ORIGINAL RESEARCH

Impact of Worsened Metabolic Syndrome on the Risk of Dementia: A Nationwide Cohort Study

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***Background*—**The relationship of alteration of metabolic syndrome (MetS) with dementia remains unclear. The purpose of study was to evaluate the association between dynamic change in MetS status around a 5-year period and dementia.

***Methods and Results*—**The cohort study was conducted from the Taiwanese Survey on Prevalence of Hypertension, Hyperglycemia, and Hyperlipidemia in 2002, with follow-up in 2007. The sample was subsequently linked to the National Health Insurance Research Database. Participants were divided into 3 groups: persistent MetS (MetS both in 2002 and 2007); nonpersistent MetS (MetS either in 2002 or 2007); and non-MetS (MetS neither in 2002 nor 2007). Furthermore, the individuals with nonpersistent MetS were categorized as improved MetS (MetS in 2002 but not in 2007) and worsened MetS (MetS not in 2002 but in 2007). Each participant was tracked until the end of 2011 to identify the development of dementia. In total, 3458 participants aged 40 to 80 years were included. Up to 10 years and 31 741 person-years of follow-up, 76 patients developed dementia. Only a relationship was found between the nonpersistent MetS and dementia (adjusted hazard ratio=1.93; 95% confidence interval =1.17–3.19; *P*=0.010). Moreover, a significantly higher dementia risk was observed in patients with worsened MetS (adjusted hazard ratio=2.22; 95% confidence interval=1.32–3.72; *P*=0.003), but not those with persistent (*P*=0.752) or improved (*P*=0.829) MetS. Similar results were detected in participants aged ≥65 years.

***Conclusions*—**Patients with worsened MetS had an increased dementia risk during the 10-year follow-up period in a population-based sample. **(*J Am Heart Assoc*. 2017;6:e004749. DOI: 10.1161/JAHA.116.004749.)**

Key Words: dementia • improved • metabolic syndrome • persistent • worsened

Global population aging has resulted in a rapid increase in the prevalence of dementia.[1–3] An association between cardiovascular risk factors and impaired cognitive function or dementia has been recognized.[4–7] Therefore, identifying patients with metabolic syndrome (MetS) is crucial. The remission rate of MetS was >50% in patients following dietary intervention and usual care.[8,9] Lifestyle modification implemented for reducing cardiovascular risk factors can improve neurocognition.[10]

The relationship between MetS and impaired cognitive function remains unclear.[11–18] Several studies have shown that MetS increases the risk of cognitive decline or dementia.[11–15] However, in other studies, patients with MetS exhibited more-favorable cognitive performance, indicating a protective ability of MetS.[16–18] These inconsistent findings might be attributed to these studies either measuring MetS at a single time point or not considering the dynamic alteration in MetS status. Moreover, a previous study indicated that long-term variability of glycated hemoglobin and blood pressure represented a risk of deteriorating health.[19] Alteration in MetS status over time might influence the link between MetS and cognition.

Limited data are available regarding the relationship between the characteristics of dynamic alteration in MetS status and cognitive function. This relationship was evaluated in only 1 study, where patients with persistent MetS for 10 years exhibited lower cognitive performance at the end of the study.[20] However, this cross-sectional study could not determine the causal effect because it applied a single-time approach for assessing cognitive function.

In this study, we evaluated whether dynamic alteration in MetS status over a 5-year period is associated with an increased dementia risk in a population-based cohort sample

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Clinical Perspective

What Is New?

- The higher risk of dementia was observed in participants with nonpersistent metabolic syndrome.
- Participants who with worsened metabolic syndrome were associated with the increased risk of dementia.
- In elderly individuals, the results were largely unchanged.

What Are the Clinical Implications?

- Management and treatment on metabolic syndrome should be administrated.
- Early detection and prevention for worsened metabolic syndrome might reduce the dementia risk.

during a 10-year follow-up period. In addition, a sensitivity analysis in participants aged ≥65 years was performed for investigating the association between dynamic alteration in MetS status and subsequent dementia risk.

Methods

Study Design and Data Sources

This study was a cohort study and was conducted using 2 independent data sources. The primary data were obtained from the Taiwanese Survey on Prevalence of Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH). Furthermore, we linked the TwSHHH data to the Taiwan National Health Insurance Research Database (NHIRD) with encrypted identification numbers to identify whether the patients in the TwSHHH were subsequently diagnosed with dementia until the end of 2011. This study was fully approved and evaluated by the institutional review board of Taipei Medical University. The informed consent was not required because participants' identities were encrypted.

The TwSHHH was a nation-wide population-based survey investigating the prevalence of hypertension, hyperglycemia, and hyperlipidemia in Taiwan in 2002. The sample characteristics and recruitment methods have been described in detail previously.[21,22] The participants included in the TwSHHH were a subsample constituting half of the sample for the National Health Interview Survey (NHIS) conducted in 2001; the NHIS had a multistaged stratified systematic sampling design by using probability proportional to size at each level.[23] The NHIS included 6592 households and 26 685 participants. In total, 10 292 participants randomly selected from the NHIS were included in the TwSHHH. Among them, 7578 completed questionnaires and 6602 provided a blood sample. Finally, 6600 participants completed the survey. A follow-up for the second visit of TwSHHH population was conducted in 2007. In addition to the original examination variables, new variables, such as orthostatic and urine screenings, were added in the second survey. Among the 6600 participants in the first TwSHHH survey, only 4682 were included in the follow-up survey after excluding participants who refused to participate (n=1095), died (n=242), or were lost to follow-up (n=581).

The NHIRD is a nation-wide research database of the Taiwan National Health Insurance program that was established in 1995. The National Health Insurance covers ≈99% of the 23 million Taiwanese residents. The National Health Insurance is a mandatory single-payer medical insurance program and provides comprehensive healthcare services. The NHIRD was released and is managed by the Taiwan National Health Insurance Administration and contains reimbursement claims data for outpatient, inpatient, and emergency services. All data in the NHIRD are anonymous and encrypted for research purposes. Researchers using the NHIRD must agree that they have no any intention of violating the privacy of the insurants. Disease diagnoses in this study were identified on the basis of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Study Sample

The study sample was recruited from the first TwSHHH survey conducted in 2002 (n=7578). Despite of the remaining 4682 (61.8%) participants in the follow-up survey of second TwSHHH in 2007, those who were lost to follow-up were obtained again by using the NHIRD database (n=2896) with meeting any 1 diagnosis of diabetes mellitus, hypertension, or hyperlipidemia within 3 years after the index date. The participants who had a history of dementia and those who did not have complete data for identifying the MetS status or covariates were excluded. In addition, to examine the causal association between MetS status and dementia, we excluded patients with dementia diagnosed during the period between the 2 surveys (n=37) to avoid the reverse causality bias. Furthermore, we enrolled adult individuals aged between 40 and 80 years. Finally, 3458 patients were included. The flow chart of patient selection in this study is presented in Figure.

Definition of MetS

MetS status was defined in the participants in the 2 TwSHHH surveys conducted in 2002 and 2007. To reduce misclassification, we also determined whether patients had diabetes mellitus (ICD-9-CM 250), hypertension (ICD-9-CM 401-405), or hyperlipidemia (ICD-9-CM 272) that were identified by linking with the NHIRD. Patients with at least 2 diagnoses received at least 30 days apart were confirmed to have a

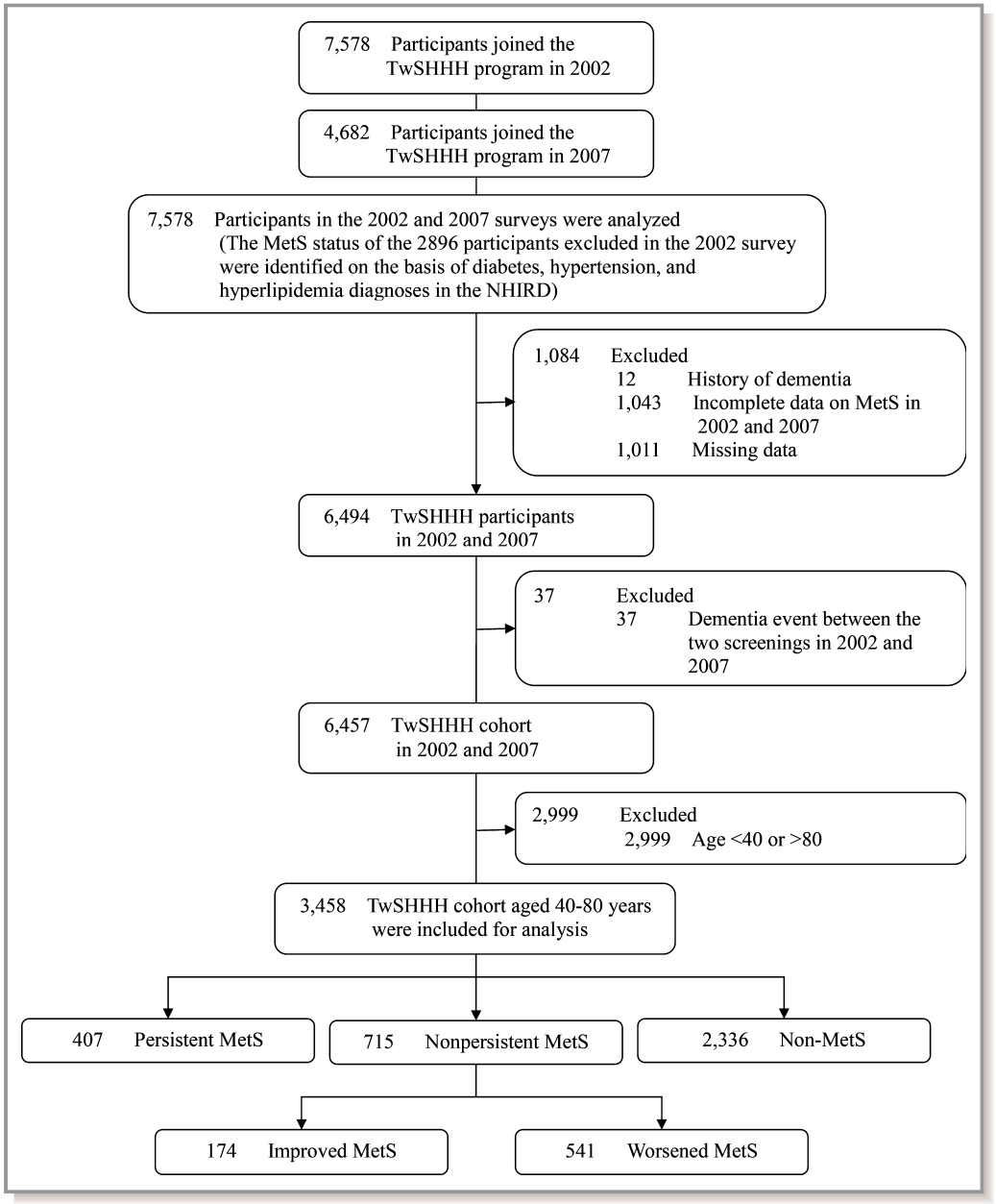

Figure. Flow chart of participant selection. MetS indicates metabolic syndrome; NHIRD, National Health Insurance Research Database; TwSHHH, Taiwanese Survey on Prevalence of Hypertension, Hyperglycemia, and Hyperlipidemia.

disease. According to the National Cholesterol Education Program Adult Treatment Panel III,[24,25] the MetS status was defined and accompanied by related prescribed drugs on the basis of the presence of any 3 or more of the following criteria: (1) elevated waist circumference (>102 cm in men and >88 cm in women); (2) elevated triglycerides (≥150 mg/dL), lipid-lowering drug use, or hyperlipidemia diagnosis; (3) reduced high-density lipoprotein cholesterol (<40 mg/dL in men and <50 mg/dL in women); (4) elevated blood pressure (≥130 mm Hg systolic or ≥85 mm Hg diastolic pressure), antihypertensive drug use, or hypertension diagnosis; and (5) elevated fasting glucose (≥100 mg/dL), antidiabetic drug use, or diabetes mellitus diagnosis.

The participants were categorized into 3 MetS groups. The period of 5 years between the screenings in 2002 and 2007 was set as the MetS exposure period. Patients diagnosed with MetS in both screenings (2002 and 2007) were included in the persistent MetS group. Patients diagnosed only once with MetS in either of the 2 screenings (2002 or 2007) were included in the nonpersistent MetS group. Participants not diagnosed with MetS in neither of the 2 screenings were included in the non-MetS group. Furthermore, we divided

patients with nonpersistent MetS into 2 groups: improved MetS (diagnosed with MetS at the first screening but not at the second screening) and worsened MetS (diagnosed with MetS at the second screening but not at the first screening).

Study Outcome and Confounders

The end point in this study was the development of dementia according to ICD-9-CM diagnosis codes in the NHIRD. The examined dementia diagnoses included senile dementia, uncomplicated (290.0), presenile dementia (290.1x), senile dementia with delusional or depressive features (290.2x), senile dementia with delirium (290.3), arteriosclerotic dementia (290.4x), dementia in conditions classified elsewhere (294.1), Alzheimer's disease (331.0), Pick's disease (331.1), and senile degeneration of the brain (331.2).[26] The index date was set as the date on which the patients were recruited from the TwSHHH in 2002. Each participant was tracked from the index date until dementia diagnosis, death, or the end of 2011. To ensure the validity of dementia diagnoses, only patients who received diagnoses in at least 3 ambulatory visits or 1 inpatient admission were considered to have dementia. The confounders defined from the questionnaire and laboratory data were obtained from the TwSHHH in 2002. Demographic factors included age and sex. We also adjusted for covariates related to lifestyle, including smoking, alcohol consumption, exercise, and betel quid chewing. In addition, we adjusted for potential confounding factors of heart disease, stroke, and depression.

Statistical Analysis

The Statistical Analysis System software (SAS System for Windows, Version 9.2; SAS Institute Inc, Cary, NC) was used for performing statistical analyses. The Kruskal–Wallis H test and chi-square test were used for exploring differences in the demographic characteristics and other comorbidities among the 4 MetS groups. The association between different MetS groups and dementia was tested using the Cox proportional hazard regression with hazard ratios (HRs) and 95% confidence intervals (CIs). In addition, multivariate Cox proportional hazard regression was used for investigating the relationship between the alteration of MetS status and dementia after adjustment for potential confounding variables, including age, sex, smoking, alcohol consumption, exercise, betel quid chewing, heart disease, stroke, and depression. Early-onset dementia was onset aged <65 years.[27] Therefore, a sensitivity analysis was repeatedly performed for examining associations in participants aged ≥65 years. A P value of <0.05 was defined as statistically significant.

Results

A total of 3458 participants aged 40 to 80 years were included in the analysis. Up to the 10 years and 31 741 person-years of follow-up, 76 participants developed dementia.

In total, 407, 715, and 2336 participants were included in the persistent MetS, nonpersistent MetS, and non-MetS, respectively (Figure). Mean age (P<0.001) and proportions of smokers (P=0.001), betel quid chewers (P=0.001), and those with heart disease (P<0.001), stroke (P<0.001), and depression (P=0.032) significantly differed among the groups. Patients with nonpersistent MetS were further divided into 2 groups: improved (n=174) and worsened (n=541) MetS. All demographic characteristics, except for exercise (P=0.380), significantly differed among all groups (all P<0.05; Table 1).

During the 10-year follow-up period, dementia risk was higher in patients with persistent (crude HR=2.37; 95% CI=1.23–4.60; P=0.010) and nonpersistent MetS (crude HR=3.37; 95% CI=2.07–5.51; P<0.001) than in those without MetS. However, compared with those without MetS, participants with persistent MetS had an increased, but nonsignificant, dementia risk after adjustment for potential confounders (adjusted HR=1.11; 95% CI=0.56–2.20; P=0.756). In addition, compared with those without MetS, participants with nonpersistent MetS had a significantly higher dementia risk (adjusted HR=1.93; 95% CI=1.17–3.19; P=0.010; Table 2).

The results showed that the persistent MetS group had a higher dementia risk (crude HR=2.37; 95% CI=1.23–4.60; P=0.010). No significantly dementia risk was observed in the improved MetS group (P=0.711). However, a higher dementia risk was observed in the worsened MetS group than in the non-MetS group (crude HR=4.13; 95% CI=2.49–6.83; P<0.001). Moreover, patients with worsened MetS had a significantly higher dementia risk (adjusted HR=2.22; 95% CI=1.32–3.72; P=0.003) after adjustment for all confounders, whereas those with persistent MetS (P=0.752) or improved (P=0.829) MetS did not show a significantly higher dementia risk (Table 3). Furthermore, difference of the HR among 4 groups by Wald tests did not reach statistical significance (P>0.05), except the comparison between groups of worsened MetS and non-MetS (P=0.003) and persistent MetS and worsened MetS (P=0.049), respectively.

A sensitivity analysis in participants aged ≥65 years (n=819) was performed. The results were similar with the total sample of adult individuals. As shown in Table 4, an adjusted statistically significant dementia risk was observed only in patients with worsened MetS in the elderly group (HR=2.00; 95% CI=1.17–3.43; P=0.012), but not in those with persistent (P=0.494) and improved groups (P=0.826).

Table 1. Distribution of Demographic Characteristics According to MetS Status

	MetS				
	Persistent (n=407)	Improved (n=174)	Worsened (n=541)	No (n=2336)	*P* Value*
Age, y, n (%)					<0.001
≥65	163 (40.05)	45 (25.86)	176 (32.53)	349 (14.94)	
<65	244 (59.95)	129 (74.14)	365 (67.47)	1987 (85.06)	
Mean (SD)	60.38 (10.67)	55.77 (10.75)	58.84 (10.67)	52.44 (10.04)	<0.001
Sex, n (%)					<0.001
Male	165 (40.54)	100 (57.47)	234 (43.25)	1126 (48.20)	
Female	242 (59.46)	74 (42.53)	307 (56.75)	1210 (51.80)	
Smoking, n (%)					0.001
Yes	31 (7.62)	30 (17.24)	48 (8.87)	302 (12.93)	
Quit	20 (4.91)	7 (4.02)	12 (2.22)	81 (3.47)	
No	356 (87.47)	137 (78.74)	481 (88.91)	1953 (83.60)	
Alcohol consumption, n (%)					0.001
Yes	34 (8.35)	28 (16.09)	38 (7.02)	265 (11.34)	
No	373 (91.65)	146 (83.91)	503 (92.98)	2071 (88.66)	
Exercise, n (%)					0.380
Yes	102 (25.06)	48 (27.59)	163 (30.13)	641 (27.44)	
No	305 (74.94)	126 (72.41)	378 (69.87)	1695 (72.56)	
Betel quid chewing, n (%)					0.001
Yes	30 (7.37)	18 (10.34)	24 (4.44)	120 (5.14)	
Quit	7 (1.72)	10 (5.75)	8 (1.48)	57 (2.44)	
No	370 (90.91)	146 (83.91)	509 (94.09)	2159 (92.42)	
Heart disease, n (%)					<0.001
Yes	70 (17.20)	17 (9.77)	84 (15.53)	146 (6.25)	
No	337 (82.80)	157 (90.23)	457 (84.47)	2190 (93.75)	
Stroke, n (%)					<0.001
Yes	34 (8.35)	4 (2.30)	26 (4.81)	22 (0.94)	
No	373 (91.65)	170 (97.70)	515 (95.19)	2314 (99.06)	
Depression, n (%)†					0.032
Yes	3 (0.74)	…	…	…	
No	404 (99.26)	…	…	…	

MetS indicates metabolic syndrome.
*Analyzed using the chi-square test and the Kruskal–Wallis H test.
†Cannot be reported when the numbers less than 3.

Discussion

In this nation-wide population-based cohort study, a significantly higher dementia risk was observed only in participants who with worsened MetS within a period of 5 years during the 10-year follow-up period. In the sensitivity analysis, similar results were observed. Patients who developed new-onset MetS had a higher dementia risk irrespective of their age.

Until now, only a single study investigated the association between dynamic change of MetS status and cognition.[20] Our results were not consistent with those of the previous study. Akbaraly et al conducted a prospective cohort study and reported that only patients with persistent MetS exhibited significantly poor cognitive performance. However, they analyzed cognitive function only at a single time point; therefore, they were unable to make a conclusion on the causality of the MetS effect on cognitive decline. In our study,

Table 2. Univariate and Multivariate Analyses of Dementia Risk Associated With MetS Status for 3 Groups

MetS Status			MetS Components (Mean, SD)*		Crude Model			Adjusted Model†		
	Event	PYs	2002	2007	HR	95% CI	*P* Value‡	HR	95% CI	*P* Value‡
Persistent	12	3475.70	3.47 (0.65)	3.61 (0.72)	2.37	1.23 to 4.60	0.010	1.11	0.56 to 2.20	0.756
Nonpersistent	31	6303.62	1.95 (1.02)	2.77 (0.94)	3.37	2.07 to 5.51	<0.001	1.93	1.17 to 3.19	0.010
No	33	21961.91	0.72 (0.76)	0.92 (0.78)	1.00			1.00		

CI indicates confidence interval; HR, hazard ratio; MetS, metabolic syndrome; PYs, person-years.
*Had complete data for all MetS components (n=2357).
†Adjusted for age, sex, smoking, alcohol consumption, exercise, betel quid chewing, heart disease, stroke, and depression.
‡Analyzed using Cox proportional hazard regression.

patients diagnosed with dementia before the first TwSHHH survey and during the time period between 2 screenings were excluded. These exclusion criteria of this study design enabled results to reduce the possibility of reverse causation bias when exploring the effect of worsened MetS on dementia. Nevertheless, our findings contradict those of Akbaraly et al.

We observed that nonpersistent MetS, but not persistent MetS, exhibited a significant effect on dementia. In most studies, patients with persistent MetS were reported to have the worst prognosis, because they have a high risk of developing conditions such as cognitive decline,[20] type 2 diabetes mellitus,[28] and increased carotid artery intima-media thickness.[29] Another study reported that both men and women with persistent MetS did not have poor health-related quality of life, whereas women with intermittent MetS had significantly poor physical health-related quality of life.[30] The inconsistent results reported in various studies remain considerably debatable. In our study, no causal relationship was observed between persistent MetS and dementia. A possible explanation for this might be adaptation through long-term exposure to MetS.[30] Also, diabetic patients with the unstable condition might accelerate health deterioration.[19]

In our study, the nonpersistent MetS group was further divided into 2 subgroups for understanding the difference in the effect of MetS status on dementia between improved and worsened MetS groups. A higher dementia risk was observed in participants with worsened MetS than in those with improved MetS. The mechanism underlying the association between MetS and dementia remains complicated and poorly understood. Several studies have hypothesized that insulin resistance is associated with a risk of cognitive decline because it might result in deregulation of signaling pathways,[31] reduction of frontal cortex function,[32] and deposition of β-amyloid.[33] Patients with MetS can recover through diet and exercise intervention.[34] A study reported a recovery rate of 30% for MetS and that the recovery group had a more-positive prognosis regarding vascular properties.[35] The significant effect of worsened MetS on dementia was in accord with the results of the aforementioned 2014 study.[30]

With regard to the mechanism of our significantly results on the groups of nonpersistent MetS and worsened MetS, several studies provide some evidence that could be explained. The increased levels of fibrinogen and C-reactive protein were associated with the elevated risk of worse outcome in patients with unstable coronary artery disease.[36] Those with MetS were likely to have coronary artery disease.[37] Increased circulating levels of fibrinogen and C-reactive protein as inflammation markers also could predict development of cognitive decline within a 5-year short-term

Table 3. Univariate and Multivariate Analyses of Dementia Risk Associated With MetS Status for 4 Groups

MetS Status			MetS Components (Mean, SD)*		Crude Model			Adjusted Model†		
	Event	PYs	2002	2007	HR	95% CI	*P* Value‡	HR	95% CI	*P* Value‡
Persistent	12	3475.70	3.47 (0.65)	3.61 (0.72)	2.37	1.23 to 4.60	0.010	1.12	0.57 to 2.21	0.752
Improved	3	1611.73	3.14 (0.39)	1.65 (0.58)	1.25	0.38 to 4.08	0.711	0.88	0.27 to 2.88	0.829
Worsened	28	4691.89	1.40 (0.69)	3.29 (0.52)	4.13	2.49 to 6.83	<0.001	2.22	1.32 to 3.72	0.003
No	33	21961.91	0.72 (0.76)	0.92 (0.78)	1.00			1.00		

CI indicates confidence interval; HR, hazard ratio; MetS, metabolic syndrome; PYs, person-years.
*Had complete data for all MetS components (n=2357).
†Adjusted for age, sex, smoking, alcohol consumption, exercise, betel quid chewing, heart disease, stroke, and depression.
‡Analyzed using Cox proportional hazard regression.

Table 4. Univariate and Multivariate Analyses of Dementia Risk Associated With MetS Status for 4 Groups Stratified in Participants Aged ≥65 Years (n=819)

MetS Status		MetS Components (Mean, SD)*		Crude Model			Adjusted Model†		
	Incidence Rate Per 10 000 PYs	2002	2007	HR	95% CI	*P* Value‡	HR	95% CI	*P* Value‡
Persistent	104.10	3.49 (0.70)	3.70 (0.77)	1.17	0.62 to 2.21	0.626	1.26	0.65 to 2.42	0.494
Improved	69.73	3.16 (0.44)	1.73 (0.45)	0.75	0.23 to 2.47	0.639	0.87	0.26 to 2.90	0.826
Worsened	179.26	1.46 (0.70)	3.35 (0.56)	2.08	1.23 to 3.51	0.006	2.00	1.17 to 3.43	0.012
No	91.23	1.03 (0.72)	1.19 (0.73)	1.00			1.00		

CI indicates confidence interval; HR, hazard ratio; MetS, metabolic syndrome; PYs, person-years.
*Had complete data for all MetS components (n=463).
†Adjusted for age, sex, smoking, alcohol consumption, exercise, betel quid chewing, heart disease, stroke, and depression.
‡Analyzed using Cox proportional hazard regression.

duration.[38] Additionally, individuals with MetS were at increased risk of cognitive impairment over the 4 years of short-term follow-up, particularly in those who with a high level of inflammation.[39] The influence of the inflammation process might be another explanation to interpret the impact of nonpersistent MetS or worsened MetS on dementia during a short duration.

Regarding the sensitivity analysis in individuals aged ≥65 years, only participants with worsened MetS had a higher dementia risk in the elderly group. The results observed in the elderly group in our study (aged ≥65) were comparable with those of previous studies.[16–18] In most studies, MetS was associated with better cognitive function or decelerated cognitive decline in elderly populations. However, these studies assessed cognitive function only at a single time point. In our study, the 5-year period between the 2 screenings was used for classifying MetS status into 4 groups. If we had included only participants from the first survey in 2002 in the analysis of MetS status, they would have been divided only into MetS and non-MetS groups. As shown in Table 4, the persistent MetS and improved MetS groups could be combined as MetS group, which had lower HRs. The other 2 groups with worsened MetS and non-MetS belonged to the non-MetS group, especially given that the worsened MetS group had the highest dementia risk. The effect of MetS in elderly patients might be moderated by combining the first 2 and second 2 groups separately, which showed that combined MetS groups exert protective effects as previous research has reported.

Our study has several strengths. First, the 2 screenings in 2002 and 2007 were used for classifying the participants into specific categories of the dynamic MetS status. To the best of our knowledge, this is the first study to examine the causal relationship between alteration of MetS status and dementia. Second, the participants were recruited from a nation-wide population-based sample. The participants in the TwSHHH were obtained from the sample for the NHIS, which was constructed using national stratified cluster sampling and has high representativeness. Most studies have enrolled participants from community-based,[11,12] institution-based,[15] or population-based samples[14,16–18] merely in specific areas, resulting in difficulty in generalizing the results. In addition, we linked the TwSHHH data with the NHIRD to increase the accuracy of the identification of MetS components and dementia events by using the ICD-9-CM codes. Therefore, the effect of underestimation might have been reduced. Third, the MetS components were defined according to the clinical laboratory data in the 2 surveys rather than obtained from a questionnaire survey, thus minimizing the measurement error in this study.

In addition, this study has several major limitations that should be addressed. First, the lower reported rates of smoking, drinking, and depression were found as compared with the national survey.[40] Therefore, it might have contributed to a lower incidence of dementia, and comparing our findings with those of other studies may yield misleading results. Second, the period for detecting the development of dementia was around 5 years after the second survey in 2007, because we excluded the dementia events between 2 screenings to reduce the possibility of reverse causation bias. As well, this study was only used 2 screenings to identify dynamic MetS status, whereas we did not know the true length of MetS exposure. Additionally, it might have a fluctuating condition and could lead to nondifferential misclassification. However, we could still observe a significant association in this study, implying that the actual relationship is likely stronger. Third, the residual effects might exist. The mild or moderate symptom related to the dementia, which is mild cognitive impairment, could not be identified from the data source. Also, the latent period time of Alzheimer's disease that might interfere with cardiometabolic processes

before dementia symptoms could not obtain. Thus, we had adjusted the cardiovascular risk factors that included smoking, heart disease, stroke, and total cholesterol in statistical analysis. Additional studies analyzing the effect of mild cognitive impairment on the association between MetS status and dementia are warranted. Finally, the diagnosis of MetS and dementia were heterogeneous. Also, the severity was difficulty to identify and could not be shown in the database. Nevertheless, we had applied the criteria of National Cholesterol Education Program Adult Treatment Panel III and ICD-9-CM diagnosis codes to define the exposure and outcome variables in our study.

In conclusion, no significant association was observed between persistent MetS and dementia. However, patients with worsened MetS within a period of 5 years had an increased dementia risk during the 10-year follow-up period. Additional studies evaluating the effect of MetS exposure time on the dementia risk should be conducted. Early detection and management of MetS might reduce the dementia risk.

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Disclosures

None.

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