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Original Article

The Shipai cohort for cardiovascular metabolic risk factors and outcome study — Design and preliminary results

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Abstract

Background: The aim of this study was to identify genotypic and phenotypic cardiovascular metabolic risk factors, and to establish risk models of diseases, including diabetes mellitus, cardiovascular disease, stroke, kidney dysfunction and psychiatric disorders, in Taiwanese adults.
Methods: In 2009, a community-based cohort study was initiated in the Shipai area of the Shilin and Beitou districts in Taipei. Residents were randomly sampled by age (young adults: 35−44 years and middle-aged adults: 45−55 years) and urbanization (rural and urban). Residents who agreed to participate were scheduled to receive examinations (physical and blood) and answer questionnaires. A ten-year follow-up is anticipated. Metabolic syndrome (MetS) was defined based on the Adult Treatment Panel III guidelines, and individuals with only one or two of the five MetS components was identified for prevention target.
Results: The response rate of the 9000 invited residents was 10.1%. After screening, 906 participants were enrolled. While 31.0% (281) had no MetS components, 29.1% (264) had only one, and 22.0% (199) had two. MetS with at least three components was diagnosed in 17.9% (162) of the cohort. Concerning gender difference, 25.4% of men and 13.2% of women had MetS ($p < 0.001$). The percentage of MetS was higher in middle-aged participants than in young adults (20.5% versus 13.4%, $p = 0.008$). Forty-six percent of participants had central obesity. After adjusting for gender, age, and urbanization, the central obesity odds ratio for MetS was 23.7, with a 95% confidence internal of 13.1−42.7.
Conclusion: Our preliminary results revealed a high MetS percentage among young and middle-aged adults in Taiwan, with central obesity being a particularly urgent prevention target. The research design and operational protocol of this cohort study may stimulate more research in the future.

Keywords: Cardiovascular diseases; Cohort studies; Community based; Metabolic syndrome

Conflicts of interest statement: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Metabolic Syndrome (MetS) is a cluster of phenotypically risky conditions that are closely linked to both type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), and which include central obesity, low high-density lipoprotein cholesterol (HDL-C) concentration, high fasting plasma glucose (FG), high blood pressure (BP), and high triglyceride (TG) levels. MetS's core pathophysiologic abnormality is insulin resistance, inflammation, and/or obesity.[1,2] Over the past 20 years, many studies have found that MetS is associated with T2DM and CVD development. Recently, the Adult Treatment Panel III (ATP III) guidelines of the National Cholesterol Education Program recommended a MetS definition for use in clinical practice. Additionally, the International Classification of Diseases, 9th Revision (ICD-9) formally included MetS as a "disease", and established a MetS code (277.7). MetS is expected to be an increasingly important driver of T2DM and CVD epidemics in the coming century.[3]

According to findings from the third National Health and Nutrition Examination Survey (NHANES) in the USA, 24% of American adults had metabolic syndrome.[4] Based on the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH), metabolic syndrome prevalence in Taiwanese adults was 15%. Age, obesity, and ethnicity were the determining risk factors.[5,6]

Although there have been many studies on MetS prevalence,[7–9] very few have focused on young and middle-aged adults.[10] The so call "golden cross" of MetS prevalence between men and women aged 50–59 years has been a recent hotspot of gender-difference studies; the golden cross phenomenon describes how, after the age of 50, MetS prevalence in women increases rapidly and eventually overtakes that in men. This change may be related to menopause, but the phenomenon has not been definitively studied.[11–14]

To develop effective public health prevention and intervention policies, an in-depth evaluation of the current MetS situation in Taiwan is needed. The Shipai area is situated in two districts, Beitou and Shilin. Shipai is approximately one-half the size of Taipei City, and has about one-fifth the population size. In addition, Shipai is also mountainous and many of its residents live a traditional agricultural lifestyle, providing a unique opportunity to compare rural and urban health. Taipei Veterans General Hospital (Taipei VGH) has been the only comprehensive tertiary health center in this area for more than 50 years, and has long had good companionship with the local community. The goal of our study is to establish a risk assessment system using data from our own local long-term follow-up population. This will be very helpful for future T2DM and CVD prevention efforts.

2. Methods

2.1. Target population, study design, and participants

We developed a long-term follow-up study with a population-based and random sampling cohort design on the Shipai area. As of December 31, 2006, the 51 neighborhoods (Li) in the Shilin district had a total population of 288,212, which included 45,767 adults aged 35–45 years and 50,017 adults aged 45–55 years. The Beitou district of 42 neighborhoods had a total population of 249,674, which included 41,127 adults aged 35–45 years and 41,594 adults aged 45–55 years. We applied for permission to access a listing of aged 35–55 years residents for random sampling from the Taipei City Bureau of Civil Affairs.

The enrolled residents were stratified into two age groups (young adults: 35–44 years old and middle-aged adults: 45–55 years old) and two levels of urbanization (rural and urban), and one return visit per two years over a 10-year follow-up period was anticipated.

A pilot sample of around 1000 residents distributed in nine neighborhoods nearest to the Taipei VGH was conducted from 2009 to 2010. These nine neighborhoods were selected in a random manner. A simple random sampling was drawn from each neighborhood, stratified by two age groups. One thousand invitations were sent out to every neighborhood, 500 per age group. Any invited resident who responded to our request to book an interview and who then completed all the examinations in the hospital was counted as a participant. The study protocol was approved by the Institutional Review Board of Taipei VGH (IRB: 97-12-06A), and each participant signed an informed consent form.

The inclusion criteria were: (1) living in the Shipai area for at least six months; (2) 35–55 years old; (3) consent to participate, including undergoing phlebotomy for biochemical testing and genotyping. There were no specific exclusion criteria.

2.2. Urbanization level of the Shipai area

To highlight the cultural and geographical features of the Shipai area, especially regarding medical resources, an urbanization level categorized by urban or rural was determined for each neighborhood. We adopted Liu et al.'s[15] 2006 method for stratifying Taiwan's townships to measure neighborhood urbanization level in the Shilin and Beitou districts (map in appendix). However, we collapsed Liu et al.'s seven categories into two levels. These data are not presented (available on request).

2.3. Measurements

Individual baseline demographic data were recorded, including birthdate, age, gender, ethnicity, marital status, education level, lifestyle (smoking, drinking, and diet), and family history of major diseases.

A physical examination was performed and recorded, this examination covered anthropometric variables (body weight, height, circumferences of waist, upper abdomen, hips, waist-hip ratio, and body mass index), BP, heart rate, grasp strength, the five MetS diagnostic components, disease history, and drug treatment records pertaining to MetS, T2DM, and CVD. Bone mineral density (BMD) was also measured with ultrasonography.

A fasting blood sample was collected to measure FG, TG, total cholesterol, and HDL-C levels; these were assessed using an automatic analyzer (Hitachi Model 736, Tokyo, Japan). Blood specimen aliquots were stored for future genomics analyses, including candidate genes and microarray analysis. **A urine sample** was also collected to measure the albumin-creatinine ratio (ACR). Albumin was assessed using an immuno-turbidimetric method (clinically reportable range (CRR): 0.94−5000 mg/dL and analytical sensitivity: 0.94 mg/dL).

The micro-albuminuria diagnosis was defined as an ACR greater than or equal to 30 mg/g and less than 300 mg/g, and overweight was defined as body mass index greater than or equal to 24 kg/cm^2.

In this study we used the same criteria for MetS as that defined by the Ministry of Health and Welfare of Taiwan in 2006.[16] Definitions for each of the five components are: (1) central obesity: waist circumference >90 cm for men and >80 cm for women; (2) high BP: SBP ≥130 mmHg and DBP ≥85 mmHg; (3) high FG level: FG ≥ 100 mg/dl; (4) low HDL-C level: HDL-C <40 mg/dl for men and <50 mg/dl for women; and (5) high TG level: TG ≥ 150 mg/dl. The drug treatment records for controlling BP, FG, HDL-C, and TG levels were also considered for the relevant components. A MetS diagnosis was defined as having three or more of the five components.

Questionnaires included (1) a quality-of-life questionnaire, which included the SF-36 (International Quality of Life Assessment (IQOLA) SF-36 Taiwan Standard Version 1.0) and the Taiwan International Physical Activity Questionnaire Short Form (IPAQ) for physical activity status; **(2) a health services accessibility and utilization questionnaire**; **(3) a psychiatric questionnaire**, including a psychiatric history evaluating the participant's personal history of insomnia, anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), depression, bipolar disorder, schizophrenia, and other psychiatric disorders; **(4) a substance use disorder questionnaire**, including abuse or dependency, amount and duration; and **(5) a family history questionnaire** of psychiatric disorders, including insomnia, anxiety disorder, depression, bipolar disorder, schizophrenia, dementia, and others.

A senior psychiatric research nurse assessed the psychiatric questionnaires, including surveys covering panic disorder, generalized anxiety disorder, PTSD, major depressive disorder, and pre-menstrual dysphoric disorder. The Pittsburg sleep questionnaire index, the restless leg syndrome questionnaire, and the mood disorder questionnaire were also administered.

2.3.1. Statistical analyses

Our predicted sample size was 20,000, approximately 4% of the target population, and our preliminary results were based on data from 906 participants, which is approximately 5% of the predicted sample size. Descriptive data were presented as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Student's t-test or ANOVA with multiple comparisons was used to compare group mean differences. The chi-square test was used to evaluate the percentage differences between or among groups. The MetS risk factors were evaluated by multivariate logistic regression with the demographic data as covariates for adjustment.

The conditional percentage was computed to evaluate the pattern of onset percentage for each individual component based on the number of MetS abnormalities (categorized from 0 to 5). A p-value less than 0.05 was considered statistically significant. SAS software, version 9.4 (SAS Institute, Cary, NC, USA) was used to perform for all analyses.

We performed a power analysis using G*Power software, version 3.1.9.2 (Franz Faul et al., Uiversität Kiel, Germany). For percentage differences between two groups evaluation, under a two-tailed alpha of 0.05, our preliminary results had nearly 99% power.

3. Results

3.1. Response rate to the posted invitation letter

In total, 906 participants completed all study procedures. The response rate for each of the nine neighborhoods varied from 7.1% to 11.8%. Among the young adults, the response rate varied from 5.2% to 9.6%, and among the middle-aged adults, the rate varied from 7.6% to 15.4%. In summary, the average response rate was 10.1% for the total sample, and 7.3% and 12.8% for the young and middle-aged adults, respectively. The middle-aged group had a higher response rate.

3.2. Demographic results

Based on 906 eligible participants, the mean age was 49.6 ± 5.5 years, and female percentage was 61.7%. There were 577 (63.7%) participants in the middle-aged group. The association of gender with age group was not statistically significant.

The majority of the participants were Han ethnicity (97.7%), married (84.9%), and had at least a college-level education (62.3%). Regarding general lifestyle habits, 59.9% of participants reported not doing ≥30 min of physical exercise per day; 16.4% did not have green vegetables in their daily diet; 74.9% did not smoke, and 83.9% did not drink alcohol. The percentage of self-reported history or drug treatment for T2DM, hypertension, and dyslipidemia was 3.1%, 8.6%, and 12.1%, respectively; however, accompanying with missing data 15.1%, 12.6%, and 4.3%, respectively.

3.3. Percentage of MetS diagnoses and the five components

The percentage of participants diagnosed with MetS was 17.9%, with significantly higher in men (25.4%, $p < 0.001$) and people in the middle-aged group (20.5%, $p = 0.008$).

Gender differences were statistically significant in all of the MetS components, except low HDL-C. Age-group differences were statistically significant for central obesity, BP, and FG

Table 1
The percentages of Diagnosed Metabolic Syndrome (MetS) and the five MetS components.

	Total	Gender		Age Group		Total
		Female	Male	35 ≤ age<45	45 ≤ age<55	
		559	347	329	577	906
Diagnosed MetS	N	74	88	44	118	162
	(%)	13.2%	25.4%	13.4%	20.5%	17.9%
	p	<0.001		0.008		
Central Obesity	N	275	142	130	287	417
	(%)	49.2%	40.9%	39.5%	49.7%	46.0%
	p	0.015		0.003		
High BP	N	121	166	82	205	287
	(%)	21.7%	47.8%	24.9%	35.5%	31.7%
	p	<0.001		0.001		
Low HDL-C	N	97	59	61	95	156
	(%)	17.4%	17.0%	18.5%	16.5%	17.2%
	p	0.892		0.426		
High FG	N	86	86	45	127	172
	(%)	15.4%	24.8%	13.7%	22.0%	19.0%
	p	0.001		0.002		
High TG	N	83	119	65	137	202
	(%)	14.9%	34.3%	19.8%	23.7%	22.3%
	p	<0.001		0.166		

BP = Blood Pressure; HDL-C = High-Density Lipoprotein Cholesterol; TG = Triglyceride; FG = Fasting Glucose.

level, but not low HDL-C and high TG. In summary, women had higher percentages of central obesity than men and the middle-aged adults had higher percentages of central obesity, BP, and FG than the young adults (Table 1).

Without adjustment, a MetS diagnosis was significantly more likely in men than women [odds ratio (OR): 2.2; 95% confidence interval (CI): 1.6–3.1], and more likely in middle-aged than young adults (OR: 1.1; 95% CI: 1.0–1.1). Among the five components, participants with high TG were more likely to have MetS than those without (OR: 19.9; 95% CI: 13.2–30.0). After adjusting for gender, age, and urbanization, participants with central obesity were most likely to be diagnosed with MetS (OR: 23.7; 95% CI: 13.1–42.7; Table 2).

The percentage of overweight (including obese) participants was 42.4%, but the percentage was higher in the middle-aged adults than in the young adults (45.6% versus 35.8%, $p = 0.010$) and among men compared with women (61.4% versus 30.6%, $p < 0.001$). The association between overweight and central obesity was statistically significant ($p < 0.001$); 77.3% of overweight participants had central obesity.

Furthermore, as the number of MetS abnormalities increased, the onset opportunity of each individual component also increased. Thus, the increasing pattern of conditional onset percentage of each individual component as the number of MetS abnormalities increased can be observed in Fig. 1. As mentioned above, the major MetS risk component was central obesity.

Table 3 describes the association of the number of MetS abnormalities with gender and age group. The percentage of the potential MetS group, which defined as participants with two abnormal components, was 22.0% (men: 24.5%, women: 20.1%; young adults: 18.4%, middle-aged adults 23.5%). The potential MetS group should be targeted for urgent preventive intervention.

3.4. Percentage of psychiatric risk factors

Post-menopausal women had a higher percentage of insomnia (25.3% versus 17.9%, $p = 0.041$) and MetS diagnosis (16.4% versus 9.7%, $p = 0.018$) than pre-menopausal women.

Table 2
Unadjusted and adjusted odds ratio for diagnosed MetS by logistic regression.

MetS Components	Unadjusted OR	95% C.I.	p[a]	Adjusted[b] OR	95% C.I.	p[a]
Central Obesity	18.1	10.3–31.6	<0.001	23.7	13.1–42.7	<0.001
High BP	9.8	6.6–14.4	<0.001	9.3	6.2–14.0	<0.001
High FG	12.7	8.6–18.8	<0.001	11.8	7.9–17.6	<0.001
Low HDL-C	13.3	8.9–19.8	<0.001	17.5	11.2–27.3	<0.001
High TG	19.9	13.2–30.0	<0.001	19.1	12.5–29.1	<0.001

BP = Blood Pressure; HDL-C = High-Density Lipoprotein Cholesterol; TG = Triglyceride; FG = Fasting Glucose.
[a] p-value of Wald test.
[b] Adjusted for gender, age group, and urbanization level.

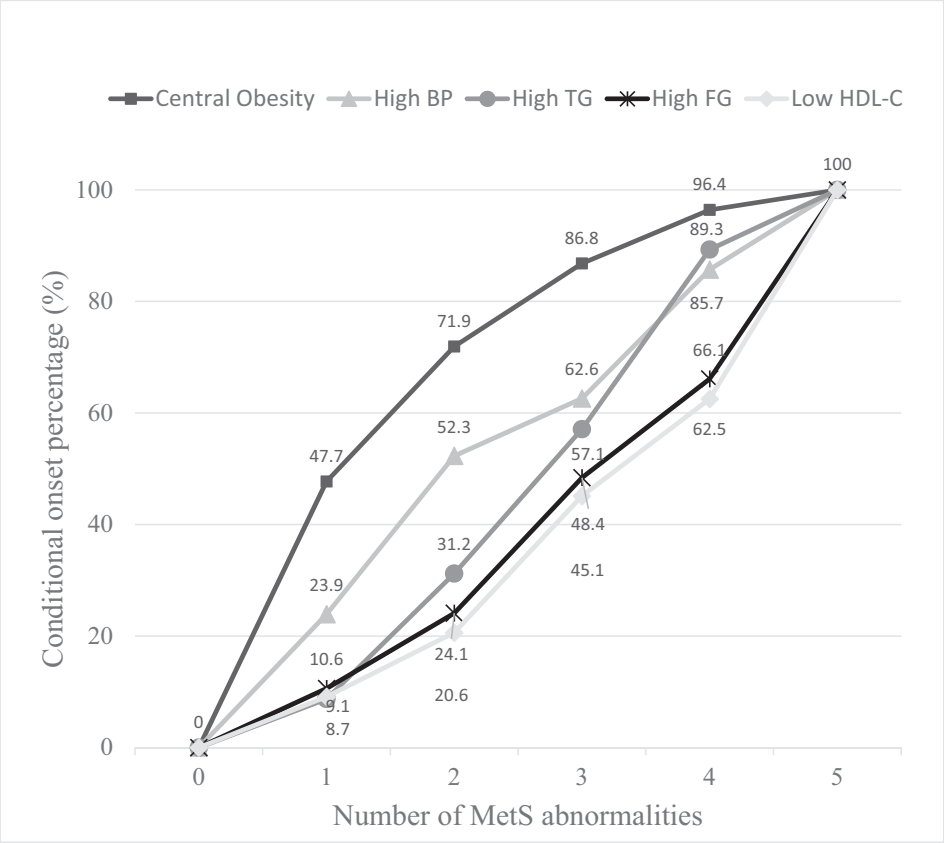

Fig. 1. The increasing pattern of conditional onset percentages for each component as the number of MetS abnormalities increased. BP: Blood Pressure; HDL-C: High-Density Lipoprotein Cholesterol; TG: Triglyceride. FG: Fasting Glucose.

4. Discussion

In Taiwan, there have been three major cohort studies focused on MetS and CVD outcomes: the Chin-Shan community cohort (CSC), set up in 1990[17]; the Nutrition and Health Survey in Taiwan (NAHSIT), in 1993–1996 and in 2005–2008[18]; and the TwSHHH cohort, in 2002.[11] Table 4 shows the age- and gender-specific MetS prevalences from these three studies alongside our cohort prevalences for comparison. The 1991 CSC survey showed a female preponderance for aged ≥35. Meanwhile, the 2008 NAHSIT survey reported similar finding in the women aged 45–65 but a reversed male dominance in the aged 31–44 group. Whereas the 2002 TwSHHH survey revealed male preponderance for aged 30–59 but reversed to female lead in aged ≥60.

In our cohort, aged 35–55, the percentage of MetS was 17.9% (men: 25.4%; women: 13.2%), which is lower than that reported by the CSC cohort and the NAHSIT survey, but is

Table 3
Associations between gender, age group, and number of MetS abnormalities.

		Diagnosed MetS	Number of MetS Abnormalities						Total
			0	1	2	3	4	5	
Gender	Female	74	191	182	112	45	24	5	559
	(%)	13.2	34.2	32.6	20.0	8.1	4.3	0.9	
	Male	88	90	82	87	46	32	10	347
	(%)	25.4	25.9	23.6	25.1	13.3	9.2	2.9	
Age	35 ≤ age<45	44	122	102	61	23	15	6	329
	(%)	13.4	37.1	31.0	18.5	7.0	4.6	1.8	
	45 ≤ age<55	118	159	162	138	68	41	9	577
	(%)	20.5	27.6	28.1	23.9	11.8	7.1	1.6	
	Total	162	281	264	199	91	56	15	906
		17.9	31.0	29.1	22.0	10.0	6.2	1.7	

Table 4
Cohort comparisons of age- and gender-specific MetS prevalence.

Cohort	Survey year	Age group (years)	Men (%)	Women (%)
CSC	1990–1991	≥35	23.0	38.0
	1995		28.3	44.7
NAHSIT	1993–1996	31–44	12.5	14.1
	2005–2008		22.9*	15.1
	1993–1996	45–65	26.5	49.0
	2005–2008		33.2	48.4
TwSHHH	2002	30–39	15.6*	5.1
		40–49	23.0*	10.7
		50–59	23.2*	22.6
		60–69	25.2	38.3
Shipai	2010	35–44	25.4*	5.5
		45–55	25.4*	17.5

Note: * men had higher MetS prevalence than women.
CSC = Chin-Shan community cohort; NAHSIT = Nutrition and Health Survey in Taiwan; TwSHHH = Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia.

similar to the TwSHHH study findings. This difference is probably attributable to there being more young enrollees in our study compared with the other studies. Nevertheless, the MetS prevalence among men in our study was comparable to all the other studies, but the prevalence among women aged 35–45 in our study was much lower compared with women in the same age group in the other studies. However, women's MetS prevalence increased rapidly with age and likely superseded men's prevalence at later ages. We also found higher MetS prevalence among post-menopausal women than in pre-menopausal women.

Compared with Japan's Watria cohort (with participants aged 30–79 years old), conducted in 2009, our result was higher than theirs (23.3% in men; 8.7% in women). A large difference of MetS prevalence in women was observed between our Shipai cohort and the Watria cohort.[19] This may be because the Watria cohort had a different criterion for central obesity, being a waist circumference >90 cm in Japanese women. Additionally, the Shipai area may be more urbanized than Watria.

Compared with our finding that 22.0% (men: 24.5%, women: 20.1%) had potential MetS (i.e., had any two MetS components), the Watria study reported a pre-MetS prevalence, which they defined as central obesity plus one other MetS component, of 21.2% in men and 10.2% in women. Although the definition of the potential MetS group is not exactly the same, the concept regarding prevention focus is similar. Central obesity is the preventive target.

In 2003, the Finnish Diabetes Association completed a national risk evaluation model, to assess the health risk of the country's entire population; it is regularly improved upon.[20] In the United States, the Framingham Heart Study tested the validity and transportability of gender-specific coronary heart disease prediction functions, and found that the Framingham functions systematically overestimated the risk of five-year coronary heart disease events among Japanese Americans, Hispanic men, and Native American women.[21] The Joint Asia Diabetes Evaluation program of the Asia Diabetes Foundation has constructed risk evaluation equations using a cohort of 8000 follow-up patients at the Chinese University of Hong Kong in which they will monitor known risk factors to evaluate DM or CVD onset, and they will employ an aggressive lifestyle modification intervention to reach their prevention targets.[22–24]

Based on 2007 patient check-up data from the Taipei VGH, MetS prevalence was 32.4% in people >65 years old, with a greater prevalence in women (40.8%) than in men (27.6%).[25] The total prevalence is higher than our study whereas the gender ratio reversed. The design of our study, which included two younger age groups, may offer an opportunity to observe the age onset point and the mechanisms responsible for the future “cross-over" of this gender discrepancy. Therefore, the high prevalence of MetS in older adults indicates an urgent need for health promotion and disease prevention strategies that are rooted in the community, especially in target early detection for middle-aged people.

Our study has some limitations. First, our sample only included pilot cohort, and was not representative of the complete northern Taipei population. Second, our preliminary findings are based on cross-sectional results. Third, our cohort did not exclude residents with previous T2DM or hypertension, the percentage of MetS would be overestimated.[26] We are looking forward to the follow-up results such as estimating the time duration of subsequent onset disorder components in individuals and identifying the progression pattern that most rapidly advances disease stages for T2DM, CVD, CKD, or mortality. With a deeper understanding of these mechanisms, a risk assessment system can be established, followed by construction of a prevention strategy to help people bypass the risky road toward disease development and to stay on a path toward healthy aging.

We also aim to continue enrolling participants to increase our sample size; this will allow us to refine MetS risk analyses by separating pre-disease and disease stages. We strongly recommend a long-term follow-up cohort study with short-term visits to better estimate the onset times of each MetS component, MetS, and disease outcomes.

In conclusion, our preliminary results revealed a high percentage of MetS among young adults and middle-aged adults in Taiwan, with central obesity being the most urgent preventive focus. The research design and operational protocol of this cohort study may stimulate more research in the future.

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Appendix.

The Map of Shipai Area: including Beitou and Shilin District of Taipei City.

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