Performance of atherosclerotic cardiovascular risk prediction models in a rural Northern Chinese population: Results from the Fangshan Cohort Study

Xun Tang, PhD, MHS,[a] Dudan Zhang, MS,[a] Liu He, PhD,[a] Na Wu, MS,[a] Yaqin Si, MS,[a] Yang Cao, MS,[a] Shaoping Huang, MD,[b] Na Li, PhD,[b] Jingrong Li, MD,[c] Huidong Dou, MD,[c] Pei Gao, PhD,[a] and Yonghua Hu, MD[a]
Beijing, China

Background Performance of Pooled Cohort Equations (PCEs) for atherosclerotic cardiovascular disease (ASCVD) risks varied across populations. Whether the recently developed Prediction for ASCVD Risk in China (China-PAR) model could accurately predict cardiovascular risks in real practice remains unclear.

Methods A population-based cohort study in rural Beijing in the "stroke belt" in North China was used to externally validate PCE and China-PAR models for 5-year ASCVD risk prediction. Expected 5-year prediction risk using China-PAR model was compared with PCE (white). The models were assessed for calibration, discrimination, and reclassification.

Results Among 11,169 adults aged 40 to 79 years over a median 6.44 years of follow-up, 1,921 participants developed a first ASCVD event during total 70,951 person-years. China-PAR model fairly predicted ASCVD risk in men but overestimated by 29.4% risk in women (calibration χ^2 = 81.4, $P < .001$). Underestimations were shown by PCE as 76.2% in men and 88.2% in women with poor calibration (both $P < .001$). However, discrimination was similar in both models: *C*-statistics in men were 0.685 (95% CI 0.660-0.710) for China-PAR and 0.675 (95% CI 0.649-0.701) for PCE; *C*-statistics in women were 0.711 (95% CI 0.694-0.728) for China-PAR and 0.714 (95% CI 0.697-0.731) for PCE. Moreover, China-PAR did not substantially improve accuracy of reclassification compared with PCE.

Conclusions China-PAR outperformed PCE in 5-year ASCVD risk prediction in this rural Northern Chinese population at average population risk level, fairly predicted risk in men, but overestimated risk in women; however, China-PAR did not meaningfully improve the accuracy of discrimination and reclassification at individual risk level. (Am Heart J 2019;211:34-44.)

Numerous risk prediction models have been developed for primary prevention of cardiovascular diseases.[1] For example, in 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) released the updated Pooled Cohort Equations (PCE) for estimating atherosclerotic cardiovascular disease (ASCVD) risks.[2] However, most risk prediction models derived primarily from Western populations might not be suitable for direct application in other ethnic populations, such as Chinese. One of the important reasons might be due to the fact that the proportion of coronary heart disease (CHD) or stroke among all forms of ASCVD in China is different from the Western population, and furthermore, the relative risk for the same risk factor for ASCVD might differ between stroke-predominant and CHD-predominant ASCVD outcomes. In China, unlike in Western countries, stroke predominates,[3] which may be caused, at least in part, by a higher population prevalence of hypertension.[4] Similar to the "stroke belt" in the southeast United States, a "stroke belt" with high stroke incidence was found in north and west China.[5]

On the other hand, China's current cardiovascular epidemic is increasing along with rapid economic development, aging population, and changing lifestyles.[6] Recently, the Prediction for ASCVD Risk in China (China-PAR) project published a new risk prediction model designed for Chinese adults in multiple contemporary Chinese cohorts.[7] However, their ability to accurately predict cardiovascular risks in

From the [a]Department of Epidemiology and Biostatistics, Peking University Health Science Center, Beijing, China, [b]Fangshan District Center for Disease Control and Prevention, Beijing, China, and [c]The First Hospital of Fangshan District, Beijing, China.
Submitted May 2, 2018; accepted January 26, 2019.
Reprint requests: Yonghua Hu, MD, or Pei Gao, PhD, Department of Epidemiology and Biostatistics, Peking University Health Science Center, 38 Xueyuan Rd, Beijing 100191, China.
E-mail: peigao@bjmu.edu.cn
0002-8703

https://doi.org/10.1016/j.ahj.2019.01.009

real practice remains unclear. Disparities in risk factor distributions, baseline survival, and composition of disease subtypes were observed within China, and patterns of risk in populations located in the "stroke belt" may be significantly different from the cohorts used to derive the China-PAR model. Consequently, evaluation and comparison of the accuracy of ASCVD risk prediction by both PCE and China-PAR models are essential for primary prevention in China.

In this study, we used a population-based cohort of 11,169 Chinese adults aged 40 to 79 years who were recruited at baseline between 2008 and 2010 in rural Beijing to investigate the ASCVD risk prediction performance when applying the original or recalibrated PCE and China-PAR models to the "stroke belt" rural populations in North China. Whether the latest China-PAR models outperform the recalibrated PCE models in this Chinese population in terms of risk prediction is of special interest.

Methods

Study population

The Fangshan Cohort Study (FCS), which is a prospective population-based cohort study in rural Beijing located in the "stroke belt" in North China, was designed to investigate the changing epidemiological characteristics of cardiovascular diseases among rural Chinese populations. Details of study design and cohort profile were published previously.[8] In brief, a total of 20,115 adults aged 40 years or older from 3 towns in the Fangshan District of Beijing were enrolled using cluster sampling between March 2008 and August 2010. For the current analysis, we used the same inclusion criteria followed for the development of the PCE,[2] that is, including the participants aged 40 to 79 years without a history of CHD, stroke, heart failure, or atrial fibrillation at baseline. We further excluded participants with missing data on components of the PCE and China-PAR models. The major reason for exclusion was missing data on measurements of lipids (n = 6,004) because some participants refused to provide overnight fasting venous blood samples at baseline. Overall, 11,169 FCS participants were included in final analysis (Supplemental Figure S1). This study was approved by the Ethics Committee of Peking University Health Science Center, and all participants provided written informed consent before beginning the survey.

Baseline assessment

Trained investigators using a structured questionnaire obtained face-to-face information on participants' age, sex, smoking status, history and family history of comorbid conditions, and use of antihypertensive and antidiabetes medications in community health care centers within residential areas. At baseline, history of CHD, stroke, heart failure, and atrial fibrillation was determined based on medical records–verified self-reported data.[9] *Diabetes* was defined as having a fasting glucose ≥126 mg/dL or self-reported current treatment with insulin or oral hypoglycemic agents. *Family history of ASCVD* was defined as at least 1 parent or 1 sibling having stroke or myocardial infarction (MI). Those who smoked more than 100 cigarettes in their lifetime were designated as smokers. Smokers who had quit more than 1 year prior to the evaluation were categorized as former smokers. Physical examinations were conducted by trained investigators following standardized protocols, and the procedure included resting blood pressure, height, weight, waist circumference, and hip circumference measurements; a 12-lead resting electrocardiogram; collection of fasting blood samples; and a review of medications used during the 2-week period prior to the study visit. Blood pressures in the right arm were measured 3 times and averaged for analysis. *Hypertension* was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of any antihypertensive medication. Overnight fasting venous blood samples were sent to the certificated central laboratory of the First Hospital of Fangshan District for measurement of total cholesterol, high-density lipoprotein cholesterol (HDLC), and blood glucose. Serum was used for the assay within 6 hours by the Hitachi 7060 Automatic Biochemical Analyzer (Hitachi High-Technologies Corp, Tokyo, Japan).

Follow-up and event definition

Living participants (or their proxy respondents) were contacted every year via telephone to assess self-reported incident stroke or CHD events. We also used the New Rural Cooperative Medical Scheme claims data to identify probable ASCVD events during January 2008 and December 2016. In addition, hospitalization medical records or death registries were retrieved by the morbidity and mortality surveillance system established by the Fangshan District Center for Disease Control and Prevention. Based on record-verified data, all suspected cases were then adjudicated by trained study clinicians following published guidelines.[10,11] *Stroke* was defined by a language or physical impairment with symptoms lasting for more than 24 hours and confirmed as being related to a cerebrovascular cause by brain computed tomography or magnetic resonance imaging. *MI* was defined as cases with changed biochemical markers of myocardial necrosis accompanied by ischemic symptoms, pathological Q waves, ST-segment elevation or depression, or coronary intervention. CHD death included all fatal events due to MI or other coronary deaths. The outcomes of hard ASCVD events that the PCE and the China-PAR were derived for were the same.[7] According to the 2013 ACC/AHA guideline, the hard ASCVD events in our study included nonfatal or fatal stroke

Table I. Comparisons of predictor variables used in the PCE and China-PAR models by sex

	Men		Women	
Predictor variables	PCE	China-PAR	PCE	China-PAR
Age	√	√	√	√
Smoking	√	√	√	√
Diabetes	√	√	√	√
Hypertension treatment	√	√	√	√
SBP	√	√	√	√
TC	√	√	√	√
HDLC	√	√	√	√
Waist circumference		√		√
Region		√		√
Urban		√		
Family history of ASCVD		√		
Age × age			√	
Age × smoking	√	√	√	
Age × SBP		√		√
Age × TC	√		√	
Age × HDLC	√		√	
Age × family history of ASCVD		√		

SBP, Systolic blood pressure; *TC*, total cholesterol.

(*International Classification of Diseases, 10th Revision* [ICD-10] codes I60, I61, I63, and I64), nonfatal MI (ICD-10 codes I21 and I22), and CHD death (ICD-10 codes I20-I25). The primary end point of this study is the first-ever fatal or nonfatal ASCVD events; that is, times were recorded as the difference between the date of the baseline examination and the date of occurrence of ASCVD event, the date of death from a cardiovascular cause, or the last follow-up date, whichever occurred first.

Risk prediction models

Comparisons of predictor variables used in the PCE and China-PAR models were summarized in Table I. Because our study followed participants for less than 10 years, we evaluated the capability of risk prediction at 5 years. The China-PAR models were originally derived from 2 cohorts (the International Collaborative Study of Cardiovascular Disease in Asia [InterASIA] and China Multi-Center Collaborative Study of Cardiovascular Epidemiology [China MUCA] 1998) for 10-year ASCVD risk prediction in Chinese (northern/southern, urban/rural) and further validated separately for both 10-year risk (in the China MUCA 1992-1994 cohort) and 5-year risk (in the Community intervention of Metabolic Syndrome in China [CIMIC] cohort).[7] Although the InterASIA study included rural Chinese in Beijing, the number of participants in the "stroke belt" was limited (only 1,913 men and 1,849 women in rural North China),[12] and there was no overlap with our FCS cohort. As one of the validation cohorts for 5-year ASCVD risk prediction by the China-PAR models, the CIMIC cohort was initiated from 2007 to 2008 with an average follow-up duration of 5.9 years. Five-year ASCVD risk predictions in our primary analysis were calculated using the equations provided in the paper by Yang et al,[7] where the $S_0(t)$ was obtained from the published 5-year Kaplan-Meier ASCVD rate of the CIMIC cohort, that is, $S_0(t)$ = exp(−5-year Kaplan-Meier ASCVD event rate) (Supplemental Table S1). We also assessed the performance affected by the baseline survival parameters of the China-PAR model. In the sensitivity analysis, $S_0(t)$ was replaced by the 5-year Kaplan-Meier ASCVD rate of China-PAR derivation cohorts (the InterASIA and China MUCA 1998), where $S_0(t)$ = exp(−10-year Kaplan-Meier ASCVD rate/2) (Supplemental Table S2). We used original PCE for 5-year risk prediction calculation. These parameters were originally obtained from the research team who developed the PCE through personal communication and were published in an article using the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study data.[13] The recalibrated PCE models were applied by adjusting the 5-year baseline survival rate to a general Chinese population (ie, using the survival rate in the China-PAR instead) and keeping other coefficient parameters the same as the original PCE model. Furthermore, we also recalibrated PCE models to our FCS (ie, using the $S_0[t]$ and the mean score derived from our high-risk Chinese population in stroke belt).

Statistical analysis

Baseline characteristics of participants were summarized for sex-specific groups as mean (SD) for continuous variables and percentage for categorical variables. Differences between sex groups were evaluated by t test (as appropriate) for continuous variables and χ^2 test for categorical variables. The Kaplan-Meier method was used to calculate the cumulative incidence of ASCVD and the observed number of ASCVD events at 5 years. The predicted numbers of events at 5 years were estimated by specific equations from PCE (white)[13] and China-PAR[7] separately. Performance of ASCVD risk prediction models was assessed by discrimination, calibration, and reclassification. Model discrimination was evaluated using the Harrell *C*-index. An overall assessment of calibration was assessed by the Hosmer-Lemeshow χ^2 test. A χ^2 value of greater than 20 or a P value of less than .05 means poor calibration. We calculated ratios of predicted to observed events among study participants in 5 categories of 5-year risk predictions: less than 2.5%, 2.5% to less than 3.75%, 3.75% to less than 5%, 5% to less than 10%, and 10% or greater, based on the 2013 ACC/AHA guideline[2] as well as risk thresholds by the World Health Organization guideline.[14] A ratio of 1.0 means perfect calibration with equal predicted and observed rates; ratios greater than 1.0 suggest overestimation, whereas those less than 1.0 indicate underestimation.[15] According to the Transparent Reporting of a Multivariable Prediction Model for Individual

Table II. Baseline characteristics and ASCVD events of study participants by sex

Characteristics	Overall (N = 11,169)	Men (n = 3578)	Women (n = 7591)	*P* value*
Age, y	55.2 ± 8.9	55.5 ± 9.0	55.1 ± 8.8	.017
Current smoker, n (%)	2661 (23.8)	1811 (50.6)	850 (11.2)	<.001
Waist circumference, cm	87.0 ± 10.2	88.6 ± 10.2	86.2 ± 10.1	<.001
SBP, mm Hg	131.2 ± 18.0	131.6 ± 17.4	131.0 ± 18.2	.135
DBP, mm Hg	82.8 ± 10.1	84.1 ± 10.6	82.1 ± 9.9	<.001
Antihypertensive treatment, n (%)	1830 (16.4)	563 (15.7)	1267 (16.7)	.203
Total cholesterol, mg/dL	189.1 ± 37.8	180.8 ± 36.0	193.0 ± 38.0	<.001
HDLC, mg/dL	48.9 ± 12.0	47.3 ± 12.2	49.6 ± 11.8	<.001
Diabetes, n (%)	1101 (9.9)	342 (9.6)	759 (10.0)	.466
Family history of ASCVD, n (%)	3874 (34.7)	1211 (33.9)	2663 (35.1)	.201

To convert total cholesterol and HDL-C to mmol/L, multiply by 0.0259. *DBP*, diastolic blood pressure.
*Compared between men and women.

Table III. Outcomes of ASCVD events in study participants by sex

Outcomes	Overall (N = 11,169)	Men (n = 3578)	Women (n = 7591)	*P* value*
Incident ASCVD events, n (%)	1921 (17.2)	671 (18.8)	1250 (16.5)	.003
Stroke events, n (%)	1064 (9.5)	437 (12.2)	627 (8.3)	<.001
CHD events, n (%)	857 (7.7)	234 (6.5)	623 (8.2)	.002
Incidence of ASCVD (n/100,000 person-year)	2707.5	3028.8	2561.6	<.001
5-y Kaplan–Meier ASCVD rate (%)	10.7	12.0	10.1	

*Compared between men and women.

Prognosis or Diagnosis guidelines,[16] we also illustrated the prediction ability of the equations by using calibration charts and plots. In addition, for model comparison in the context of clinical relevance, change in risk reclassification between the PCE and the China-PAR model was analyzed using the continuous net reclassification improvement and integrated discrimination improvement (IDI) methods.[17] Moreover, to further explore the heterogeneity in effects of predictors, PCE (white) and China-PAR models were refitted in our FCS population using sex-specific Cox proportional-hazards models with all continuous variables natural log-transformed. We used centering continuous predictors by subtracting the mean from each variable in the regression model. Regression coefficients for components in the PCE (white)[13] and China-PAR[7] were compared with those in our FCS population, and hazard ratios were illustrated by forest plots. Two-sided *P* values of less than .05 were considered statistically significant, and 95% CI was used. All statistical analyses were conducted using the STATA version 14 (Stata Corporation, College Station, TX).

Sources of funding

This study was supported by the National Natural Sciences Foundation of China (81573226, 91546120, and 81230066) and Beijing Natural Science Foundation (7162107). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Results

Baseline characteristics of total 11,169 participants were presented in Table II. At baseline, the average age of participants was 55.2 years, and 68% of adults were women. Men were slightly older, had higher levels of waist and diastolic blood pressure, and were more likely to be smokers, whereas women had a higher level of total cholesterol and lower level of HDLC (all $P < .05$). Comparisons of participants included and excluded in final analysis were shown in the Supplemental Table S3 and suggested that baseline characteristics were broadly similar between the 2 groups, except educational level and family history of ASCVD. Among 11,169 adults without history of ASCVD included in our study, 1,921 participants (671 men and 1,250 women) had an incident fatal or nonfatal ASCVD event over a total follow-up of 70,951 person-years (median follow-up 6.44 years). Observed incidence rate were 3,028.8 (95% CI 2,807.1-3,263.0) and 2,561.6 (95% CI 2,423.3-2,705.7) for men and women, respectively, per 100,000 person-years (Table III).

Predicted 5-year incidence using original PCE and recalibrated PCE by CIMIC was lower than that using China-PAR, whereas recalibrated PCEs by FCS were higher in both men and women (Table IV). Sex-specific *C*-statistics for China-PAR model were 0.685 (95% CI 0.660-0.710) for men and 0.711 (95% CI 0.694-0.728)

Table IV. External validation of 5-year ASCVD risk prediction by the PCE and China-PAR models

Model	Predicted ASCVD events* (n)	Kaplan-Meier adjusted events† (n)	Expected-observed ratio	Calibration χ^2 (*P* value)	Discrimination *C*-statistic (95% CI)
Men (418 cases/3578 participants during 5 y)					
Original PCE (white)	102.5	430.1	0.238	2218.7 ($P < .001$)	0.675 (0.649-0.701)
Recalibrated PCE (white) by CIMIC	76.0	430.1	0.177	3260.3 ($P < .001$)	0.675 (0.649-0.701)
Recalibrated PCE (white) by FCS	734.0	430.1	1.707	489.8 ($P < .001$)	0.675 (0.649-0.701)
Original China-PAR	429.3	430.1	0.998	6.7 ($P = .57$)	0.685 (0.660-0.710)
Women(749 cases/7591 participants during 5 y)					
Original PCE (white)	90.2	765.9	0.118	6432.1 ($P < .001$)	0.714 (0.697-0.731)
Recalibrated PCE (white) by CIMIC	129.7	765.9	0.169	4067.5 ($P < .001$)	0.714 (0.697-0.731)
Recalibrated PCE (white) by FCS	1205.0	765.9	1.573	386.9 ($P < .001$)	0.714 (0.697-0.731)
Original China-PAR	990.7	765.9	1.294	81.4 ($P < .001$)	0.711 (0.694-0.728)

*Expected number of events based on the 5-year ASCVD prediction models.
†Observed number of ASCVD events after Kaplan-Meier adjustment through follow-up.

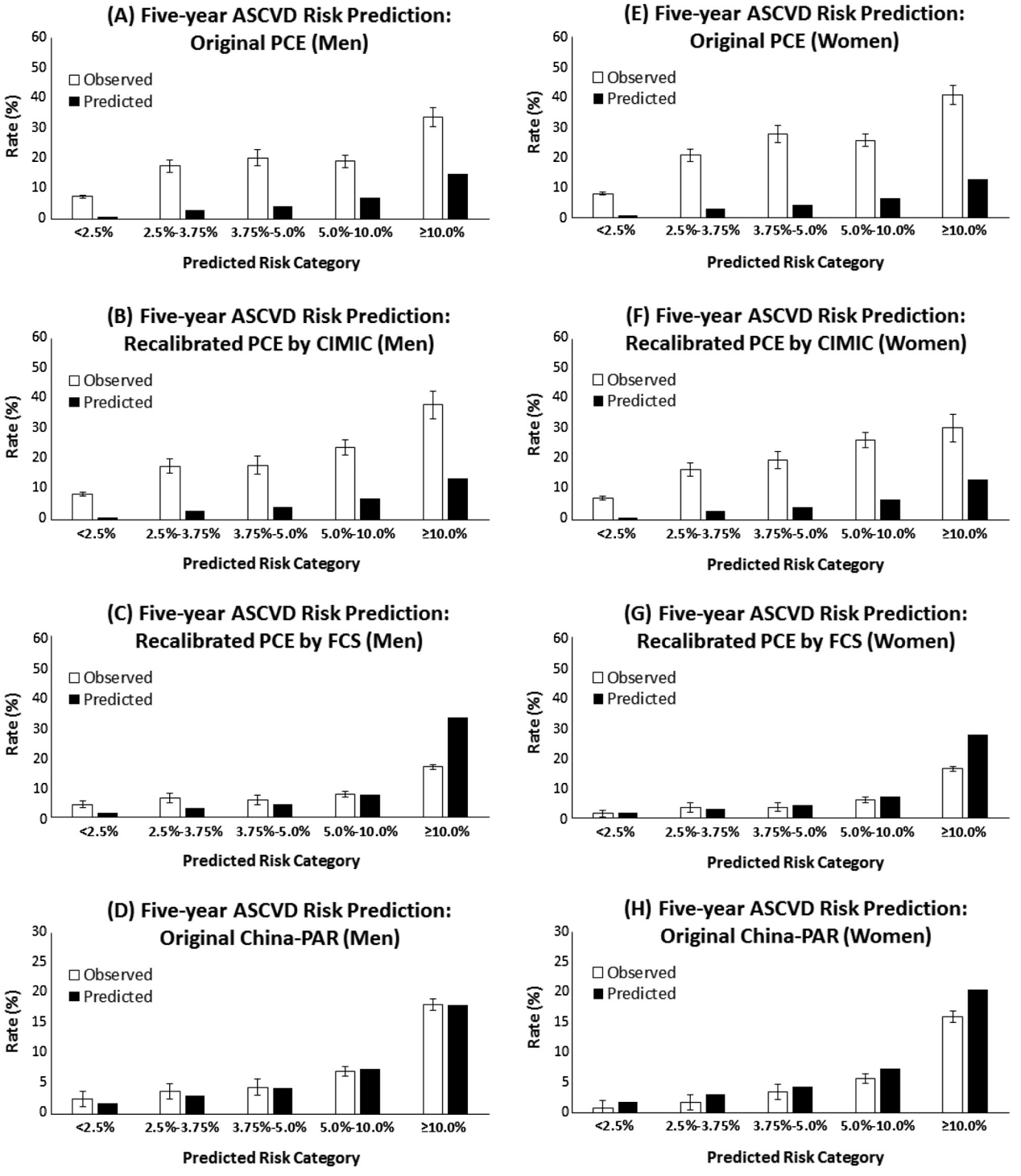
for women, which were similar to 0.675 (95% CI 0.649-0.701) for men and 0.714 (95% CI 0.697-0.731) for women using original PCE or recalibrated PCE. The original PCE underestimated the 5-year risk of ASCVD by 76.2% and 88.2% in men and women with poor calibration (both $P < .001$). The recalibrated PCE model by CIMIC which adjusted the baseline survival to that in a general Chinese population did not improve the performance, that is, the underestimations were still as high as 82.3% in men and 83.1% in women with poor calibration (both $P < .001$). On the contrary, the recalibrated PCE model by FCS which adjusted to a high-risk Chinese population in stroke belt indicated that the overestimations were 70.7% in men and 57.3% in women with poor calibration (both $P < .001$). In contrast, the China-PAR model fairly predicted ASCVD risk in men but overestimated risk in women by 29.4% (calibration $\chi^2 = 81.4$, $P < .001$). China-PAR outperformed PCE at average population risk level in men.

As shown in Figure 1, in predicted 5-year ASCVD risk categories using China-PAR of <2.5%, 2.5% to <3.75%, 3.75% to <5%, 5% to <10%, and ≥10%, the observed rates in those categories were 2.54%, 3.85%, 4.49%, 7.05%, and 18.17% in men and 0.86%, 1.76%, 3.49%, 5.71%, and 15.96% in women. However, their counterparts in above categories using recalibrated PCE by CIMIC were 8.56%, 17.81%, 18.11%, 23.92%, and 38.12% in men and 7.28%, 16.75%, 19.94%, 26.56%, and 30.62% in women, respectively. The calibration plots also illustrated that there were no substantial differences between the observed and the predicted rate in men, whereas overestimation occurred in the highest-risk category in women using China-PAR. However, significant underestimations were observed in both men and women using original PCE or recalibrated PCE by CIMIC, whereas overestimations were indicated using recalibrated PCE by FCS (Figure 2) or recalibrated China-PAR by FCS (Supplemental Figure S2).

In the context of clinically relevant improvements in prediction, we compared the China-PAR model with the reference of original PCE and found that reclassification measured with the continuous net reclassification improvement was not significant in men (0.14%; 95% CI −8.26% to 8.53%) and in women (0.03%; 95% CI −6.03% to 6.10%). IDIs comparing China-PAR versus original PCE were both significant at 2.97% (2.30%-3.64%) in men and 6.58% (5.87%-7.30%) in women; however, IDIs for China-PAR versus recalibrated PCE by FCS were both significant at −9.24% (−11.30% to −7.18%) in men and −5.14% (−6.01% to −4.27%) in women (Supplemental Table S4). These results indicated that, after adjustment for the baseline risk in our FCS population, the China-PAR model inversely predicted worse than the recalibrated PCE by FCS in both men and women at individual risk level. Even after the China-PAR model was also recalibrated by FCS, the results seemed broadly similar (Supplemental Table S5), so the results suggested that the China-PAR model was not necessary to be recalibrated by FCS.

In the sensitivity analyses using the $S_0(t)$ from the China-PAR derivation cohorts, the China-PAR model underestimated the risk by 16.7% in men and overestimated the risk by 10.9% in women with poor calibration (both $P < .001$) (Supplemental Table S6 and Figure S3). In terms of reclassification measures, similar results were shown (Supplemental Table S7) and also

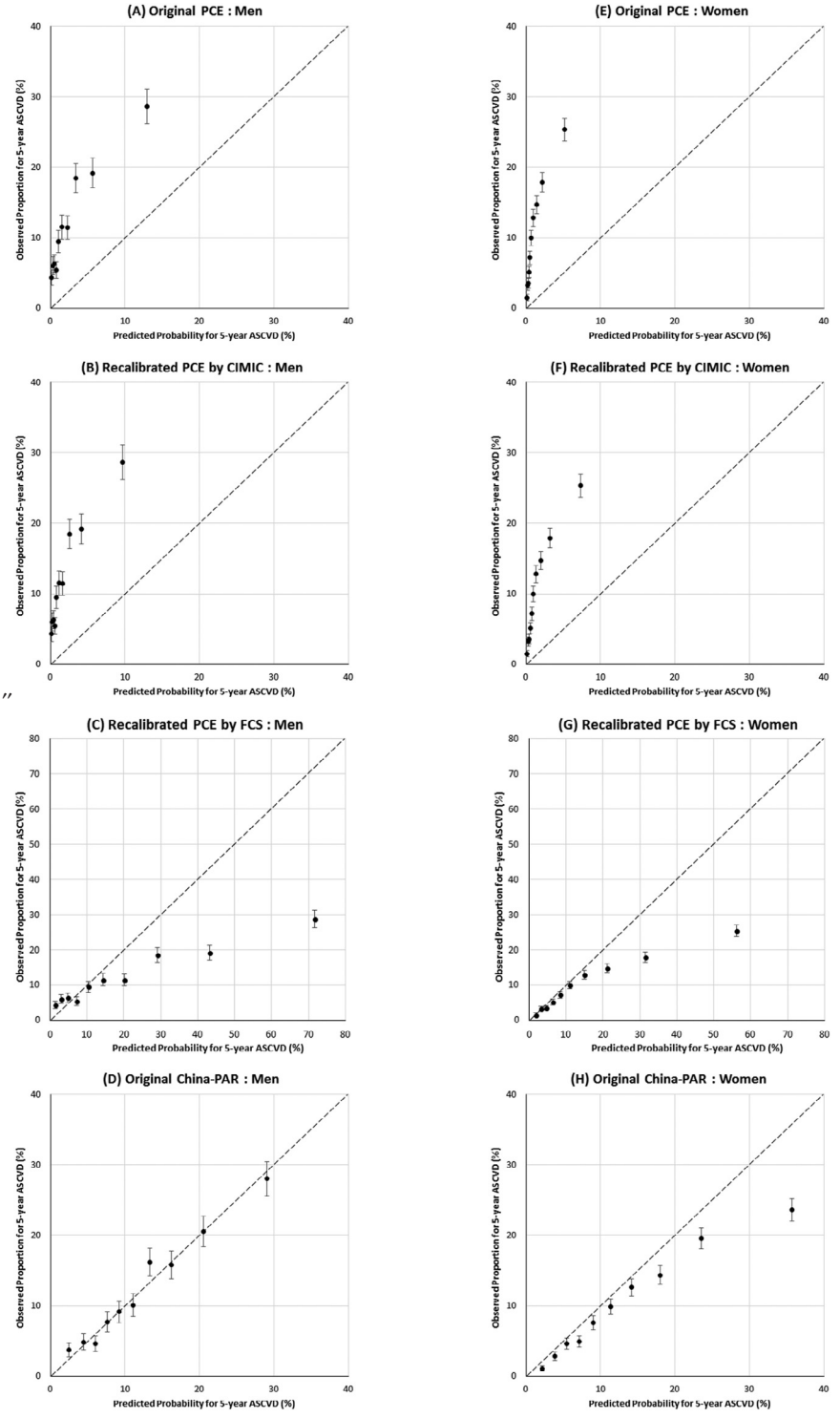
Figure 1



Five-year Kaplan-Meier observed and predicted ASCVD event rates using the China-PAR and PCE.

indicated that, after adjustment for the baseline risk in our FCS population, the China-PAR model inversely predicted worse than the recalibrated PCE in both men and women at individual risk level.

Figure 2



Calibration plots for the external validation of 5-year ASCVD risk prediction using the China-PAR and PCE.

To better understand what components of the PCE or China-PAR influenced the association the most in our rural Chinese population, we compared the regression coefficients in the models and found that the level of systolic blood pressure has major effects besides age (Supplemental Table S8-S9 and Figure S4).

Discussion

To the best of our knowledge, this study is among the first to externally validate the performance of both PCE and China-PAR when applied to data collected in a rural Chinese population located in the "stroke belt" in China. The current analysis suggested that both original PCE and recalibrated PCE by CIMIC using a general Chinese population underestimated the 5-year risk of ASCVD with poor calibration in our study; however, recalibrated PCE by FCS using our high-risk Chinese population in the stroke belt overestimated the 5-year risk of ASCVD with poor calibration.

Researches on performance of the PCE in Asian populations, especially in Chinese, are limited. The Hong Kong Cardiovascular Risk Factor Prevalence Study[18] validated the PCE among 1,476 Chinese adults who were aged 40 to 79 years at baseline recruited in 1995. Model discrimination was moderate (*C*-index was 0.714 for men and 0.765 for women) with poor calibration in men (χ^2 was 24.1 for men and 10.1 for women). The Korean Heart Study (KHS) validated the PCE (white) among 192,605 participants and indicted that 10-year risk was overestimated by 56.5% in men and underestimated by 27.9% in women.[19] Moreover, the KHS developed a Korean Risk Prediction Model for ASCVD and showed an appropriate predictive ability in the KHS cohort. They concluded that PCE should not be directly applied for cardiovascular risk prediction in the Korean population.[19] Besides, the Japan Atherosclerosis Society also commented that it is not necessary to change their guidelines because applying PCE to the Asian population can overestimate the risk.[20] The Japan Public Health Center–based prospective study developed own risk equations for coronary artery disease and ischemic stroke incidence in Japanese.[21] However, all these specific prediction models for the Asian population should be further validated independently by others before they are adopted as the ASCVD risk calculator by the guidelines. Similarly, the China-PAR model for Chinese was published in 2016; however, the recently updated Chinese guidelines for the prevention of cardiovascular diseases (2017)[22] still recommended cardiovascular risk assessment only based on count of the total number of risk factors instead of the quantitative risk assessment calculator such as the China-PAR. In addition, we used Markov models to compare the effectiveness of different screening strategies for primary prevention of cardiovascular diseases in this rural Chinese population in the "stroke belt" and found that screening strategy based on China-PAR risk calculator could gain more health benefit than that based on count of the total number of risk factors by the Chinese guidelines (2017) at the population risk level.[23] These results were consistent with the current study and suggested the implications of validation of cardiovascular risk prediction models in real-world circumstances.

The long-term trend shows a decline in age-standardized cardiovascular mortality in the United States from 300 deaths per 100,000 in 1990 to 176 deaths per 100,000 in 2015,[24] whereas cardiovascular death rates in China are estimated to have declined from 389.93 only to 307.18 per 100,000 between 1990 and 2013.[25] Age-standardized rates of death (per 100,000 people) for stroke in China were 188.8 and 127.5 for men and women in 2013; however, there is substantial province-level variability in stroke mortality with increased rates in the north and west of China.[5] For example, the age-standardized death rates for stroke were higher in Hebei province, which is in the northern Chinese region neighboring Beijing, that is, 258.0 and 160.7 per 100,000 people for men and women.[25] Mortality rates of CHD range from overall 137.6 deaths per 100,000 people in China to 186.0 per 100,000 people in Hebei for men and from 95.1 per 100,000 people in China to 120.1 per 100,000 people in Hebei for women. A relatively clear north-to-south gradient also exists, with the highest rates in the north, and may be explained by differences in cardiovascular risk factors across populations.[25] Thus, the higher rates for ASCVD events in North China as compared with the United States might partially explain why the PCE underestimated the ASCVD risk in our study.

Most of the published studies in some contemporary US cohorts found that PCE overestimated the observed risk for ASCVD due to decline in cardiovascular incidence in Western population, which may in part be due to increased use of statins.[15,26] Although the Multi-Ethnic Study of Atherosclerosis showed overestimation in all ethnic groups and especially in Chinese Americans (252% for women and 314% for men),[27,28] the PCE was never intended to be applied in a rural Chinese population. The population in China might be quite different from US whites and blacks, as well as Chinese Americans, regarding levels of cardiovascular risk factors. For example, blood pressure levels are higher with low rates of awareness, treatment, and control of hypertension in China. This may be responsible for China's high stroke prevalence.[4] Because the average blood pressure levels in our population were more than 130/80 mm Hg, it is not surprising that the original PCE and recalibrated PCE by CIMIC using a general Chinese population underestimated ASCVD risk in this "stroke belt" population in North China. Using the baseline survival and mean score derived from our high-risk population in the FCS, the recalibrated PCE by FCS showed overestimations which were consistent with most of other published studies.

Another plausible reason suggested for the underestimation by both original and recalibrated PCE by CIMIC in our population may be related to the socioeconomic status of the population. A recent published large population-based study in New Zealand indicated that measures of socioeconomic deprivation should be included as predictors to identify vulnerable high-risk subpopulations in prediction models.[29] Recently, Dalton et al[30] suggested that PCE systematically underestimated 5-year ASCVD risk among participants from disadvantaged communities of the Cleveland Clinic Health System, and model discrimination was also poor among participants from socioeconomically disadvantaged neighborhoods (*C*-index was 0.70 [95% CI 0.67-0.74]). In addition, the REGARDS study found that PCE underestimated the 5-year ASCVD risk among participants with more social deprivation, whereas it overestimated risk among those without deprivation. Social deprivation in their evaluation was defined using information on annual household income, education, and relationship status.[31] The PCE overestimated risk in prior validation studies, such as the Women's Health Study, Physicians' Health Study, and Women's Health Initiative observational study, which usually included participants without social deprivation.[32] Notably, the REGARDS study was known to elucidate regional and racial differences in residents of the stroke belt, located in southeastern United States. Given that our participants were based on rural populations also located in the stroke belt but in China with less education (eg, 39.5% participants have educational levels of only primary school or lower in the Supplemental Table S3) and lower income,[33] our results are consistent with the conclusion of the REGARDS study and demonstrated that even after recalibration using Chinese populations, the PCE in the 2013 ACC/AHA guideline might not be appropriate for rural Chinese population.

Furthermore, the current study indicated that the China-PAR model fairly predicted ASCVD risk in men but overestimated risk in women at average population risk level. With the addition of geographical (northern/southern, urban/rural) information, family history of ASCVD, and waist circumference in the China-PAR model, average population risk was shown to have good fit over the calibration plot.[34,35] Geographical (northern/southern, urban/rural) risk factors were generally correlated with neighborhood social deprivation status we discussed above in China. Furthermore, family history of ASCVD has been shown to be a strong predictor of ASCVD events, that is, the Canadian Cardiovascular Society recommended that a person's calculated risk should be doubled when a family history of ASCVD is positive.[36] In addition, a high proportion (34.7%) of participants were observed to have family history of ASCVD in our "stroke belt" population. However, family history of ASCVD was included in the China-PAR model only for men, which may explain why China-PAR models outperformed the PCE models at population risk level, especially in men.

Nevertheless, at individual risk level, China-PAR model did not meaningfully improve the capability of either discrimination or reclassification in our population. The CIMIC study showed that China-PAR models overestimated 5-year ASCVD risk by 12.0% in men and 27.5% in women among 70,838 Chinese participants aged 35-74 years who were free of ASCVD at baseline.[7] Our study was comparative to the CIMIC in terms of cohort initiation period, follow-up time, sex proportion, and average age of participants. The consistent overestimation for China-PAR in women might also be ascribed to some sex-specific cardiovascular risk factors. Further investigations are required to confirm whether additional enhancement to include novel risk markers in women could add value to risk prediction models for clinical practice.[37,38] Using local electronic health records data, such as data from the Veterans Affairs ambulatory care services,[39] physicians might constantly recalibrate and readily updated risk scores; however, most general practitioners could hardly recalibrate flawed risk equations for their own population in practice. Performance of risk prediction models varied across changing populations, and there are too many unique risk factors to consider. At individual risk level, some researchers suggested assessing atherosclerosis directly such as with coronary artery calcium scores, which have been shown to have superior risk prediction than many of the risk scores.[40]

The main strengths of the current analysis include the large number of participants in a genetically homogenous population, thus enhancing the internal validity of our findings. Furthermore, ASCVD events were all adjudicated by trained physicians. Several limitations in our study should also be addressed. Twice as many women as men were included, likely because men in the labor force tend to move to cities such as downtown Beijing for better work opportunities and higher wages. Other studies enrolling subjects in rural China, such as the Asia Pacific Cohort Studies Collaboration,[41] had similar proportions of women and men as in our study. In addition, many participants (29.8%) in FCS cohort were excluded because of missing lipids, and this is common in Asian cohort studies, for example, the Japan Public Health Center-based prospective study also excluded 26.3% (16,310/61,984) and 22.1% (12,009/54,360) participants because of missing biochemical data in their derivation and validation cohorts, respectively.[21] However, comparisons of participants included and excluded in the final analysis suggested that baseline characteristics were broadly similar between the 2 groups in our study, except educational level and family history of ASCVD (Supplemental Table S3). Moreover, our validation study only focused on estimating risk of ASCVD within a 5-year period because of the limited follow-up period of the FCS. Whether the 10-year risk assessment could have better performance is to be evaluated in the future. Finally, our study was based only on a distinct Chinese population

located in the "stroke belt" in North China. Therefore, additional studies in other populations in China are still needed to independently validate the ASCVD risk prediction models for primary prevention.

Conclusions

In summary, our findings suggested that at average population risk level, China-PAR model outperformed PCE in 5-year ASCVD risk prediction in this rural Northern Chinese population, fairly predicted risk in men, but overestimated risk in women; however, in contrast to the PCE, China-PAR model did not meaningfully improve the accuracy of discrimination and reclassification at individual risk level. Therefore, future ASCVD risk prediction models specifically aiming to improve the accuracy at individual risk level, especially for women, are still demanded.

Acknowledgments

The authors thank all the investigators, staff, and participants of the Fangshan Cohort Study for their valuable contributions.

Conflict of interest disclosures

The authors declare that they have no conflicts of interests.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.01.009.

References

1. Zhao D, Liu J, Xie W, et al. Cardiovascular risk assessment: a global perspective. Nat Rev Cardiol 2015;12:301-11.
2. Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:S49-73.
3. Wu Z, Yao C, Zhao D, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, part I: morbidity and mortality monitoring. Circulation 2001;103:462-8.
4. Lu Y, Wang P, Zhou T, et al. Comparison of prevalence, awareness, treatment, and control of cardiovascular risk factors in China and the United States. J Am Heart Assoc 2018;7, e007462.
5. Xu G, Ma M, Liu X, et al. Is there a stroke belt in China and why? Stroke 2013;44:1775-83.
6. Wu Y, Benjamin EJ, MacMahon S. Prevention and control of cardiovascular disease in the rapidly changing economy of China. Circulation 2016;133:2545-60.
7. Yang X, Li J, Hu D, et al. Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population: the China-PAR Project (Prediction for ASCVD Risk in China). Circulation 2016;134:1430-40.
8. Wu N, Tang X, Wu Y, et al. Cohort profile: the Fangshan Cohort Study of cardiovascular epidemiology in Beijing, China. J Epidemiol 2014;24:84-93.
9. He L, Tang X, Song Y, et al. Prevalence of cardiovascular disease and risk factors in a rural district of Beijing, China: a population-based survey of 58,308 residents. BMC Public Health 2012;12:34.
10. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ 1976;54:541-53.
11. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108:2543-9.
12. He J, Neal B, Gu D, et al. International collaborative study of cardiovascular disease in Asia: design, rationale, and preliminary results. Ethn Dis 2004;14:260-8.
13. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA 2014;311:1406-15.
14. World Health Organization. Prevention of cardiovascular disease: guidelines for assessment and management of total cardiovascular risk. World Health Organization: http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf 2007. Accessed November 16, 2018.
15. Cook NR, Ridker PM. Calibration of the pooled cohort equations for atherosclerotic cardiovascular disease: an update. Ann Intern Med 2016;165:786-94.
16. Collins GS, Reitsma JB, Altman DG, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.
17. Pencina MJ, D'Agostino Sr RB, Demler OV. Novel metrics for evaluating improvement in discrimination: net reclassification and integrated discrimination improvement for normal variables and nested models. Stat Med 2012;31:101-13.
18. Lee CH, Woo YC, Lam JK, et al. Validation of the pooled cohort equations in a long-term cohort study of Hong Kong Chinese. J Clin Lipidol 2015;9:640-6. e2.
19. Jung KJ, Jang Y, Oh DJ, et al. The ACC/AHA 2013 pooled cohort equations compared to a Korean Risk Prediction Model for atherosclerotic cardiovascular disease. Atherosclerosis 2015;242:367-75.
20. Kinoshita M, Yokote K, Arai H, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb 2018;25:846-984.
21. Yatsuya H, Iso H, Li Y, et al. Development of a risk equation for the incidence of coronary artery disease and ischemic stroke for middle-aged Japanese—Japan Public Health Center–based prospective study. Circ J 2016;80:1386-95.
22. Task Force on Chinese Guidelines for the Prevention of Cardiovascular Diseases (2017), Editorial Board of Chinese Journal of Cardiology. Chinese guidelines for the prevention of cardiovascular diseases (2017). Chin J Cardiol 2018;46:10-25. [in Chinese].
23. Si YQ, Tang X, Zhang DD, et al. Effectiveness of different screening strategies for primary prevention of cardiovascular diseases in a rural northern Chinese population. J Peking Univ (Health Sci) 2018;50:443-9. [in Chinese].

24. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol 2017;70:1-25.
25. Zhou M, Wang H, Zhu J, et al. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet 2016;387:251-72.
26. Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. JAMA Intern Med 2014;174:1964-71.
27. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association–American College of Cardiology–Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. Eur Heart J 2017;38:598-608.
28. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med 2015;162:266-75.
29. Pylypchuk R, Wells S, Kerr A, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. Lancet 2018;391:1897-907.
30. Dalton JE, Perzynski AT, Zidar DA, et al. Accuracy of cardiovascular risk prediction varies by neighborhood socioeconomic position: a retrospective cohort study. Ann Intern Med 2017;167:456-64.
31. Colantonio LD, Richman JS, Carson AP, et al. Performance of the atherosclerotic cardiovascular disease pooled cohort risk equations by social deprivation status. J Am Heart Assoc 2017;6, e005676.
32. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet 2013;382:1762-5.
33. Tang X, Laskowitz DT, He L, et al. Neighborhood socioeconomic status and the prevalence of stroke and coronary heart disease in rural China: a population-based study. Int J Stroke 2015;10:388-95.
34. Copas JB. Using regression models for prediction: shrinkage and regression to the mean. Stat Methods Med Res 1997;6: 167-83.
35. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology 2010;21:128-38.
36. Anderson TJ, Gregoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2013;29:151-67.
37. Akintoye E, Briasoulis A, Afonso L. Biochemical risk markers and 10-year incidence of atherosclerotic cardiovascular disease: independent predictors, improvement in pooled cohort equation, and risk reclassification. Am Heart J 2017;193:95-103.
38. Daniels LB, Clopton P, de Filippi CR, et al. Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2015;170:1170-83.
39. Sussman JB, Wiitala WL, Zawistowski M, et al. The Veterans Affairs cardiac risk score: recalibrating the atherosclerotic cardiovascular disease score for applied use. Med Care 2017;55: 864-70.
40. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol 2015;66: 1643-53.
41. Asia Pacific Cohort Studies CollaborationBarzi F, Patel A, et al. Cardiovascular risk prediction tools for populations in Asia. J Epidemiol Community Health 2007;61:115-21.