Original Article

Clustering of Cardiovascular Risk Factors and Diabetes: A Prospective Cohort Study on the Inner Mongolian Population in China*

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Abstract

Objective To evaluate the effect of clustering of cardiovascular risk factors (CVRFs) on type 2 diabetes mellitus (T2DM) incidence and identify some high predictive clusters in the Inner Mongolian population in China.

Methods A total of 1,884 Mongolian individuals aged 20 years or above were followed up from 2002 to 2013 and included in the final analysis. We categorized the participants into two subgroups according to the study outcome event. A Cox proportional hazards model was used to evaluate the effect of clustering of CVRFs on the incidence of T2DM. Areas under the curve were used to compare the effect of every cluster on T2DM and identify those having higher predictive value.

Results We found 203 persons with T2DM. Subjects with incident T2DM tended to be older, had a higher prevalence of drinking, had higher systolic and diastolic pressures; total cholesterol, triglyceride, low-density lipoprotein cholesterol, and C-reactive protein levels; waist circumference; body mass index; and heart rate and lower HDL-C level than did those without T2DM. The multivariable adjusted hazard ratio (95% confidence interval) of T2DM was calculated based on comparisons with subjects with 0 CVRFs; in participants with 2 and ≥ 3 factors, the adjusted hazard ratios were 2.257 (1.448, 3.518) and 3.316 (2.119, 5.188), respectively.

Conclusion The clustering of CVRFs increased the risk of T2DM. On the basis of fast heart rate, the cluster of abdominal obesity and other CVRFs had higher predictive value for T2DM than the other three CVRF clusters.

Key words: Type 2 diabetes; Cardiovascular risk factors; Abdominal obesity; Heart rate

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a worldwide epidemic with an estimated prevalence projected to approach 366 million cases worldwide by 2030[1]. The prevalence of T2DM is high and increasing rapidly in China[2]. A national survey of Chinese adults published in 2010 has shown that the prevalence of T2DM and prediabetes are 9.7% and 15.5%, respectively[3]. The risk of cardiovascular disease (CVD) in subjects with T2DM is about two- to fourfold greater than in those without T2DM[4-6]. Moreover, some cardiovascular risk factors (CVRFs) are associated with T2DM incidence, especially the components of metabolic syndrome, such as dyslipidemia, hypertension, and obesity[7-9]. Some cross-sectional studies have indicated that there was clustering of CVRFs in individuals with impaired fasting glucose (IFG) and T2DM[10-11]. However, no prospective study has evaluated the relationship between clustering of CVRFs and T2DM incidence in the Mongolian population. Considering that heart rate is easily measured but an important indicator of CVDs[12], we used heart rate, family history of CVD, dyslipidemia, hypertension, abdominal obesity, and general obesity as CVRFs and obtained heart rate as a fixed factor in analyzing whether the clustering of CVRFs increases the risk of T2DM. Moreover, we compared the associations of different clusters of fast heart rate and other CVRFs with T2DM incidence to identify some clusters that have a high predictive value for T2DM in the Mongolian population.

METHODS

Study Participants

This study was established to evaluate potential risk factors for chronic diseases in a rural population of 32 villages in 2 townships, Kezuohou Banner (county) and Naiman Banner, Inner Mongolia, China, in the period between July 2002 and September 2003. The methods of recruitment of study participants and baseline data collection have been described previously[13]. Briefly, 2,589 Mongolian people aged 20 years and above were recruited from Inner Mongolia. Individuals with CVDs and endocrine diseases were excluded. In addition, 94 patients with T2DM and 56 without complete key variables were excluded in the present study. Finally, 2,439 individuals were included in this study at baseline. During the follow-up, 276 died and 279 were lost; 1,884 participants were eventually included in the final analysis. This study was approved by the Soochow University Ethics Committee in China. Written informed consent was obtained for all study participants.

Data Collection

The trained staff interviewed participants using a standard questionnaire to obtain information on demographic characteristics and lifestyle risk factors. Cigarette smoking was defined as having smoked at least 1 cigarette per day for 1 year or more[14]. Alcohol drinking was defined as having consumed at least 50 g of alcohol per day for 1 year or more[15].

Three sitting blood pressure measurements were taken for each participant using a mercury sphygmomanometer according to a standard protocol[16]. The first and fifth Korotkoff sounds were recorded as systolic (SBP) and diastolic blood pressures (DBP), respectively. Hypertension was defined as an SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, a self-reported history of hypertension, or the use of any antihypertensive drugs in the past two weeks[17]. Waist circumference (WC) was measured horizontally at the umbilical level at the end of normal expiration by trained staff. Abdominal obesity was defined as WC ≥ 85 cm for men and ≥ 80 cm for women. Weight and height were measured by standard methods, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). General obesity was defined as BMI ≥ 28 kg/m^2. Heart rates were measured three times using a stethoscope at the apex of the heart and counted for 60 s, 1 min apart, following at least 30 min rest. Fast heart rate was classified as heart rate greater than the upper quartile (≥ 84 bpm).

Blood samples were collected in the morning after at least 8 h of fasting. Plasma and serum samples were frozen at -80 °C. Fasting plasma glucose levels were examined using a modified hexokinase enzymatic method[18]. C-reactive protein (CRP) concentrations were determined by an immunoturbidimetric assay on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter, Fullerton, California, USA) using commercial reagents. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were analyzed enzymatically on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter) using commercial reagents[19]. Low-density

lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation for participants who had TG level < 400 mg/dL[20]. Dyslipidemia was defined as TC level ≥ 6.22 mmol/L, TG level ≥ 2.26 mmol/L, LDL-C level ≥ 4.14 mmol/L, and/or HDL-C level < 1.04 mmol/L[21].

Follow-up and Outcome Definitions

Cohort members were reinvestigated between 2013 and 2014. If participants reported that T2DM had developed during the period between baseline survey and follow-up, the staff contacted the subjects' general practitioners and reviewed records or death certificates to confirm. All other living participants were instructed to maintain their usual physical activity and diet (more than 150 g of carbohydrates per day) for at least 3 days before undergoing the oral glucose tolerance test according to a standard protocol. After at least 10 h of overnight fasting, fasting venous blood glucose levels were measured, and standard 75-g glucose solutions were administered. Blood samples were drawn 120 min after the glucose load to measure glucose concentrations. Plasma glucose levels were also measured with the use of a modified hexokinase enzymatic method. Incident T2DM was defined based on the 1999 World Health Organization[22] criteria (≥ 7.0 mmol/L fasting or ≥ 11.1 mmol/L 2-h glucose), validated physician diagnosis, use of antidiabetic medication at any investigation, or diagnosis of T2DM in the medical records or death certificate.

Statistical Analysis

Participants were classified into two groups: participants with T2DM and those without T2DM according to the study outcome status. Categorical data were summarized using percentages and compared using chi-square tests. Normally distributed continuous data were summarized as mean with standard deviations and compared using the *t*-test. Skewed data were presented as median (interquartile range) and compared using the Wilcoxon test. Further analysis was based on these six CVRFs: family history of CVD, fast heart rate, abdominal obesity, general obesity, hypertension, and dyslipidemia. According to different CVRF clusters, the participants were categorized into four groups: participants with 0, 1, 2, and ≥ 3 CVRFs. We used Cox proportional hazards model to compute hazard ratios (HR) of T2DM incidence among four groups by adjusting the important confounding factors including age, sex, smoking, drinking, and CRP level. We also assessed the predictive value of different clusters for T2DM incidence by computing the area under the receiver operating characteristic curve (AUC) and 95% confidence interval (*CI*). First, we only combined two CVRFs, which included fast heart rate and another factor, and compared the difference in AUC between different clusters. Second, we combined three CVRFs, which included fast heart rate and two other factors, and compared the difference in AUC between different clusters. Statistical analyses were performed using SAS (version 9.4) and MedCalc statistical software (used to compare the AUC in different clusters). All *P*-values were two-tailed, and a significance level of 0.05 was used.

RESULTS

Among 1,884 participants, 203 developed T2DM during the follow-up. The cumulative incidence rate of T2DM was 10.8%, and the incidence density was 1,001 per 100,000 person-years.

Table 1 presents the baseline characteristics of participants with incident T2DM and those without T2DM. Conventional CVRFs, such as age, blood pressure, lipids, WC, BMI, and CRP level, were significantly different between the two groups. Subjects with incident T2DM had higher SBP; DBP; TC, TG, LDL-C, and CRP levels; WC; BMI; and heart rate and lower HDL-C level (all $P < 0.05$). Moreover, the mean age and rate of drinking in subjects with incident T2DM were also higher than that in those without T2DM (both $P < 0.05$).

Table 2 summarizes the unadjusted and adjusted HRs and 95% *CI* of the risk of T2DM according to the number of CVRF clusters. Compared with those without CVRF, the unadjusted HRs (95% *CI*) in subjects with 1, 2, and ≥ 3 risk factors were 0.997 (0.620, 1.602), 2.632 (1.711, 4.048), and 4.089 (2.677, 6.245), respectively. After adjusting for age, sex, smoking, drinking, and CRP level, the HRs (95% *CI*) in subjects with 1, 2, and ≥ 3 factors were 0.932 (0.577, 1.505), 2.257 (1.448, 3.518), and 3.316 (2.119, 5.188), respectively. A positive dose-response relationship is likely to present for T2DM with increasing number of CVRF clusters (*P* for trend < 0.0001).

The clustering of two CVRFs and AUC (95% *CI*) of each cluster are presented in Table 3. The result showed that the AUC of clustering of fast heart rate and abdominal obesity was 0.701 (0.661, 0.741),

which was significantly higher than any other clustering (all $P < 0.05$).

Table 4 presents the clustering of three CVRFs and AUC (95% *CI*) of each cluster. It is noted that the cluster of fast heart rate with abdominal obesity and other risk factors had significantly higher AUC than other clusters (all $P < 0.05$). The AUCs (95% *CI*) were 0.701 (0.661, 0.741), 0.711 (0.671, 0.750), 0.713 (0.673, 0.753), and 0.702 (0.662, 0.741) for the clusters of fast heart rate with abdominal obesity and general obesity, fast heart rate with abdominal obesity and hypertension, fast heart rate with abdominal obesity and dyslipidemia, and fast heart rate with abdominal obesity and family history, respectively.

Table 1. Baseline Characteristics of 1,884 Participants with and without T2DM

Characteristics	With T2DM	Without T2DM	*P* Value
n	203	1,681	
Age, y	47.71 ± 11.09	43.65 ± 10.90	< 0.0001
Male, %	40.39	37.83	0.4782
SBP, mmHg	133.28 ± 22.18	125.70 ± 21.78	< 0.0001
DBP, mmHg	87.42 ± 12.21	82.87 ± 12.08	< 0.0001
TG, mmol/L	1.27 (0.79, 2.21)	0.90 (0.62, 1.30)	< 0.0001
TC, mmol/L	3.81 (3.12, 4.78)	3.51 (2.94, 4.23)	0.0004
HDL-C, mmol/L	1.00 (0.86, 1.22)	1.17 (0.96, 1.38)	< 0.0001
LDL-C, mmol/L	2.41 (1.82, 3.15)	2.10 (1.57, 2.74)	< 0.0001
Smoker, %	40.89	42.53	0.6536
Drinker, %	37.44	29.63	0.0223
WC, cm	86.42 ± 10.74	79.51 ± 8.76	< 0.0001
BMI, kg/m^2	24.23 ± 3.85	22.11 ± 3.23	< 0.0001
Heart rate, beat per minute	78.07 ± 10.68	75.80 ± 11.05	0.0058
CRP (P_{25}, P_{75}, mg/L)	9.40 (4.92, 16.63)	5.43 (3.63, 9.76)	< 0.0001

Note. SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WC, waist circumference; BMI, body mass index; CRP, C-reactive protein.

Table 2. Hazard Ratios for T2DM Incidence According to the Number of CVRFs

Numbers	Cases	Person-years	Unadjusted HR (95% *CI*)	Adjusted HR (95% *CI*)*
0	31	333.54	1.00 (reference)	1.00 (reference)
1	38	420.18	0.997 (0.620, 1.602)	0.932 (0.577, 1.505)
2	63	674.40	2.632 (1.711, 4.048)	2.257 (1.448, 3.518)
≥ 3	71	727.77	4.089 (2.677, 6.245)	3.316 (2.119, 5.188)
P for trend			< 0.0001	< 0.0001

Note. *Adjusted for age, gender, smoking, drinking, and CRP.

Table 3. The Cluster of two CVRFs and the AUC (95% *CI*) of Each Cluster

Clusters	AUC	95% *CI*
[a]Fast heart rate + Abdominal obesity	0.701	0.661-0.741
Fast heart rate + General obesity	0.616	0.572-0.660
Fast heart rate + Hypertension	0.625	0.582-0.667
Fast heart rate + Dyslipidemia	0.613	0.568-0.657
Fast heart rate + Family history	0.569	0.526-0.613

Note. AUC, area under curve; *CI*, confidence interval. [a]AUC is significantly higher than that of other clusters and $P < 0.05$.

DISCUSSION

In this population-based prospective cohort study on the Inner Mongolian population, we found that the clustering of CVRFs at baseline significantly increased the risk of T2DM in the future. Subjects with ≥ 3 CVRFs had 3.316-fold higher risk of T2DM than those without CVRF. In addition, abdominal obesity is an important CVRF, which has a high predictive value for T2DM incidence. On the basis of fast heart rate, abdominal obesity suggests a greater risk of T2DM. Our study is the first to analyze the relationship between clustering of CVRFs and T2DM incidence in the Inner Mongolian population, an ethnic minority in China. Compared with previous studies analyzing CVRFs separately with T2DM risk, the novelty of this study is to identify some concrete clusters including two or three CVRFs that had higher predictive value for T2DM.

Several studies have indicated that the clustering of CVRFs was associated with increased risk of T2DM. The community-based study on Hispanic adults living in the San Juan Metropolitan Area of Puerto Rico showed that those with previous T2DM had significantly (P < 0.05) higher adjusted prevalence of all CVRFs compared with participants with normoglycemia[11]. A longitudinal population-based study in the eastern Mediterranean region reported that the 5.6 mmol/L cutoff value of IFG in combination with other risk factors significantly increased its predictive power for T2DM [AUC (95% *CI*), 0.78 (0.74-0.83)][23]. Our previous cross-sectional study has found that there was a positive and significant association between the number of CVRFs clusters and T2DM[10]. *OR*s of T2DM associated with 1, 2, and ≥ 3 factors was 2.01 (0.70, 5.76), 5.47 (2.03, 14.71), and 14.30 (5.55, 36.83), respectively. The findings reported here are consistent with our previous results, which indicated that continuous accumulation of various risk factors would lead to T2DM in the subsequent years.

In addition, we focused in depth on some exact clusters with higher predictive value for T2DM. A number of epidemiologic studies point to fast heart rate as a major risk factor for T2DM and CVD. Shigetoh et al.[24] reported that fast heart rate may predispose an individual to the development of obesity and T2DM. The Kailuan prospective study in China observed a dose-response association between higher heart rate and higher risk of developing T2DM and IFG and progression of IFG to T2DM[25]. Heart rate is influenced by sympathetic nerve activities, and reflex sympathetic activation can elicit acute insulin resistance in normotensive individuals[26-27]. The Framingham Heart Study (FHS) suggested that individuals with a higher heart rate has an elevated long-term risk for cardiovascular events [HR (95% *CI*), 1.15 (1.07-1.24), P = 0.0002], in particular, heart failure [HR (95% *CI*), 1.32 (1.18-1.48), P < 0.0001], and all-cause death [HR (95% *CI*), 1.17 (1.11-1.24), P < 0.0001][28]. Meanwhile, higher heart rate also has been associated with many other CVRFs, including hypertension, obesity, dyslipidemia, and metabolic syndrome[29-31], which are intermediate risk factors for T2DM. Given the established observational data and randomized recent trial evidence, it is now appropriate to aim to reduce elevated resting heart rate by lifestyle and pharmacological therapy like ivabradine, a pure heart rate-lowering agent[32-33]. Nonetheless, increased heart rate is not yet a primary medical goal for T2DM. In part, this is due to a lack of evidence

Table 4. The Cluster of Three CVRFs and the AUC (95% *CI*) of Each Cluster

Clusters	AUC	95% *CI*
[a]Fast heart rate + Abdominal obesity + General obesity	0.701	0.661-0.741
[a]Fast heart rate + Abdominal obesity + Hypertension	0.711	0.671-0.750
[a]Fast heart rate + Abdominal obesity + Dyslipidemia	0.713	0.673-0.753
[a]Fast heart rate + Abdominal obesity + Family history	0.702	0.662-0.741
Fast heart rate + General obesity + Hypertension	0.653	0.610-0.696
Fast heart rate + General obesity + Dyslipidemia	0.655	0.611-0.699
Fast heart rate + General obesity + Family history	0.623	0.579-0.667
Fast heart rate + Hypertension + Dyslipidemia	0.651	0.607-0.694
Fast heart rate + Hypertension + Family history	0.629	0.587-0.671
Fast heart rate + Dyslipidemia + Family history	0.624	0.580-0.668

Note. [a]AUC is significantly higher than that of other clusters and P < 0.05.

supporting heart rate lowering as a therapeutic strategy in T2DM. However, all known controllable risk factors (hypertension, increased body weight, lipid levels, etc.) have to be treated first-line. Therefore, our analysis included heart rate in every cluster to identify which CVRF cluster may generate higher predictive value. This might help individuals with fast heart rate deal with other CVRFs better.

In the two CVRF clustering models, abdominal obesity combined with fast heart rate had the highest predictive value for T2DM, and in the three CVRF clustering models, on the basis of heart rate, abdominal obesity combined with dyslipidemia had higher predictive value than other clusters without abdominal obesity. This result indicated that abdominal obesity was a core CVRF for participants with fast heart rate. It has been recognized that central obesity is a major risk factor for T2DM. Ford et al.[34] support the use of WC as a measure of obesity to predict health risk, due to the rapid increase in obesity incidence, especially abdominal obesity, among US adults. In two prospective, nested case-control studies on US women and men, Huang et al. reported that the genetic predisposition to central obesity was significantly associated with an increased T2DM risk independent of BMI, dietary, and lifestyle risk factors[35]. In addition, a recent cohort study indicated that abdominal obesity is a major risk factor for T2DM in China and accounted for 28.1% [95% *CI* (14.8%, 40.5%)] of incident T2DM in men and 41.2% [95% *CI* (28.3%, 52.6%)] in women[36]. Our study also showed that abdominal obesity plays an important role in predicting T2DM incidence in the future. Furthermore, a hypertriglyceridemia study from the University of California, Los Angeles (UCLA) Risk Factor Obesity Program reported that the presence of elevated level of TG, an important part of dyslipidemia, is a likely predictor for insulin resistance in individuals with increased WC[37], which means hypertriglyceridemic waist increased the risk of incident T2DM[38]. Our previous study also found that dyslipidemia was an independent risk factor for diabetes in the Mongolian population[39]. In this study, we have shown that the cluster of heart rate, abdominal obesity, and dyslipidemia had higher predictive value than other clusters without abdominal obesity. This indicated that further research such as interaction on the relationship between abdominal obesity and dyslipidemia is needed.

To our knowledge, T2DM is considered to be an incurable disease that causes generalized vascular damage affecting the heart, eyes, kidneys, and nerves and imposes a significant economic impact on the society, healthcare systems, and individuals with diabetes and their families[40]. Therefore, it is obvious that targeted prevention and intervention are the most effective strategies for diabetes and its complications. Clustering of CVRFs is a useful tool in assessing abnormal glucose metabolism in adults. The current study suggests the promise of this simple tool as part of the overall diagnostic method for T2DM and to identify those who are at risk for glucose abnormality. Our results indicated that individuals with relatively fast heart rate should pay more attention to maintaining normal WC to reduce T2DM risk in our study population.

This study has several strengths that deserve mention. It is the first prospective study to analyze the clustering of different CVRFs and their predictive value for T2DM in the Mongolian population, a minority in China. The study participants were homogeneous in many respects. All individuals have similar lifestyles and gene characteristics. Moreover, the data were collected with explicit inclusion and exclusion criteria, and rigid quality control for important covariables was carried out. In addition, our follow-up time was relatively long, which enabled us to minimize bias from confounding factors. However, there still exist some limitations in this study. Information on CVRFs was measured only at baseline. Nevertheless, because of the impeded economic development and insufficient health consciousness in Inner Mongolia, lifestyle changes and cultivation of good habits in this stable population are low. Thus, CVRFs are not expected to have varied greatly during the follow-up. In addition, the possibility of residual confounding cannot be fully eliminated in an observational study, although several important potential confounders have been controlled for in multivariable-adjusted models.

CONCLUSIONS

In conclusion, our study indicated that the clustering of CVRFs increased the risk of T2DM. On the basis of fast heart rate, the cluster of abdominal obesity and other CVRFs had higher predictive value for T2DM than the other three CVRF clusters.

CONFLICT OF INTEREST

No conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All authors contributed to the results of the research. WANG Ting Ting wrote the manuscript with the help of LIN Bo; CUI Wen Xiu and ZHANG Ming Zhi participated in the analysis and interpretation of data; ZHANG Yong Hong participated in the whole research process and designed the study; ZHANG Shao Yan designed the study, collected and analyzed the data, and revised the manuscript.

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