Impact of Metabolic Syndrome on the Development of Cardiovascular Disease among Kazakhs in Remote Rural Areas of Xinjiang, China: A Cohort Study

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Abstract

Background: Metabolic syndrome (MS) could promote the development of cardiovascular disease(CVD). The aim of this study was to examine the association of MS and its components with CVD among Kazakhs in Xinjiang.

Methods: According to the geographical distribution of the minority populations in Xinjiang, we selected the representative prefecture (Yili). A total of 2,644 participants completed the baseline survey between April 2010 and December 2012. The follow-up survey was conducted from April 2016 to December 2016. Only 2,286 out of 2,644 participants were followed-up on, with a follow-up rate of 86.46%. Cox regression was used to evaluate the association of each component and the number of combinations of MS components on the development of CVD.

Results: Multivariate Cox regression analysis showed that blood pressure (BP), waist circumference (WC), and triglycerides (TG) were independently associated with CVD. Participants with 1–5 MS components had an increased hazard ratio for developing CVD, from 1.82 to 8.59 (trend P<0.001), compared with those without any MS components. This trend persisted after adjusting for other general risk factors. The risk of developing CVD increased when TG and WC coexisted, or when TG/WC and BP coexisted. However, no significant interactions were found between BP , WC , and TG.

Conclusions: BP , WC, and TG were independent risk factors for CVD in Kazakhs. In clinical practice, a more informative assessment may be obtained by taking into account the number of MS components.

Background

Cardiovascular disease (CVD) has become the leading cause of death in China [1]. Although medical treatments are available for CVD, they are not a lasting solution and the long-term harmful impact of the disease on patient health is challenging to treat. Therefore, prevention of CVD is now identified as an urgent public health issue. However, the underlying cause of CVD has not yet been discovered, posing a danger for individuals at high risk of developing the disease.

Metabolic syndrome (MS) is a highly prevalent constellation of vascular risk factors, including elevated blood pressure, elevated blood glucose, obesity and dyslipidemia[2]. Several studies have demonstrated the association of MS with CVD among Asian populations in Hong Kong[3], Japan[4], mainland China[5], and Taiwan[6]. However, the differential clustering of MS components and their association with CVD in a Kazakh population in Xinjiang province is not clearly understood, and whether this population bears the highest hazard for CVD development in the presence of MS is yet unclear. Accordingly, there is a need for studies on risk of CVD in the Kazakh population in order to identify effective methods of disease prevention for these individuals.

Xinjiang, a province in northwestern China, is a multiethnic settlement that includes nomadic Kazakh individuals. There is a growing double epidemic of dysarteriotony/obesity and dyslipidemia in Kazakhs,

owing to their special ethnicity, living environment, and genetic characteristics[7–9]. To our knowledge, there have been no studies investigating the association of MS with future risks of CVD in the Kazakh population due to limited public health care resources and poor transportation in the rural regions of Xinjiang. Therefore, the aim of our study was to conduct such an investigation using a longitudinal data set from Kazakhs living in a rural region of Xinjiang. Our findings may have important implications in preventive public health for the medically underserved Kazakh minority.

Materials And Methods

Study population

First, according to the geographical distribution of the minority populations in Xinjiang, we selected the representative prefecture (Yili), which is approximately 4407 km(2739 miles) from Beijing and in which approximately 98% of the population belong to the Kazakh minority. Second, we randomly selected one county in the Yili Prefecture and one township from that county (viz., Nalati Township in Xinyuan County). Finally, a multistage (prefecture-county-township-village) stratified, and cluster random sampling method was used to select the corresponding villages in each township (i.e., 6 villages in Nalati Township). We interviewed local Kazakhs aged ≥ 18 years who had resided in their village for at least 12 months. We excluded those with serious illness, lack of awareness, and unwillingness to cooperate, as well as pregnant women. A total of 2,644 participants completed the baseline survey between April 2010 and December 2012. In order to improve the rate of follow-ups, we interviewed the subjects by face to face inquiry and household surveys. The follow-up survey was conducted from April 2016 to December 2016. Only 2,286 of the 2,644 participants were followed up on, with a follow-up rate of 86.46%. The median follow-up period was 5.49 person-years (in total 11014.92 person-years). Furthermore, we then excluded 281 participants who had a history of CVD (coronary heart disease [CHD], stroke, and hypertension) or lack of information at baseline. Thus, as of December 2016, 2,005 participants were eligible for the final analyses. Within the follow-up period, a total of 278 individuals developed CVD. The person-years were calculated as the sum of the individual follow-up times until the occurrence of a CVD incident or the end of 2016.

Epidemiological Survey and Biochemical Detection

All of the study subjects completed a demographic information survey during face-to-face interviews. Detailed information about diet, drinking, details of existing disease, and family history of disease was collected by trained investigators. Trained staff measured weight, height, waist circumference (WC), and blood pressure(BP) according to standardized methods[10]. Blood samples were drawn from the cubital vein into tubes containing heparin sodium in the morning after an overnight fast. Blood samples were cryopreserved before being transported. Fasting plasma glucose (FPG), triglyceride(TG) and high density lipoprotein cholesterol (HDL-C) levels were measured using a biochemical auto-analyzer (Olympus AU 2700; Olympus Diagnostics, Hamburg, Germany) in the clinical laboratory the First Affiliated Hospital of Shihezi University School of Medicine. All described methods were performed according to the approved

guidelines and regulations. All participants signed informed consent forms before joining the study. This study was approved by the Institutional Ethics Review Board (IERB) of the First Affiliated Hospital of Shihezi University School of Medicine (IERB no.:SHZ2010LL01).

Diagnostic criteria for CVD

The participants who had one of the following clinical events were diagnosed as having CVD: the first-ever occurrence of stroke, CHD, or hypertension during the follow-up period. Stroke was classified as either ischemic or hemorrhagic attack. Subjects were hospitalized for CHD during the follow-up period; coronary intervention (cardiac catheterization or coronary bypass surgery) was performed; there was angina (or nitroglycerin was initiated after cohort study); the first occurrence of myocardial infarction, and congestive heart failure. Data on CVD events were obtained from patients' hospital medical records and questionnaire responses. If the same type of event occurred two or more times, the first occurrence was considered as the end event.

CVD events

Before the follow-up, we conducted a qualitative survey among the leaders of local health institutions in Nalati Township and Xinyuan County, and asked them about the hospitals in which the patients would most likely be hospitalized. As they have lived in remote mountain pastures for generations, with limited contact with the outside world, they are less likely to go to Yili prefecture's hospitals, even to hospitals outside. Moreover, Xinyuan County People's Hospital and Xinyuan County Chinese Medicine Hospital are two relatively large hospitals with a high level of medical care. As such after the qualitative investigation, we collected the medical files from the Xinyuan County People's Hospital and traditional Chinese Medicine Hospital. Therefore, CVD events were obtained from hospitalization data. The collection of CVD outcomes in these two hospitals is almost complete.

Definition of MS

According to the Third Report of the Adult Treatment Unit with a Modified US National Cholesterol Education Program (2005 NCEP-ATP)[11]. MS is defined as meeting three or more of the following factors: (1) central obesity: WC ≥ 90 cm for men and ≥ 80 cm for women; (2) elevated TG level ≥ 150 mg/dL(1.70 mmol/L); (3) reduced HDL-C < 40 mg/dL(1.03 mmol/L) for men and < 50 mg/dL(1.30 mmol/L) for women (4) elevated BP ≥ 130/85 mmHg, or have received the appropriate treatment for or was previously diagnosed with hypertension; (5) elevated FPG ≥ 100 mg/dL (5.6 mmol/L) or have received the appropriate treatment for or was previously diagnosed with type 2 diabetes.

Confounding factors

Traditional risk factors used in the data analysis included age, sex, drinking (drinker/non-drinker), and family history of hypertension, diabetes, and CVD.

Statistical analysis

EpiData3.02 software was used to establish a database, and we used a double entry data-in and logic error detection method. Results were presented as mean ± standard deviation for continuous variables and as numbers (percentages) for categorical variables. Continuous variables between groups were compared by Student's t-test, while categorical variables were analyzed using Chi-square test. Cox proportional hazards regression model was used to evaluate the association of each component and the number of combinations of MS components on the development of CVD. A trend test was performed using the Breslow and Day method[12].

Next, we evaluated the interactions between TG and WC and those between TG/WC and BP. Therefore, subjects were divided on the basis of 2 separate factors, and each group was further divided into 4 different subgroups, in order to determine the risks of different combinations on the development of CVD and the interactions between them:

(1) without WC [WC (-)] and without BP [BP(-)]; (2) with WC [WC (+)] and BP(-); (3) WC (-) and with BP [BP(+)]; (4) WC (+) and BP(+).

(1) without TG [TG(-)] and BP(-); (2) with TG [TG(+)] and BP(-); (3) TG(-) and BP(+); (4) TG(+) and BP(+).

(1) TG(-) and WC (-); (2) TG(+) and WC (-); (3) TG(-) and WC (+); (4) TG(+) and WC (+).

Multiplicative interactions among BP, WC, and TG were evaluated by incorporation of the dummy variable into a Cox regression model. We then tested each interaction on an additive scale by calculating the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI) according to the methods proposed by Andersson et al[13]. Values of RERI > 0, AP > 0, and SI > 1 indicate biological interaction. We assessed both the point estimation and the 95% confidence interval (CI) of RERI, AP, and SI values using a method that accounts for the asymmetric distribution of confidence limits for risk ratio[14]. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL,USA). All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study subjects

Table 1 shows the baseline characteristics of the participants. Those with MS were significantly older and had higher WC, SBP, DBP, TG, FPG than those without MS. The prevalence of smoking and drinking was significantly higher in the MS group than in the non-MS group.

Table 1
Baseline general characteristics of the study subjects

Risk factor	MS	Non-MS	*P*
Sex, female/male	330/198	847/630	0.039
Age,years	46.33 ± 12.04	38.71 ± 11.83	< 0.001
WC,cm	91.24 ± 10.67	79.40 ± 9.36	< 0.001
SBP,mmHg	135.74 ± 18.78	122.97 ± 17.95	< 0.001
DBP,mmHg	87.42 ± 12.91	78.71 ± 11.94	< 0.001
HDL-C,mmol/L	1.21 ± 0.38	1.41 ± 0.54	< 0.001
TG,mmol/L	1.79 ± 1.56	1.06 ± 0.96	< 0.001
FPG,mmol/L	5.75 ± 1.66	5.01 ± 0.93	< 0.001
Smoking rate,n(%)	195(36.93)	434(29.38)	0.001
Drinking rate,n(%)	80(15.15)	147(9.95)	0.001
Family history of hypertension,n(%)	206(39.02)	501(33.92)	0.035
Family history of diabetes,n(%)	9(1.70)	9(0.61)	0.022
Family history of CVD,n(%)	56(10.61)	113(7.65)	0.036
Incidence of CVD,n(%)	114(21.59)	164(11.10)	< 0.001

WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FPG, fasting plasma glucose; MS, metabolic syndrome; CVD, cardiovascular diseases.

Adjusted hazard ratio for CVD and MS with its components in a Cox proportion hazard regression model

As was expected, MS and individual components of MS were significantly associated with the risk of developing CVD, independent of age, sex, drinking, and family history of hypertension, diabetes, and CVD. After adjusting for 4 other MS components and the traditional risk factors above, the BP, WC and TG were still independently associated with CVD(Table 2).

Table 2
Adjusted HR for CVD and MS with components in a Cox proportion hazard regression model

Risk factor	Population exposure ratio,(%)	Incidence of CVD,(%)	HR(95%CI)[a]	aHR(95%CI)[b]	aHR(95%CI)[c]
MS	26.33	21.59	2.22(1.75,2.83)	1.46(1.14,1.87)	
WC	43.99	20.07	2.28(1.78,2.91)	1.59(1.23,2.05)	1.60(1.19,2.15)
BP	45.89	19.57	2.07(1.61,2.64)	1.49(1.11,2.00)	1.50(1.08,2.08)
TG	19.75	18.69	1.78(1.36,2.32)	1.55(1.19,2.03)	1.44(1.04,2.01)
FPG	28.08	16.70	1.33(1.04,1.70)	1.07(0.83,1.38)	1.14(0.86,1.53)
HDL-C	40.00	15.09	1.48(1.17,1.88)	1.36(1.07,1.74)	1.34(0.99,1.82)

HR, hazard ratio; a, univariate analysis; b, adjusted for age, sex, drinking, and family history of hypertension, diabetes, and CVD; c, adjusted for 4 other MS components and the age, sex, drinking, and family history of hypertension, diabetes, and CVD.

Adjusted hazard ratio of the number of MS components associated with CVD

In contrast with the participants without any MS components, those with MS components had an increased incidence of CVD, ranging from 5.56–37.50%. Participants with 1–5 MS components had an increased hazard ratio (HR) for developing CVD, from 1.82 (95%CI: 1.07–3.11) to 8.59 (95%CI:4.43–16.67) (trend $P < 0.001$), compared to those without any MS components. This trend persisted even after adjusting for age, sex, drinking, and family history of hypertension, diabetes, and CVD(Table 3).

Table 3
Adjusted HR of the number of MS components associated with CVD

	CVD(n)	Incidence of CVD,(%)	HR(95%CI)	aHR**(95%CI)
0 component	17	5.56	1.00	1.00
1 component*	62	10.25	1.82(1.07,3.11)	1.49(0.87,2.55)
2 components*	85	15.02	2.86(1.70,4.82)	1.76(1.03,2.99)
3 components*	60	17.96	3.58(2.09,6.13)	1.89(1.08,3.29)
4 components*	36	24.66	5.68(3.19,10.12)	2.56(1.41,4.65)
5 components*	18	37.50	8.59(4.43,16.67)	4.25(2.16,8.39)
P for trend			p < 0.001	p < 0.001

*Compared with those with 0 components of MS; HR, univariate analysis; **adjusted for age, sex, drinking, and family history of hypertension, diabetes, and CVD; Abbreviations are defined in Tables 1 and 2.

Analysis of interactions between BP, WC and TG associated with CVD

We evaluated the effect of the interaction between WC and TG on CVD development. These 2 separate factors, arranged into 4 different subgroups according to their individual absence or presence, were analyzed in pairs by a Cox regression model. Relative to the subgroup without TG and without WC, the HRs associated with CVD were 1.45 (95% CI: 1.08–1.94), 1.27 (95% CI: 0.74–2.21), and 2.16 (95% CI: 1.54–3.04) for the subgroups without TG and with WC, with TG and without WC, and with TG and WC, respectively(Table 4). Moreover, with regard to the indexes of additive interaction, the RERI value was 0.53 (95%CI, -0.40–1.46), AP was 0.25 (95%CI, -0.15–0.65) and SI was 1.91 (95%CI, 0.47–7.70), which indicated no additive interaction between the 2 risk factors. The interaction analysis between TG/WC and BP on CVD development was performed, where upon no additive interactions were found (Table 5).

Table 4
Multiplying interactions analysis among BP, WC and TG associated with CVD

Factor1	Factor2	CVD(n)	Incidence of CVD,(%)	aHR(95%CI)
WC	TG			
□	□	59	23.79	2.16(1.54,3.04)
□	-	118	18.61	1.45(1.08,1.94)
-	□	15	10.14	1.27(0.74,2.21)
-	-	86	8.82	1.00
BP	TG			
□	□	52	25.00	1.92(1.32,2.79)
□	-	128	17.98	1.22(0.90,1.66)
-	□	22	11.70	1.49(0.93,2.40)
-	-	76	8.47	1.00
BP	WC			
□	□	122	24.90	1.93(1.33,2.82)
□	-	55	14.03	1.40(0.93,2.11)
-	□	58	13.49	1.86(1.24,2.79)
-	-	43	6.20	1.00

aHR, adjusted for age, sex, drinking, family history of hypertension, diabetes, and CVD; Abbreviations are defined in Tables 1 and 2.

Table 5
Additive interactions among BP, WC and TG

	Relative excess risk		Attributable proportion		Synergy index	
	Point estimation	95%CI	Point estimation	95%CI	Point estimation	95%CI
WC and TG	0.53	(-0.40,1.46)	0.25	(-0.15,0.65)	1.91	(0.47,7.70)
BP and TG	0.31	(-0.66,1.27)	0.15	(-0.30,0.60)	1.42	(0.43,4.70)
BP and WC	0.03	(-0.89,0.94)	0.01	(-0.38,0.40)	1.02	(0.51,2.03)

Abbreviations are defined in Tables 1 and 2.

Discussion

Numerous studies have suggested that MS is a cluster of CVD risk factor[15–18]. A meta-analysis by Mottillo et al[19]. that included 87 different studies found that MS was associated with an increased risk of CVD(relative risk: 2.35; 95% CI: 2.02–2.73). The predictive value of MS and its contribution to CVD should be ascertained in region-specific populations[20], considering that its effects have been studied in select populations[21]. However, longitudinal data regarding the predictive value of MS in Kazakh population are sparse. In this study, MS was associated with CVD in Kazakh subjects, and the increased risks of CVD remained significant after adjusting for age, sex, drinking, and family history of hypertension, diabetes, and CVD. These findings were also reported in some earlier studies[22–25]. These results imply a significant role of MS in the development of CVD in this ethnic population. However, McNeill et al[26]. found no significant correlation between MS and CVD in a biracial cohort of Whites and Blacks, even after adjusting for risks associated with MS components, a finding that was also highlighted in the West of Scotland Coronary Prevention Study[27]. These discrepancies may be explained in part by the different MS definitions used and the prevalence of individual components of MS in the studied populations.

Our present study suggested that each component of MS was associated with an increased prospective risk of CVD. Furthermore, as the number of MS components increased, the risk of CVD also increased, exhibiting a significant and cumulative-component response trend. This suggests the presence of a cumulative effect of MS components in elevating the CVD risk. These findings are vital because the relationships between clustering patterns of MS and CVD risk have not been thoroughly characterized in Kazakh populations. This synergistic association is also noteworthy as it provides valuable information

for the establishment of appropriate policies in preventive public health care for the inhabitants of Xinjiang. This linear synergistic correlation has been previously reported in other ethnic groups[24, 25].

Recently, there has been an increase in research concerning the independent association of MS and its components for predicting CVD. However, which MS component is associated with CVD to a larger degree remains unclear. In the Asia Pacific region, up to 66% of some subtypes of CVD can be attributed to hypertension[28]. Numerous studies have suggested a more important role for BP than other components in determining cardiovascular events[29, 30]. Likewise, the present study found that after adjusting for 4 other MS components as well as age, sex, drinking, and family history of hypertension, diabetes, and CVD, the BP factor was still independently associated with increased risks of CVD in Kazakh population. A report by Iso et al[31]. suggested that the National Cholesterol Education Program-defined MS was associated with CVD, even though the body mass index(BMI) was used instead of the Asian criterion for WC. Therefore, adjusting for BMI in models where WC may be entered would be an over adjustment. we did not adjust the BMI in the Cox regression models. The above studies were relatively consistent in finding that BP was an independent risk factor for the development of CVD.

Moreover, our results showed that BP, WC and TG were independent risk factors for CVD in the Kazakh population. Suh et al[18]. found that BP and abdominal obesity were key predictors of CVD in Koreans when adjusted for general risk factors and MS components. For subjects in the National Health and Nutrition Examination Survey III, BP and HDL-C were associated with CHD when adjusted for general risk factors and MS components[32]. Hadaegh et al.[33]studied Middle-East Caucasian residents in Tehrani and highlighted that the FPG level in women and WC in men were independently associated with CVD. These reports are inconsistent in terms of the MS components that predict CVD. These discrepancies may be explained in part by the different study populations, follow-up periods, MS definition used, and prevalence of individual components of MS in different populations.

The present study found that BP, WC and TG were independent risk factors for CVD in Kazakhs, which requsted further consideration of whether WC and TG, WC / TG and BP interact for cardiovascular risk. As a result, we analyzed the interaction between TG and WC or between WC / TG and BP and explored whether their coexistence is an additional risk factor for CVD. Our results showed that when TG and WC coexisted, the aOR was 2.16, which indicated that the accumulation of TG and WC fortifies CVD risk. Therefore, it is plausible that the coexistence of TG and WC contribute to the highest CVD risk, as observed in this study. This indicates that the growing double epidemic of obesity and dyslipidemia among Kazakh people may greatly and rapidly increase their burden of developing CVD. However, the additive interaction indexes indicated no additive interaction between TG and WC. This result was consistent with the results obtained by Kang et al[34]. The above phenomenon indicated that when multiple metabolic abnormalities occur at the same time, the risk of CVD caused by MS is not greater than the sum of their components, indicating that the presence of MS does not provide a clinician with more or better information. This may be because the MS components have a common physiological basis, such as inflammation[35], or central obesity[36], or are closely related to one another.

Study Limitations

This study is a large-scale prospective cohort study of a Kazakh population with a long follow-up period that reports the association of MS with CVD incidence. Our study had some limitations. First, the diagnosis of MS was based on a single measurement of its components at baseline, as was the case in other epidemiological studies[37]. Second, because of site-specific limitations, the CVD outcomes analyzed here failed to include hospitalization or outpatient visits due to a transient myocardial ischemia that prevented symptom remission, which may have led to the underestimation of CVD incidence. Nevertheless, our findings may be generalized to populations who reside in low-income rural areas of Xinjiang. In addition, our findings may provide some important insights regarding issues related to the relationship between MS and CVD in rural Kazakh populations living in other countries, such as Kazakhstan and Uzbekistan owing to similarities in religion, culture, lifestyle, diet, and genetic background in these ethnic groups. Last, Kazakh is a large nomadic nation in Xinjiang and the fluidity is relatively large, physical activity was not assessed and therefore not accounted for in the multivariate model.

Conclusions

BP, WC, and TG were independent risk factors for CVD in the Kazakh populations. In clinical practice, a more informative assessment may be obtained by taking into account the number of MS components. No significant interactions were found between BP, WC, and TG.

Abbreviations

Abbreviations	Full name
CVD	Cardiovascular disease
MS	Metabolic syndrome
CHD	Coronary heart disease
WC	Waist circumference
BP	Blood pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
TG	Triglyceride
HDL-C	High density lipoprotein cholesterol
IERB	Institutional Ethics Review Board
WC (-)	Without WC
BP(-)	Without BP
TG(-)	Without TG
WC (+)	With WC
BP (+)	With BP
TG (+)	With TG
RERI	Relative excess risk due to interaction
AP	Attributable proportion due to interaction
SI	Synergy index
CI	Confidence interval
HR	Hazard ratio

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Ethics Review Board (IERB) of the First Affiliated Hospital of Shihezi University School of Medicine (IERB no.:SHZ2010LL01). All participants signed informed consent forms before joining the study.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: We thank all the individuals who participated in the present study. S G,W Y, and J H had the original idea for the study and all co-authors carried out the design. H W, Y L, X Z, Y H, and H G were responsible for recruitment and follow-up of study participants. K W, Y Y, J Z, J M, L M, and L M were responsible for data cleaning, and J L,Y S ,C L, Z M , R M carried out the analyses. W Y and J H drafted the manuscript, which was revised by all authors. All authors read and approved the final manuscript.

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