Research Article

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Comparative Analysis of Cardiovascular disease risk prediction Models: A Population-based Assessment of the Efficacy of ACC/AHA, Framingham, and QRISK.

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ABSTRACT

Objectives: Different models have been developed for the assessment of cardiovascular risks, most of which are based in the western countries. To ensure the applicability of these models in non-Western nations, these models should be studied in such populations. The present study aimed to determine their applicability in a population-based study in Iran.

Methods: The population in this study were the 9704 adults aged 35–65 years included in the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study. Mashhad study was a 10-year cohort on a population in Iran. The main outcomes in this study were the predicted and observed 10-year CVD risks for the population; the tools used were the ACC/AHA, Framingham, and the QRISK models.

Results: Of the research subjects, 5819 (59.97%) were females with an average age of 46.9 ± 7.7 years, and 3885 (40.03%) were men with an average age of 48.3 ± 8.2 years. 1060 (10.9%) CVD events in total were reported by the research participants, with 514 (13.3%) males and 546 (10.7%) women. The estimated CVD risk at baseline was determined by the ACC/AHA to be 5.19±5.91 and 9.27±8.61 for those with and without a CVD incident, the Framingham to be 3.45±4.67 and 6.55±6.45, and the QRISK to be 9.92±8.59 and 10.33±10.52 %.

Conclusions: The performance of the QRISK model was moderately better than the two other models, both in men and women. However, all three models performed underestimation in roughly all risk ranges.

Keywords: *atherosclerotic cardiovascular disease risk, Framingham, ACC/AHA, QRISK.*

INTRODUCTION

Atherosclerotic cardiovascular diseases (ASCVD) are currently one of the significant non-communicable diseases in the Middle East (1). Furthermore, the death rate due to ASCVD is on the rise with a death toll of 17.5 million in 2012 and 17.9 million in 2016, and an expected 22.2 million by 2030 (2, 3). The increased rate of death is considered a result of the increased prevalence of traditional risk factors of cardiovascular diseases (CVD) such as risk obesity, smoking, elevated cholesterol, and diabetes (4). Given the modifiable nature of these risk factors

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and thus preventable death, primary prevention of ASCVDs is crucial. For that purpose, physicians need accurate tools for the risk assessment of individuals in terms of cardiovascular events.

Several models have been introduced over the years for the assessment of ASCVD risk among patients. The generalized Framingham risk score was proposed in the Framingham study in 2008 (5). This tool provides the 10-year estimated risk of CVD events. The QRISK is another risk estimator, primarily developed in 2007 with the aim of including patients of different races living in England and Wales (6). This calculator was later updated in 2018, which is its latest recommended version (7). The other risk-predicting model is the equation developed by the American College of Cardiology and the American Heart Association (ACC/AHA) in 2013 (8).

These risk estimators are inherently different and each provides a score based on different. However, given that the study samples of the original studies were not mainly White Europeans or White Americans, the application of these estimators in different populations needs to be studied. For example, previous studies have shown that the Framingham risk estimators overestimated in some populations (9, 10). Such a drawback has also been reported for the ACC/AHA calculator (11).

On the other hand, a limited number of studies have compared the predictive value of the available risk estimators (12) and few have conducted such a study on the Iranian population (13, 14). Therefore, given the lack of a consensus on what risk estimator fits the Iranian population the most, the present study was conducted to compare the predictive value of the ACC/AHA, Framingham, and QRISK calculators in an Iranian population.

METHODS AND MATERIALS

Study population

The present study was conducted on the data derived from the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study, a cohort conducted in three regions of a city in North-Eastern Iran, Mashhad. The study design of the MASHAD cohort has previously been reported (15). The study was conducted in two phases, initiated in 2010 and terminated in 2020. The data in this cohort included demographic, anthropometric, and lifestyle data which were collected during formal appointments with the eligible participants. The initial number of participants yielded by stratified cluster random sampling was 11,247, which after the exclusion of non-responders and prevalent cases of coronary artery disease (CAD), stroke, and peripheral arterial diseases, and omitting cases due to the unavailability of data required for risk assessment, the total number of subjects included 9704 adults between the ages of 35 and 65 years.

Risk model calculations

The present study used three risk estimators to obtain the 10-year predicted CVD risk for the subjects: the 2008 the ACC/AHA (8), Framingham (5), and the QRISK3 risk predicting algorithm (7). The data required by these models included gender, age, race, height, weight, systolic blood pressure, diastolic blood pressure, drug history of hypertension, statins, aspirin, atypical antipsychotic medication, steroid, use of smoking status, history of vascular disorders, diabetes, chronic kidney disease, atrial fibrillation, migraines, rheumatoid arthritis, systemic lupus erythematous (SLE), severe mental illness, total cholesterol, HDL cholesterol, and LDL cholesterol. An overview of the variables used, the risk range recommended, and outcomes defined for each of these risk prediction models is shown in Table 1.

Data collection

Gender, age, and race were according to the self-report. Height and weight were measured during the physical examination appointments using standard a measurement device and technique. Furthermore, systolic and diastolic blood measures were the means of the second and third sequential measurements while satisfying the conditions for standard measurements. The medical, drug, and social history of the participants were obtained in the interview appointments by two certified healthcare professionals and a nurse. Furthermore, the biochemical reports of patients were obtained by testing blood and mid-stream urine samples. Diabetes was defined as FBG ≥ 126 mg/dL or being treated with existing oral hypoglycemic agents or insulin. A current smoker was defined as smoking cigarettes at least once a day; an ex-smoker was formerly a daily smoker, but someone who currently did not smoke, and a non-smoker was a person who belonged to none of the groups.

Atherosclerotic cardiovascular events

According to the definition provided by the WHO, stroke was defined in this study as "rapidly developing signs of focal or global disturbance of cerebral function lasting (24 h) with no apparent cause other than of vascular origin (16)." Also, a CAD outcome was determined using a history of myocardial infarction or angina pectoris, or the presence of a definitive Q wave in an electrocardiogram using the Minnesota Code.

Statistics

The chi-square, analysis of variance (ANOVA), and Kruskal-Wallis tests were used to report distribution differences for qualitative and quantitative (normal and non-normal) data, respectively. To assess the performance of the three risk prediction models, we assessed the calibration of each model in the total population, and men and women separately. For this purpose, the Loess calibration plots were used for each

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decile of predicted risk for each risk model. The most optimal calibration is observed once a linear equation with slope=1 is obtained. The significance level in this study was defined as less than 0.05. The statistical analyses were conducted using SPSS version 21 and R version 3.4.2.

Ethics

The MASHAD study was approved by the Ethics Committee of Mashhad University of Medical Sciences.

RESULTS

Baseline characteristics

This study was primarily conducted on 9704 adults between the ages of 35 and 65 years. (Figure 1). 3885 (40.03%) of the study subjects were males and with an average age of 48.3 ± 8.2 years; 5819 (59.97%) were females with an average age of 46.9 ± 7.7 years. Regarding the smoking status, 1060 (27.3%) of the men and 1032 (17.7%) of the women were current smokers. Among the men, 521 (13.7%) had diabetes, 1140 (29.4%) were on anti-hypertensive medication, and 668 (17.2%) were categorized as obese. On the other hand, 848 (14.8%) of the women had diabetes, 1895 (32.6%) were hypertensive, and 2249 (38.7%) were obese (**Table 1**). The female and male participants were significantly different in the variables studies except for the FBG and diabetes status (p-value= 0.26 and 0.15, respectively). A total of 1060 (10.9%) CVD events were reported among the study subjects with 514 (13.3%) among the men and 546 (10.7%) among the women (**Table 2**). At baseline, the estimated CVD risk for those without a CVD event and those with a CVD event was calculated 5.19±5.91 and 9.27±8.61 for the ACC/AHA, 3.45±4.67 and 6.55±6.45 for the Framingham, and 9.92±8.59 and 10.33±10.52 for the QRISK. These measurements were significantly different between the two groups for all three risk estimators (p-value <0.001 for all) (**Table 3**).

Table 1. A summary of the risk estimation models used in this study.

CVD estimation model	Variables used	Risk ranges recommended	Outcomes defined
ACC/AHA (1)	Sex, age, race, total cholesterol, HDL cholesterol, systolic blood pressure, receiving treatment for high blood pressure, diabetes, smoking	Low risk: <5% Borderline risk: 5-7.4% Intermediate risk: 7.5-19.9% High risk: ≥20%	acute myocardial infarction, coronary heart disease death, and fatal or non-fatal ischemic stroke
Framingham (2)	Age, sex, smoking status, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure being treated with medicines	Low-risk: <10% Intermediate risk: 10-19% High risk: ≥20%	coronary death, myocardial infarction, coronary insufficiency, and angina, cerebrovascular events, peripheral artery disease, and heart failure
QRISK (3)	Age, sex, ethnicity, smoking, diabetes, Angina or heart attack in a 1st degree relative < 60?, CKD, AF, on blood pressure treatment, migraines, RA, SLE, severe mental illness, on atypical antipsychotic medication, steroid drug history, ED, cholesterol/HDL ratio, systolic blood pressure, BMI	Low-risk: <10% Intermediate risk: 10-19% High risk: ≥20%	coronary heart disease, ischaemic stroke, or transient ischaemic attack

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Table 2. The demographic, anthropometric and clinical features in total population by sex.

		Male (3885)	Female (5819)	P value
Age, y		48.3 ± 8.2	46.9 ± 7.7	<0.001
Marriage	Single	19 (0.5%)	40 (0.7%)	<0.001
	Married	3834 (98.7%)	5204 (89.4%)	
	Divorced	17 (0.4%)	117 (2%)	
	Widow	14 (0.4%)	458 (7.9%)*	
Job status	Employed	2860 (73.6%)	745 (12.8%)	<0.001
	Unemployed	330 (8.5%)	4815 (82.8%)*	
	Retired	694 (17.9%)	256 (4.4%)	
Education	Low	1609 (41.4%)	3679 (63.3%)	<0.001
	Moderate	1600 (41.2%)	1748 (30.1%)	
	High	676 (17.4%)*	385 (6.6%)	
Smoking status	Non smoker	2236 (57.6%)	4418 (75.9%)	<0.001
	Ex-smoker	589 (15.2%)*	369 (6.3%)	
	Current smoker	1060 (27.3%)	1032 (17.7%)	
BMI, kg/m2		26.4 ± 4.1	28.8 ± 4.7	<0.001
SBP, mmHg		121.5 ± 16.4	120.5 ± 18.6	0.01
DBP, mmHg		79.8 ± 10.4	78.2 ± 12.4	<0.001
Glucose (FBG), mg/dL		90.5 ± 35.2	91.5 ± 37.6	0.26
Cholesterol, mg/dL		186.4 ± 37.2	193.7 ± 39.1	<0.001
TG, mg/dl		147.8 ± 97.7	135.8 ± 85.8	<0.001
HDL, mg/dl		39.7 ± 9.1	44.8 ± 9.7	<0.001
LDL, mg/dl		113.4 ± 34.3	118.4 ± 35.4	<0.001
Hs-CRP, mg/L		3.4 ± 7.7	4.2 ± 8.7	<0.001
PAL		1.4 ± 0.30	1.6 ± 0.22	<0.001
ACC/AHA		7.8 ± 7	3.3 ± 4	<0.001
Framingham		6.4 ± 5.5	1.5 ± 2.3	<0.001
QRISK		13.3 ± 9	7.5 ± 7	<0.001
Diabetes	No (8195)	3294 (86.3%)	4901 (85.2%)	0.15
	Yes (1369)	521 (13.7%)	848 (14.8%)	
HTN	No (6640)	2731 (70.6%)	3909 (67.4%)	<0.01
	Yes (3035)	1140 (29.4%)	1895 (32.6%)*	
Obesity	No (6768)	3207 (82.8%)	3561 (61.3%)	<0.001
	Yes (2917)	668 (17.2%)	2249 (38.7%)*	
Mets	No (5934)	2719 (70.1%)	3215 (55.4%)	<0.001
	Yes (3748)	1157 (29.9%)	2591 (44.6%)*	

Abbreviations:

Student t-test was used for the analysis.

* significance in this point

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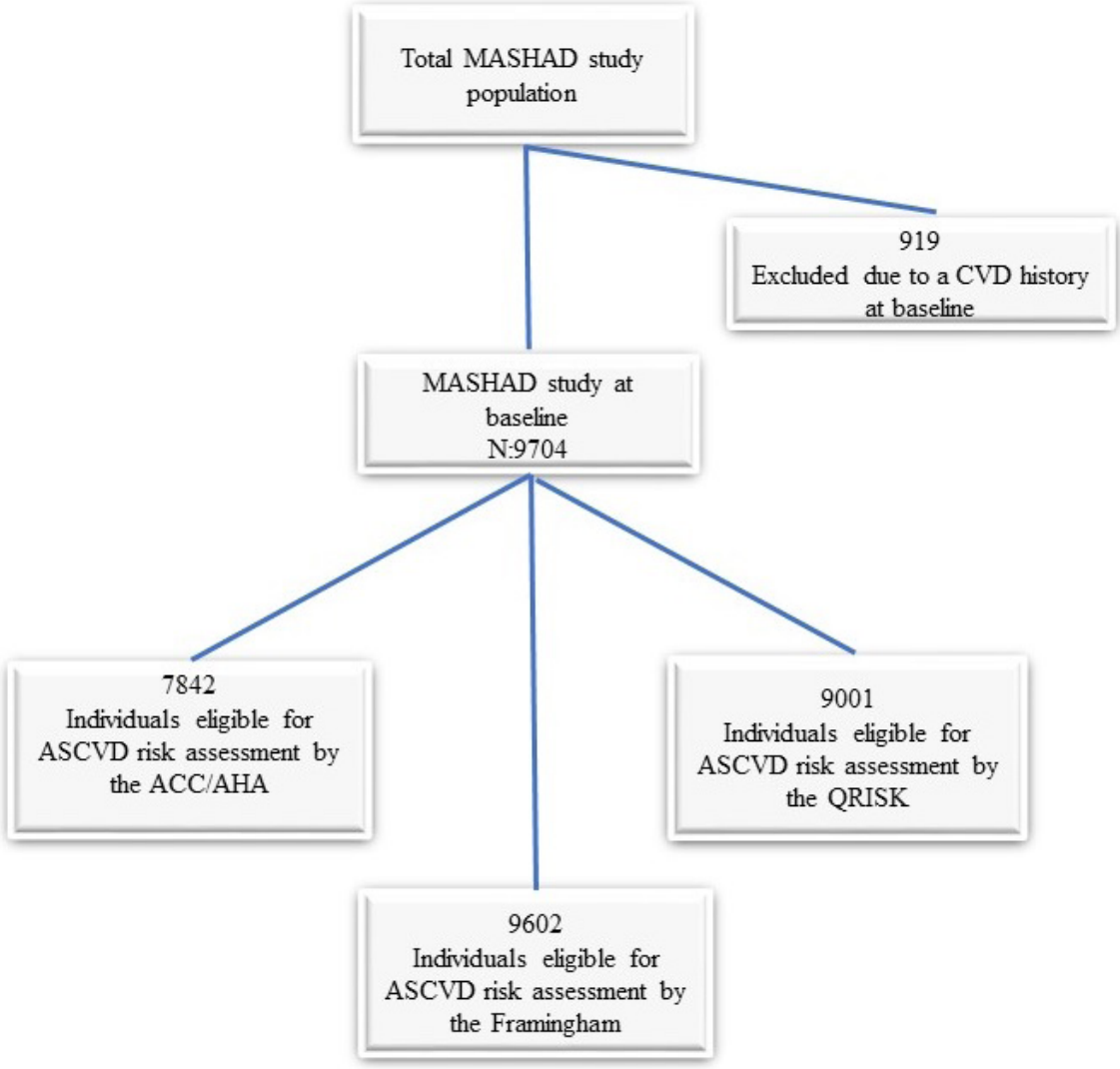
Table 3. Baseline mean of risk scores according to event.

		ACC/AHA	Framingham	QRISK
CVD total	Healthy (8644)	5.19±5.91	3.45±4.67	9.92±8.59
	CVD (With death) (1060)	9.27±8.61	6.55±6.45	10.33±10.52
p-value		<0.001	<0.001	<0.001

Figure 1. The overview of patients included for risk assessment by each of the three models.



Calibration

The QRISK model showed the most accurate concordance between the predicted and observed risks. The discordance between the observed and the predicted risks for the QRISK model peaked in risks above 23% (Figure 2G). Gender-wise, Framingham and ACC/AHA models showed minimal discordance among the men while for the women, QRISK was the only model with acceptable discrepancy. Unlike the men, the discordance in the QRISK model for women were the greatest in 2-3 and 6-10 risk ranges. Interestingly, the risks predicted by Framingham and ACC/AHA models were underestimated in almost all risk ranges in both genders, while QRISK showed minimal underestimation up to a point and then performed overestimation as the risk range increased among the men and in total subjects (Figure 2A-I). Furthermore, Loess calibration plots showed the greatest agreement between the estimated and observed risks for the QRISK model in the total population, and among the men and women separately (Figure 3). Overall, the present study revealed that compared to the QRISK model, the Framingham and the ACC/AHA models showed unacceptable performance particularly among the women.

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Figure 2. The predicted and observed 10-year cardiovascular risk among the study population by deciles of predicted risk, for the ACC/AHA, Framingham, and QRISK estimators.

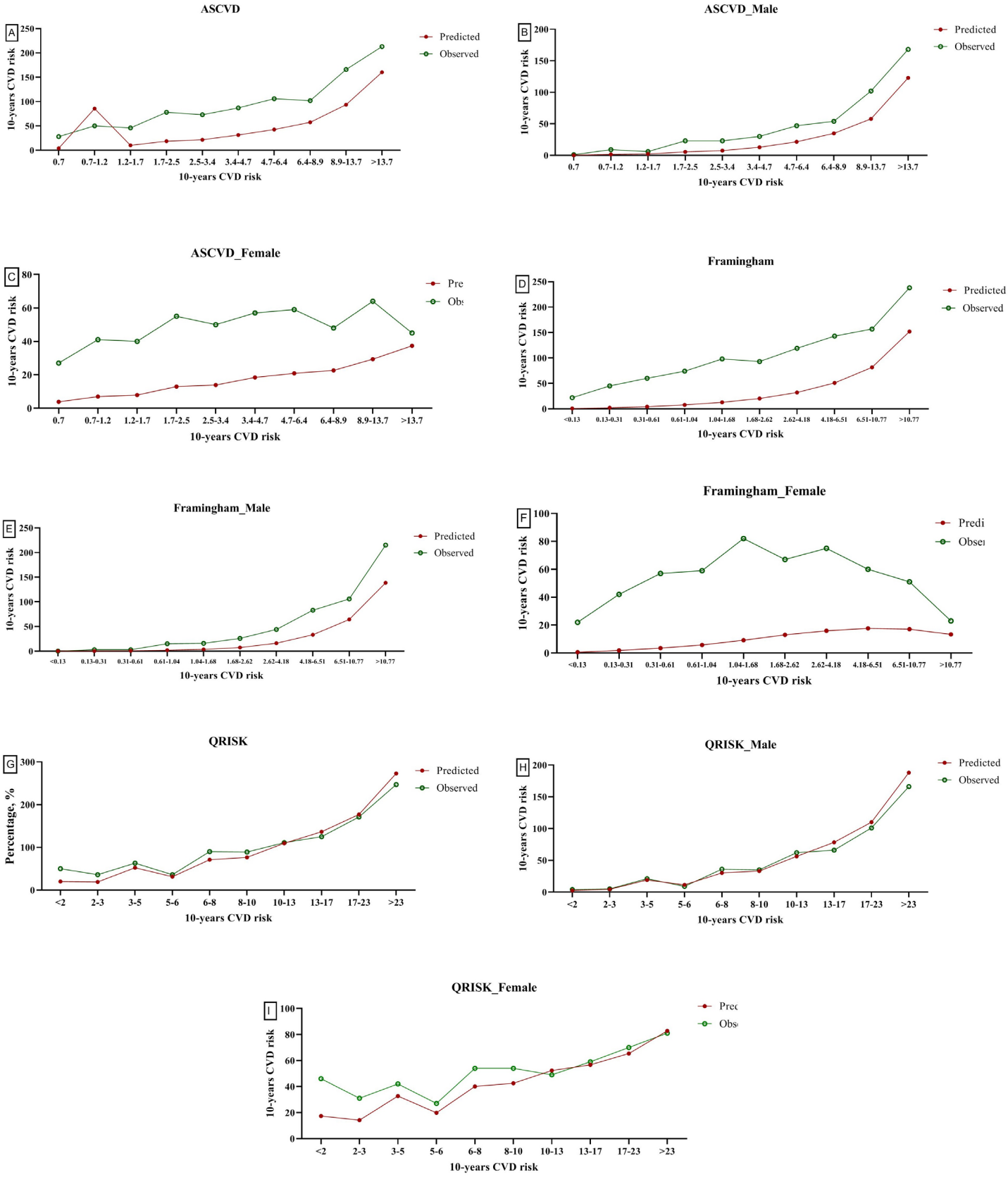

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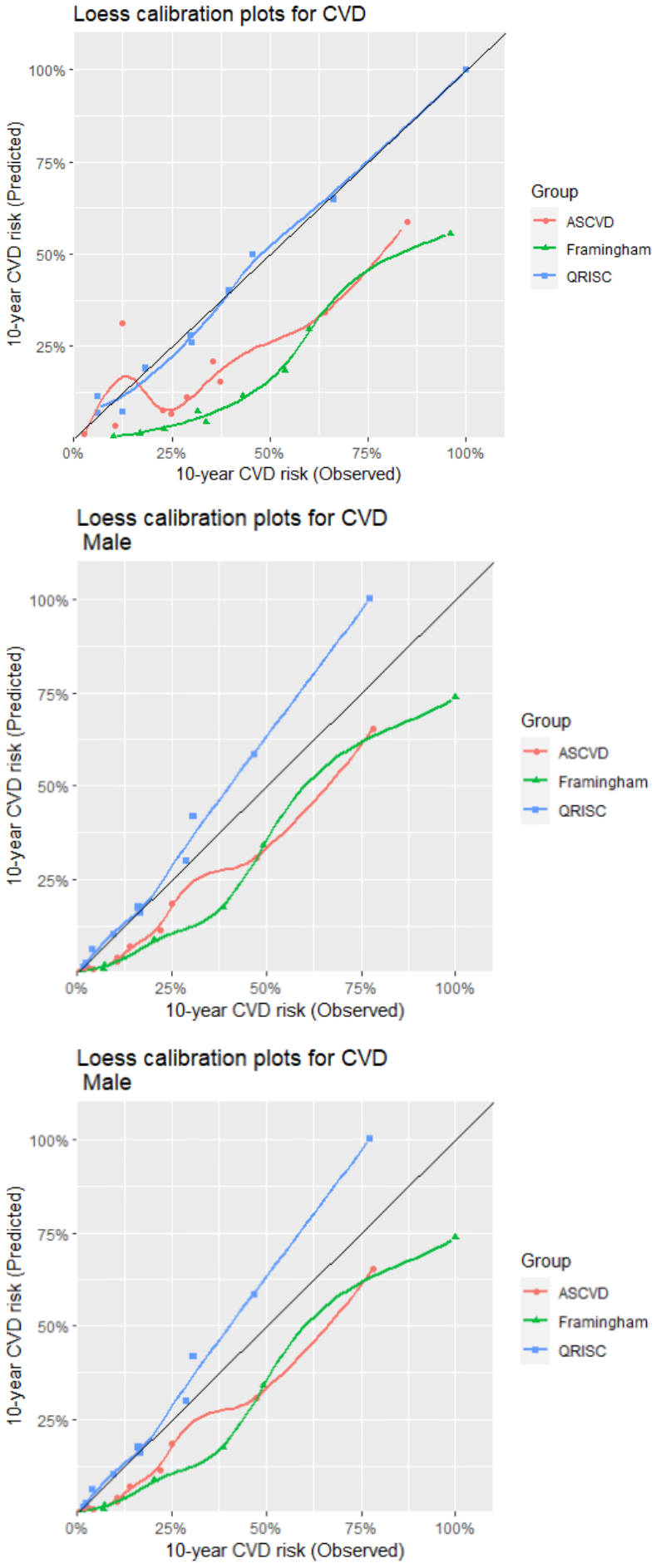
Figure 3. Loess calibration plots for the three CVD risk estimators in among females, males, and the total subjects.



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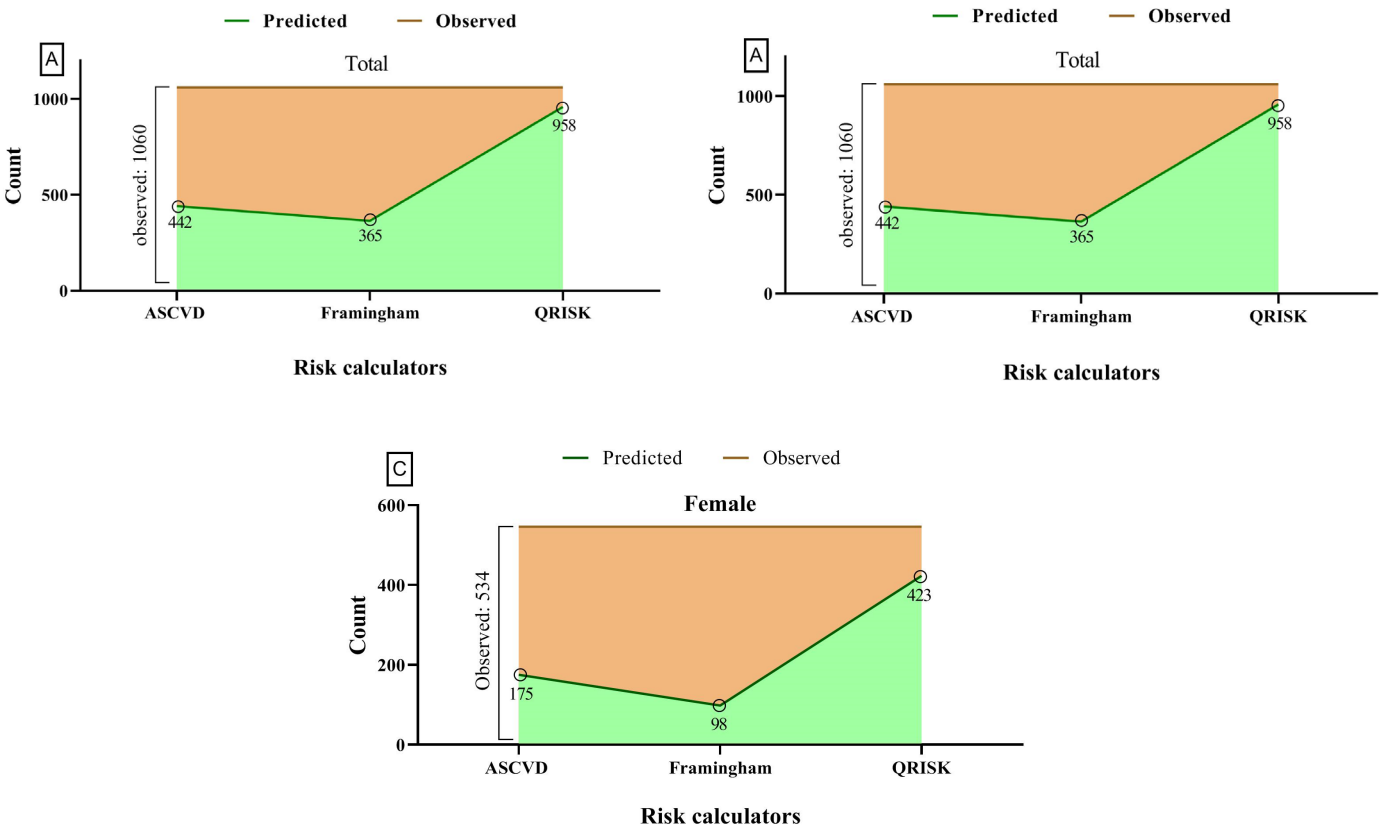
Risk classification

Using the three risk estimation models, 331 (4.2%), 142 (1.4%), and 1403 (15.5%) were considered to be at high risk for a CVD event in the next 10 years by the ACC/AHA, Framingham, and the QRISK models, respectively. Accordingly, the ACC/AHA model predicted the largest portion of CVD events (24.1%) compared to the two other models. QRISK predicted a ≥20% risk of CVD event for 1403 individuals, of whom 1112 (79.2%) did not have such an experience. Figure 4 shows the comparison between the number of predicted and observed cases by the three models in the total population, men, and women. According to this figure, QRISK covered the highest and the Framingham covered the lowest number of the observed cases.

Figure 4. The performance of the three CVD risk estimators in predicting the observed CVD events among the total subjects, males, and females.



DISCUSSION

The present study compared the clinical performance of three CVD risk prediction tools commonly used in Iran, namely the ACC/AHA, Framingham, and the QRISK ASCVD risk prediction models. The results showed that none of these tools performed ideally among the population studied. None of these models have primarily been modeled based on an Iranian population; hence, the perfect performance of these risk estimators on our population is unexpected.

Given that the ASCVD risk assessment is a measure for clinical decision making on initiating statin therapy, the models used should be precisely calibrated. The findings of the present study showed all the three models studied in this study are not calibrated for the population studied. It is anticipated that the risk prediction models will be miscalibrated when used in populations other than the ones they were originally developed for (17). The imperfect calibration may be attributed to variations in the attributes of the new populations, such as varying degrees of baseline risk, to which the risk prediction model is applied. Overall, the QRISK risk assessment model showed a considerably better performance than the two other models.

Although the QRISK model showed the highest concordance, its performance was still limited. Given that QRISK model labels patients with an ASCVD score ≥ 20% as high risk, the present study showed that this threshold is very low for our population. Applying these risk ranges to our population resulted in the highest number of high-risk patients compared to the other two models. However, only a minority of these patients experienced a CVD event. This raises the importance of the unknown

balance between the risks and benefits of treating patients at lower risks of CVD (18).

Collectively, the results showed that QRISK was the most accurate among the three models in this study for the prediction of CVD events in the male and female population separately, or the total population. However, this study highlighted that even QRISK performed considerable underestimation at some risk ranges. Motamed et al. conducted a study on an Iranian population similar to the present study, the results of which showed a better performance for the ACC/AHA model (13). However, it should be mentioned that they did not include the QRISK model in their comparison.

Several studies in different continents have shown a discrepancy between the predicted and the observed CVD risk for the ACC/AHA model (19-23). Some attribute such a discordance to the more frequently applied cardiovascular prevention measures such as statin therapy. However, some studies that adjusted the use of statin mediation also showed such a discrepancy (20). Furthermore, some studies have denied a possible role for the preventive measures to lead to such a discrepancy (24).

Furthermore, this study showed all three models worked more accurately among the men than in women. This, however, is in contrast to another Iranian cohort study which reported a better performance for the ACC/AHA and Framingham models in women, than in men (13). On the other hand, an older similar Iranian study in 2014 showed poor calibration for the ACC/AHA model for both sexes (19).

The present study had some strengths. The sample size in this study was relatively large compared to the previous similar studies, which when accompanied by a long follow-up, resulted in robust data. Furthermore, we included the QRISK model, which was commonly not included in the previous national studies. However, this study also had some limitations. The CVD outcomes were determined through medical history and the possibility of missing a silent MI (which is diagnosed with ECG) cannot be denied. Also, the number of individuals with missing data for the analysis were considerable, which may have impacted the final results.

CONCLUSION

The present study showed that the QRISK risk prediction model was a better tool for the assessment of the ASCVD risk among the population in this study. Furthermore, this study showed that the underestimation observed in the two other models (i.e., the Framingham and the ACC/AHA) was considerably more significant among the women. Therefore, it seems that using the QRISK risk assessment model fits better to the population studied in this work and further adjustments should be made to decrease the underestimation.

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Declarations section

Ethical Approval and Consent to participate: this project supports by Mashhad University of Medical Sciences. Funding number: 4000030 and ethical approval cod: IR.MUMS.MEDICAL.REC.1398.228. All individuals were well-informed, and their written consent was drawn.

Competing interests: The Authors declare that there is no conflict of interest.

Consent for publication: It is not applicable to the Consent of Image Publication for this manuscript. The figures were designed only in this manuscript for presenting the results of the current paper.

Availability of data and materials: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Authors' contributions

Vahid Mahdavizadeh, Moloud Asadi, Susan Darroudi, Mostafa Mansouri (wrote manuscript)

Reihaneh Alizadeh, Reihaneh Aryan, Hussein Ahmed Shamkhi Alnayyef (data gathering)

Susan Darroudi, Nasrin Talkhi, (Data analysis and study design)

Habibollah Esmaeili, Majid Ghayour-Mobarhan (study design, scientific edition)

Mohsen Moohebati, Bahram Shahri (corresponding author, confirm patients)

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