by International Diabetes Federation criteria[25]							
No	1158	6	5.2	1 [Reference]	NA	1 [Reference]	NA
Yes	371	8	21.6	5.03 (1.63-15.50)	.005	4.25 (1.29-14.00)	.002
Type 2 diabetes mellitus							
No	1182	8	6.8	1 [Reference]	NA	1 [Reference]	NA
Yes	347	6	17.3	3.16 (1.06-9.46)	.04	2.47 (1.92-4.19)	.13
Central obesity							
No	836	5	6.0	1 [Reference]	NA	1 [Reference]	NA
Yes	693	9	13.0	2.98 (0.92-9.71)	.07	2.97 (0.85-10.40)	.09
Hypertension							
No	711	5	7.0	1 [Reference]	NA	1 [Reference]	NA
Yes	819	9	11.0	2.08 (0.64-6.76)	.22	1.84 (0.55-6.22)	.32
Dyslipidemia							
No	671	5	7.5	1 [Reference]	NA	1 [Reference]	NA
Yes	858	9	10.5	1.63 (0.54-4.90)	.38	2.04 (0.61-6.78)	.25
Component cardiovascular risk factors							
<3	1083	5	4.6	1 [Reference]	NA	1 [Reference]	NA
≥3	446	9	20.2	5.78 (1.78-18.8)	.004	4.92 (1.39-17.40)	.001

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] Adjusted for sex, age, education, *APOE-ε4* genotype, smoking, and physical, social, and productive activities score.

a-MCI.[21] However, 2 prospective cohort studies[22,23] failed to find a convincing association between the MetS and the risk of incident MCI. In one cohort study[22] of postmenopausal women (mean age, 66 years), the MetS was associated with incident cognitive impairment but not with MCI per se. The Italian prospective cohort study by Solfrizzi et al[23] (mean age, 72 years) reported no association of the MetS with incident MCI but positively reported that the MetS was associated with a 4-fold higher risk of MCI progression to dementia.

In this study, significantly increased risks of incident MCI were found to be associated with diabetes mellitus, central obesity, dyslipidemia, and 3 or more component CVRFs but not with hypertension. This result is in keeping with the strong evidence that diabetes mellitus throughout the life course is causally associated with dementia.[2] Evidence is limited but consistent in suggesting that central obesity in midlife but not late life may be a risk factor for late-life dementia, but evidence for body mass index is inconsistent.[44-46] For dyslipidemia, the published findings are inconsistent in supporting an association with dementia.[2,5] Hypertension in midlife has been shown to be consistently strongly associated with incident dementia in later life overall, particularly vascular dementia; however, inverse or no associations between late-life hypertension and dementia are reported in cohort studies of older persons with short follow-up.[2]

This study has important clinical and therapeutic implications. The predementia syndrome of MCI is widely regarded to be a critical new focus for early intervention. Many potential antidementia treatments have been shown in clinical trials to be ineffective for slowing cognitive decline associated with advanced neuropathological disease. Early intervention in patients with MCI represents a paradigmatic shift in clinical trial interventions aimed at preventing or slowing progression to dementia. There is already good and consistent evidence that individuals with diabetes mellitus have a higher prevalence of cognitive impairment and are at increased risk of developing dementia. Identifying individuals with diabetes mellitus or the MetS with or without MCI is a promising approach in early interventions to prevent or slow progression to dementia.

The study population was optimally powered by its sample size and demographics to detect a significant association of the MetS with incident MCI, with adjustment for important confounding risk factors. However, the number of cases of incident dementia was small. Therefore, the study lacks the power to determine the risk of incident dementia associated with the MetS. Among those who were free of dementia at baseline (cognitively normal and MCI included), with only 26 cases of incident dementia from 6654 person-years of follow-up, elevated but statistically nonsignificant risks of incident dementia were associated with the MetS (adjusted HR, 1.37; 95% CI, 0.60-3.12; $P = .49$) and diabetes mellitus (adjusted HR, 2.07; 95% CI, 0.78-5.50; $P = .14$) (eTable 2 in the Supplement). The estimated excess risk of incident dementia was concentrated in the cohort subset with MCI at baseline but, based on a total of 14 cases with progression to dementia, was surrounded by wide 95% CIs. There were also insufficient numbers in subgroups to demonstrate statistically significant

effect modification by age groups and *APOE-ε4* genotype. Among cognitively normal individuals, there were 13 cases of dementia that were diagnosed without prior detection of MCI status during follow-up, suggesting less than optimal case detection of this elusive predementia condition. Assuming that these dementia cases were all undetected MCI cases, we re-estimated the HR of association with the MetS (see the first footnote to Table 2) and obtained similar results. Data permitting the neurocognitive and etiological subtyping of MCI and dementia were not available for about half of the participants with MCI or dementia who declined further in-person detailed examinations. Based on data for 17 a-MCI cases and 39 na-MCI cases that were successfully classified, we found similarly elevated adjusted odds of association for the MetS with a-MCI (HR, 1.41; P = .56) and na-MCI (HR, 1.42; P = .31) and for diabetes mellitus with a-MCI (HR, 1.83; P = .31) and na-MCI (HR, 1.68; P = 19).

Conclusions

The MetS was associated with an increased incidence of MCI and progression to dementia. Identifying individuals with diabetes mellitus or the MetS with or without MCI is a promising approach in early interventions to prevent or slow progression to dementia. Further studies of the association of the MetS with neurocognitive subtypes of MCI or etiological subtypes of AD or vascular dementia are needed.

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Author Affiliations: Gerontological Research Programme, Department of Psychological Medicine, National University of Singapore, Singapore (Ng, Liang Feng, Nyunt, Lei Feng, Gao, M. L. Lim); Department of Psychology, National University of Singapore, Singapore (Collinson); Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore (Chong, W. S. Lim); Neuroscience and Behavioral Disorders Program, Duke-National University of Singapore Graduate Medical School, Singapore (Lee); Department of Geriatric Medicine, Khoo Teck Puat Hospital, Singapore (P. Yap); Department of Geriatric Medicine, Alexandra Hospital, Singapore (K. B. Yap).

Author Contributions: Dr Ng 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: Ng, Nyunt, Collinson, Lee.
Acquisition, analysis, or interpretation of data: Ng, Liang Feng, Lei Feng, Gao, M. L. Lim, Chong, W. S. Lim, P. Yap, K. B. Yap.
Drafting of the manuscript: Ng.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ng, Nyunt.
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Study supervision: Ng, Gao, Collinson, Chong, Lee.

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REFERENCES

1. Grundy SM, Cleeman JI, Daniels SR, et al; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published corrections appear in *Circulation*. 2005;112(17):e298 and 2005;112(17):e297]. *Circulation*. 2005;112(17):2735-2752.

2. Alzheimer's Disease International. *World Alzheimer Report* 2014*: Dementia and Risk Reduction: An Analysis of Protective and Modifiable Factors*. http://www.alz.co.uk/research/world-report-2014. Published September 2014. Accessed January 19, 2016.

3. Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology*. 2002;58(8):1175-1181.

4. Skoog I. Highs and lows of blood pressure: a cause of Alzheimer's disease? *Lancet Neurol*. 2003;2(6):334.

5. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol*. 2004;61(5):705-714.

6. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. *Neurology*. 2005;65(6):892-897.

7. Luchsinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. *Arch Neurol*. 2007;64(3):392-398.

8. Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA, West N. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. *J Am Geriatr Soc*. 2007;55(5):758-762.

9. Dik MG, Jonker C, Comijs HC, et al. Contribution of metabolic syndrome components to cognition in older individuals. *Diabetes Care*. 2007;30(10):2655-2660.

10. Komulainen P, Lakka TA, Kivipelto M, et al. Metabolic syndrome and cognitive function: a population-based follow-up study in elderly women. *Dement Geriatr Cogn Disord*. 2007;23(1):29-34.

11. Ho RC, Niti M, Yap KB, Kua EH, Ng TP. Metabolic syndrome and cognitive decline in Chinese older adults: results from the Singapore Longitudinal Ageing studies. *Am J Geriatr Psychiatry*. 2008;16(6):519-522.

12. van den Berg E, Biessels GJ, de Craen AJ, Gussekloo J, Westendorp RG. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. *Neurology*. 2007;69(10):979-985.

13. Vanhanen M, Koivisto K, Moilanen L, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology*. 2006;67(5):843-847.

14. Razay G, Vreugdenhil A, Wilcock G. The metabolic syndrome and Alzheimer disease. *Arch Neurol*. 2007;64(1):93-96.

15. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men: the Honolulu-Asia Aging Study. *Arterioscler Thromb Vasc Biol*. 2000;20(10):2255-2260.

16. Raffaitin C, Gin H, Empana JP, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. *Diabetes Care*. 2009;32(1):169-174.

17. Solfrizzi V, Scafato E, Capurso C, et al; Italian Longitudinal Study on Ageing Working Group. Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. *J Neurol Neurosurg Psychiatry*. 2010;81(4):433-440.

18. Muller M, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Metabolic syndrome and dementia risk in a multiethnic elderly cohort. *Dement Geriatr Cogn Disord*. 2007;24(3):185-192.

19. Forti P, Pisacane N, Rietti E, et al. Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc*. 2010;58(3):487-492.

20. Roberts RO, Geda YE, Knopman DS, et al. Metabolic syndrome, inflammation, and nonamnestic mild cognitive impairment in older persons: a population-based study. *Alzheimer Dis Assoc Disord*. 2010;24(1):11-18.

21. Feng L, Chong MS, Lim WS, et al. Metabolic syndrome and amnestic mild cognitive impairment:

Singapore Longitudinal Ageing Study-2 findings. *J Alzheimers Dis*. 2013;34(3):649-657.

22. Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol*. 2009;66(3):324-328.

23. Solfrizzi V, Scafato E, Capurso C, et al; Italian Longitudinal Study on Aging Working Group. Metabolic syndrome, mild cognitive impairment, and progression to dementia. *Neurobiol Aging*. 2011;32(11):1932-1941.

24. Niti M, Yap KB, Kua EH, Tan CH, Ng TP. Physical, social and productive leisure activities, cognitive decline and interaction with *APOE-ε4* genotype in Chinese older adults. *Int Psychogeriatr*. 2008;20(2):237-251.

25. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. *Lancet*. 2005;366(9491):1059-1062.

26. Ng TP, Niti M, Chiam PC, Kua EH. Ethnic and educational differences in cognitive test performance on Mini-Mental State Examination in Asians. *Am J Geriatr Psychiatry*. 2007;15(2):130-139.

27. Feng L, Chong MS, Lim WS, Ng TP. The Modified Mini-Mental State Examination test: normative data for Singapore Chinese older adults and its performance in detecting early cognitive impairment. *Singapore Med J*. 2012;53(7):458-462.

28. Rey A. *L'Examen Clinique en Psychologie [Clinical Examination in Psychology]*. Paris: Presses Universitaires de France; 1964.

29. Wechsler D. *Wechsler Memory Scale*. 3rd ed. San Antonio, TX: Psychological Corp; 1997.

30. Smith A. *Symbol Digit Modality Test*. Los Angeles, CA: Western Psychological Services; 1991.

31. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System*. San Antonio, TX: Psychological Corp; 2001.

32. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*. 2nd ed. South Tucson, AZ: Neuropsychology Press; 1993.

33. Wechsler D. *WAIS-III Administration and Scoring Manual*. San Antonio, TX: Psychological Corp; 1997.

34. Feng L, Ng TP, Chuah L, Niti M, Kua EH. Homocysteine, folate, and vitamin B-12 and cognitive performance in older Chinese adults: findings from the Singapore Longitudinal Ageing Study. *Am J Clin Nutr*. 2006;84(6):1506-1512.

35. Lee CK, Collinson SL, Feng L, Ng TP. Preliminary normative neuropsychological data for an elderly Chinese population. *Clin Neuropsychol*. 2012;26(2):321-334.

36. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med*. 2004;256(3):183-194.

37. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment: beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256(3):240-246.

38. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61-65.

39. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.

40. Laudisio A, Marzetti E, Pagano F, et al. Association of metabolic syndrome with cognitive function: the role of sex and age. *Clin Nutr*. 2008;27(5):747-754.

41. Hassenstab JJ, Sweat V, Bruehl H, Convit A. Metabolic syndrome is associated with learning and recall impairment in middle age. *Dement Geriatr Cogn Disord*. 2010;29(4):356-362.

42. White H, Pieper C, Schmader K, Fillenbaum G. Weight change in Alzheimer's disease. *J Am Geriatr Soc*. 1996;44(3):265-272.

43. Luchsinger JA, Gustafson DR. Adiposity, type 2 diabetes, and Alzheimer's disease. *J Alzheimers Dis*. 2009;16(4):693-704.

44. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol*. 2005;62(10):1556-1560.

45. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. 2008;71(14):1057-1064.

46. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med*. 2003;163(13):1524-1528.