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Adding risk-enhancing factors improves risk assessment of atherosclerotic cardiovascular disease in middle-aged and elderly Chinese: Findings from the Chinese Multi-provincial Cohort Study

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Abstract

Objective To examine whether risk-enhancing factors integrating with the Chinese Society of Cardiology-recommended clinical risk assessment tool (i.e., the CSC model) for atherosclerotic cardiovascular disease (ASCVD) improves 10-year ASCVD risk stratification in Chinese adults.

Methods A total of 4,910 Chinese participants aged 50-79 years 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., Harrel'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 among all individuals or those at intermediate risk. Risk-enhancing factors, including the 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 in the current analysis. 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 of 10-year follow-up, 449 (9.1%) ASCVD events were recorded. Adding ≥ 2 risk-enhancing factors to the CSC model yielded significant improvement in C-index (1.0%, 95% confidence interval [CI]: 0.2% to 1.7%) and modest improvement in NRI (2.0%, 95% CI: -1.2% to 5.4%) in the total population. For intermediate-risk individuals, significant improvements in NRI were observed by adding ≥ 2 risk-enhancing factors (17.4%, 95% CI: 5.6% to 28.5%) to the CSC model, particularly among those at high risk of developing ASCVD.

Conclusions Adding ≥ 2 risk-enhancing factors refines 10-year ASCVD risk stratification, particularly for intermediate-risk individuals, demonstrating their potential to help tailor targeted interventions in clinical practice.

Keywords Atherosclerotic cardiovascular disease; Reclassification; Risk-enhancing factors; Risk assessment

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 the foundation for tailoring personalized preventive (e.g., lifestyle and pharmacological interventions) strategies for CVD [2]. To date, several well-established risk assessment tools, incorporating traditional risk factors solely, have been recommended by the current guidelines to prevent CVD in China [3, 4] and Western countries [2, 5]. However, for individuals with intermediate ASCVD risk, the actual risk may be higher or lower than the predicted risk due to the multiple levels and combinations of cardiovascular risk factors. Consequently, suboptimal preventive strategies were often recommended [4].

Some emerging risk factors [2, 4, 5] have shown great potential to refine ASCVD risk stratification. However, most studies were conducted among the Western populations [6-12] but only some among Chinese adults [13-16]. Furthermore, the inclusion of risk factors with less accessibility and laboratory standardization (e.g., Lipoprotein (a) [Lp(a)] and high-sensitivity C-reactive protein [hs-CRP]) limits their application in the primary care setting, 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] when tailoring personalized preventions for individuals with intermediated estimated 10-year risk adults (IIa, B), mainly depending on evidence from Western populations.

Therefore, we conducted this study to assess whether the individual risk-enhancing factors (i.e., the family history of CVD, overweight/obesity, central obesity, 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 improves the prediction of 10-year ASCVD risk than the current ASCVD risk assessment tool (referred to as the CSC model [17, 18]), particularly among intermediate-risk adults, based on a large population-based cohort, i.e., 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 using a standardized questionnaire modified based on the WHO-MONICA protocol [21] in the 2007-2008 Survey after obtaining informed consent. All participants were actively followed up for the onset of CVD events or deaths every 1 to 2 years till now, supplemented via 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 5,961 participants who were free of CVD in the 2007-2008 Survey. We excluded 479 participants with a history of disease or revascularization therapy and 572 with incomplete data. Finally, 4,910 participants aged 50-79 were included in the final analysis, as detailed in **Figure 1**.

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., the 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 ≥ 1 cigarette per day. Height, weight, waist circumference, and BP were measured during physical examinations. Body mass index (BMI) was calculated as 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 a midpoint between the lower rib margin and the iliac crest. Central obesity was defined as a waist circumference ≥ 90 cm for males or ≥ 85 cm for females [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 first-degree relatives having a 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. Precisely, glucose, TC, and TG were measured using enzymatic methods, and HDL-C and LDL-C were measured using homogeneous methods, with which

non-HDL-C was calculated as TC−LDL-C. Moreover, hs-CRP and Lp(a) were measured using an immunoturbidimetric assay. Diabetes was defined as fasting blood glucose levels ≥ 7.0 mmol/L or pre-diagnosed diabetes.

Conventional risk factors

Per the 2020 CSC guideline 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 utilized to predict the 10-year ASCVD risk, with the additional inclusion of antihypertensive therapy due to its high prevalence in CMCS (29.80%), referred to as the CSC model [18].

Risk-enhancing Factors

Furthermore, risk-enhancing factors (e.g., the 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) were also suggested by the CSC to improve ASCVD risk stratification for individuals with intermediated estimated risk [4], for whom there needs to be more clear evidence for the benefit-to-harm of pharmaceutical interventions. All thresholds of these risk-enhancing factors were utilized based on the *Chinese Guideline on the Primary Prevention of Cardiovascular Diseases*. We also considered overweight/obesity and central obesity risk-enhancing factors as the 2021 ESC guideline recommended [5]. Finally, we explored whether the number (i.e., < 1 *vs.* ≥ 1 and < 2 *vs.* ≥ 2) of risk-enhancing factors improves ASCVD risk stratification. In CMCS, the family history of CVD was obtained by asking participants whether any member of first-degree relatives 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 from the current analysis.

ASCVD events ascertainment

From the 2007-2008 survey, all fatal and nonfatal acute coronary and stroke events were recorded and supplemented via 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 following advances in diagnostic technology of myocardial infarction [19, 21, 24, 25] and adjudicated by a panel of trained physicians. Till 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 1,000 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 adding risk-enhancing factors solely or the number of risk-enhancing factors. Baseline characteristics of study participants were described as mean (± standard deviation [SD]), median (interquartile range), or frequency (proportion) as appropriate 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 using the conventional risk factors based on a Cox proportional hazards model. The 10-year observed ASCVD event 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 adding risk-enhancing factors individually or with a different number of risk-enhancing factors 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 base and updated models using the DeLong test [26]. Moreover, to quantify the uncertainty of these performance measures, the 95% confidence intervals (CIs) of NRI were calculated using 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 adding risk-enhancing factors.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cray, NC) and R version 4.1.2 (2021-11-01), with a two-sided P value < 0.05 being considered statistical significance.

Results

Baseline characteristics

Table 1 presents characteristics of study participants from the 2007-2008 Survey stratified by 10-year estimated ASCVD risk using the CSC model. The mean age of the participants in the 2007-2008 Survey was 60.9 ± 7.7 years, of whom 47.4% were men. For conventional risk

factors, participants with higher ASCVD risk were more likely to be older and men, had a higher prevalence of smoking and diabetes, and had higher levels of SBP, DBP, fasting blood glucose, TC, LDL-C, and 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, had a higher prevalence of TG ≥ 2.3 mmol/L, hs-CRP ≥ 2 mg/L, non-HDL-C ≥ 4.9 mmol/L, overweight/obesity, central obesity, and no differences in the 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 of the risk-enhancing factors with 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. Such associations remained except for TG ≥ 2.3 mmol/L after adjusting for sex, age, smoking, diabetes, SBP, HDL-C, LDL-C, and antihypertensive treatment. Notably, the inclusion 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 stratifications regarding changes in C-indexes and NRI by adding risk-enhancing factors or the number of risk-enhancing factors compared to 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 when adding the risk-enhancing factors individually among the whole population. However, when 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% to 1.7%; *P*=0.014).

Table 4 shows the reclassification performance in refining ASCVD risk stratification regarding the changes in NRI (including event NRI and nonevent NRI) by adding risk-enhancing factors or the number of risk-enhancing factors to the CSC model in participants with intermediated estimated risk. Adding overweight/obesity (total NRI 10.1%, 95% CI: 0.8% to 19.9%; *P*=0.041), ≥ 1 risk-enhancing factor (6.5%, 95% CI: 0.6% to 12.8%; *P*=0.033), or ≥ 2 risk-enhancing factors (17.4%, 95% CI: 5.6% to 28.5%; *P*=0.002) improved

ASCVD risk stratification, particularly for those with ASCVD events. Consistent results were also observed for males and females, particularly for ≥ 2 risk-enhancing factors for participants at intermediate risk, as shown in **Supplementary Table 1**.

Discussion

Principal findings

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

Comparison with other studies

Risk-enhancing factors have previously been reported to improve ASCVD risk prediction in Western populations [6, 7, 28-31] but with relatively small improvements in ASCVD risk assessment tools' reclassification capability. For instance, the Multi-Ethnic Study of Atherosclerosis [6] showing adding the family history of CVD or hs-CRP to the pooled cohort equation (PCE) didn't improve ASCVD risk assessment, which was consistent with our results. The Tehran lipid and glucose study [28] has also reported similar results in the Middle East population with an ASCVD-PCE score of 5-20%. However, the Bruneck study [9] showing that additional using Lp(a) improves CVD risk prediction in the general community, particularly in the intermediate-risk group, was inconsistent with our results. The ethnic difference of Lp(a) levels, base models, and the threshold for ASCVD risk stratification may explain such discrepancies.

Furthermore, another cohort study used pooled individual-level data from 8 community-based cohort studies showing adding BMI, waist circumference, or hs-CRP individually to the PCE failed to improve its discrimination and net reclassification, but the combinations of these three risk-enhancing factors, yielding a consistent with our results [29]. Similar results were also noted in the Aerobics Center Longitudinal Study regarding the Framingham Risk Score [30] and a systematic review [31] showing no additional value for adding BMI to the base risk prediction models, although with different BMI and waist circumference forms.

Finally, the potential of risk-enhancing factors in improving ASCVD risk re-stratification was seldom evaluated in Chinese adults [15]. A recent study showing adding ≥ 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 was consistent with our results, though hard-to-measure risk-enhancing factors were used. Such results are expected since the more risk-enhancing factors, the more likely the high-risk individuals would be.

Strengths and limitations

The major strengths of the current study include the large population-based prospective cohort, long follow-up, and rich and well-defined risk-enhancing factors that enabled us to comprehensively evaluate their values in improving ASCVD risk assessment. However, several limitations should also be noted. First, the current study doesn't 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 they are hardly available in the primary care setting. Second, participants in the 2007-2008 Survey were 50-79 years, so they may not represent the whole Chinese adults. However, young adults < 50 years are more likely to be at low risk, while older adults ≥ 80 years are almost at high risk. Therefore, the participants aged 50-79 years largely represent the targeted intermediate-risk population, among which risk-enhancing factors may refine risk stratification. Third, genetic differences across ethnic groups may influence the ASCVD risk assessment; however, such an impact would be minimal since 95% of all participants in CMCS were the Chinese Han population.

Conclusions

Adding ≥ 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.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Table 1. Characteristics of study participants stratified by 10-year estimated ASCVD risk using the Chinese Socie

Characteristics	Total (n=4910)	10-year ASCVD risk strati	
		Low risk (n=868)	Intermediate risk (n=16
Conventional risk factors			
Age, years	60.9 ± 7.7	54.3 ± 4.4	59.1 ± 6.6
Sex			
Male, n (%)*	2329 (47.4)	131 (15.1)	675 (41.1)
Female, n (%)*	2581 (52.6)	737 (84.9)	969 (58.9)
Smoking, n (%)*	899 (18.3)	5 (0.6)	202 (12.3)
SBP, mm Hg	138.6 ±19.9	119.8 ± 11.4	132.4 ± 13.8
DBP, mm Hg	83.0 ± 10.6	75.6 ± 7.9	81.6 ± 9.2
Fasting blood glucose, mmol/L	5.7 ± 1.5	5.1 ± 0.7	5.4 ± 1.2
Diabetes, n (%)*	730 (14.9)	6 (0.7)	102 (6.2)
TC, mmol/L	5.2 ± 1.0	5.0 ± 0.8	5.2 ± 1.0
HDL-C, mmol/L	1.4 ± 0.3	1.5 ± 0.3	1.4 ± 0.3
LDL-C, mmol/L	3.3 ± 0.9	2.9 ± 0.7	3.2 ± 0.8
Risk-enhancing factors			
Family history of CVD, n (%)*	1490 (30.4)	284 (32.7)	489 (29.7)
TG, mmol/L	1.5 (1.1, 2.1)	1.2 (0.9, 1.7)	1.4 (1.0, 2.0)
Hs-CRP, mg/L	1.0 (0.5, 2.3)	0.7 (0.3, 1.5)	1.0 (0.5, 2.0)
Lp(a), mg/dL	12.0 (7.0, 26.0)	12.0 (6.0, 26.0)	12.0 (6.0, 25.0)

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Non-HDL-C, mmol/L	3.9 ± 0.9	3.5 ± 0.7	3.8 ± 0.9
BMI, kg/m^2	24.9 ± 3.3	23.6 ± 3.2	24.6 ± 3.2
Waist circumference, cm	84.8 ± 9.4	79.2 ± 8.6	83.6 ± 8.7
TG ≥ 2.3 mmol/L, n (%)*	963 (19.6)	106 (12.2)	308 (18.7)
Hs-CRP ≥ 2 mg/L, n (%)*	1397 (28.5)	166 (19.1)	418 (25.4)
Lp(a) ≥ 50 mg/dL, n (%)*	453 (9.2)	65 (7.5)	153 (9.3)
Non-HDL-C ≥ 4.9 mmol/L, n (%)*	602 (12.3)	27 (3.1)	169 (10.3)
Overweight/obesity, n (%)*	2897 (59.0)	364 (41.9)	932 (56.7)
Central obesity, n (%)*	1975 (40.2)	200 (23.0)	600 (36.5)
Antihypertensive treatment, n (%)*	1465 (29.8)	21 (2.4)	256 (15.6)
Lipid-lowering treatment, n (%)*	307 (6.3)	15 (1.7)	90 (5.5)

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; DBP: diastolic blood pres
lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol;
non-high-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides.

* Frequency and percentage of variables with only 'Yes' value presented.

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Table 2. The associations of risk-enhancing factors with atherosclerotic cardiovascular disease risk.

Risk-enhancing factors	Univariable		
	HR (95% CI)	*P* value	HR
Family history of CVD	1.13 (0.93, 1.38)	0.212	1.20
Overweight/obesity	1.76 (1.43, 2.16)	< 0.001	1.39
Central obesity	1.64 (1.37, 1.98)	< 0.001	1.26
TG ≥ 2.3 mmol/L	1.31 (1.06, 1.63)	0.014	1.16
Hs-CRP ≥ 2 mg/L	1.50 (1.24, 1.82)	< 0.001	1.26
Lp(a) ≥ 50 mg/dL	1.40 (1.05, 1.85)	0.022	1.34
Non-HDL-C, mmol/L*	1.29 (1.18, 1.41)	< 0.001	1.28
Numbers of risk-enhancing factors			
≥ 1 risk-enhancing factors	1.71 (1.27, 2.31)	< 0.001	1.33
≥ 2 risk-enhancing factors	2.14 (1.72, 2.65)	< 0.001	1.66

Multivariable Cox models were adjusted for sex, age, smoking, diabetes mellitus, SBP, HDL-C, LDL-C, and

Abbreviations: Hs-CRP: high-sensitivity C-reactive protein; Lp(a): Lipoprotein(a); Non-HDL-C: non-high-de
triglycerides.

* In multivariable cox models, LDL-C was replaced with non-HDL-C.

Table 3. Measures of discrimination and reclassification for predicting the atherosclerotic cardiovascular dise the risk-enhancing factors to the current ASCVD risk assessment tool (i.e., the CSC model) in the total popula

Models	C-index (95% CI)	C-index changes (95% CI)
The CSC model	0.703 (0.679, 0.728)	
+ Family history of CVD	0.704 (0.680, 0.729)	0.001 (-0.002,0.004)
+ Overweight/obesity	0.708 (0.684, 0.732)	0.005 (-0.001, 0.010)
+ Central obesity	0.705 (0.681, 0.730)	0.002 (-0.002, 0.007)
+ TG ≥ 2.3 mmol/L	0.703 (0.679, 0.727)	0.000 (-0.002, 0.002)
+ hs-CRP ≥ 2 mg/L	0.704 (0.680, 0.729)	0.001 (-0.003, 0.005)
+ Lp(a) ≥ 50 mg/dL	0.704 (0.680, 0.729)	0.001 (-0.002, 0.005)
Replace LDL-C with non-HDL-C	0.701 (0.676, 0.725)	-0.002 (-0.006, 0.002)
Numbers of risk-enhancing factors		
+ ≥ 1 risk-enhancing factors	0.704 (0.680, 0.728)	0.001 (-0.002, 0.004)
+ ≥ 2 risk-enhancing factors	0.713 (0.689, 0.737)	0.010 (0.002, 0.017)

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; Lp(a): Lipoprotein(a); non-HDL-C: non-high-den net reclassification improvement; TG: triglycerides; the CSC model: the Chinese Society of Cardiology-recon tool.

Table 4. Reclassification measures for predicting the atherosclerotic cardiovascular disease events risk by a current ASCVD risk assessment tool (i.e., the CSC model) in intermediate-risk participants.

Models	Event NRI (95% CI)	Nonevent NRI (95% C
The CSC model		
+ Family history of CVD	0.021 (-0.057, 0.104)	-0.005 (-0.020, 0.012)
+ Overweight/obesity	0.128 (0.037, 0.221)	-0.027 (-0.052, -0.005
+ Central obesity	0.085 (0.004, 0.171)	-0.024 (-0.043, -0.006
+ TG ≥ 2.3 mmol/L	0.043 (-0.005, 0.094)	-0.007 (-0.019, 0.006)
+ hs-CRP ≥ 2 mg/L	0.053 (-0.019, 0.126)	-0.015 (-0.031, 0.003)
+ Lp(a) ≥ 50 mg/dL	-0.011 (-0.067, 0.049)	-0.001 (-0.014, 0.012)
Replace LDL-C with non-HDL-C	0.074 (0.019, 0.137)	-0.026 (-0.041, -0.012
+ ≥ 1 risk-enhancing factors	0.074 (0.012, 0.133)	-0.009 (-0.026, 0.009)
+ ≥ 2 risk-enhancing factors	0.191 (0.077, 0.296)	-0.017 (-0.047, 0.011)

Abbreviations: hs-CRP: high-sensitivity C-reactive protein; Lp(a): Lipoprotein(a); non-HDL-C: non-high-den net reclassification improvement; TG: triglycerides; the CSC model: the Chinese Society of Cardiology-recom tool.

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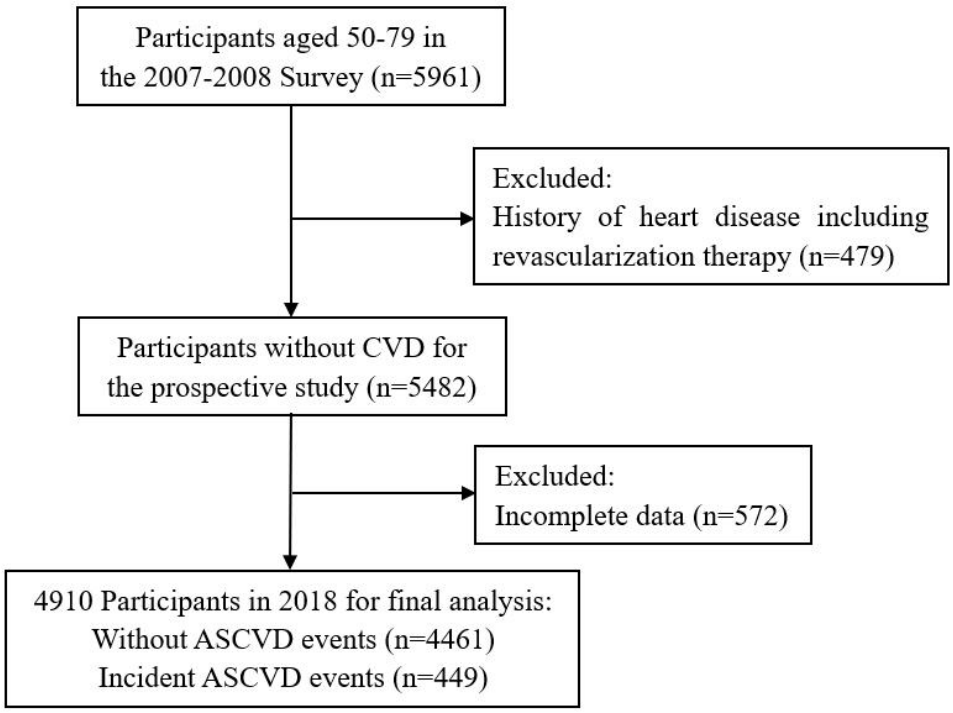

Figure 1. Flow chart of study participants selection in the 2007-2008 Survey from the Chinese Multi-provincial Cohort Study.

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CVD: cardiovascular disease.

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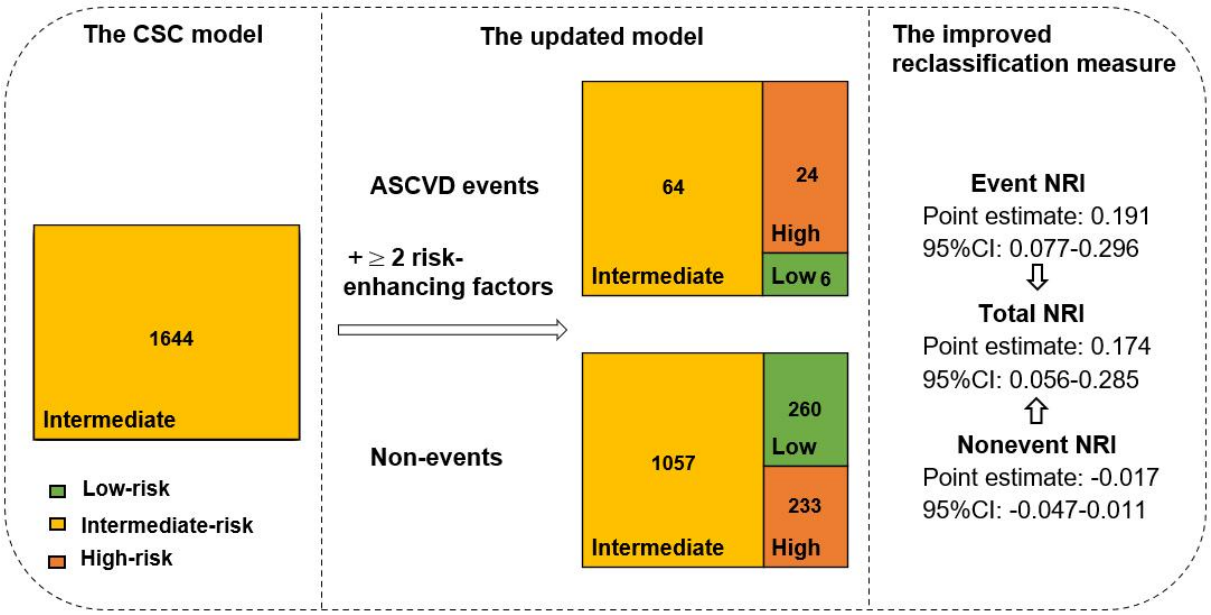

Figure 2. Central illustration. The updated model by adding ≥ 2 risk-enhancing factors to the CSC model improves ASCVD risk stratification for individuals at intermediate risk. Abbreviations: NRI: net reclassification improvement; The CSC model: the Chinese Society of Cardiology-recommended clinical risk assessment tool.