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Original Article

An Exploratory Analysis of Dynamic Change of Metabolic Syndrome in Relation to the Risk of Developing Cardiovascular Disease in a Chinese Cohort

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Abstract

Background: Metabolic syndrome (MS) is the syndrome closely related to cardiovascular disease (CVD) risk factors. Few prospective studies have compared the impact of dynamic changes of MS on the development of cardiovascular diseases (CVD).

Methods: Overall, 3461 subjects were recruited from a cohort study on Prevention of Multiple Metabolic disorders and MS in Jiangsu of China (PMMJS) with a follow up of 3.8 years. The associations between the dynamic changes (Difference, the value at first follow-up subtract the value at baseline) of MS, component numbers, components and relative risk (RR) of CVD were analyzed by using Cox regression model.

Results: The total incidence standardized rate of CVD was 2.58%,and the incidence standardized rates of CVD in MS-/follow-up MS-,baseline MS-/follow-up MS+, baseline MS+/follow-up MS- and baseline MS+/follow-up groups were 2.05%,5.01%,1.65% and 4.39% separately. After adjustment confounding factors Difference in FPG, BP and TG have significantly effects on the incidence of CVD.

Conclusion: Difference of MS component numbers had the prediction ability of CVD, but MS groups based on baseline and first follow-up MS and/or non-MS had not. In Chinese, the dynamic change of MS component numbers was a useful predict factor for CVD.

Keywords: Metabolic syndrome, Cardiovascular disease, Dynamic change, Age, China

Introduction

Since Reaven proposed "X syndrome" in 1988(1), it has been much concerned about the syndrome closely related to cardiovascular disease (CVD) risk factors. Metabolic syndrome (MS) is a combination of medical disorders that, including obesity, insulin resistance,impaired glucose metabolism, dyslipidemia of high triglycerides (TG), low level of high density lipoprotein cholesterol (HDL-C) and elevated blood pressure (BP), when occurring together, increase the risk of developing cardiovascular disease and diabetes(1).It has become a major public health challenge worldwide (2). The best available evidence suggests that people with MS are at increased risk of cardiovascular disease (CVD) (3-5). Thus, there has been growing interest in this constellation of closely related cardio-

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vascular risk factors. To intervene early the common pathophysiological basis of metabolic syndrome (MS) can delay or prevent the formation of multiple CVD risk factors. It is the important reason that the concept of MS is widely accepted in the field of CVD prevention and control. Now clinical treatment options of MS mainly focus on lifestyle interventions (such as improving diet quality and increasing physical activity) or take targeted therapies (such as lowering blood pressure, lowering cholesterol or modest weight-loss). This may lead to that the population meets the diagnostic criteria for MS change dynamically. In a way, changes in MS components because of lifestyle or treatment can be approximated as a natural result of intervention. In cohort studies, for example, MS patients at baseline may change to non-MS during follow-up; on the other hand, part of Non-MS people in the baseline will meet the MS diagnosis in the process of follow-up. Previous prospective studies on the relationship between MS and CVD just carried out once follow-up, and investigated the association between incidence of follow-up CVD and baseline MS. As a result, the impact of the dynamic changes of MS on incidence of CVD was poorly understood, which might be caused by the change of life-style or targeted intervention (6-9). Therefore, the aim of this study was to compare the influence of dynamic changes of MS on incident CVD using cohort data of Prevention of Multiple Metabolic Disorders and MS in Jiangsu Province project (PMMJS).

Materials and Methods

Study cohort

PMMJS was a cohort study, aimed to estimate the MS prevalence in Jiangsu province at the baseline investigation, and to evaluate the incidence of CVD and T2DM during the follow-up survey. The information and methods of the program were described in detail in the previous publications (10, 11).

The multi-stage sampling method was used in the present study. In stage one; we randomly selected three districts from 13 urban districts and nine counties from 52 counties in Jiangsu province based on the economic condition in different regions. In the second stage, one community (similar as a street district or a residential committee) from each city and one rural township from each county were sampled randomly, respectively. In the final stage, households were randomly chosen from the selected communities and townships; only one participant was randomly selected from each household, without replacement. Simple random sampling methods were used at each stage. The local public health administrative institutes possess the household registration including address and telephone for all participants in order to track his or her health status easily in follow-up; individuals who suffered from the cancer, severe disability, and severe psychiatric disturbance were excluded. Overall, 8685 participants aged 35–74 years old were randomly selected from 12 primary units (each unit was about 1000–2000 households), stratified by sex and age (10 years per group).

All the participants were informed of the objectives and the procedures of the study. Further, they were also informed of their rights to withdraw at any stage or to prohibit their data from being used analyses. The investigation was only initiated after receiving written consent from the participants. This research was licensed by the ethical committee of Jiangsu Provincial Center for Disease Prevention and Control, China.

Measurement

All the measurements were performed during the morning of a health examination after the examinees fasted overnight. Automatical recording instrument was used to measure height and weight. All plasma and serum samples were frozen at –80°C until laboratory testing. Three sitting blood pressure (BP) measurements with an interval of 30 seconds were taken by trained observers using a standard mercury sphygmomanometer according to a standard protocol, after the subjects had been resting for 5 min. The first and fifth Korotkoff sounds were recorded as systolic and diastolic BP, respectively. Waist circumference (WC) was measured by the same physician at the umbilical

level with the subjects standing and breathing normally during the physical examination. Lipid biomarkers and fasting plasma glucose were analyzed in the center laboratory, which is certified by the centers for disease control of Jiangsu province. Fasting plasma glucose (FPG) was detected by Hitachi 7020 analyzer (Roche).Concentrations of TG (12) and HDL-C (13) were analyzed simultaneously on the Hitachi 7020. Low-density lipoprotein cholesterol (LDL-C) (14) was determined by a homogenous direct method. Quality control data were generated from a fresh sample of the samples. Quality control data were generated from a fresh sample of the samples.

Follow-up survey

Amongst 5888 subjects whose follow-time meets 2 years, total 4582 participants (77.82%) received the first follow-up investigation and measurements between January 2002 and August 2003. The contents and methods for investigation and measurements in the first follow-up investigation were the same as those at baseline. In addition, the data on blood pressure and information on incidence of hypertension and CVD based on questionnaire were collected at the first follow-up. Amongst 4582 subjects who received first follow-up investigation and whose follow-time meets 5 years, total 3847 participants (83.96%) received the second follow-up investigation between March 2006 and November 2007. In this investigation, we mainly collected the information on incidence of CVD, which happened in five years. Those who did not attend twice follow-ups examination were similar to those who attended twice follow-ups in terms of age, sex, smoking, alcohol, family history of hypertension and metabolic variables. A total of 3847 participants undergo twice follow-ups, after excluding subjects who were found to have T2DM at baseline or the first follow-up investigation (n=332), missing data (n=133), CVD (n=32), and BMI<18.5kg/m2 (n=22), total 3461 participants (males 1406, females 2055) were included in this analysis, the median duration of follow-up was 3.8 years from the first follow-up to the second follow-up.

Definition of MS

MS was diagnosed in the presence of any three of the following according to ATPIII (AHA/NHLBI amended in 2005) (15): WC≥90cm in men and≥80cm in women; TG≥1.7mmol/l; HDL-C<1.0mmol/l in men and<1.3mmol/l in women; BP≥130/85 mmHg; or FPG≥5.6 mmol/l.

Validation of CVD

Diagnosis of CVD were validated with hospital physician repeated investigation or validation of patients' reports. We also relied on the daily monitoring system for chronic disease surveillance and death registration at local district, which was set up as an operational function of center for disease prevention and control in China. The diagnosis of CVD was based on clinical symptoms, cardiac enzymes, electrocardiogram (ECG) findings, necropsy findings, and previous history of CVD. The coronary heart disease (CHD) events were classified as definite acute myocardial infarction, possible acute myocardial infarction or coronary death, no acute myocardial infarction, or unclassifiable coronary death. The definition of stroke was rapidly developing signs of focal (or global) disturbance of cerebral function lasting >24 h (unless interrupted by surgery or death), with no apparent nonvascular cause. The CHD and stroke were defined using the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (MONICA) criteria (16); the diagnosis methods of this study are consistent with previous studies (17).

Definition of risk factors

Family history of diseases was defined as the presence of parents with history of CVD, type 2 diabetes (T2DM), hypertension, obesity or dyslipidemia (10,11). Participants who used more than 100 cigarettes were considered as smokers, and those consumed less than 100 considered were considered as non-smokers. The drinking definition was defined similarly with a threshold of drinking 12 times per year with more than 50 g (every drink-contained alcohol) each time.

Statistical analysis

The difference value (Difference, the value at the first follow-up subtract the value at baseline) In WC, TG, HDL-C, BP or FPG was calculated to evaluate change of those from baseline to the first follow-up. For example, Difference >0 meant that WC increased from baseline to the first follow-up, the greater the Difference was, the more WC increased. Difference <0 meant that WC decreased from baseline to the first follow-up, the less the Difference was, the more WC decreased.

Difference in MS component number was the difference between the number of compositions consistent with MS the first follow-up and one of baseline. Difference >0 meant that MS compositions increased from baseline to the first follow-up, the greater the Difference was, the more MS compositions increased. Difference <0 meant that MS compositions decreased from baseline to the first follow-up, the less the Difference was, the more MS compositions decreased.

Statistical analyses were performed with the SPSS 13.0 statistical software system. Continuous variables were tested using the t-test and noparametric test. Frequencies of categorical variables were tested using the chi-square test. The incidence of the disease was standardized with the fifth national population census constitutes (18). Cox proportional hazards regression model was used to examine the association between components and MS, Difference in WC, TG, HDL-C, BP or FPG and Difference in MS component number on the development of CVD. Potential confounding factors included age, sex, smoking, alcohol status, and family history of diseases. All reported P-values were two-tailed, and those less than 0.05 were considered statistically significant.

Results

Overall, 3461 subjects (male=1406, female=2055) at baseline were included, and the median of follow-up time was 3.8 years from the first follow-up to the second follow-up. Using ATPIII definition, the subjects included 2098 baseline MS-/follow-up MS- individuals, 547 baseline MS-/follow-up MS+, 313 baseline MS+/follow-up MS- and 503 baseline MS+/follow-up MS+. Baseline characteristics of four groups were shown in Table 1.

Table1: Clinical and biochemical characteristics of the subjects of four groups on the basis of baseline and first follow-up ms and/or non-ms

Characteristic	Baseline MS-/followup MS-	Baseline MS-/followup MS+	Baseline MS+/followup MS-	Baseline MS+/followup MS+	*P**
n	2098	547	313	503	-
AGE (year) **	49.7 (9.9)	49.0 (9.4)	51.4 (10.4)	52.6 (10.3)	>0.05
Gender (male,%)	48	30.7	27.2	28.8	<0.01
FPG (mmol/L) **	5.0 (0.6)	5.2 (0.6)	5.4 (0.7)	5.5 (0.7)	<0.01
HDL-C (mmol/L) **	1.3 (0.4)	1.3 (0.3)	1.1 (0.3)	1.1 (0.3)	<0.01
WC (cm) **	73.1 (7.4)	77.6 (8.3)	81.1 (8.5)	86.6 (8.2)	<0.01
TG (mmol/L) *	1.3 (0.9)	1.5 (0.9)	2.2 (1.6)	2.7 (1.8)	<0.01
SBP (mmHg) **	120.9 (17.8)	124.9 (18.1)	135.1 (18.7)	139.8 (21.4)	<0.01
DBP (mmHg) **	77.5 (10.5)	79.3 (9.4)	84.9 (9.8)	86.3 (11.0)	<0.01
Smoking rate (%)	24.1	21.2	18.5	22.9	<0.01
Drinking rate (%)	25.8	18.3	16.9	15.7	<0.01
Family history of CVD (%)	1.3	2	2.6	1	>0.05

** Means (SD) showed the data of normal distribution. * Median (range) indicated the data of abnormal distribution

There were significant statistical difference ($P<0.05$) among four groups, except for age and family history. At second follow-up, the subjects included 87 new CVD patients and 3374 without CVD. Between two groups, there were significant statistical difference ($P<0.05$), except for difference of WC, HDL-C and family history (Table 2).

Table2: Clinical and biochemical characteristics of the subjects of non-CVD and CVD at follow-up

Characteristic	CVD		non-CVD		*P**
n(male)	87	(39)	3374	(1367)	-
AGE (year) **	56.93	(7.80)	50.04	(9.96)	<0.01
Difference of ms	0.14	(1.28)	-0.26	(1.29)	<0.01
Difference in wc(cm)**	-2.24	(7.30)	-3.19	(7.40)	>0.05
Difference in tg(mmol/L)*	0.36	(1.15)	0.03	(1.31)	<0.01
Difference in hdlc(mmol/L)**	-0.06	(0.42)	-0.02	(0.43)	>0.05
Difference in glu(mmol/L)**	0.39	(0.98)	0.04	(1.26)	<0.01
Difference in sbp(mmHg)**	2.93	(21.53)	-5.43	(20.05)	<0.01
Difference in dbp(mmHg)**	3.64	(12.64)	-0.65	(11.95)	<0.01
Smoking rate （n,%）	39	(44.83)	756	(22.41)	<0.01
Drinking rate （n,%）	28	(32.18)	745	(22.08)	<0.05
Family history of CVD （n,%）	5	(5.75)	93	(2.76)	>0.05

** Means (SD) showed the data of normal distribution.*Median (range) indicated the data of abnormal distribution

Table 3 showed that the total incidence standardized rate of CVD was 2.58%,and the incidence standardized rates of CVD in MS-/follow-up MS-,baseline MS-/follow-up MS+, baseline MS+/follow-up MS- and baseline MS+/follow-up groups were 2.05%,5.01%,1.65% and 4.39% separately. Cox regression model was used to examine RR of CVD and Difference in these four groups (Table 3). Model adjusted for sex, age, smoking, drinking and relevant family history. After adjustment for confounding factors, the result showed that MS subject numbers in four groups was not significantly associated with risk of CVD.

Table 3: Adjusted RR for CVD and four groups based on baseline and first follow-up MS and/or non-MS

	N	N of CVD	Incidence standardized rate(%)	*P*
Baseline MS-/followup MS-	2098	42	2.05	-
Baseline MS-/followup MS+	547	15	5.01	-
Baseline MS+/followup MS-	313	9	1.65	-
Baseline MS+/followup MS+	503	21	4.39	-
Total	3461	87	2.58	-
aRR(95.0% CI) *	1.02	(0.80-	1.30)	0.87

*Adjusted for gender, age, smoking, drinking and relevant family history at baseline in a Cox proportion hazard regression model.

After adjustment confounding factors in Cox regression hazard model, the result showed that baseline MS-/ first follow-up MS+ participants had not a significantly poorer prognosis of CVD than baseline MS-/ first follow-up MS- participants (aRR, 1.02, 95% CI, 0.52-2.01), and non-MS participants at baseline who were followed up into MS did not increase the risk of CVD significantly. Baseline MS+/ first follow-up MS+ participants had not a significantly poorer prognosis of CVD than baseline MS+/ first follow-up MS- participants (aRR, 1.02, 95% CI, 0.67-1.91), and showed that MS patients at baseline who were first followed up to control to normal did not reduce the risk of CVD significantly. Additionally, we further analyzed the risk for CVD of Difference in MS components (WC, TG, HDL-C, BP or FPG) and MS component numbers (Table 4).

Table 4: Adjusted RR for CVD and the control of different in MS components and MS

Difference	*P*	aRR	(95.0% CI)	
WC*	0.376	0.987	(0.959-	1.016)
TG*	0.015	1.216	(1.039-	1.423)
HDL-C*	0.596	1.145	(0.694-	1.889)
FPG*	0.023	1.239	(1.030-	1.490)
SBP*	0.002	1.015	(1.005-	1.024)
DBP*	0.018	1.02	(1.004-	1.037)
MS*	0.003	1.288	(1.088-	1.524)

*Adjusted for gender, age, smoking, drinking and relevant family history at baseline in a Cox proportion hazard regression model.

After adjusting for baseline sex, age, smoking, drinking and relevant family history, excepting Different in WC and HDL-C, the aRR of Different in MS was 1.288(95%CI 1.088-1.524), and Different in SBP (aRR 1.015; 95%CI 1.005-1.024), DBP(aRR1.020;95%CI 1.004-1.037), Different in TG (aRR 1.216; 95%CI 1.039-1.423) and Different in FPG (aRR 1.239; 95%CI 1.030-1.490) were associated with CVD.

Discussion

In recent years, many prospective studies have reported MS had an important role in predicting the risk of CVD independently, and Meta-analyses have concluded that MS increased risk of CVD (6-8). However, the population who are consistent with diagnosis of MS is not fixed. Our results showed that the change is there. For example, baseline MS-/ first follow-up MS+ participants were 547, which is 20.7% of the non-MS participants at baseline, and baseline MS+/ first follow-up MS- participants were 313, which is 38.4% of the MS participants at baseline. In addition, MS component numbers of the participants, who were diagnosed as MS or non-MS at baseline and first follow-up, would have changed. If the incidences of CVD in the dynamic changes of MS at baseline and follow-up can be compared, which can demonstrate that ,the Causation and Causal Inference in Epidemiology, an increase in the amount of cause leads to an increase in disease and reduction in the amount of cause leads to a reduction in disease. In this study, the dynamic changes of MS from baseline to follow-up showed that baseline MS-/ first follow-up MS- participants had a lower standardized incidence of CVD than baseline MS-/ first follow-up MS+ participants(2.05% vs. 5.01%), the standardized incidences of CVD in baseline MS+/ first follow-up MS+ and baseline MS+/first follow-up MS- participants were 4.39% and 1.65% separately. It indicated that the dynamic changes of MS had an impact on the incidence of CVD. In addition, the more MS component numbers was, the more the incidence of CVD increased. After adjustment, there was not statistically significant between MS subject numbers in these four groups and risk of CVD. However, Difference in MS component numbers had a significantly prognosis of CVD after adjustment confounding factors. In MS components, except Different in WC and HDL-C, Difference in SBP, DBP, TG, FPG was still independently associated with CVD. Our study still confirmed that determining the dynamic change of the MS is a useful tool for predicting CVD.

Which component has actually the closest association with CVD in MS components? PAMELA study showed that WC, TG, and HDL were not a predictor of CVD after adjusting for MS components (19). Wilson and others reported that FPG and BP had more effects on CVD than other components (20). Eddy and others used

NHANES data and found that FPG was successful to predict myocardial infarction than MS, which was defined by ATPIII, IDF AND WHO (21). Alexander and Lawlor reported that after adjustment for confounding factors and MS components only BP and HDL-C had a significantly poorer prognosis of CHD, but MS had no significantly relationship of CHD (22, 23). In a 13-year follow-up prospective cohort study in Finns, only low HDLC was independently associated with CVD (24). Similarly, China's 2003 National Nutrition Survey showed that only hypertension had considerable contribution to stroke than MS (25). Girman found that in MS components only hypertension associated with CVD in the Air Force/Texas Coronary Atherosclerosis Intervention Study among population-received placebo (26). Kang GD and others showed that in MS components BP is the only independent risk factors for CVD (27). Yu Hao reported that BP had the largest impact on CVD in MS components (28). These phenomena has prompted that the role of MS on predicting CVD is not independent to the individual components, and it is consistent that BP is an independent risk factor for CVD in MS components. In our study, we have confirmed FPG, BP and TG (continuous variable) has been shown that the dynamic changes have significantly effects on the incidence of CVD.

Each component in MS diagnosis, a risk item of CVD, is used by binary categorization, which will leads to loss of information of intensity and size of risk factor. MS patients have different levels of cardiovascular risk. A MS patient, whose dangerous levels are just over the critical point, has a much lower risk of CVD than MS patient whose dangerous levels are far beyond the critical point (29). Therefore, there firmly are some populations to predict CVD risk may be difficult to show by diagnosing MS or component number (30,31). However, increasing research concerning the independent association of the MS and its components for predicting CVD has been reported (32). In Swedish men, after adjusting for traditional risk factor and 5 MS components, the relationship between the MS and CVD disappeared (33). In the British Women Heart and Health Study, the MS was not a predictor of CVD after adjusting for its components, and only BP and low HDL-C had a relationship with CVD (34). Our results showed that the CVD rick of baseline MS-/ first follow-up MS+ was higher than one of baseline MS+/follow-up MS+. Dynamic changes of MS component numbers (continuous variable) had the prediction ability of CVD, but MS groups (Categorical variable) based on baseline and first follow-up MS and/or non-MS had not. Therefore, in view of the prevention and control of MS, preventing dynamic changes of MS (especially dynamic change in FPG, BP, and TG) can effectively reduce the risk of developing CVD.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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Abbreviations footnotes

metabolic syndrome(MS)
cardiovascular diseases(CVD)
relative risk (RR)
the value at the first follow-up subtract the value at baseline (Difference)
blood pressure(BP)
systolic (SBP) and diastolic (DBP)
waist circumference (WC)

fasting plasma glucose (FPG)
triglycerides (TG)
high density lipoprotein cholesterol (HDL-C)
low density lipoprotein cholesterol(LDL-C)
the coronary heart disease (CHD)
type 2 diabetes (T2DM)
adjusted RR(aRR)
relative risk(RR)
confidence interval(CI)
Framingham Risk Score(FRS)

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