Letter to the Editor

Validation of the China-PAR Equations for Cardio-cerebrovascular Risk Prediction in the Inner Mongolian Population*

ZENG Ni Mei[1,^], ZHENG Xiao Wei[1,^], PENG Hao[1], JIAO Yang[2], LI Hong Mei[1], ZHANG Ming Zhi[1], WANG Ai Li[1], and ZHANG Yong Hong[1,#]

The objective of this study was to evaluate the usefulness of the China-PAR equations in predicting the 10-year risk of cardiovascular disease (CVD) in the Inner Mongolians population. A population-based, prospective cohort of 2,589 Mongolians were followed up from 2003 to 2012. Participants were categorized into 4 subgroups according to their 10-year CVD risks calculated using the China-PAR equations: < 5%, 5%-9.9%, 10%-19.9%, and ≥ 20%. The China-PAR equations discriminated well with good C statistics (range, 0.76-0.86). The adjusted hazard ratios for CVD showed an increasing trend among the 4 subgroups (*P* for trend < 0.01). However, the China-PAR equations underestimated the 10-year CVD risk in Mongolians, and the calibration was unsatisfactory (Hosmer-Lemeshow χ^2 = 19.98, *P* < 0.01 for men, χ^2 = 46.58, *P* < 0.001 for women). The performance of the China-PAR equations warrants further validation in other ethnic groups in China.

Cardiovascular disease (CVD) remains the leading cause of premature death worldwide and have imposes a heavy disease and economy burden in China[1]. Risk prediction plays a central role in clinical guidelines for both primary and secondary prevention of CVD. The sex-specific China-PAR equations for 10-year risk prediction of atherosclerotic cardiovascular disease were successfully developed and validated in Han populations in China[2]. However, China is a multi-ethnic country comprising Han and other minority groups which may or may not share similar CVD characteristics with the Han people. The aim of this study is to evaluate whether the China-PAR equations could be used to predict the 10-year risk of cardio-cerebrovascular disease (CCVD) in Mongolians, a minority population in northern China.

This prospective cohort study was conducted from June 2002 to July 2012 in Inner Mongolia, an autonomous region in northern China. Briefly, a total of 3,475 Mongolian people aged 20 years and older were recruited from 32 villages. The majority of local residents were Mongolians who had lived there for many generations and maintained a traditional diet and lifestyle. Among them, 886 people were excluded because they refused to participate, or had cardiovascular or endocrine diseases, including hyper/hypothyroidism. Finally, a total of 2,589 individuals (1,064 men and 1,525 women) free of baseline CVD were included in our study.

Written informed consent was obtained for all participants. This study was approved by the Soochow University Ethics Committee.

Data on demographic characteristics, lifestyle risk factors, family history of CVD, and personal medical history were collected by trained staff. Family history of CVD was defined as having at least 1 parent or sibling with myocardial infarction (MI) or stroke. Current smokers was defined as having smoked at least 1 cigarette per day for 1 year or more. Alcohol consumption was defined as consuming at least 1 unit (50 g) of alcohol per day on average for 1 year or more.

Three consecutive blood pressure (BP) measurements were taken, and the means of the 3 measurements were used for data analysis. Hypertension was defined as a systolic BP of at least 140 mmHg and/or diastolic BP of at least 90 mmHg, or taking antihypertensive medication. Waist circumference (WC) was measured at the level of 1 cm above the umbilicus.

doi: 10.3967/bes2018.061

*This study was supported by the National Natural Science Foundation of China [Grant No. 30972531]; and a Project of the Priority Academic Program Development of Jiangsu Higher Education Institutions of China.

1. Department of Epidemiology, School of Public Health, Medical College of Soochow University, Suzhou 215123, Jiangsu, China; 2. Department of Cardiovascular Disease, Second Affiliated Hospital, Soochow University, Suzhou 215004, Jiangsu, China

Overnight fasting blood samples were obtained to test fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C). Diabetes was defined as the presence of one of the following: 1) FPG ≥ 7.0 mmol/L or 2) a self-reported history of diabetes and current use of either insulin or oral diabetes medication.

All participants were followed up from June 2003 to July 2012. CVD events were defined as a composite of coronary heart disease (CHD) (coronary death, myocardial infarction) and stroke (ischemic stroke and hemorrhagic stroke). Since 2003, household surveys of all participants were conducted on average every 2 years to identify new CVD events. Trained staff interviewed either the participants or their relatives, if participants were dead or unable to communicate, and completed a medical status questionnaire. If any participant reported the occurrence of a CVD event during the period since the last survey, the staff reviewed the patient's hospital records.

The 10-year predictive risk of CVD was calculated for each participant using the China-PAR equations. Participants were categorized into 4 subgroups according to their 10-year CVD risks: < 5%, 5%-9.9%, 10%-19.9%, and ≥ 20%. Baseline characteristics were described separately in each CVD risk subgroup and the cumulative incidence of CVD was estimated using Kaplan-Meier curves and compared by log-rank test. Furthermore, hazard ratios (HR) and 95% confidence intervals (*CI*) of observed CVD events were computed across each subgroup compared with the < 5% category in a multiple Cox proportional hazard model, adjusting for other variables not included in the China-PAR equations, such as hypertension, alcohol drinking and BMI. Age was the most heavily weighted variable in the 10-year risk model[3]; therefore, the model was adjusted for age as a covariate.

We evaluated the calibration and discrimination ability of the China-PAR equations for 10-year CVD risk prediction in Mongolians. For this purpose, we divided the participants into 10 deciles according to their 10-year CVD risks based on the China-PAR equations. We evaluated calibration graphically by comparing the average predicted CVD rates to the observed CVD rates among participants in each decile. Model fit was assessed by using a modified Hosmer-Lemeshow 'goodness-of-fit' test. Discrimination was estimated by calculating the concordance (C) statistic. The above analyses were performed for the overall population and separately for men and women.

The study included 2,589 participants (mean age: 46.4 ± 12.3 years, men: 40.79%) without previous CVD at baseline. The participants had been followed up for an average of 9.2 years and 23,400 person-years. Six participants were lost to follow-up and 48 were excluded for missing key variables; thus, a total of 2,535 persons were included in the final analysis. A total of 195 CVD events, including 120 strokes and 75 cases of CHD were observed, and the cumulative incidence rate was 7.69%. The cumulative incidence of CVD in the < 5%, 5%-9.9%, 10%-19.9%, and ≥ 20% subgroups was 2.56%, 12.96%, 20.54%, and 40.00%, respectively (log-rank $P < 0.001$).

In discriminatory assessment, as shown in Table 1, the adjusted hazard ratios of CVD were 4.94 (95% *CI*: 3.15-7.74), 7.78 (95% *CI*: 4.88-12.39), and 15.37 (95% *CI*: 9.13-25.87), respectively, using the < 5% category as a reference (P for trend < 0.01). The hazard ratios of CVD events significantly and positively increased with the levels of 10-year predicted CVD risk obtained from the China-PAR equations, even after adjustment for age, hypertension, alcohol drinking, and BMI as covariates. The C statistics were 0.816 (95% *CI*: 0.769-0.849) for all participants, 0.808 (95% *CI*: 0.766-0.856) for men, and 0.810 (95% *CI*: 0.787-0.846) for women. The China-PAR equations discriminated well between low and high-risk participants and had a good ability to distinguish CVD cases from non-cases. There was no indication that the performance of the China-PAR equations differed between men and women.

Figure 1 showed comparisons between the observed and predicted incidence of CVD in each decile of the predicted CVD risk for all participants, men only, and women only. The predicted CVD incidence rates were significantly lower than those observed according to deciles of risk, indicating that the China-PAR equations may underestimate 10-year CVD risk in the Mongolian population. The Hosmer-Lemeshow 'goodness-of-fit' test was also unsatisfactory calibrated for all participants (χ^2 = 64.80, $P < 0.001$), men (χ^2 = 19.98, $P < 0.01$), and women (χ^2 = 46.58, $P < 0.001$) (Table 2).

The discrepancy in performance of the China-PAR equations between Chinese Mongolian and Chinese Han populations may be attributed to different genetic determinants and environmental

Table 1. Hazard Ratios and Discrimination among Mongolians by 10-year Predicted Risk

10-year Predicted Risk of CVD, %	Observed Events/ Person-year	Un-adjusted HR (95% *CI*)	Adjusted* HR (95% *CI*)	C Statistics (95% *CI*)
All participants				
< 5	45/16786.52	1.00 (reference)	1.00	0.816 (0.769-0.849)
5-9.9	49/3367.03	5.52 (3.68-8.28)	4.94 (3.15-7.74)	
10-19.9	61/2472.55	9.43 (6.41-13.86)	7.78 (4.88-12.39)	
≥ 20	40/774.83	20.11 (13.12-30.81)	15.37 (9.13-25.87)	
P value for trend		< 0.0001	< 0.0001	
Men				
< 5	15/5356.05	1.00 (reference)	1.00	0.808 (0.766-0.856)
5-9.9	21/1639.41	4.63 (2.39-8.99)	4.40 (2.20-8.78)	
10-19.9	39/1598.44	8.75 (4.82-15.88)	7.90 (4.04-15.45)	
≥ 20	33/665.79	18.48 (10.03-34.06)	15.45 (7.51-31.75)	
P value for trend		< 0.0001	0.0309	
Women				
< 5	30/11430.47	1.00	1.00	0.810 (0.787-0.846)
5-9.9	28/1727.62	6.26 (3.74-10.48)	4.91 (2.65-9.07)	
10-19.9	22/874.11	10.22 (5.89-17.72)	7.89 (4.00-15.58)	
≥ 20	7/119.04	23.14 (10.15-52.76)	17.82 (6.87-46.25)	
P value for trend		< 0.0001	0.0007	

Note. *Adjusted for age, hypertension, alcohol drinking, and BMI.

Table 2. Comparison of Observed and Predicted Incidence of CVD in Mongolians by 10-year CVD Risk

10-year Predicted Risk of CVD, %	Incidence of Observed CVD Risk (%)	Incidence of Predicted CVD Risk (%)	Calibration χ^2	*P* Value
All participants				
< 5	2.56	1.55	64.80	< 0.001
5-9.9	12.96	7.20		
10-19.9	20.54	14.03		
≥ 20	40.00	27.79		
Men				
< 5	2.62	2.00	19.98	< 0.01
5-9.9	11.35	7.18		
10-19.9	20.42	14.20		
≥ 20	38.82	28.39		
Women				
< 5	2.53	1.34	46.58	< 0.001
5-9.9	14.51	7.23		
10-19.9	20.75	13.72		
≥ 20	46.67	24.37		

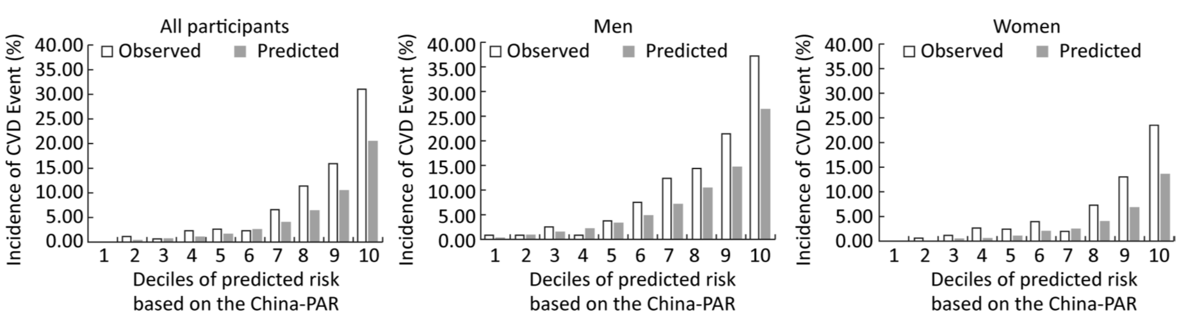

Figure 1. Observed and predicted incidence of CVD event among Mongolians by deciles of predicted risk based on the China-PAR.

exposure. First, the susceptibility to CVD was higher in Mongolians than in the Chinese Han population, as suggested by a higher occurrence of the apolipoprotein *E* gene ε4 allele[4] and *RGS5* gene variants (rs16849802 and haplotype GAA)[5]. Second, the Mongolian participants in our study had a higher prevalence of current smoking (44% *vs*. 33%) and hypertension (37.39% *vs*. 25.73%) than the Chinese Han cohort[6]. In addition, the higher prevalence of CVD in Mongolians may be attributed to differences in lifestyle. In China, the epidemic of CVD and risk factors, including occupation and lifestyle, have changed vastly in the past decade. However, Chinese Mongolian retain traditional dietary habits, which are characterized by heavy drinking, high consumption of saturated fatty acids, and few fresh vegetables[7].

It is worthy of mention that the Framingham General Cardiovascular Score, which was designed for the American population, has been found to perform well in the Mongolian population in China. A previous study indicated that the risk of CVD in Mongolians is as high as that in the Framingham population[8]. Investigators have identified hypertension, diabetes, dyslipidemia, and smoking as key risk factors that account for most of the CVD burden in the community. Chinese Mongolian people had a higher prevalence of hypertension and other cardiovascular risk factors, as well as risk factor clustering, than Chinese Han people. Thus, risk factors which were not included in the China-PAR equations should also be taken into consideration in predicting 10-year CVD risk in Mongolians. The clustering of multiple risk factors has more detrimental cardiovascular effects than a single risk factor[9,10].

There were some limitations to our study. First, our study only included Mongolian farmers and herdsmen and excluded urban Mongolian residents. The risk score for urbanization included in the China-China-PAR equations requires validation to determine its predictive utility. Second, treatment details, especially for high blood-pressure patients during follow-up period, were not obtained; therefore, it is possible that residual confounding factors affected our results, although we collected data on major cardiovascular risk factors at baseline. Third, we did not collect data on dynamic changes in risk factors for the participants and not adjust for the change status.

In summary, the China-PAR equations underestimated the 10-year risk of CVD among Chinese Mongolians. The performance of the China-PAR equations warrants further validation in other ethnic groups in China.

We are deeply appreciative of the participants in the study, and we thank the Kezuohouqi Banner Center for Disease Prevention and Control and the Naiman Banner Center for Disease Prevention and Control for their support and assistance.

^These authors contributed equally to this work.

#Correspondence should be addressed to ZHANG Yong Hong, Tel: 86-512-6588-0078, E-mail: yhzhang@suda.edu.cn

Biographical notes of the first authors: ZENG Ni Mei, female, born in 1993, master degree candidate, majoring in cardio-cerebrovascular epidemiology; ZHENG Xiao Wei, male, born in 1992, master degree candidate, majoring in cardio-cerebrovascular epidemiology.

Received: November 22, 2017;

Accepted: March 29, 2018

REFERENCES

1. Yang ZJ, Liu J, Ge JP, et al. Prevalence of cardiovascular disease risk factor in the Chinese population: the 2007-2008 China National Diabetes and Metabolic Disorders Study. Eur Heart J, 2012; 33, 213-20.
2. Yang X, Li J, Hu D, et al. Predicting the Ten-Year Risks of Atherosclerotic Cardiovascular Disease in Chinese Population: The China-PAR Project. Circulation, 2016; 134, 1430-40.
3. Chia YC. Review of tools of cardiovascular disease risk stratification: interpretation, customisation and application in clinical practice. Singapore Med J, 2011; 52, 116-23.
4. Svobodova H, Kucera F, Kvasilova M, et al. T06-P-019 Apolipoprotein *E* gene polymorphism in the Mongolian population. Folia Biol (Praha), 2007; 53, 138.
5. Chang PY, Qin L, Zhao P, et al. Association of regulator of G protein signaling (RGS5) gene variants and essential hypertension in Mongolian and Han populations. Genet Mol Res, 2015; 14, 17641-50.
6. Liu J, Hong Y, Sr DAR, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA, 2004; 291, 2591-9.
7. Ganmaa D, Rich-Edwards JW, Frazier LA, et al. A comparison of migrants to, and women born in, urban Mongolia: demographic, reproductive, anthropometric and lifestyle characteristics. Int Health, 2013; 5, 244-50.
8. Peng H, Jiao Y, Zeng Q, et al. Utility of Framingham general cardiovascular disease risk score for predicting 10-year cardiovascular risk in an Inner Mongolian population: a prospective cohort study. Int J Cardiol, 2014; 172, 274-5.
9. Batu ZB, Tong W. Prehypertension and Cardiovascular Risk Factor ClusteringAmong Mongolian Population in Rural and AnimalHusbandry Area, Inner Mongolia, China. Circ J, 2009; 73, 1437-41.
10. Zhou Y, Tian Y, Zhong C, et al. Clustering of cardiovascular risk factors and stroke: a prospective cohort study in Inner Mongolia. Neurol Res, 2016; 38, 1-6.