

Incremental Prognostic Value of Exertional Chest Pain Beyond PREVENT-Based Cardiovascular Risk Stratification: A Nationwide Prospective Cohort Study of Middle-Aged and Older Chinese Adults (CHARLS 2011–2020)

Zhenghui Wang

The People's Hospital Affiliated to Jiangsu University

Tianfeng Zhang

The People's Hospital Affiliated to Jiangsu University

Yiming Wang

The People's Hospital Affiliated to Jiangsu University

Long Zhao

The People's Hospital Affiliated to Jiangsu University

Dongli Shen

The People's Hospital Affiliated to Jiangsu University

Biao Kong

The People's Hospital Affiliated to Jiangsu University

Yongwei Yao

The People's Hospital Affiliated to Jiangsu University

Chenghua Wang

The People's Hospital Affiliated to Jiangsu University

Junfang Guo

The People's Hospital Affiliated to Jiangsu University,

Aibin Tao

aibinTao@outlook.com

The People's Hospital Affiliated to Jiangsu University

Research Article

Keywords: exertional chest pain, angina, PREVENT equations, cardiovascular-kidney-metabolic syndrome, risk prediction, CHARLS

Posted Date: October 20th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11416880/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: The authors declare no competing interests.

Abstract

Aims

The 2026 AHA/ACC/ADA/ASN cardiovascular-kidney-metabolic (CKM) guideline stratifies stage 3 by PREVENT-predicted risk but identifies the prognostic value of patient-reported symptoms, including exertional chest pain, as an evidence gap. This study assessed the incremental prognostic value of exertional chest pain beyond PREVENT-based risk stratification.

Methods

The China Health and Retirement Longitudinal Study (2011–2020) included 7,813 participants aged 30–79 years without baseline heart disease or stroke and with complete PREVENT inputs and symptom data. Over 9 years, 1,916 developed cardiovascular disease (CVD). Two questionnaire items assessed exertional chest pain. Cox models compared symptom ×PREVENT-risk (< 20% vs. ≥20%) groups. Incremental prediction was assessed using ΔC , integrated discrimination improvement (IDI), and net reclassification improvement (NRI).

Results

Exertional chest pain was associated with incident CVD in a dose-response pattern (fully adjusted hazard ratios: single-item-positive, 1.42 [95% confidence interval 1.25–1.62]; double-positive, 1.51 [1.29–1.77]; unable-to-exert, 1.96 [1.54–2.49]). Low-risk symptomatic participants had higher risk than high-risk asymptomatic participants (1.51 vs. 1.24), with a 9-year event rate of 31.4% versus a median predicted risk of 5.7%. The association was stronger in females (interaction $P = 0.03$). Adding symptoms improved discrimination (ΔC 0.019; IDI 0.011; NRI 0.036). Lag analysis and inverse-probability weighting confirmed robustness, while negative-control analyses suggested a general symptom-reporting component.

Conclusion

Two zero-cost questions assessing exertional chest pain provide prognostic information beyond PREVENT-based stratification, addressing a guideline-identified evidence gap and supporting evaluation of exertional chest pain as a CKM risk enhancer in resource-limited settings.

Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome staging, formalised by the American Heart Association in 2023 (1) and operationalised in the 2026 AHA/ACC/ADA/ASN guideline (2), stratifies individuals by risk factors, kidney function, and cardiovascular status. As stage 3 (subclinical cardiovascular disease [CVD]) is asymptomatic by definition, classification relies on imaging, biomarkers, or predicted risk. The guideline defines stage 3 using a PREVENT-CVD 10-year risk $\geq 20\%$ and prioritises cardiorenal-protective therapy at $\geq$

7.5% (2, 3), an architecture that parallels the risk-factor–based stratification underlying the 2021 ESC prevention guideline (4).

This framework has two gaps. First, coronary artery calcium scoring and cardiac biomarkers, despite their prognostic value (5, 6), are largely unavailable in community and resource-limited settings, leaving predicted risk as the only scalable approach. Second, the guideline explicitly identifies the prognostic value of patient-reported symptoms, including exertional chest pain, as CKM risk enhancers as an evidence gap (2, 7, 8).

Symptoms have established prognostic value. The Renfrew–Paisley study demonstrated that Rose angina predicted 20-year coronary outcomes beyond electrocardiographic (ECG) evidence of ischaemia, with combined symptoms and ECG findings identifying the highest-risk group (9). The Rose questionnaire remains widely used for angina assessment in population surveys (10). Contemporary primary-care evidence extends this principle: chest pain recorded without a specific attribution nevertheless identifies patients at excess cardiovascular risk (11). However, whether symptoms improve prediction beyond contemporary multivariable equations incorporating age, blood pressure, lipids, glycaemia, smoking, and kidney function remains unclear. Furthermore, symptomatic individuals may seek care and receive diagnoses more frequently, introducing detection bias that requires formal assessment (12).

Using the nationally representative CHARLS cohort (13), this study examined whether exertional chest pain, assessed using two items reflecting core Rose dimensions (location and exertional provocation) (14), predicts incident CVD beyond PREVENT-based stratification, improves risk reclassification at guideline thresholds, and withstands prespecified bias diagnostics, including negative-control outcomes.

Methods

Study Population

CHARLS is a nationwide Chinese cohort established in 2011 ($n = 17,708$), with follow-up in 2013, 2015, 2018, and 2020 (13). Participants were restricted to those aged 30–79 years (PREVENT applicability; $n = 16,941$), excluding those with baseline self-reported physician-diagnosed heart disease or stroke ($n = 14,365$). Eligibility required complete PREVENT inputs (blood pressure, lipids, creatinine, smoking, diabetes, and medication use; $n = 8,038$), valid symptom responses ($n = 8,005$), and ≥ 1 follow-up contact (final $n = 7,813$; loss to follow-up, 2.4%) (Fig. 1). Most attrition reflected the 2011 blood-sampling subsample. Only 33 participants were excluded for missing symptom responses because preceding exclusions had largely removed proxy respondents, for whom symptom data were unavailable.

Exposure

Two 2011 questionnaire items prohibited proxy responses: “Do you ever feel pain on the left side of your chest?” (DA003) and “Do you ever feel chest pains when climbing stairs/uphill or walking quickly?” (DA004; yes/no/not applicable) (13). Exposure was classified as asymptomatic, single-positive, double-positive, or “not applicable” (unable to exert). The latter was analysed separately because inability to climb stairs may

indicate functional limitation or cardiopulmonary disease. As these items omit the Rose relief-with-rest criterion (14), the exposure was termed exertional chest pain rather than Rose angina.

Risk Stratification

PREVENT-CVD 10-year risk was calculated using published AHA base-model coefficients (15). Inputs included mean systolic blood pressure from the second and third seated measurements; non-HDL-C and HDL-C from 2011 venous samples; smoking; diabetes (physician diagnosis, fasting glucose ≥ 126 mg/dL among those with fasting samples, or HbA1c $\geq 6.5\%$); estimated glomerular filtration rate using the CKD-EPI 2021 creatinine Eq. (16); and antihypertensive and lipid-lowering Western medication use. Implementation exactly reproduced the development paper's worked example (10-year CVD risk, 5.4%) and predicted risks for the 55-year-old female reference and optimal risk-factor profiles (3.5% and 2.7%, respectively) (15). High risk was defined as $\geq 20\%$ per the 2026 guideline [2].

Outcomes

Incident CVD was defined as the first post-baseline report of physician-diagnosed heart disease or stroke (1,916 events). Components were analysed separately, with incident stroke (652 events) considered least susceptible to detection bias. Negative-control outcomes included incident gastric/digestive disease and arthritis (12), assessed among participants without the respective baseline condition using fully adjusted M3 models. Events were interval-censored between waves (17). Primary analyses used midpoint-approximation Cox models, assigning final-interval events to the 2020 interview wave. Hazard ratios remained unchanged to three decimal places under pure-midpoint assignment. Interval-specific hazard ratios assessed temporal variation.

Covariates and Bias Diagnostics

To avoid tautological adjustment, models included only non-PREVENT covariates: M1 adjusted for age and sex to address residual confounding within risk strata; M2 additionally adjusted for education, rurality, marital status, and alcohol use; and M3 further adjusted for chronic lung disease, peak expiratory flow (PEF; distinct from forced expiratory volume at 1 second [FEV1]), recent outpatient visits, hospitalisation, and insurance.

Prespecified diagnostics included: (i) excluding events within two years; (ii) interval-specific hazard ratios (2011–2013, 2013–2015, 2015–2018, 2018–2020); (iii) negative-control outcomes; (iv) comparing exertional chest pain (any positive exertional-symptom item or inability to exert vs. neither) with previous-month chest pain (DA042 site item) and pain at any of 14 other sites; (v) sex interaction using a Wald test of the low-risk symptomatic $\times$ male term in M3, including all four symptom-group $\times$ male interaction terms; (vi) inverse-probability weighting (IPW) for loss to follow-up (18); and (vii) E-values for unmeasured confounding (19).

Incremental Prediction

Three models were compared: A (continuous PREVENT risk), B (symptom grades), and C (A + B). Performance was assessed using Harrell's C statistic, integrated discrimination improvement (IDI), and category-based net reclassification improvement (NRI) at guideline thresholds of 7.5% and 20% (20, 21). To preserve the guideline's absolute-risk scale and distinguish symptom-driven reclassification from in-sample recalibration, NRI applied M3-adjusted symptom-group hazard ratios to individual PREVENT predictions under proportional hazards; 95% confidence intervals were estimated from 200 bootstrap resamples. Reporting followed TRIPOD guidelines (22, 23). Calibration compared predicted and observed event rates overall and by quadrant. The prediction sample (n = 7,569) excluded 244 participants with missing education (n = 4) or PEF (n = 240). Analyses used Python 3.12 (pandas, numpy, statsmodels), with two-sided $P < 0.05$ indicating statistical significance.

Ethics

CHARLS was approved by the Peking University Institutional Review Board (IRB00001052-11015), and all participants provided written informed consent. This analysis used de-identified, publicly available data.

Results

Study Flow

Of 17,708 baseline participants, 7,813 met eligibility criteria and completed follow-up (Fig. 1). Most exclusions (n = 6,327) resulted from missing PREVENT inputs associated with the 2011 blood-sampling subsample. The final groups comprised 5,664 low-risk asymptomatic, 1,346 low-risk symptomatic, 496 high-risk asymptomatic, 135 high-risk symptomatic, and 172 unable-to-exert participants.

Table 1
Baseline characteristics by symptom × PREVENT 2×2 group (CHARLS 2011 eligible sample, n = 8,005)

Variable	Low-risk asymptomatic	Low-risk symptomatic	High-risk asymptomatic	High-risk symptomatic	Unable to exert	P value
n	5,771	1,371	535	145	183	
Age, years	56.8 ± 8.0	56.9 ± 8.1	71.1 ± 6.8	71.2 ± 6.9	61.0 ± 9.6	< 0.001
Female, %	54.7	57.3	32.5	37.9	61.2	< 0.001
Rural residence, %	64.8	71.2	61.5	66.9	73.2	< 0.001
Less than primary education, %	44.9	51.1	61.0	68.3	54.1	< 0.001
Current smoking, %	29.0	28.2	52.9	53.1	25.7	< 0.001
Systolic blood pressure, mm Hg	126.4 ± 19.3	125.6 ± 19.5	148.9 ± 25.2	149.1 ± 23.5	130.8 ± 23.9	< 0.001
Total cholesterol, mg/dL	192.9 ± 37.7	194.1 ± 38.8	192.3 ± 42.8	187.6 ± 40.4	192.8 ± 37.8	0.247
HDL-C, mg/dL	51.5 ± 15.1	53.1 ± 16.0	47.0 ± 14.9	47.0 ± 13.5	52.5 ± 14.5	< 0.001
Diabetes, %	10.4	13.3	40.6	46.9	13.7	< 0.001
eGFR, mL/min/1.73 m ²	98.3 ± 12.5	97.7 ± 12.9	83.4 ± 17.0	84.7 ± 18.6	95.5 ± 16.4	< 0.001
hs-CRP, mg/L, median (IQR)	0.9 (0.5, 1.9)	0.9 (0.5, 2.1)	1.5 (0.8, 3.5)	1.7 (0.8, 3.6)	1.1 (0.6, 2.6)	< 0.001
PEF, L/min	310.2 ± 121.4	285.8 ± 125.1	252.2 ± 118.5	255.2 ± 107.3	245.6 ± 120.5	< 0.001
Chronic lung disease, %	6.7	14.4	11.4	18.6	11.5	< 0.001
Outpatient visit, past month, %	16.8	25.7	15.3	20.7	15.8	< 0.001
Hospitalisation, past year, %	6.7	10.9	9.2	13.8	10.9	< 0.001
Medical insurance, %	93.9	94.6	92.5	93.8	90.7	0.398

Variable	Low-risk asymptomatic	Low-risk symptomatic	High-risk asymptomatic	High-risk symptomatic	Unable to exert	P value
Antihypertensive Western medication, %	11.9	13.4	42.2	41.4	19.1	< 0.001
Lipid-lowering Western medication, %	2.8	3.5	6.7	3.4	6.0	< 0.001
PREVENT-CVD risk, %, median (IQR)	5.8 (3.0, 10.1)	5.8 (3.0, 10.4)	23.9 (21.8, 27.4)	24.2 (21.7, 28.2)	7.9 (4.1, 15.2)	< 0.001

Continuous variables are presented as mean $\pm$ SD (ANOVA), hs-CRP and PREVENT risk as median (IQR) (Kruskal–Wallis), and categorical variables as percentages (chi-square). P values compare the four 2 $\times$ 2 groups. The baseline-eligible sample included 8,005 participants; requiring follow-up reduced the analytic sample to 7,813 (group sizes: 5,664 / 1,346 / 496 / 135 / 172). Education codes were verified against the 2011 Demographic Background module (bd001): level 1, less than primary education (illiterate, incomplete primary school, or traditional private school; bd001 = 1–3); level 2, primary school graduate; level 3, middle school; level 4, high school or above.

Among low-risk participants, symptomatic and asymptomatic groups had similar mean ages (56.9 vs. 56.8 years). However, symptomatic participants were more often rural (71.2% vs. 64.8%) and less educated, with greater chronic lung disease prevalence (14.4% vs. 6.7%), lower PEF (285.8 vs. 310.2 L/min), and more outpatient visits (25.7% vs. 16.8%; Table 1).

Table 2
Symptom grade and incident CVD (reference = asymptomatic)

Exposure	M1 (age + sex)	M2 (+ socioeconomic/behavioural)	M3 (+ lung disease/PEF/healthcare contact)
Asymptomatic	1.00	1.00	1.00
Single-positive	1.48 (1.30–1.68)	1.49 (1.31–1.69)	1.42 (1.25–1.62)
Double-positive	1.62 (1.39–1.89)	1.65 (1.42–1.92)	1.51 (1.29–1.77)
Unable to exert	2.01 (1.59–2.55)	1.98 (1.56–2.51)	1.96 (1.54–2.49)

All $P < 0.0001$. Attenuation from M1 to M3 was modest ($\leq 15\%$ on the log-hazard scale).

Table 3
Symptom × PREVENT 2×2 and outcomes (M3, reference = low-risk asymptomatic) † denotes the primary contrast of interest.

Outcome	Low-risk symptomatic †	High-risk asymptomatic	High-risk symptomatic	Unable to exert
Incident CVD (n = 1,916)	1.51 (1.35–1.70)***	1.24 (1.02–1.49)*	1.29 (0.94–1.77)	2.01 (1.57–2.56)***
Incident heart disease (n = 1,479)	1.61 (1.42–1.83)***	1.02 (0.81–1.28)	1.34 (0.94–1.91)	1.75 (1.31–2.33)***
Incident stroke (n = 652)	1.22 (0.99–1.50)	1.71 (1.29–2.26)***	1.02 (0.58–1.80)	2.07 (1.39–3.08)***

Symptom-grade hazard ratios increased monotonically and remained robust after adjustment (Table 2). Crude 9-year CVD event rates were 21.6%, 31.4%, 31.5%, and 32.6% across the low-risk asymptomatic, low-risk symptomatic, high-risk asymptomatic, and high-risk symptomatic groups, respectively, reaching 41.9% among those unable to exert (Table 3).

Table 4
Symptom × PREVENT group and incident CVD stratified by sex (M3) † denotes the primary contrast of interest.

Outcome: incident CVD	Low-risk symptomatic †	High-risk asymptomatic	High-risk symptomatic	Unable to exert
Female	1.67 (1.45–1.93)***	1.33 (1.00–1.76)	1.71 (1.11–2.66)*	1.89 (1.39–2.56)***
Male	1.28 (1.06–1.56)*	1.18 (0.91–1.53)	1.02 (0.65–1.61)	2.28 (1.53–3.39)***

The symptom × male interaction was significant (HR 0.77, P = 0.03; Wald test of the low-risk symptomatic × male term in M3, including all four group × male interactions; Table 4).

Figure 2A presents Kaplan–Meier cumulative CVD incidence using midpoint-approximated event times. Figure 2B compares PREVENT-predicted risk quintiles with observed rates. All quintiles exceeded the ideal calibration line (Q5: 20% predicted vs. 32% observed), indicating systematic underprediction. Median predicted risk versus observed incidence was 5.7% vs. 31.4% in low-risk symptomatic participants and 7.6% vs. 41.9% among those unable to exert. Adding symptom grades significantly improved discrimination and reclassification (Table 5). Prespecified bias diagnostics and sensitivity analyses are presented in Table 6.

Table 5
Incremental prediction statistics (outcome = incident CVD, n = 7,569)

Model	C statistic	ΔC (95% CI)	IDI (95% CI)	NRI at 7.5%/20% (95% CI)
A: PREVENT (continuous)	0.598	—	—	—
B: Symptom grades	0.548	—	—	—
C: A + B	0.617	0.019 (0.012–0.028)	0.011 (0.007–0.016)	0.036 (0.019–0.055)

CIs were derived from 200 bootstrap resamples. Reclassification moved 421 participants above an action threshold (219 across 7.5%; 202 across 20%), with none moving down (event-side NRI + 0.08; non-event-side NRI – 0.05). The prediction sample (n = 7,569) excluded 244 participants with missing education (n = 4) or PEF (n = 240) from the analytic cohort (n = 7,813).

Table 6
Bias diagnostics and sensitivity analyses

#	Analysis	Result (HR for low-risk symptomatic quadrant unless noted)	Verdict
S1	Lag analysis (excluding first 2 years)	1.49 (1.31–1.69)	Pass
S2	Time-dependence (interval-specific HRs)	1.49 / 2.13 / 1.47 / 1.19 (ns) (2011–13 / 13–15 / 15–18 / 18–20)	Final-interval attenuation
S3	Negative control: incident gastric disease	1.68 (1.48–1.92)	Reporting component detected
S3	Negative control: incident arthritis	1.66 (1.47–1.88)	Reporting component detected
S3'	Negative controls × unable-to-exert group	Gastric 0.97; arthritis 1.16 (both ns)	No reporting component
S4	Head-to-head (mutual adjustment)	Exertional chest pain (symptomatic or unable to exert vs. neither) 1.43 vs. other-site pain 1.26 vs. last-month chest pain 1.11 (ns)	Exertional dimension strongest
S5	IPW for loss to follow-up	1.51 (1.35–1.70) (identical to unweighted)	Pass
S6	E-values	Low-risk symptomatic 2.39; unable-to-exert 3.33	Reference

Discussion

In this nationally representative Chinese cohort, two exertional chest pain questions identified community-dwelling adults whose observed cardiovascular event rates matched or exceeded those of guideline-defined high-risk individuals, despite median predicted risks of approximately 6%. Associations were dose-dependent, persisted after extensive adjustment, lag analysis, and loss-to-follow-up weighting, and were strongest for exertional symptoms. Significant improvements in discrimination (ΔC and IDI) and net reclassification (NRI) directly address the 2026 CKM guideline's evidence gap concerning symptom-based risk enhancers (2).

Three findings warrant consideration. First, negative-control analyses revealed more non-cardiac diagnoses among symptomatic participants, suggesting a general symptom-reporting/healthcare-engagement component. Thus, the prognostic increment was partly non-ischaemia-specific: CVD hazard ratios (1.42–1.51) were lower than those for negative-control outcomes (1.66–1.68). Nevertheless, exertional symptoms outperformed other pain measures, while inability to exert showed the highest CVD risk (1.96) but null negative-control associations (0.97 and 1.16), suggesting a cardiopulmonary signal beyond reporting propensity. Previous CHARLS research similarly associated pain dynamics with cardiovascular outcomes (24), while self-reported gait speed demonstrated prognostic utility in primary prevention (25). Second, the association with stroke, which is less susceptible to detection bias, was attenuated (1.22, borderline), whereas PREVENT remained predictive (1.71), suggesting predominantly cardiac prognostic information. Third, PREVENT substantially underestimated observed event rates (8.5% predicted vs. 24.6% observed), consistent with CHARLS-based external validation showing reduced discrimination (AUC 0.61–0.62) and calibration slopes of 0.47–0.51 (26). In US national data, the PREVENT equations have been shown to estimate risk accurately(27);by contrast, external validations in Chinese and Swiss populations report attenuated discrimination and systematic risk underestimation(26, 28), indicating that recalibration may be required when the equations are transported beyond their US derivation populations. Within Asia specifically, these findings reinforce the guideline's call for external validation and echo the rationale behind Chinese-specific prediction models such as China-PAR (29, 30). The discrepancy between predicted (approximately 6%) and observed (approximately 31–42%) risks further highlights potentially overlooked symptom-defined groups.

The stronger association in females (1.67 vs. 1.28; interaction $P = 0.03$) aligns with sex differences in symptom presentation and pain reporting (31). Angina without obstructive coronary artery disease, more prevalent in females, also carries increased cardiovascular risk (32–34). Symptoms may therefore capture prognostic information beyond conventional risk factors, particularly in females (35).

Clinically, these findings support incorporating exertional chest pain as a potential zero-cost risk enhancer rather than modifying CKM staging. Where coronary artery calcium scoring and biomarkers are unavailable, two questions may identify individuals whose observed risk exceeds the 20% action threshold. Symptomatic individuals with low predicted risk warrant objective cardiovascular evaluation (36), rather than reassurance based solely on risk scores.

Strengths include nationwide representativeness, minimal loss to follow-up, robustness confirmed by IPW, validated implementation of official PREVENT coefficients, prespecified bias diagnostics, and formal sex-interaction testing. Limitations include self-reported, non-adjudicated outcomes, with angina included among

heart disease diagnoses and potentially introducing detection bias, addressed through stroke and negative-control analyses; interval-censored events, with proportional hazards evaluated using interval-specific estimates rather than formal testing; lack of external validation; omission of survey weights and clustering; a two-item assessment rather than the full Rose questionnaire (14); PEF instead of FEV1 for respiratory adjustment; and medication data restricted to Western medication checkboxes.

Conclusions

Exertional chest pain improves prognostic prediction beyond PREVENT-based stratification, with increments exceeding typical biomarker gains but partly reflecting non-specific factors. This zero-cost candidate CKM risk enhancer may be particularly useful in resource-limited settings, prompting objective cardiovascular evaluation rather than replacing it. Future studies should address these limitations: external validation in independent cohorts with adjudicated endpoints and the full Rose questionnaire; benchmarking against recalibrated or China-specific equations such as China-PAR, with sex-specific analyses; and implementation studies testing whether these two zero-cost questions improve risk classification and outcomes in resource-limited settings.

Data Availability

The CHARLS data used in this study are publicly available upon registration at <https://charls.charlsdata.com>.

Declarations

Conflict of Interest

The authors declare no conflict of interest.

Funding

This work was supported by the National Natural Science Foundation of China (grant no. 81971817).

Author Contributions

Conception and design: Zhenghui Wang and Aibin Tao. Methodology: Zhenghui Wang, Tianfeng Zhang and Yiming Wang. Data acquisition: Zhenghui Wang and Long Zhao. Data analysis and interpretation: Zhenghui Wang and Dongli Shen. Writing of the article: Zhenghui Wang, Biao Kong and Yongwei Yao. Review of the article: Chenghua Wang, Junfang Guo and Aibin Tao. All authors read and approved the final manuscript.

Acknowledgements

We thank the CHARLS research team, field interviewers, and all study participants for their contributions.

References

1. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS et al (2023) Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. *Circulation* 148(20):1606–1635
2. Ndumele CE, Rodriguez F, Dixon DL, Khan SS, Mukherjee D, Bajaj M et al (2026) 2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 154(4):e50–e158
3. Khan SS, Bhavne N, Blumenthal RS, Coresh J, Huang X, Joseph JJ et al (2026) Use of Predicted Risk and Expected Benefit to Guide Decision-Making in Cardiovascular-Kidney-Metabolic Syndrome for the Primary Prevention of Cardiovascular Disease: A Scientific Statement From the American Heart Association and American College of Cardiology. *Circulation* 154(4):e159–e80
4. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M et al (2022) 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *Rev Esp Cardiol (Engl Ed)* 75(5):429
5. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR et al (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 358(13):1336–1345
6. McClelland RL, Jorgensen NW, Budoff M, Blaha MJ, Post WS, Kronmal RA et al (2015) 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* 66(15):1643–1653
7. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ et al (2019) 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* 140(11):e596–e646
8. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA et al (2018) /ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e143
9. Murphy NF, Stewart S, Hart CL, MacIntyre K, Hole D, McMurray JJ (2006) A population study of the long-term consequences of Rose angina: 20-year follow-up of the Renfrew-Paisley study. *Heart* 92(12):1739–1746
10. Cook DG, Shaper AG, MacFarlane PW (1989) Using the WHO (Rose) angina questionnaire in cardiovascular epidemiology. *Int J Epidemiol* 18(3):607–613
11. Jordan KP, Rathod-Mistry T, van der Windt DA, Bailey J, Chen Y, Clarson L et al (2023) Determining cardiovascular risk in patients with unattributed chest pain in UK primary care: an electronic health record study. *Eur J Prev Cardiol* 30(11):1151–1161

12. Lipsitch M, Tchetgen Tchetgen E, Cohen T (2010) Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 21(3):383–388
13. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G (2014) Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol* 43(1):61–68
14. Rose GA (1962) The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 27(6):645–658
15. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A et al (2024) Development and Validation of the American Heart Association's PREVENT Equations. *Circulation* 149(6):430–449
16. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y et al (2021) New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med* 385(19):1737–1749
17. Lindsey JC, Ryan LM (1998) Tutorial in biostatistics methods for interval-censored data. *Stat Med* 17(2):219–238
18. Seaman SR, White IR (2013) Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 22(3):278–295
19. VanderWeele TJ, Ding P (2017) Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 167(4):268–274
20. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB Jr., Vasan RS (2008) Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 27(2):157–172 discussion 207 – 12
21. Kerr KF, Wang Z, Janes H, McClelland RL, Psaty BM, Pepe MS (2014) Net reclassification indices for evaluating risk prediction instruments: a critical review. *Epidemiology* 25(1):114–121
22. Collins GS, Reitsma JB, Altman DG, Moons KG (2015) Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 350:g7594
23. Collins GS, Moons KGM, Dhiman P, Riley RD, Beam AL, Van Calster B et al (2024) TRIPOD + AI statement: updated guidance for reporting clinical prediction models that use regression or machine learning methods. *BMJ* 385:e078378
24. Yang Z, Zheng L, Zhao H, Zhang H, Zhu Y, Ma Y et al (2025) Impact of dynamic changes in pain on cardiovascular disease in Chinese middle and elderly people: results from China Health and Retirement Longitudinal Study (CHARLS). *BMC Public Health* 25(1):3489
25. Ueno K, Kaneko H, Kamiya K, Itoh H, Okada A, Suzuki Y et al (2022) Clinical utility of simple subjective gait speed for the risk stratification of heart failure in a primary prevention setting. *Sci Rep* 12(1):11641
26. Fan WQ, Hu YW, Yu CY, Liu YK, Li H (2026) External validation of American heart association predicting risk of cardiovascular disease EVENTS (PREVENT) equations in a Chinese population. *Sci Rep.* ;16(1)
27. Khan SS, Sang Y, Huang X, Petito LC, Hong C, Pencina MJ et al (2026) External Validation of the PREVENT Equations in a National Sample of US Adults. *Circ Popul Health Outcomes* 19(9):e012988
28. Roxane H, Pedro MV, Julien V (2025) External validation of the 2023 American Heart Association Predicting Risk of cardiovascular disease EVENTS equations for atherosclerotic cardiovascular disease in primary cardiovascular prevention setting and comparison with 2021 Systematic COronary Risk Evaluation and 2013 Pooled Cohort Equations. *Eur J Prev Cardiol*

29. Zhao D, Liu J, Wang M, Zhang X, Zhou M (2019) Epidemiology of cardiovascular disease in China: current features and implications. *Nat Rev Cardiol* 16(4):203–212
30. Yang X, Li J, Hu D, Chen J, Li Y, Huang J et al (2016) Predicting the 10-Year Risks of Atherosclerotic Cardiovascular Disease in Chinese Population: The China-PAR Project (Prediction for ASCVD Risk in China). *Circulation* 134(19):1430–1440
31. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V et al (2012) Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 307(8):813–822
32. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK et al (2012) Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 33(6):734–744
33. Gulati M, Cooper-DeHoff RM, McClure C, Johnson BD, Shaw LJ, Handberg EM et al (2009) Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 169(9):843–850
34. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL (2017) Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. *Circulation* 135(11):1075–1092
35. Hemingway H, Langenberg C, Damant J, Frost C, Pyörälä K, Barrett-Connor E (2008) Prevalence of angina in women versus men: a systematic review and meta-analysis of international variations across 31 countries. *Circulation* 117(12):1526–1536
36. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, AHA/ACC/ASE/CHEST et al (2021) /SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;144(22):e368-e454

Figures

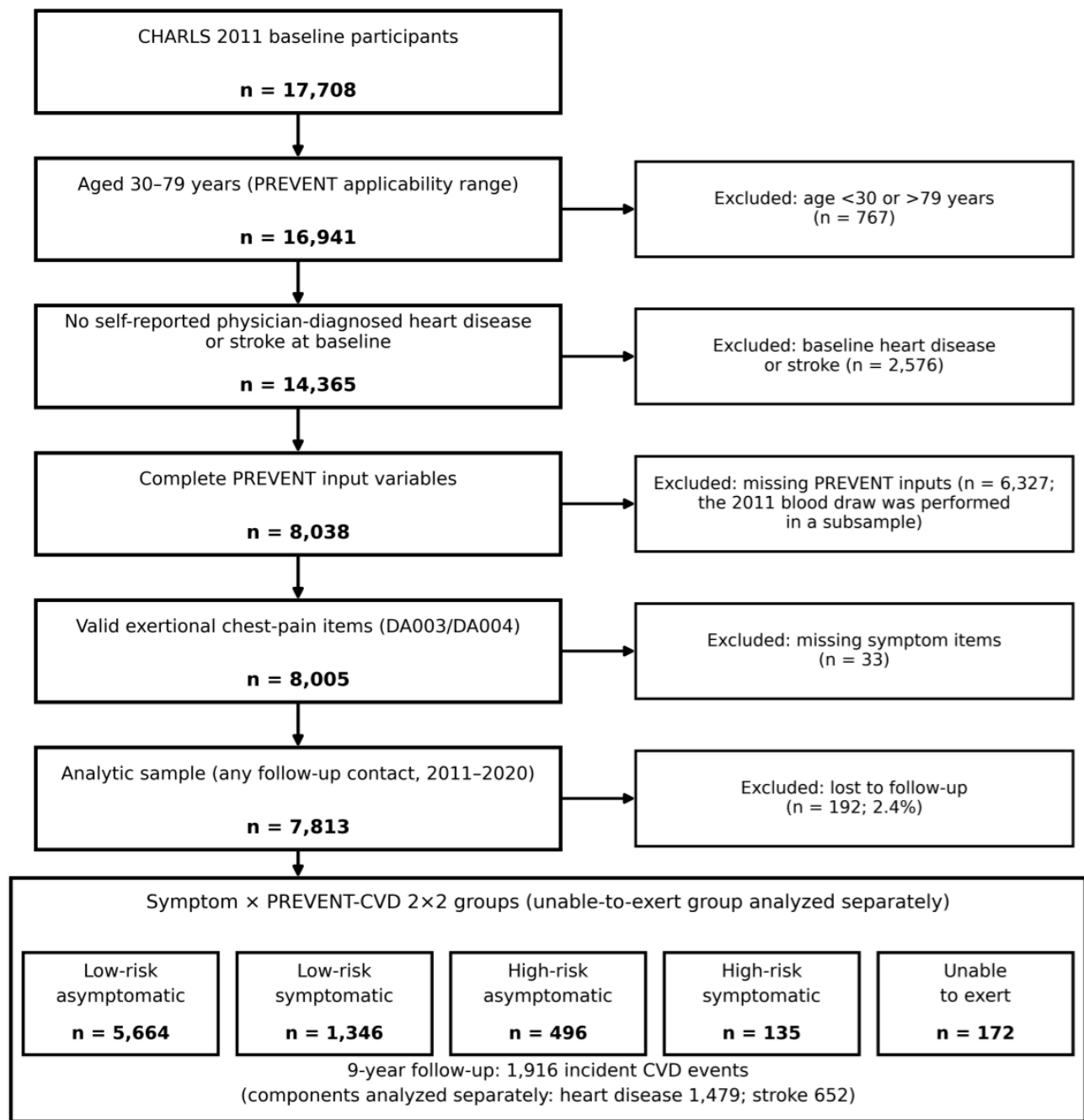


Figure 1

Study flowchart. Sequential eligibility criteria applied to 17,708 baseline participants (2011)—aged 30–79 years, no baseline physician-diagnosed heart disease or stroke, complete PREVENT inputs, valid symptom responses, and ≥1 follow-up contact—yielded 7,813 participants.

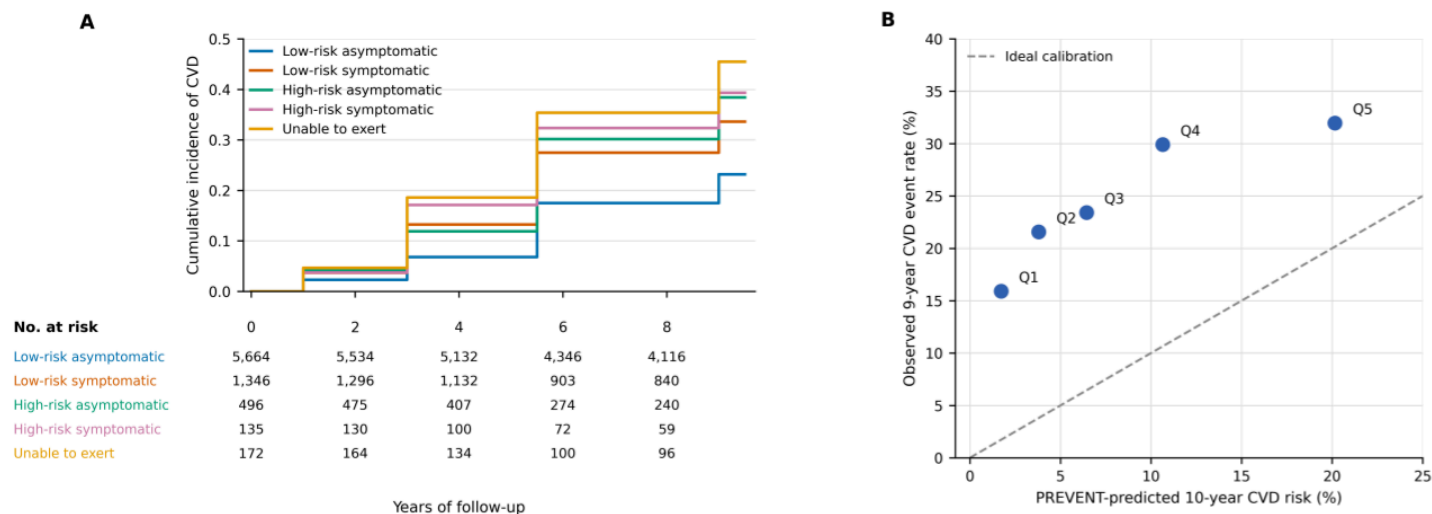


Figure 2

Cumulative incidence and PREVENT calibration. (A) Cumulative incidence of CVD by symptom × PREVENT group (Kaplan–Meier analysis using midpoint-approximated event times), with numbers at risk below the panel. (B) Observed event rates versus PREVENT-predicted risk quintiles relative to the ideal calibration line, demonstrating systematic underprediction.