Cardiovascular Innovations and Applications

Vol. 8 (2023) 27
ISSN 2009-8618
DOI 10.15212/CVIA.2023.0036

RESEARCH ARTICLE

Addition of Risk-enhancing Factors Improves Risk Assessment of Atherosclerotic Cardiovascular Disease in Middle-aged and Older Chinese Adults: Findings from the Chinese Multi-provincial Cohort Study

Haimei Wang[1,a], Zhao Yang[1,a], Yue Qi[1], Yulin Huang[1], Luoxi Xiao[1], Yiming Hao[1], Jiayi Sun[1], Miao Wang[1], Qiuju Deng[1], Yongchen Hao[1], Na Yang[1] and Jing Liu[1]

[1]*Center for Clinical and Epidemiologic Research, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, People's Republic of China*

Received: 4 February 2023; Revised: 15 March 2023; Accepted: 17 May 2023

Abstract

Objective: This study aimed to examine whether integrating risk-enhancing factors into the Chinese Society of Cardiology-recommended clinical risk assessment tool (i.e., the CSC model) for atherosclerotic cardiovascular disease (ASCVD) might improve 10-year ASCVD risk stratification in Chinese adults.

Methods: A total of 4910 Chinese participants who were 50–79 years of age and free of cardiovascular disease in the 2007–2008 Survey from the Chinese Multi-provincial Cohort Study were included. We assessed the updated model's clinical utility (i.e., Harrell's C-index and net reclassification improvement [NRI]) by adding risk-enhancing factors individually or the number of risk-enhancing factors to the CSC model, for all individuals or those at intermediate risk. Risk-enhancing factors, including a family history of CVD, triglycerides ≥2.3 mmol/L, high-sensitivity C-reactive protein ≥2 mg/L, Lipoprotein (a) ≥50 mg/dL, non-high-density lipoprotein cholesterol ≥4.9 mmol/L, overweight/obesity, and central obesity, were evaluated. ASCVD events were defined as a composite endpoint comprising ischemic stroke and acute coronary heart disease events (including nonfatal acute myocardial infarction and all coronary deaths).

Results: During a median 10-year follow-up, 449 (9.1%) ASCVD events were recorded. Addition of ≥2 risk-enhancing factors to the CSC model yielded a significant improvement in the C-index (1.0%, 95% confidence interval [CI]: 0.2–1.7%) and a modest improvement in the NRI (2.0%, 95% CI: −1.2–5.4%) in the total population. For intermediate-risk individuals, particularly individuals at high risk of developing ASCVD, significant improvements in NRI were observed after adding ≥2 risk-enhancing factors (17.4%, 95% CI: 5.6–28.5%) to the CSC model.

Conclusions: Addition of ≥2 risk-enhancing factors refined 10-year ASCVD risk stratification, particularly for intermediate-risk individuals, supporting their potential in helping tailor targeted interventions in clinical practice.

Keywords: atherosclerotic cardiovascular disease; reclassification; risk-enhancing factors; risk assessment

[a]Haimei Wang and Zhao Yang contributed equally to this research.

Correspondence: Jing Liu, MD, PhD, Center for Clinical and Epidemiologic Research, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, China,
E-mail: jingliu@ccmu.edu.cn

Introduction

The tremendously increasing burden of atherosclerotic cardiovascular disease (ASCVD) has been a prominent feature of cardiovascular disease (CVD) epidemiology in China [1]. Accurate risk assessment of the development of ASCVD lays a foundation for tailoring personalized preventive (e.g., lifestyle and pharmacological interventions) strategies for CVD [2]. To date, several well-established risk assessment tools incorporating solely traditional risk factors have been recommended by the current guidelines to prevent CVD in China [3, 4] and Western countries [2, 5]. However, the actual risk for individuals with intermediate ASCVD risk may be higher or lower than the predicted risk, owing to the multiple levels and combinations of cardiovascular risk factors that may be present. Consequently, suboptimal preventive strategies are often recommended [4].

Several emerging risk factors [2, 4, 5] have shown great potential to refine ASCVD risk stratification. However, most related studies have been conducted in Western populations [6–12], with few conducted in Chinese adults [13–16]. Furthermore, the inclusion of risk factors with low testing accessibility and a lack of laboratory standardization (e.g., Lipoprotein (a) [Lp(a)] and high-sensitivity C-reactive protein [hs-CRP]) has seen only limited adoption in primary care settings, particularly in less developed areas. Therefore, these factors have been defined as risk-enhancing factors, as suggested by the Chinese Society of Cardiology (CSC) in 2020 [4], for tailoring personalized prevention for adults with intermediate estimated 10-year risk (IIa, B), mainly on the basis of evidence from Western populations.

Therefore, we conducted this study to assess whether adding individual risk-enhancing factor (i.e., family history of CVD, overweight/obesity, central obesity, and high levels of triglycerides [TG], hs-CRP, Lp(a), or non-high-density lipoprotein cholesterol [non-HDL-C]) or the number of risk-enhancing factors might improve the prediction of 10-year ASCVD risk beyond that of the current ASCVD risk assessment tool (referred to as the CSC model [17, 18]), particularly among intermediate-risk adults, on the basis of a large population-based cohort, the Chinese Multi-provincial Cohort Study (CMCS).

Methods

Study Population

Study participants were recruited from the 2007–2008 Survey of the CMCS, a nationwide, multicenter, population-based cohort study on CVD. Details of the study design have been described elsewhere [19, 20]. Information on demographics, lifestyle characteristics, medical history, and clinical measurements was collected with a standardized questionnaire modified on the basis of the WHO-MONICA protocol [21] in the 2007–2008 Survey, after informed consent was obtained from participants. All participants were actively followed up to determine the onset of CVD events or deaths every 1 to 2 years to date, and the data were supplemented by information from the local disease surveillance systems. The study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

In the current analysis, we initially included 5961 participants who were free of CVD in the 2007–2008 Survey. We excluded 479 individuals with a history of disease or revascularization therapy and 572 individuals with incomplete data. Finally, 4910 participants 50–79 years of age were included in the final analysis (Figure 1).

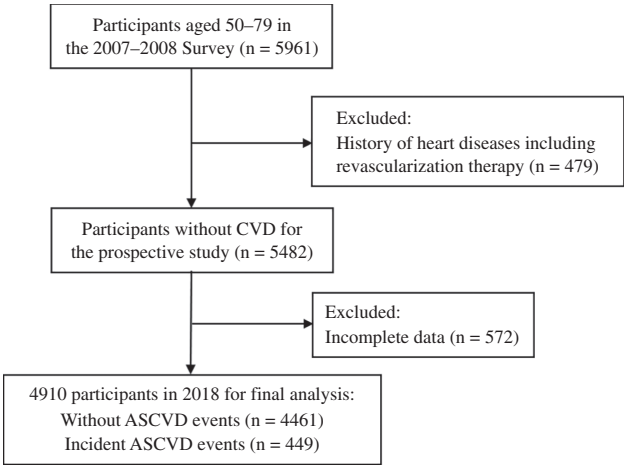

Figure 1 Flow Chart of Study Participants Selection in the 2007–2008 Survey from the Chinese Multi-provincial Cohort Study.
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease.

Risk Measures at Baseline

In the 2007–2008 Survey, information on demographics (i.e., age and sex), lifestyle characteristics (e.g., smoking status), medical history (e.g., family history of CVD, diabetes, antihypertensive treatment, and lipid-lowering medication), and clinical measurements (e.g., blood pressure [BP], fasting blood glucose, total cholesterol [TC], Lp(a), hs-CRP, and anthropometry) was collected by trained researchers following the WHO-MONICA protocol [21] to achieve better quality control. Specifically, current smoking was defined as smoking one or more cigarettes per day. Height, weight, waist circumference, and BP were measured during physical examinations. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Overweight/obesity was defined as BMI ≥24 kg/m^2 [22]. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest. Central obesity was defined as a waist circumference ≥90 cm for men or ≥85 cm for women [23]. BP was measured on the right-side brachial artery after at least a 5-min rest in a sitting position, and the mean value of the consecutive reads was used for analysis. A family history of CVD was defined as having a first-degree relative with stroke or acute myocardial infarction.

Eight-hour fasting venous blood samples were used to measure glucose, TC, TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Lp(a), and hs-CRP. Glucose, TC, and TG were measured with enzymatic methods. HDL-C and LDL-C were measured with homogeneous methods as described in the previous study [24], and non-HDL-C was calculated as TC–LDL-C. Moreover, hs-CRP and Lp(a) were measured with an immunoturbidimetric assay. Diabetes was defined as a fasting blood glucose (FBG) level ≥7.0 mmol/L or pre-diagnosed diabetes.

Conventional Risk Factors

According to the 2020 CSC guidelines on preventing CVD [4], the conventional risk factors, including age, sex, smoking, diabetes, systolic blood pressure (SBP), HDL-C, and LDL-C, were recommended and used to predict the 10-year ASCVD risk. Antihypertensive therapy was additionally included because of its high prevalence in CMCS (29.80%). This model is referred to as the CSC model [18].

Risk-enhancing Factors

Further risk-enhancing factors (e.g., family history of CVD, TG ≥2.3 mmol/L, hs-CRP ≥2 mg/L, Lp(a) ≥50 mg/dL, and non-HDL-C ≥4.9 mmol/L) have also been suggested by the CSC to improve ASCVD risk stratification for individuals with intermediate estimated risk [4], for whom clearer evidence of the benefit-to-harm of pharmaceutical interventions is needed. All thresholds of these risk-enhancing factors were used according to the *Chinese Guideline on the Primary Prevention of Cardiovascular Diseases*. We also considered overweight/obesity and central obesity risk-enhancing factors, as recommended in the 2021 ESC guidelines [5]. Finally, we explored whether the number (i.e., <1 *vs.* ≥1 and <2 *vs.* ≥2) of included risk-enhancing factors improved ASCVD risk stratification. In CMCS, the family history of CVD was determined by asking participants whether any first-degree relative had experienced a fatal or nonfatal myocardial infarction or stroke. Notably, we found a strong positive correlation between non-HDL-C and LDL-C in CMCS, and thus replaced LDL-C with non-HDL-C in the current analysis.

Determination of ASCVD Events

From the 2007–2008 Survey, all fatal and nonfatal acute coronary and stroke events were recorded and supplemented with data from the local disease surveillance systems. ASCVD events were defined as a composite endpoint comprising ischemic stroke and acute coronary heart disease events (including nonfatal acute myocardial infarction and all coronary deaths). All CVD events were diagnosed after advances in diagnostic technology of myocardial infarction became available [19, 21, 24, 25], as adjudicated by a panel of trained physicians. As of December 31, 2018, a total of 43,907 person-years' follow-up with a median of 10.0 years and 449 ASCVD events were recorded, yielding a crude incidence rate of 10.23 events per 1000 person-years.

Statistical Analysis

Participants enrolled in the 2007–2008 Survey from CMCS were used to evaluate the potential to improve ASCVD risk stratification by the addition of individual or the number of risk-enhancing factors. The baseline characteristics of the study participants are described as mean (± standard deviation [SD]), median (interquartile range), or frequency (proportion), as appropriate, stratified by risk stratification (i.e., <5.0% [low risk], 5.0–9.9% [intermediate risk], and ≥10.0% [high risk]) derived from the CSC model.

We first developed the CSC model with the conventional risk factors, on the basis of the Cox proportional hazards model. The 10-year observed ASCVD events rate was estimated via the Kaplan-Meier estimator in CMCS, which was further used in all candidate models in this study. Secondarily, we updated the CSC model by addition of risk-enhancing factors individually or in combination and evaluated their improvements in refining 10-year ASCVD risk via discrimination (i.e., Harrell's C-index) and reclassification measures (i.e., the net reclassification index [NRI]). Specifically, we evaluated the improvement in the whole population and the intermediate-risk group. We compared Harrell's C-indexes between the CSC and updated models with the DeLong test [26]. Moreover, to quantify the uncertainty of these performance measures, we calculated the 95% confidence intervals (CIs) of NRI with the 2.5th and 97.5th percentiles of a nonparametric bootstrap distribution based on 1000 bootstrap samples [27]. Finally, we explored the sex-specific improvements in 10-year ASCVD risk stratification by the addition of risk-enhancing factors.

All statistical analyses were performed in SAS software version 9.4 (SAS Institute, Cray, NC) and R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), and a two-sided P value < 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

Table 1 presents the baseline characteristics of study participants from the 2007–2008 Survey, stratified by 10-year estimated ASCVD risk using the CSC model. The mean age of participants in the 2007–2008 Survey was 60.9 ± 7.7 years, and 47.4% were men. For conventional risk factors, participants with higher ASCVD risk were more likely to be older and men; to have a higher prevalence of smoking and diabetes; to have higher levels of SBP, DBP, FBG, TC, and LDL-C; and to have lower levels of HDL-C. For risk-enhancing factors, participants with higher ASCVD risk had higher TG, hs-CRP, Lp(a), non-HDL-C, BMI, and waist circumference; a higher prevalence of TG ≥2.3 mmol/L, hs-CRP ≥2 mg/L, non-HDL-C ≥4.9 mmol/L, overweight/obesity, and central obesity; and no differences in family history of CVD and Lp(a) ≥50 mg/dL. Participants with higher ASCVD risk had a higher prevalence of antihypertensive and lipid-lowering treatment.

Risk-enhancing Factors and ASCVD Risk

Table 2 shows the associations between risk-enhancing factors and ASCVD. Overweight/obesity, central obesity, TG ≥ 2.3 mmol/L, hs-CRP ≥ 2 mg/L, Lp(a) ≥ 50 mg/dL, and non-HDL-C level were significantly associated with an increased ASCVD risk. These associations persisted except for TG ≥ 2.3 mmol/L after adjustment for sex, age, smoking, diabetes, SBP, HDL-C, LDL-C, and antihypertensive treatment. Notably, the addition of ≥2 risk-enhancing factors was also associated with an increased ASCVD risk, even after accounting for the conventional risk factors.

Risk-enhancing Factors and Improvements in ASCVD Risk Stratification

Table 3 shows the reclassification performance in refining ASCVD risk stratification, on the basis of changes in the C-index and NRI, after addition of risk-enhancing factors individually or the number of risk-enhancing factors, as compared with that of the CSC model. The C-index for the CSC model was 0.703 (95% CI 0.679, 0.728). No significant improvements in refining ASCVD risk were observed after addition of the risk-enhancing factors individually among the whole population. However, after adding ≥2 risk-enhancing factors to the CSC model, a significant improvement in the change of C-index was noted (i.e., 1.0%, 95% CI: 0.2–1.7%; P = 0.014).

Table 1 Characteristics of Study Participants Stratified by 10-year Estimated ASCVD Risk with the Chinese Society of Cardiology-recommended Model.

Characteristics	Total (n = 4910)	10-year ASCVD risk stratification			P value
		Low risk (n = 868)	Intermediate risk (n = 1644)	High risk (n = 2398)	
Conventional risk factors					
Age, years	60.9 ± 7.7	54.3 ± 4.4	59.1 ± 6.6	64.5 ± 7.3	<0.001
Sex					<0.001
Male, n (%)*	2329 (47.4)	131 (15.1)	675 (41.1)	1523 (63.5)	
Female, n (%)*	2581 (52.6)	737 (84.9)	969 (58.9)	875 (36.5)	
Smoking, n (%)*	899 (18.3)	5 (0.6)	202 (12.3)	692 (28.9)	<0.001
SBP, mmHg	138.6 ±19.9	119.8 ± 11.4	132.4 ± 13.8	149.6 ± 19.0	<0.001
DBP, mmHg	83.0 ± 10.6	75.6 ± 7.9	81.6 ± 9.2	86.7 ± 10.8	<0.001
FBG, mmol/L	5.7 ± 1.5	5.1 ± 0.7	5.4 ± 1.2	6.1 ± 1.8	<0.001
Diabetes, n (%)*	730 (14.9)	6 (0.7)	102 (6.2)	622 (25.9)	<0.001
TC, mmol/L	5.2 ± 1.0	5.0 ± 0.8	5.2 ± 1.0	5.4 ± 1.0	<0.001
HDL-C, mmol/L	1.4 ± 0.3	1.5 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	<0.001
LDL-C, mmol/L	3.3 ± 0.9	2.9 ± 0.7	3.2 ± 0.8	3.5 ± 0.9	<0.001
Risk-enhancing factors					
Family history of CVD, n (%)*	1490 (30.4)	284 (32.7)	489 (29.7)	717 (29.9)	0.244
TG, mmol/L	1.5 (1.1, 2.1)	1.2 (0.9, 1.7)	1.4 (1.0, 2.0)	1.6 (1.2, 2.2)	<0.001
Hs-CRP, mg/L	1.0 (0.5, 2.3)	0.7 (0.3, 1.5)	1.0 (0.5, 2.0)	1.2 (0.6, 2.6)	<0.001
Lp(a), mg/dL	12.0 (7.0, 26.0)	12.0 (6.0, 26.0)	12.0 (6.0, 25.0)	13.0 (7.0, 27.0)	0.033
Non-HDL-C, mmol/L	3.9 ± 0.9	3.5 ± 0.7	3.8 ± 0.9	4.1 ± 1.0	<0.001
BMI, kg/m^2	24.9 ± 3.3	23.6 ± 3.2	24.6 ± 3.2	25.5 ± 3.3	<0.001
Waist circumference, cm	84.8 ± 9.4	79.2 ± 8.6	83.6 ± 8.7	87.7 ± 9.0	<0.001
TG ≥ 2.3 mmol/L, n (%)*	963 (19.6)	106 (12.2)	308 (18.7)	549 (22.9)	<0.001
Hs-CRP ≥ 2 mg/L, n (%)*	1397 (28.5)	166 (19.1)	418 (25.4)	813 (33.9)	<0.001
Lp(a) ≥ 50 mg/dL, n (%)*	453 (9.2)	65 (7.5)	153 (9.3)	235 (9.8)	0.130
Non-HDL-C ≥ 4.9 mmol/L, n (%)*	602 (12.3)	27 (3.1)	169 (10.3)	406 (16.9)	<0.001
Overweight/obesity, n (%)*	2897 (59.0)	364 (41.9)	932 (56.7)	1601 (66.8)	<0.001
Central obesity, n (%)*	1975 (40.2)	200 (23.0)	600 (36.5)	1175 (49.0)	<0.001
Antihypertensive treatment, n (%)*	1465 (29.8)	21 (2.4)	256 (15.6)	1188 (49.5)	<0.001
Lipid-lowering treatment, n (%)*	307 (6.3)	15 (1.7)	90 (5.5)	202 (8.4)	<0.001

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a); non-HDL-C: non-high-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

*Frequencies and percentages of variables with only a "yes" value are presented.

Table 2 Associations of Risk-enhancing Factors with Atherosclerotic Cardiovascular Disease Risk.

Risk-enhancing factors	Univariable Cox model		Multivariable Cox model	
	HR (95% CI)	P value	HR (95% CI)	P value
Family history of CVD	1.13 (0.93, 1.38)	0.212	1.20 (0.98, 1.46)	0.077
Overweight/obesity	1.76 (1.43, 2.16)	<0.001	1.39 (1.12, 1.73)	0.003
Central obesity	1.64 (1.37, 1.98)	<0.001	1.26 (1.04, 1.54)	0.020
TG ≥ 2.3 mmol/L	1.31 (1.06, 1.63)	0.014	1.16 (0.93, 1.46)	0.198
Hs-CRP ≥ 2 mg/L	1.50 (1.24, 1.82)	<0.001	1.26 (1.03, 1.53)	0.024
Lp(a) ≥ 50 mg/dL	1.40 (1.05, 1.85)	0.022	1.34 (1.01, 1.79)	0.046
Non-HDL-C, mmol/L*	1.29 (1.18, 1.41)	<0.001	1.28 (1.17, 1.41)	<0.001
Number of risk-enhancing factors				
≥1 risk-enhancing factor	1.71 (1.27, 2.31)	<0.001	1.33 (0.97, 1.81)	0.075
≥2 risk-enhancing factors	2.14 (1.72, 2.65)	<0.001	1.66 (1.32, 2.10)	<0.001

The multivariable Cox model was adjusted for sex, age, smoking, diabetes mellitus, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and antihypertensive treatment. Abbreviations: CVD: cardiovascular disease; Hs-CRP: high-sensitivity C-reactive protein; Lp(a): Lipoprotein(a); non-HDL-C: non-high-density lipoprotein cholesterol; TG: triglycerides; 95% CI: 95% confidence interval.
*In the multivariable Cox model, LDL-C was replaced with non-HDL-C.

Table 3 Measures of Discrimination and Reclassification for Predicting the Atherosclerotic Cardiovascular Disease (ASCVD) Event Risk by Addition of Risk-enhancing Factors to the Chinese Society of Cardiology-recommended Clinical Risk Assessment Tool (i.e., the CSC model) in the Total Population.

Models	C-index (95% CI)	C-index changes (95% CI)	Total NRI (95% CI)
CSC model	0.703 (0.679, 0.728)		
+ Family history of CVD	0.704 (0.680, 0.729)	0.001 (−0.002,0.004)	−0.012 (−0.035, 0.012)
+ Overweight/obesity	0.708 (0.684, 0.732)	0.005 (−0.001, 0.010)	0.023 (−0.005, 0.052)
+ Central obesity	0.705 (0.681, 0.730)	0.002 (−0.002, 0.007)	−0.002 (−0.027, 0.024)
+ TG ≥ 2.3 mmol/L	0.703 (0.679, 0.727)	0.000 (−0.002, 0.002)	0.001 (−0.016, 0.018)
+ hs-CRP ≥ 2 mg/L	0.704 (0.680, 0.729)	0.001 (−0.003, 0.005)	0.003 (−0.021, 0.027)
+ Lp(a) ≥ 50 mg/dL	0.704 (0.680, 0.729)	0.001 (−0.002, 0.005)	−0.013 (−0.031, 0.004)
Replacement of LDL-C with non-HDL-C	0.701 (0.676, 0.725)	−0.002 (−0.006, 0.002)	0.004 (−0.016, 0.024)
Number of risk-enhancing factors			
+ ≥1 risk-enhancing factor	0.704 (0.680, 0.728)	0.001 (−0.002, 0.004)	0.005 (−0.016, 0.024)
+ ≥2 risk-enhancing factors	0.713 (0.689, 0.737)	0.010 (0.002, 0.017)	0.020 (−0.012, 0.054)

Abbreviations: CVD: cardiovascular disease; Hs-CRP: high-sensitivity C-reactive protein; Lp(a): Lipoprotein(a); LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; NRI: net reclassification improvement; TG: triglycerides; 95% CI: 95% confidence interval.

Table 4 shows the reclassification performance in refining ASCVD risk stratification regarding the changes in NRI (including event NRI and nonevent NRI) by adding individual risk-enhancing factor or the number of risk-enhancing factors to the CSC model in participants with intermediate estimated risk. Addition of overweight/obesity (total NRI 10.1%, 95% CI: 0.8–19.9%; P = 0.041), ≥1 risk-enhancing factor (6.5%, 95% CI: 0.6–12.8%; P = 0.033), or ≥2 risk-enhancing factors (17.4%, 95% CI: 5.6–28.5%; P = 0.002) improved ASCVD risk stratification, particularly for participants with ASCVD events, as illustrated by Figure 2. Consistent results were also observed for men and women, particularly with inclusion of ≥2 risk-enhancing factors for participants at intermediate risk (Supplementary Table 1).

Table 4 Reclassification Measures for Predicting Atherosclerotic Cardiovascular Disease (ASCVD) Event Risk by Addition of Risk-enhancing Factors to the Chinese Society of Cardiology-recommended Clinical Risk Assessment Tool (i.e., the CSC model) in Intermediate-risk Participants.

Models	Event NRI (95% CI)	Nonevent NRI (95% CI)	Total NRI (95% CI)
CSC model			
+ Family history of CVD	0.021 (−0.057, 0.104)	−0.005 (−0.020, 0.012)	0.017 (−0.058, 0.103)
+ Overweight/obesity	0.128 (0.037, 0.221)	−0.027 (−0.052, −0.005)	0.101 (0.008, 0.199)
+ Central obesity	0.085 (0.004, 0.171)	−0.024 (−0.043, −0.006)	0.061 (−0.021, 0.151)
+ TG ≥ 2.3 mmol/L	0.043 (−0.005, 0.094)	−0.007 (−0.019, 0.006)	0.035 (−0.015, 0.086)
+ hs-CRP ≥ 2 mg/L	0.053 (−0.019, 0.126)	−0.015 (−0.031, 0.003)	0.038 (−0.034, 0.112)
+ Lp(a) ≥ 50 mg/dL	−0.011 (−0.067, 0.049)	−0.001 (−0.014, 0.012)	−0.012 (−0.069, 0.050)
Replacement of LDL-C with non-HDL-C	0.074 (0.019, 0.137)	−0.026 (−0.041, −0.012)	0.048 (−0.010, 0.112)
+ ≥1 risk-enhancing factor	0.074 (0.012, 0.133)	−0.009 (−0.026, 0.009)	0.065 (0.006, 0.128)
+ ≥2 risk-enhancing factors	0.191 (0.077, 0.296)	−0.017 (−0.047, 0.011)	0.174 (0.056, 0.285)

Abbreviations: Hs-CRP: high-sensitivity C-reactive protein; Lp(a): Lipoprotein(a); non-HDL-C: non-high-density lipoprotein cholesterol; NRI: net reclassification improvement; TG: triglycerides.

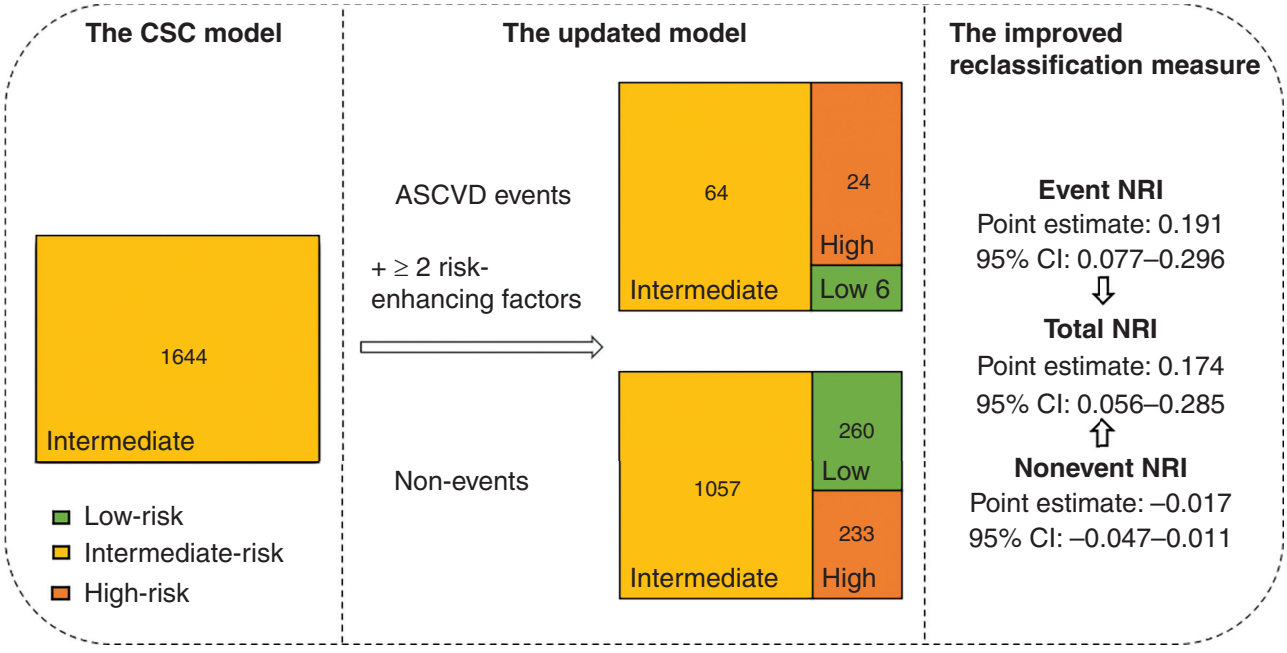

Figure 2 Central Illustration.
The updated model incorporating ≥2 risk-enhancing factors into the Chinese Society of Cardiology-recommended clinical risk assessment tool (i.e., the CSC model) improves atherosclerotic cardiovascular disease (ASCVD) risk stratification for individuals at intermediate risk. Abbreviations: NRI: net reclassification improvement.

Discussion

Principal Findings

This study demonstrates that incorporating ≥2 risk-enhancing factors into the CSC model improved discrimination and reclassification of ASCVD risk over a prospective 10-year follow-up in Chinese adults 50–79 years of age, particularly in intermediate-risk individuals. These findings suggest that adding ≥2 risk-enhancing factors may reclassify individuals from intermediate to high risk, thus guiding decisions regarding personalized preventive strategies.

Comparison with other Studies

Risk-enhancing factors have been reported to improve ASCVD risk prediction in Western populations [6, 7, 28–31] but with relatively small improvements in the reclassification ability of ASCVD risk assessment tools. For instance, the Multi-Ethnic Study of Atherosclerosis [6] has shown that adding family history of CVD or hs-CRP to the pooled cohort equation (PCE) did not improve ASCVD risk assessment, in line with our results. The Tehran lipid and glucose study [28] has also reported similar results in a Middle Eastern populations with an ASCVD-PCE score of 5–20%. However, the Bruneck study [9] has shown that addition of Lp(a) improves CVD risk prediction in the general community, particularly in the intermediate-risk group, in contrast with our results. Ethnic differences in Lp(a) levels, base models, and the threshold for ASCVD risk stratification might explain these discrepancies.

Furthermore, another cohort study using pooled individual-level data from eight community-based cohort studies has reported that incorporating BMI, waist circumference, or hs-CRP individually into the PCE did not improve its discrimination and net reclassification, but combinations of these three risk-enhancing factors yielded improvements, in line with our results [29]. Similar results have also been noted in the Aerobics Center Longitudinal Study regarding the Framingham Risk Score [30], and a systematic review [31] showing no additional value with the addition of BMI to the base risk prediction models, although continuous, categorized, or dichotomized predictors of BMI were used.

Finally, the potential of risk-enhancing factors to improve ASCVD risk re-stratification has rarely been evaluated in Chinese adults [15]. A recent study has indicated that addition of ≥2 negative risk markers (i.e., Lp(a) ≤5 mg/dL, normal electrocardiogram, and carotid intima-media thickness ≤0.5) improves ASCVD reclassification in intermediate- and high-risk Chinese adults, in line with our results, although that study used difficult-to-measure risk-enhancing factors. Such results are expected since the more risk-enhancing factors present, the more likely the high-risk individuals would be.

Strengths and Limitations

The major strengths of our study include the large population-based prospective cohort, long follow-up, and availability of extensive well-defined risk-enhancing factors. Consequently, we comprehensively evaluated the value of these factors in improving ASCVD risk assessment. However, several study limitations should also be noted. First, the current study did not include measurements of target organ damage, such as coronary artery calcium score [6, 10], ankle-brachial index [6, 10], and left ventricular hypertrophy [32], because their analysis is rarely possible in the primary care settings. Second, participants in the 2007–2008 Survey were 50–79 years of age and therefore may not represent the entire population of Chinese adults. However, young adults <50 years of age are likely to be at low risk, whereas older adults ≥80 years of age are likely at high risk. Therefore, the participants 50–79 years of age largely represent the targeted intermediate-risk population, among which risk-enhancing factors may refine risk stratification. Third, genetic differences across ethnic groups may influence ASCVD risk assessment; however, such effects should be minimal in this study, because 95% of all participants in CMCS were Chinese Han population.

Conclusions

Addition of ≥2 risk-enhancing factors to the CSC model may improve ASCVD risk stratification and help tailor personalized preventive strategies for individuals with intermediate estimated 10-year risk, for whom the ASCVD risk-based treatments are uncertain.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

The study was approved by the Ethics Committee of Beijing An Zhen Hospital, Capital Medical University. All participants provided written informed consent.

Author Contributions

JL, YQ, and ZY contributed to the overall conception and designed the study; JS, MW, YLH, LX, and YMH collected and cleaned the data; HW analyzed the data; HW and ZY wrote the manuscript; JL, YQ, QD, YCH, and NY provided suggestions for the analysis and helped improve the manuscript. All authors reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the staff members and participants of the Chinese Multi-provincial Cohort Study for their participation and contributions.

Funding

This work was supported by the National Natural Science Foundation of China (grant numbers 82073635, 82103962, and 12226005); National Key Research and Development Program of China (grant number 2022YFC3602501); Beijing Municipal Medical Research Institutes Pilot Reform Project (grant number 2021-07); and Beijing Natural Science Foundation (grant number 7212006).

Conflict of interest

The authors declare that there are no conflicts of interest.

REFERENCES

1. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in China: current features and implications. Nat Rev Cardiol 2019;16(4):203–12.
2. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;140(11):e596–646.
3. Yang X, Li J, Hu D, Chen J, Li Y, Huang J, 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(19):1430–40.
4. Chinese Society of Cardiology of Chinese Medical Association, Cardiovascular Disease Prevention and Rehabilitation Committee of Chinese Association of Rehabilitation Medicine, Cardiovascular Disease Committee of Chinese Association of Gerontology and Geriatrics, Thrombosis Prevention and Treatment Committee of Chinese Medical Doctor Association. Chinese Guideline on the Primary Prevention of Cardiovascular Diseases. Cardiology Discovery 2021;1:70–104.
5. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42(34):3227–337.
6. Yeboah J, Young R, McClelland RL, Delaney JC, Polonsky TS, Dawood FZ, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. J Am Coll Cardiol 2016;67(2):139–47.
7. Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, et al. Lipid-related markers and cardiovascular disease prediction. J Am Med Assoc 2012;307(23):2499–506.
8. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes 2011;4(3):337–45.
9. Willeit P, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. J Am Coll Cardiol 2014;64(9):851–60.
10. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the multi-ethnic study of atherosclerosis (MESA). Circulation 2016;133(9):849–58.
11. Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi AA, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. J Am Med Assoc 2016;316(20):2126–34.
12. den Ruijter HM, Peters SA, Groenewegen KA, Anderson TJ, Britton AR, Dekker JM, et al. Common carotid intima-media thickness does not add to Framingham risk score in individuals with diabetes mellitus: the

USE-IMT initiative. Diabetologia 2013;56(7):1494–502.
13. Xia J, Guo C, Cao H, Liu K, Peng W, Sun Y, et al. Impact of lipoprotein(a) level on cardiometabolic disease in the Chinese population: the CHCN-BTH study. Eur J Clin Invest 2022;52(2):e13689.
14. Dong Y, Wang X, Zhang L, Chen Z, Zheng C, Wang J, et al. High-sensitivity C reactive protein and risk of cardiovascular disease in China-CVD study. J Epidemiol Community Health 2019;73(2):188–92.
15. Bie L, Niu J, Wu S, Zheng R, Xu M, Lu J, et al. Negative risk markers for cardiovascular risk evaluation in Chinese adults. Front Cardiovasc Med 2022;9:800671.
16. Xie W, Liang L, Zhao L, Shi P, Yang Y, Xie G, et al. Combination of carotid intima-media thickness and plaque for better predicting risk of ischaemic cardiovascular events. Heart 2011;97(16):1326–31.
17. Joint Committee Issued Chinese Guideline for the Management of Dyslipidemia in Adults. 2016 Chinese guideline for the management of dyslipidemia in adults. Zhonghua Xin Xue Guan Bing Za Zhi 2016;44(10):833–53.
18. Wang M, Liu J, Zhao D. A new scheme for risk assessment of atherosclerotic cardiovascular disease in China. Zhonghua Xin Xue Guan Bing Za Zhi 2018;46(2):87–91.
19. Liu J, Hong Y, D'Agostino RB, Sr., Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. J Am Med Assoc 2004;291(21):2591–9.
20. Qi Y, Han X, Zhao D, Wang W, Wang M, Sun J, et al. Long-term cardiovascular risk associated with stage 1 hypertension defined by the 2017 ACC/AHA hypertension guideline. J Am Coll Cardiol 2018;72(11):1201–10.
21. Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J, 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(3):462–8.
22. Gao M, Lv J, Yu C, Guo Y, Bian Z, Yang R, et al. Metabolically healthy obesity, transition to unhealthy metabolic status, and vascular disease in Chinese adults: a cohort study. PLoS Med 2020;17(10):e1003351.
23. Bao Y, Lu J, Wang C, Yang M, Li H, Zhang X, et al. Optimal waist circumference cutoffs for abdominal obesity in Chinese. Atherosclerosis 2008;201(2):378–84.
24. Wang Y, Liu J, Wang W, Wang M, Qi Y, Xie W, et al. Lifetime risk for cardiovascular disease in a Chinese population: the Chinese Multi-Provincial Cohort Study. Eur J Prev Cardiol 2015;22(3):380–8.
25. Luepker RV, Apple FS, Christenson RH, Crow RS, Fortmann SP, Goff D, 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(20):2543–9.
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837–45.
27. Kerr KF, Wang Z, Janes H, McClelland RL, Psaty BM, Pepe MS. Net reclassification indices for evaluating risk prediction instruments: a critical review. Epidemiology 2014;25(1):114–21.
28. Hadaegh F, Asgari S, Moosaie F, Orangi M, Sarvghadi F, Khalili D, et al. The risk and added values of the atherosclerotic cardiovascular risk enhancers on prediction of cardiovascular events: Tehran lipid and glucose study. J Transl Med 2021;19(1):25.
29. Khera R, Pandey A, Ayers CR, Carnethon MR, Greenland P, Ndumele CE, et al. Performance of the Pooled Cohort Equations to Estimate Atherosclerotic Cardiovascular Disease Risk by Body Mass Index. JAMA Netw Open 2020;3(10):e2023242.
30. Nelms MW, Day AG, Sui X, Blair SN, Ross R. Waist circumference does not improve established cardiovascular disease risk prediction modeling. PLoS One 2020;15(10):e0240214.
31. van Bussel EF, Hoevenaar-Blom MP, Poortvliet RKE, Gussekloo J, van Dalen JW, van Gool WA, et al. Predictive value of traditional risk factors for cardiovascular disease in older people: a systematic review. Prev Med 2020;132:105986.
32. Du Z, Xing L, Ye N, Lin M, Sun Y. Complementary value of ECG and echocardiographic left ventricular hypertrophy for prediction of adverse outcomes in the general population. J Hypertens 2021;39(3):548–55.

Supplementary Material: Supplementary material for this paper can be found at https://cvia-journal.org/wp-content/uploads/2023/05/Supplementary_Table_1.pdf.