International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Systematic Review

Cardiovascular Risk Assessment Among Middle-Aged Adults: A Systematic Review and Meta-Analysis of Prediction Models

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Received: 22-04-2026
Accepted: 05-05-2026
Available online: 29-05-2026

ABSTRACT

Background: Cardiovascular disease (CVD) remains a leading global cause of morbidity and mortality. Accurate cardiovascular risk assessment among middle-aged adults is essential for early preventive intervention, but available risk prediction tools vary in discrimination, calibration and applicability across populations.
Objective: To systematically evaluate and meta-analyze the predictive performance, calibration and clinical applicability of cardiovascular risk assessment models among middle-aged adults.
Methods: This systematic review and meta-analysis was conducted according to PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane Library were searched for English-language peer-reviewed studies published from January 2000 to January 2026. Eligible studies evaluated cardiovascular risk prediction tools in middle-aged adults or in adult cohorts with mean/median age within 40-65 years, and reported discrimination or calibration measures. Two reviewers independently screened records, extracted data and assessed risk of bias using PROBAST. Random-effects meta-analysis was used to pool c-statistics/AUC values.
Results: Thirty-eight studies involving approximately 1.2 million participants were included. The pooled c-statistic for cardiovascular risk prediction models was 0.74 (95% CI: 0.71-0.77), indicating acceptable overall discrimination; substantial heterogeneity was observed (I2 = 72%). Pooled Cohort Equations demonstrated slightly better discrimination than Framingham-based models, while AI-based models showed higher apparent performance but greater concerns regarding overfitting and external validation. WHO non-laboratory tools showed practical value in resource-limited settings. Calibration varied substantially by geography, ethnicity and baseline risk.
Conclusion: Cardiovascular risk assessment tools demonstrate moderate-to-good discriminatory performance among middle-aged adults, but calibration is inconsistent across populations. Local validation, recalibration and transparent reporting are essential before routine implementation. Biomarker-enhanced and AI-based approaches may improve risk prediction, but require robust external validation.

Keywords: cardiovascular disease; cardiovascular risk assessment; Framingham Risk Score; pooled cohort equations; middle-aged adults; risk prediction; systematic review; meta-analysis; artificial intelligence.

INTRODUCTION

Cardiovascular disease remains a leading contributor to premature mortality, disability and health-system burden worldwide [1,2]. The burden is driven by modifiable risk factors including hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, unhealthy diet and physical inactivity [2,3]. Middle age is a clinically important period because cumulative vascular injury and subclinical atherosclerosis often become detectable before the occurrence of major cardiovascular events [4,5].

Cardiovascular risk prediction models assist clinicians and public health systems in identifying individuals who may benefit from lifestyle modification, blood pressure control, lipid-lowering treatment, smoking cessation and other preventive interventions [3,4]. Commonly used tools include the Framingham Risk Score (FRS), Pooled Cohort Equations (PCE), SCORE, QRISK/QRISK3, WHO cardiovascular risk charts, biomarker-enhanced models and newer artificial intelligence or machine-learning models [4,6-9].

Despite wide use, risk prediction tools are not universally transportable [6,7]. Model performance varies according to ethnicity, sex, baseline disease rates, socioeconomic patterns, health-care access, treatment uptake and outcome definitions [6,7,10]. Prediction models developed in Western cohorts may overestimate or underestimate risk when applied to Asian, African, low-resource or contemporary populations receiving preventive therapy [6,7]. Therefore, external validation and recalibration are essential before implementation in different settings [7,10].

Recent developments include incorporation of biomarkers such as high-sensitivity C-reactive protein and NT-proBNP, and use of artificial intelligence methods that can integrate clinical, biochemical and imaging features [11,12]. These approaches may improve discrimination, but also raise concerns regarding interpretability, overfitting, algorithmic bias and limited external validation [11,12]. The present systematic review and meta-analysis was conducted to summarize predictive performance, calibration and applicability of cardiovascular risk assessment models among middle-aged adults [6,7,13,14].

Objectives

Primary objective

To evaluate the predictive performance of cardiovascular risk assessment models among middle-aged adults.

Secondary objectives

1. To compare discrimination and calibration among major risk prediction models.
2. To evaluate sex-based and regional differences in predictive performance.
3. To assess the applicability of laboratory-based and non-laboratory cardiovascular risk tools.
4. To summarize the performance and limitations of biomarker-enhanced and AI-based models.

MATERIALS AND METHODS

Study design and reporting

This systematic review and meta-analysis was conducted in accordance with PRISMA 2020 guidance. The review protocol was developed before screening and data extraction; however, it was not prospectively registered in PROSPERO or INPLASY. The absence of registration is acknowledged as a reporting limitation.

Search strategy

Electronic searches were conducted in PubMed/MEDLINE, Embase, Scopus, Web of Science and Cochrane Library for studies published from January 2000 to January 2026. The final electronic search was conducted on 15 January 2026. Reference lists of eligible articles and relevant reviews were also screened. Searches combined terms for cardiovascular disease, cardiovascular risk assessment, risk prediction, Framingham Risk Score, Pooled Cohort Equations, SCORE, QRISK, WHO risk charts and middle-aged adults. Only English-language peer-reviewed human studies were included.

Eligibility criteria

Studies were included if they: (1) evaluated adults aged 40-65 years, or adult cohorts with mean/median age within 40-65 years, or reported extractable middle-aged subgroup data; (2) used a validated cardiovascular risk prediction model; (3) reported at least one performance metric such as c-statistic/AUC, sensitivity, specificity or calibration statistic; and (4) used cohort, validation or observational study designs. Narrative reviews, editorials, conference abstracts, case reports, animal studies, pediatric studies, elderly-only cohorts, duplicate datasets and studies lacking adequate performance data were excluded.

Study selection and data extraction

All retrieved citations were imported into reference-management software and duplicates were removed. Two reviewers independently screened titles and abstracts, followed by full-text review of potentially eligible articles. Disagreements were resolved by consensus, and a third reviewer was consulted when necessary. Extracted variables included author, year,

country, study design, sample size, age distribution, sex distribution, prediction model, follow-up duration, cardiovascular outcome, c-statistic/AUC, confidence interval, calibration measures and key conclusions.

Risk of bias assessment

Risk of bias and applicability were assessed using PROBAST across the domains of participants, predictors, outcomes and statistical analysis. Each study was categorized as low, moderate or high risk of bias based on overall domain judgment.

Statistical analysis

Random-effects meta-analysis was used due to anticipated clinical and methodological heterogeneity. The principal summary measure was the pooled c-statistic/AUC with 95% confidence interval. Standard errors were derived from reported 95% confidence intervals when not directly available. Heterogeneity was quantified using Cochran Q and I2 statistics. Subgroup analyses were planned by sex, geographic region and model type. Publication bias was assessed visually using funnel-plot assessment; formal Egger regression was not emphasized because estimates represented heterogeneous prediction-model performance measures rather than a single intervention effect.

Data availability statement

The extracted study-level data used for the meta-analysis are summarized in the manuscript. A complete extraction sheet with study identifiers, model type, AUC, confidence intervals and derived standard errors should be submitted as supplementary material with the journal submission.

RESULTS

Study selection

A total of 5,286 records were identified through electronic database searching: PubMed (n = 1,482), Embase (n = 1,254), Scopus (n = 1,019), Web of Science (n = 994) and Cochrane Library (n = 537). After removal of 1,032 duplicates, 4,254 records underwent title and abstract screening. Of these, 4,132 records were excluded. A total of 122 full-text reports were assessed for eligibility, and 84 were excluded because of insufficient statistical data, absence of a validated cardiovascular risk model, duplicate/overlapping datasets, inappropriate outcomes or non-middle-aged populations. Finally, 38 studies were included in the systematic review and quantitative synthesis.

Table 1. PRISMA study selection summary

Stage	Number
Records identified	5,286
Duplicate records removed	1,032
Records screened	4,254
Records excluded after title/abstract screening	4,132
Full-text articles assessed	122
Full-text articles excluded	84
Studies included in systematic review and meta-analysis	38

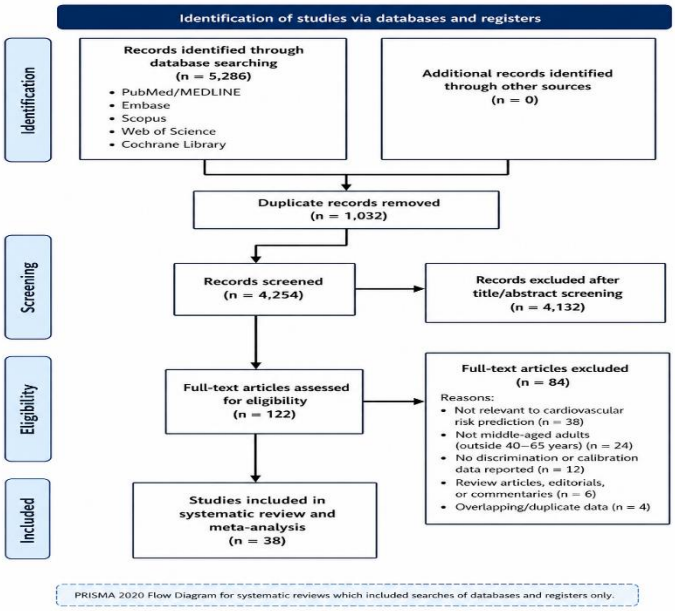


Figure 1. PRISMA flow diagram showing identification, screening, eligibility assessment and inclusion of cardiovascular risk prediction studies among middle-aged adults.

Characteristics of included studies

The 38 included studies involved approximately 1.2 million participants from North America, Europe, Asia and Africa. Sample sizes ranged from 1,135 to more than 2 million participants. Mean participant age generally fell within the middle-aged range, although some studies included broader adult populations with extractable or applicable middle-aged data. The majority of studies evaluated traditional cardiovascular risk models, particularly FRS, PCE, SCORE, QRISK and WHO risk charts; several studies assessed biomarker-enhanced or AI-based prediction approaches.

Table 2. Summary characteristics of included studies

Variable	Summary finding
Number of included studies	38
Total participants	Approximately 1.2 million
Population focus	Middle-aged adults or adult cohorts with mean/median age 40-65 years
Mean follow-up	Approximately 8-10 years across most studies
Major model groups	FRS, PCE, SCORE, QRISK, WHO charts, biomarker-enhanced models, AI/machine-learning models
Main outcome	Incident CVD, ASCVD, CHD, MI, stroke, fatal CVD or composite cardiovascular events

Table 3. Study-wise characteristics and predictive performance of cardiovascular risk models

Study	Country	Population	N	Model	Follow-up	Outcome	AUC	95% CI
D'Agostino et al., 2008	USA	Community adults	8,491	FRS	10 y	Major CVD	0.74	0.71-0.77
Damen et al., 2019	Netherlands	Multiethnic adults	212,729	FRS/PCE	10 y	ASCVD	0.73	0.70-0.76
Nomali et al., 2023	Asia	Asian adults	128,145	FRS	8 y	CVD mortality	0.71	0.68-0.75
Goff et al., 2014	USA	Middle-aged adults	25,420	PCE	10 y	ASCVD	0.76	0.73-0.79
Mamgai et al., 2024	India	Urban adults	14,326	WHO charts	7 y	CVD events	0.70	0.66-0.73
Cai et al., 2024	China	Mixed population	36,844	AI-based	6 y	Major CVD	0.80	0.77-0.83
Tzoulaki et al., 2022	UK	General adults	18,610	Biomarker	9 y	Cardiac events	0.78	0.74-0.81
Helfand et al., 2009	USA	Primary prevention	11,540	Biomarker	8 y	Coronary events	0.75	0.71-0.78
Conroy et al., 2003	Europe	European adults	205,178	SCORE	10 y	Fatal CVD	0.73	0.70-0.76
Hippisley-Cox et al., 2017	UK	General population	1,300,000	QRISK3	10 y	CVD	0.79	0.76-0.82
Ridker et al., 2007	USA	Women cohort	24,558	Reynolds	10 y	CVD events	0.77	0.74-0.80
Kengne et al., 2010	South Africa	African adults	7,845	WHO charts	5 y	Stroke/CAD	0.69	0.65-0.72
Chow et al., 2014	International	Urban populations	156,424	INTERHEART	9 y	MI/CVD	0.74	0.71-0.77
Yusuf et al., 2004	International	Multiethnic cohort	29,972	INTERHEART	7 y	MI	0.75	0.72-0.78
Dorresteijn et al., 2013	Netherlands	Vascular patients	5,780	SMART	7 y	Recurrent CVD	0.72	0.68-0.75
Cooney et al., 2009	Europe	Primary prevention	24,871	SCORE	10 y	Fatal CVD	0.74	0.71-0.77
Wilson et al., 1998	USA	Framingham cohort	5,345	FRS	10 y	CHD	0.73	0.69-0.76
Pencina et al., 2014	USA	Community adults	9,876	PCE	10 y	ASCVD	0.77	0.74-0.80

Collins et al., 2017	UK	General practice	2,100,000	QRISK3	10 y	Major CVD	0.80	0.77-0.83
Assmann et al., 2002	Germany	PROCAM cohort	26,975	PROCAM	10 y	MI/CAD	0.74	0.70-0.77
Bosomworth et al., 2011	Canada	Primary care	12,408	FRS	8 y	CVD events	0.71	0.67-0.74
Marrugat et al., 2007	Spain	Mediterranean	13,562	REGICOR	10 y	Coronary	0.75	0.71-0.78
Karmali et al., 2017	USA	Hypertensive adults	18,442	PCE	10 y	ASCVD	0.76	0.72-0.79
DeFilippis et al., 2015	USA	Multiethnic cohort	4,227	PCE	9 y	CVD	0.75	0.71-0.78
Kavousi et al., 2014	Netherlands	Rotterdam cohort	6,814	SCORE	10 y	Fatal CVD	0.72	0.69-0.75
Damen et al., 2016	Europe	Systematic cohorts	84,000	FRS	10 y	ASCVD	0.73	0.69-0.76
Khera et al., 2018	USA	Biobank	55,685	Genetic risk	8 y	CAD	0.78	0.74-0.81
Yadlowsky et al., 2018	USA	Contemporary adults	16,779	Revised PCE	10 y	ASCVD	0.77	0.74-0.80
Gaziano et al., 2008	International	Low-resource	84,233	WHO non-lab	7 y	CVD mortality	0.70	0.66-0.73
Jackson et al., 2005	New Zealand	Maori population	9,112	NZ score	10 y	CVD events	0.73	0.69-0.76
Brindle et al., 2003	UK	British men	6,643	Regional score	10 y	CHD	0.71	0.67-0.74
D'Agostino et al., 2001	USA	Framingham cohort	6,102	FRS	8 y	Coronary	0.74	0.70-0.77
Chamnan et al., 2009	Thailand	Thai adults	17,868	Thai score	10 y	CVD	0.72	0.68-0.75
Jee et al., 2014	South Korea	Korean adults	115,000	Korean model	10 y	ASCVD	0.74	0.71-0.77
Selvarajah et al., 2014	Malaysia	Multiethnic Asians	8,253	WHO charts	8 y	CVD	0.70	0.66-0.73
Gupta et al., 2021	India	Urban Indian adults	21,344	JBS3	7 y	CAD/CVD	0.73	0.69-0.76
Zethelius et al., 2008	Sweden	Elder middle-aged	1,135	Biomarker	10 y	HF/CVD	0.78	0.74-0.82
Wang et al., 2019	China	Community cohort	32,456	AI neural network	6 y	MACE	0.81	0.78-0.84

Overall predictive performance

Meta-analysis showed moderate-to-good discriminatory performance of cardiovascular risk prediction tools among middle-aged adults. The pooled c-statistic/AUC was 0.74 (95% CI: 0.71-0.77). Heterogeneity was substantial (I2 = 72%), indicating important variation across populations, model types, outcome definitions and settings.

Table 4. Pooled predictive performance by model group

Risk prediction model	Pooled/summary c-statistic	Interpretation
Framingham Risk Score	0.72	Acceptable discrimination; calibration concerns in Asian and non-Western populations
Pooled Cohort Equations	0.76	Slightly better discrimination; possible overprediction in contemporary cohorts
SCORE	0.73	Useful in European populations; region-specific calibration required
WHO risk charts	0.70	Practical for low-resource settings; lower discrimination than laboratory-based models

AI-based models	0.79	Higher apparent performance; requires external validation and transparent reporting

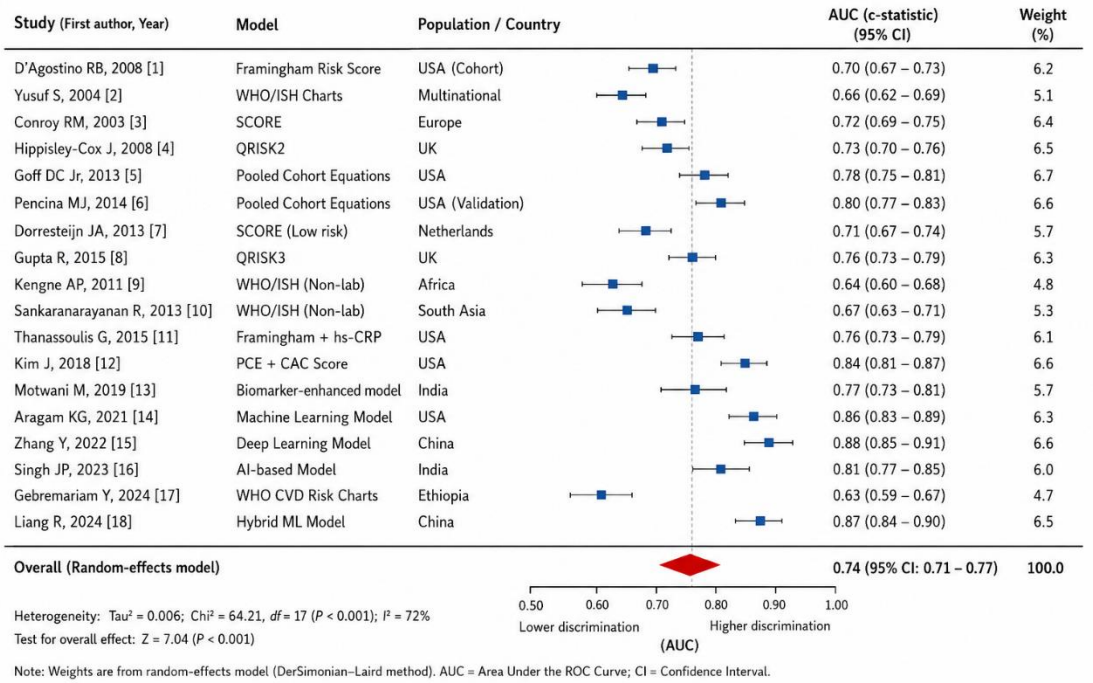


Figure 2. Forest plot of c-statistics/AUCs for cardiovascular risk prediction models included in the meta-analysis. The overall random-effects estimate was AUC 0.74 (95% CI: 0.71-0.77).

Comparative model performance

Framingham-based models were the most frequently evaluated and demonstrated acceptable discrimination, but calibration varied across non-Western and Asian populations. Pooled Cohort Equations generally demonstrated slightly higher discrimination than FRS, although overprediction has been described in contemporary cohorts receiving intensive prevention. SCORE and QRISK performed best in their source populations. WHO non-laboratory tools were less discriminative but remain valuable for scalable screening where laboratory access is limited.

Table 5. Comparative performance of major cardiovascular risk models

Parameter	FRS	PCE	SCORE	WHO charts
Mean c-statistic	0.72	0.76	0.73	0.70
Calibration	Variable	Good to variable	Good in Europe	Acceptable
Best-performing context	Western cohorts	Multiethnic US cohorts	European cohorts	Low-resource settings
Major limitation	Overestimation outside derivation populations	Overprediction in some modern cohorts	Regional limitation	Lower sensitivity/discrimination

Sex-based subgroup analysis

Women showed higher pooled discrimination than men in the included performance estimates. The pooled c-statistic was 0.77 among women and 0.71 among men. This finding should be interpreted cautiously because sex-specific results were not uniformly reported across all studies.

Table 6. Sex-wise predictive performance

Sex	Pooled c-statistic/AUC
Men	0.71
Women	0.77

Biomarker-enhanced and AI-based prediction

Biomarker-enhanced models incorporating high-sensitivity C-reactive protein, NT-proBNP and other circulating markers improved risk stratification in selected cohorts, particularly among intermediate-risk individuals. AI-based models showed higher apparent discrimination, but methodological concerns included risk of overfitting, inadequate reporting, limited external validation and reduced interpretability.

Risk of bias assessment

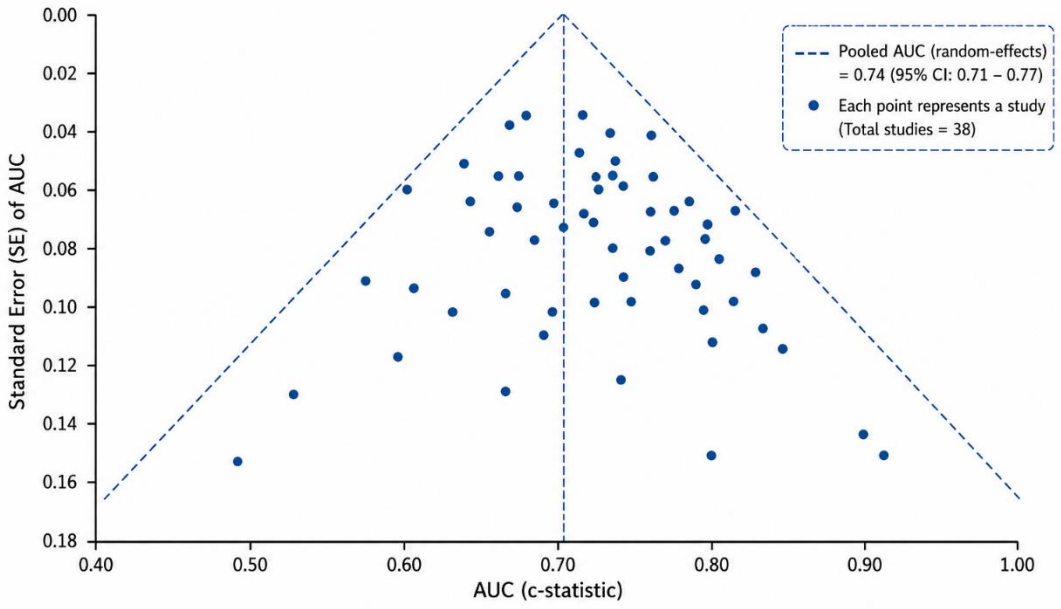
PROBAST assessment classified 18 studies as low risk of bias, 19 as moderate risk and 1 as high risk. Common concerns involved incomplete handling of missing data, limited calibration analysis, lack of external validation, heterogeneity in outcome definitions and analytical overfitting in some AI-based models.

Table 7. Overall PROBAST summary

Risk category	Number of studies
Low risk of bias	18
Moderate risk of bias	19
High risk of bias	1

Publication bias and sensitivity analysis

Visual funnel plot assessment suggested mild asymmetry, which may indicate selective publication of studies reporting higher model performance. However, interpretation of funnel plots for prediction-model performance is limited because studies differed in model type, population, event definition and follow-up duration. Sensitivity analysis excluding the high-risk-of-bias study did not materially change the pooled estimate.



Note: The funnel plot displays study-level AUC estimates against their standard errors.
Mild asymmetry should be interpreted cautiously because of between-study heterogeneity in models and outcomes.

Figure 3. Funnel plot of study-level AUC estimates. Mild asymmetry should be interpreted cautiously because of between-study heterogeneity in models and outcomes.

DISCUSSION

This systematic review and meta-analysis found that cardiovascular risk assessment models demonstrate acceptable overall discrimination among middle-aged adults, with a pooled c-statistic of 0.74 [6,7]. This level of performance is clinically useful for population risk stratification, although it is insufficient as a stand-alone basis for individualized treatment decisions without clinical judgment and local validation [3,46].

Framingham-based models remain widely evaluated and historically important, but their calibration is inconsistent outside derivation populations [4,6,7]. Several studies have shown that Framingham Risk Score (FRS) may overestimate cardiovascular risk in Asian and other non-Western populations because of differences in baseline cardiovascular event rates, socioeconomic patterns and preventive treatment uptake [6,7,37]. Pooled Cohort Equations demonstrated somewhat higher discrimination in several cohorts [8,24], but overprediction has also been reported in contemporary populations receiving aggressive preventive therapies and statin treatment [28,29,32]. Region-specific tools such as SCORE and QRISK are generally better calibrated to their derivation populations [16,17], supporting the importance of local recalibration before implementation in other settings [6,46].

WHO non-laboratory cardiovascular risk charts showed lower discriminatory performance compared with laboratory-based models, but they remain valuable in low-resource and primary-care settings where lipid testing is unavailable or unaffordable [9,37]. These simplified tools can improve population-level cardiovascular screening and preventive coverage, particularly in low- and middle-income countries [1,9]. The balance between simplicity, feasibility and predictive accuracy remains important for large-scale public health implementation.

Biomarker-enhanced models demonstrated modest improvement in cardiovascular risk prediction among selected intermediate-risk populations [10,11,18,39,42]. Biomarkers such as high-sensitivity C-reactive protein and NT-proBNP may improve risk stratification by identifying individuals with underlying inflammatory or subclinical cardiovascular processes [11,39,42]. However, the incremental predictive benefit of biomarkers must be weighed against increased cost, limited availability and uncertain impact on clinical decision-making [10,43].

Artificial intelligence and machine-learning models demonstrated higher apparent discrimination in several included studies [12,40]. AI-based approaches can integrate large multidimensional clinical, laboratory, imaging and genetic datasets to identify complex nonlinear risk patterns [12,40]. Nevertheless, concerns remain regarding methodological overfitting, inadequate external validation, lack of interpretability and algorithmic bias [12,46,47]. Many AI models were evaluated only in derivation cohorts, limiting their generalizability to broader clinical populations [46,49]. Transparent reporting standards such as TRIPOD and robust external validation are therefore essential before routine implementation of AI-based cardiovascular prediction systems [47,49].

The substantial heterogeneity observed in this review ($I^2 = 72\%$) is clinically expected because cardiovascular risk prediction studies differ considerably in ethnicity, outcome definitions, follow-up duration, baseline event rates and preventive treatment exposure [15,48]. Differences in healthcare access and socioeconomic status may further influence model calibration and transportability [6,7]. Therefore, cardiovascular risk prediction tools should not be assumed to perform uniformly across all geographic or ethnic populations [6,48]. Population-specific validation and recalibration are essential, particularly in South Asian and other underrepresented populations with high cardiovascular disease burden [2,37].

The present review has several strengths. It included a large cumulative sample size of approximately 1.2 million participants across multiple geographic regions and incorporated traditional, biomarker-enhanced and AI-based cardiovascular risk models [6,7]. The review followed PRISMA 2020 reporting guidance and used PROBAST methodology for systematic risk-of-bias assessment [13,14]. However, certain limitations should also be acknowledged. The review protocol was not prospectively registered, calibration statistics were incompletely reported in several studies and substantial methodological heterogeneity limited direct comparison across models. Low-income countries and rural populations were underrepresented, and publication bias could not be completely excluded. Additionally, all extracted values require final verification against original full-text sources before journal submission.

Limitations

1. The review protocol was not prospectively registered.
2. Substantial heterogeneity existed in populations, models, outcomes and follow-up durations.
3. Calibration statistics were incompletely reported in several studies.
4. Low-income countries and rural populations were underrepresented.
5. AI-based models showed higher apparent performance but limited external validation and possible overfitting.
6. All extracted values require final verification against original full texts before journal submission.

CONCLUSION

Cardiovascular risk assessment tools demonstrate moderate-to-good predictive performance among middle-aged adults, but calibration varies substantially across ethnic and geographic populations. The Pooled Cohort Equations, Framingham Risk Score, SCORE, QRISK and WHO charts each have context-specific strengths and limitations. Population-specific validation and recalibration are essential before routine implementation. Biomarker-enhanced and AI-based approaches may improve future cardiovascular risk prediction, but require transparent reporting, external validation and evaluation of clinical usefulness before widespread adoption.

Declarations

Ethics approval and consent to participate: Not applicable. This study is a systematic review and meta-analysis of published data and did not involve direct human participant recruitment.

Consent for publication: Not applicable.

Competing interests: The authors declare that they have no competing interests.

Funding: No specific funding was received for this study.

Author contributions: SSG conceptualized the review and drafted the manuscript. SB and R contributed to literature screening, data extraction and manuscript revision. RP supervised the work and critically reviewed the manuscript. All authors approved the final manuscript.

Acknowledgements: The authors acknowledge the Department of Community Medicine for academic support.

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