Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART Modifiable Risk Score

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Aims	Summating risk factor burden is a useful approach in the assessment of cardiovascular risk among apparently healthy individuals. We aimed to derive and validate a new score for myocardial infarction (MI) risk using modifiable risk factors, derived from the INTERHEART case–control study (*n* = 19 470).
Methods and results	Multiple logistic regression was used to create the INTERHEART Modifiable Risk Score (IHMRS). Internal validation was performed using split-sample methods. External validation was performed in an international prospective cohort study. A risk model including apolipoproteins, smoking, second-hand smoke exposure, hypertension, and diabetes was developed. Addition of further modifiable risk factors did not improve score discrimination in an external cohort. Split-sample validation studies showed an area under the receiver-operating characteristic (ROC) curve *c*-statistic of 0.71 [95% confidence interval (CI): 0.70, 0.72]. The IHMRS was positively associated with incident MI in a large cohort of people at low risk for cardiovascular disease [12% increase in MI risk (95% CI: 8, 16%) with a 1-point increase in score] and showed appropriate discrimination in this cohort (ROC *c*-statistic 0.69, 95% CI: 0.64, 0.74). Results were consistent across ethnic groups and geographic regions. A non-laboratory-based score is also supplied.
Conclusions	Using multiple modifiable risk factors from the INTERHEART case–control study, we have developed and validated a simple score for MI risk which is applicable to an international population.
Keywords	Risk score • Myocardial infarction • Prediction • Ethnic • Global • Risk factors

Introduction

The World Health Organization estimates that in 2010, coronary heart disease (CHD) will be the leading cause of death globally, causing 30.8% of all deaths per annum and with about 80% of all cardiovascular disease deaths occurring in developing countries.[1] The INTERHEART case–control study has shown that nine modifiable risk factors account for more than 90% of the population attributable risk for acute myocardial infarction (MI) globally, a finding which was consistent in all regions of the world.[2]

Risk stratification is widely suggested as best practice in the management of individual cardiovascular disease risk.[3,4] Coronary heart disease risk estimation tools estimate the effects of multiple risk factors to obtain an overall estimate of a person's own risk of disease. Such tools have been shown to be more accurate at predicting risk than physician assessment alone.[5] A number of risk estimation tools are currently in use, such as the functions based on the Framingham cohort[6] and the European SCORE.[7] However, both tools use a limited number of risk factors in their risk estimation, and neither includes lifestyle factors such as dietary

intake and physical activity. Modifiable lifestyle risk factors are of importance to clinicians and patients alike, and there is an inherent appeal to develop a score which integrates such factors.

The INTERHEART study was a large standardized case–control study involving cases of first MI from 52 different countries, and their sex- and age-matched controls ($\pm$ 5 years).[2] Nine modifiable risk factors were found to have a globally consistent association with MI: apolipoprotein levels, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, dietary factors, physical exercise, and alcohol consumption. This study aims to examine the utility of the modifiable CHD risk factors in risk assessment and to derive and validate an appropriate 'modifiable risk' equation using the multifactor data collected in INTERHEART. The consistency of the association of this risk factor equation with MI is then assessed within both the INTERHEART population, by ethnicity and geographical area, and an external validation cohort. 'Non-laboratory' and lipoprotein-based equations are also derived.

Methods

Details of the participants and data collection procedures used are described in detail elsewhere.[2] Briefly, INTERHEART was a case–control study which recruited cases of first acute MI admitted to coronary care or equivalent units, and at least one sex- and age-matched (within 5 years) control, who had no history of heart disease. Participants were recruited from 252 centers in 52 countries worldwide.

Data on lifestyle and other risk factors were collected by a structured questionnaire, and a standardized physical examination was performed.[2] Non-fasting blood samples were drawn from every participant, centrifuged within 2 h of extraction, and frozen immediately at -20 or $-70°$C. For cases, samples were to be drawn within 24 h of symptom onset, although due to delayed presentation, especially in lower income countries, this was only achieved in two-thirds of cases. Samples were shipped in liquid nitrogen to the core laboratories in Hamilton, Canada and Beijing, China. Apolipoprotein concentrations were measured using immunoturbidmetric assays (Roche/Hitachi 917 analyser with Tina/quant Apo B version 2 and ApoA1 version 2 kits; Roche Diagnostics, Mannheim, Germany).[8]

INTERHEART was approved by the appropriate Ethics Committee in all participating study countries and centres. Informed consent was provided by all participants before taking part in the study.

Statistical methods

Stage 1: Assessment of each proposed risk factor

After data cleaning and exclusion of subjects with missing risk factor data, the data set was split into a 2/3s derivation set and a 1/3 test set.[9] Splitting of the data was performed in a paired manner, to maintain the matched nature of the data, and was stratified by sex and geographic area.

Using the 2/3s derivation set, each of the nine modifiable risk factors was examined in a simple logistic regression model, adjusting for sex, age, and geographic region, and with acute MI as the dependent or outcome variable. The variables relating to each risk factor were chosen from the questionnaire data based both on the variables used in previous INTERHEART analyses and publications[2,10–12] and on the expected clinical utility of the variable. Categorical variables were examined using design variables. Proposed variables were retained if they achieved the set criterion of $\alpha \leq 0.05$ for statistical significance in the simple model.

Stage 2: Creation of risk factor definitions to be used in the INTERHEART Modifiable Risk Score

The following risk factor definitions were selected. The apolipoprotein B:A1 ratio (included as a continuous variable in the final model and as quartiles for the final score) was selected as the measure of lipid status of choice. A secondary model (the 'cholesterol' score) replaced apolipoproteins with low-density lipoprotein and high-density lipoprotein measurements, for use in regions where apolipoprotein testing is not readily available. Current smokers were defined as individuals who had smoked any tobacco in the last 12 months, including those people who had quit within that time. Current smoking was categorized into number of cigarettes or beedies smoked per day. Former smokers were those persons who had quit 12 or more months prior to the interview. Second-hand smoke was defined as exposure for one or more hours per week, vs. less or no exposure. Hypertension and diabetes were both defined by self-report. Waist–hip ratio was chosen as the optimal index of abdominal obesity (included as a continuous variable in the final model and as quartiles for the final score).[12]

Psychosocial factors included details of work/home stress, depression, perceived locus of control, incidence of adverse life events, and financial stress. Diet-related variables chosen were those which had previously been identified as having the strongest association with case status.[13] Consumption was measured in the frequency of eating the foodstuff in question, and the diet variables were ultimately included as dichotomous variables. Physical exercise was defined as the level of regular physical activity during leisure time. Family history was defined as a history of MI in either parent, at any age. This variable was only used in the 'non-laboratory'-based score. A variable on alcohol was not included, because of the potential for a 'mixed' public health message.

Stage 3: Calculation of the risk equation

Methods similar to those of Sullivan *et al.*[14] from the Framingham Heart study were used to develop the IHMRS. The risk factor variables were examined in multivariable unconditional logistic regression models, with MI case status as the dependent variable. Variables were added to the multivariable model in a forward stepwise method, with variable entry chosen manually by the investigators as per the relative importance and effect size attributed to each risk factor from the INTERHEART study. The criterion for statistical significance was set at $\alpha \leq 0.05$. The effect of interaction terms was assessed, with terms relating to risk factor*age/sex included in the model building. Model fit was checked at each step using the area under the receiver-operating characteristic (ROC) curve *c*-statistic, and the integrated discrimination index (IDI) was used to measure the improvement in model discrimination as variables were added.[15] INTERHEART used a matched design for age ($\pm$ 5 years) and sex, with the result that the true effects of age and sex cannot be accurately estimated in this analysis. Nevertheless, we wished to include an age- and sex-related variable, to maintain optimal face validity of the score. Furthermore, because matching was not achieved in all recruited subjects, an effect of both age and sex was evident on logistic regression analysis. Therefore, unconditional logistic regression was used to optimize the use of the data, and all models were adjusted by age and sex. A single age and sex variable was created which classified men and women into younger vs. older groups (men younger than 55 and women younger than 65, or else older) based on epidemiological evidence of this age gap of risk from both INTERHEART[2] and the Framingham study.[16,17] After the risk factor variable panel for the equation was selected, a base or reference category was assigned for each variable. The other categories were then valued on how far they were from the base category and this value was weighted by

multiplying it by the β coefficient from the multiple regression equation. The points were derived by multiplying by an empirical constant and rounding to the nearest integer, for ease of use of the risk score. Three models were developed: a 'short' score, a 'full' score, and a 'non-laboratory'-based score. A secondary model, the 'cholesterol' score, was also created. Analyses were performed using Intercooled Stata 9 (StataCorp, TX, USA).

Stage 4: Internal validation

Validation of the scores was assessed in the 1/3 test set using measures of calibration and discrimination. Calibration is the agreement between the expected probabilities of disease and the actual event rate seen in the test set and refers to the extent that bias influences the model. Calibration is often assessed by the Hosmer–Lemeshow test.[18] However, the results of the Hosmer–Lemeshow test can vary by the statistical software used[19] and the test is over-sensitive to small deviations in fit as the sample size increases.[20] To address these problems, the deciles of risk were compared separately and displayed as a calibration plot of the observed vs. expected events. Discrimination, or refinement, is a measure of a model's ability to rank subjects correctly in terms of risk. Model discrimination (i.e. the model's ability to rank persons appropriately, from low to high risk) was assessed using the c-statistic from ROC testing,[21] and further estimates of model discrimination were made on subgroups of the population. Measures of global fit were also examined, including the Akaike information criteria,[22] the Bayesian information criteria,[23] and the Brier score.[24] The Brier score quantifies the overall accuracy of predictions and ranges from 0 (perfect accuracy) to 0.25 (worthless). Competing risk equation scores were examined and compared using these measures, and the final model was determined as that which provided the best fit in terms of the ROC c-statistic, with due regard to the aim of model parsimony.

Stage 5: External validation

The final score (termed the IHMRS) was assessed in an independent study population. EpiDREAM is an international prospective cohort study which includes follow-up data on 18 990 participants who were screened for eligibility for the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) clinical trial.[25] Subjects were recruited from 21 countries and 191 centers, from North America, South America, Europe, Australia, and Asia. All participants completed a questionnaire with information collected on medical history, physical activity, and diet. Furthermore, all participants underwent a 75 g oral glucose tolerance test, and physical measurements including weight, height, and waist and hip circumference were taken using a standardized protocol. Six thousand and eight hundred subjects (35.8%) had impaired fasting glucose or impaired glucose tolerance (5269 of whom were randomized into DREAM), 2563 subjects (13.5%) had type-2 diabetes, and 9627 subjects (50.7%) were normoglycaemic. The IHMRS was evaluated against incident MI ($n = 95$) and incident CHD (including MI, new angina, and revascularization) ($n = 289$). The models were adjusted for trial status and region.

Results

Data from 27 043 INTERHEART participants were available for analysis, 14 605 controls and 12 438 cases. When those participants with missing data were excluded, the final number available for analysis was 19 470. Of those excluded with missing data, 5714 had missing apolipoprotein data (no blood sample had been taken). After data splitting, there were 12 772 subjects in the derivation set, 5349 cases (41.9%) and 7423 controls

(58.1%); and 6698 subjects in the test set, 2868 cases (42.8%) and 3830 controls (57.2%); 75.3% of the participants in the derivation set were males ($n = 9615$), compared with 77.2% in the test set ($n = 5,168$). Mean age in the derivation set was 57.46 years (standard deviation or SD 12.13) and in the test set, 57.16 (SD 11.99).

Modifiable risk factors contributing to CHD risk which were identified in the INTERHEART study (Table 1) were examined in univariable and multivariable logistic regression models. Variables which were not retained in the multivariable model included 'adverse life events' (which did not maintain statistical significance in the multivariable model), and 'locus of control' and financial stress variables (excluded because there was a large missing data burden and little incremental predictive ability with these factors). Interaction terms for both age and sex with hypertension, diabetes, and apolipoprotein B:A1 ratio were statistically significant in the multivariable model, but were omitted from the final model because of the lack of incremental value associated with their inclusion, and the potential complexity of a risk score were they to be retained. The risk factors were then assessed for their incremental predictive ability with their addition to the final model (Table 2). A risk model including age, sex, apolipoproteins,

Table 1 Variables examined in the risk score derivation process

Variable	Definition
Apolipoprotein B: A1 level	Included in the model as a continuous variable, split into quartiles at the score development stage
Smoking status	Never smoked, former smoker (ceased smoking 12 or more months ago), or current smoker (smoked regularly in the last 12 months: by average number of cigarettes smoked daily)
Second hand smoke exposure	More than 1 h of passive smoke exposure per week
Diabetes mellitus	Self-report of diabetes mellitus
Hypertension	Self-report of hypertension
Abdominal obesity: waist-to-hip ratio (WHR)	Included in the model as a continuous variable, split into quartiles at the score development stage
General stress	How often have you felt stress in the last year? Never/some periods OR several periods/permanently
Depression	During the past 12 months, was there ever a time when you felt sad, blue, or depressed for 2 weeks or more in a row?
Dietary factors	Salty foods or snacks ≥1 time a day (%) Deep fried foods/snacks/fast foods ≥3 times a week (%) Fruit: ≥1 time fruit daily Vegetables: ≥1 time vegetables daily Meat and poultry: ≥2 times daily
Physical activity	Activity during leisure time: none or mild, or moderate or strenuous

smoking, hypertension, and diabetes had an ROC *c*-statistic of 0.72 [95% confidence interval (CI): 0.72, 0.73]. Addition of further variables significantly increased the ROC *c*-statistic to 0.73 (95% CI: 0.72, 0.74) (Pearson's χ^2 54.87, $P < 0.0001$); however, it did so at the expense of model parsimony. Four risk score versions were therefore created. The two scores for consideration as the primary INTERHEART risk scores were a 'short' score, which was the most parsimonious, and a 'full' score, including all the risk factors. Two supplemental scores were derived: a 'cholesterol' score, for settings in which laboratory measurements of apolipoproteins were not available, and a 'non-laboratory-based' score, which did not include any lab-based measures of lipid status. *Table 3* shows the internal validation for the four scores. The ROC *c*-statistic in the 1/3 test set was greater for the 'full' score than for the 'short' score (Pearson's $\chi^2 = 6.28$, $P = 0.012$), but the absolute difference in *c*-statistic was small, and was outweighed by the loss of model parsimony and increased complexity of the 'full' model. Therefore, the 'short' score was accepted as the primary IHMRS, and *Table 4* shows the odds ratios for this IHMRS model. Although for clarity in this table, the apolipoproteins are presented as quartile 4 vs. quartile 1 comparisons, these were included as continuous variables in the final model. Similarly, smoking status is shown as current or former smoking, whereas current smokers were included in the final model as categorical variables by the number of cigarettes smoked. Checks of

Table 2 Building the multivariable model: forward stepped approach, using logistic regression in the derivation set, with case status as the dependent variable

Model examined	ROC *c*-statistic (95% confidence interval)	Integrated discrimination index (z, *P*-value)[a]	Brier score
Model adjusted for region and the age/sex variable	0.559 (0.549, 0.569)	—	0.241
Above + apo B:A1 ratio	0.633 (0.623, 0.643)	0.034 (z = 3.828, P < 0.001)	0.232
+smoking variables	0.681 (0.672, 0.690)	0.048 (z = 1.759, P < 0.001)	0.221
+diabetes	0.702 (0.693, 0.711)	0.024 (z = 1.759, P = 0.039)	0.215
+hypertension	0.719 (0.710, 0.728)	0.019 (z = 1.290, P = 0.099)	0.210
+abdominal obesity	0.721 (0.712, 0.730)	0.004 (z = 0.257, P = 0.399)	0.209
+dietary factors	0.726 (0.717, 0.735)	0.007 (z = 0.359, P = 0.359)	0.208
+physical activity	0.727 (0.718, 0.736)	0.001 (z = 0.049, P = 0.480)	0.207
+psychosocial factors	0.733 (0.718, 0.736)	0.008 (z = 0.364, P = 0.358)	0.205

Each step shows the associated change in model discrimination. *Note.* Independent variables are added in a forward stepwise manner.
[a]IDI is for each successive model when compared with the preceding model.

collinearity on the final model revealed a variance inflation factor of 1.2, indicating that collinearity was not present.[26,27] The 'full', 'non-laboratory', and 'cholesterol' versions of the score are available in the Supplementary material online, *Tables S1–S3*.

The probability of MI increased as the IHMRS increases, in the 1/3 test set (*Figure 1*). The assessment of IHMRS calibration (the Hosmer–Lemeshow test) in the 1/3 test set suggests a significant lack of fit (Hosmer–Lemeshow $\chi^2 = 28.69$, $P = 0.0004$). However, ranking the observations by deciles of predicted risk and performing the Hosmer–Lemeshow test on each group separately show that the lack of fit occurs predominantly at the extremes of predicted risk (Supplementary material online, *Table S4*). A calibration plot (*Figure 2*) similarly shows good agreement between observed vs. predicted events in the groups where the majority of the subjects lie. The validation of the score by the ethnic group is shown in *Table 5* and by the geographic region in *Table 6*. Discrimination as assessed by the ROC *c*-statistic is best among the South East Asian and Japanese (ROC *c*-statistic 0.79, 95% CI: 0.76, 0.83), North American (0.76, 95% CI: 0.73, 0.80), South American and Mexican (0.76, 95% CI: 0.73, 0.80), and South Asian (0.74, 95% CI: 0.71, 0.78) geographic regions and acceptable in the Middle East and Egypt, Western European, and China/Hong Kong regions. Discrimination was poorest in the Australia/ New Zealand and Central and Eastern European geographic areas, and also in the European and other ethnic groups. We also examined the discriminative ability of the IHMRS in men and women and in the older and younger groups (*Table 7*). The ROC *c*-statistic was higher in women than in men (Pearson's $\chi^2 = 6.10$, $P = 0.014$) and higher in the younger group than in the older group (Pearson's $\chi^2 = 41.05$, $P < 0.0001$).

The IHMRS is presented in *Table 8*. The categories of the risk factors are presented in the first column, and the specific questions to be asked in the middle columns. Only one answer is chosen for every question and inserted into the 'points' column. All questions must be answered for the most accurate risk score estimate. The mean score in the derivation set is 9.47 (SD 5.59; min 0, max 32), and in the test set, the mean score is 9.97 (SD 5.65), Student's *t*-test $t = -5.90$, $P < 0.001$. Examining the derived score in the test set ($n = 6687$), the mean score is higher in the cases than in the controls (12.37, SD 5.55 vs. 8.17, SD 5.02, Student's $t = -32.37$, $P < 0.0001$), higher in the older than in the younger groups (10.63, SD 5.36, vs. 9.30, SD 5.86, Student's $t = -9.65$, $P < 0.0001$) and higher in men than in women (10.44, SD 5.64 vs. 8.37, SD 5.37, Student's $t = -12.71$, $P < 0.0001$).

An external validation procedure was undertaken in an independent cohort study. The characteristics of the EpiDREAM and the INTERHEART derivation set populations are shown in Supplementary material online, *Table S5*. Definitions of modifiable risk factors in EpiDREAM were matched to the INTERHEART definitions (see Supplementary material online, *Table S6*). In the EpiDREAM cohort, among 18 838 persons who had no prior history of MI, there were 95 first MI events and a median follow-up of 3.5 years (inter-quartile range 3.0–4.0). The mean IHMRS in EpiDREAM participants is 8.1 (SD 5.4). For a 1-point increase in the IHMRS, the odds of MI increased by 1.12 (95% CI: 1.08, 1.16). This association between MI risk and IHMRS in EpiDREAM is linear (see Supplementary material online, *Table S7*) and is seen consistently across

Table 3 Internal validation studies of the three tested modifiable risk scores: the 'short' score, the 'full' score, and the 'non-laboratory-based' score

	'Short' INTERHEART Modifiable Risk Score	'Full' INTERHEART Modifiable Risk Score	'Cholesterol' risk score	'Non-laboratory-based' INTERHEART Modifiable Risk Score
Validation studies within the 2/3 derivation set				
Odds increase of MI for a 1-point increase in score (95% CI)	15.2% (14.4%, 16.1%)	14.3% (13.5%, 15.1%)	12.9% (12.2%, 13.7%)	14.4% (13.9%, 15.3%)
ROC c-statistic (95% CI)	0.71 (0.70, 0.72)	0.72 (0.71, 0.73)	0.69 (0.68, 0.70)	0.71 (0.70, 0.72)
Brier score	0.21	0.21	0.22	0.21
Validation studies within the 1/3 test set				
Odds increase of MI for a 1-point increase in score (95% CI)	15.8% (14.7%, 17.0%)	14.0% (13.0%, 15.1%)	13.0% (12.0%, 14.3%)	14.2% (13.1%, 15.3%)
ROC c-statistic (95% CI)	0.71 (0.70, 0.73)	0.71 (0.71, 0.73)	0.69 (0.68, 0.71)	0.71 (0.70, 0.72)
Brier score	0.21	0.21	0.22	0.21

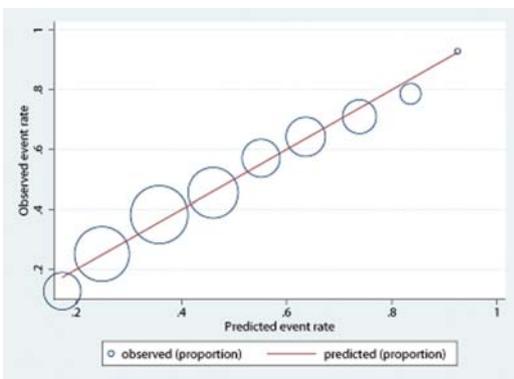**Table 4** The INTERHEART Modifiable Risk Score model

Risk factor		Odds ratio	95% confidence interval	Standard error	z	P-value
Age and sex	Male sex and age ≥ 55 years or female sex and age ≥ 65 years vs. younger	1.25	1.15, 1.35	0.05	5.40	<0.001
Apolipoprotein B:A1 ratio	Quartile 4 vs. Quartile 1	2.98	2.66, 3.34	0.17	18.64	<0.001
Smoking	Current smoking vs. never smoking	2.33	2.13, 2.55	0.11	18.54	<0.001
	Former smoking vs. never smoking	1.31	1.18, 1.46	0.07	5.07	<0.001
	Second-hand smoke exposure (≥1 h/week)	1.50	1.38, 1.63	0.06	9.50	<0.001
Self-report of diabetes		2.50	2.21, 2.82	0.15	14.90	<0.001
Self-report of hypertension		2.04	1.87, 2.22	0.09	16.30	<0.001

Multivariable logistic regression in the derivation set with case status as the dependent variable and the risk factors as independent variables. *Note.* Model is adjusted for geographic region and age and sex.
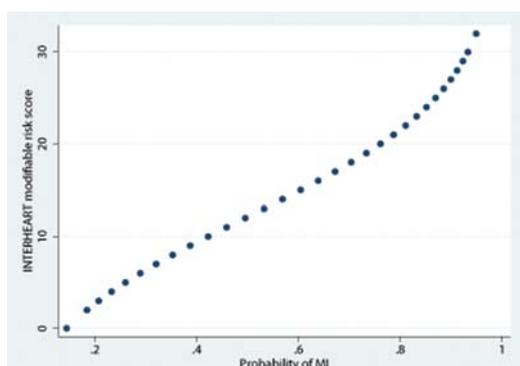
Figure 1 Two-way plot of the INTERHEART Modifiable Risk Score and the observed probability of myocardial infarction, in the INTERHEART test set.

geographical regions (see Supplementary material online, *Table S8*). The ROC curve c-statistic for the IHMRS in EpiDREAM was 0.69 (95% CI: 0.64, 0.74) (*Figure 3*). The score showed good calibration using the Hosmer−Lemeshow goodness-of-fit test ($\chi^2 = 3.08$, $P = 0.93$). Comparing the top tertile of the IHMRS (score ≥10) to the lowest tertile (≤4), the odds ratio for MI is 5.67 (95% CI: 2.77, 11.59), and comparing the middle tertile of score to the lowest the odds ratio is 2.22 (95% CI: 1.02, 4.82) (*Figure 4*). The IHMRS shows a graded increase in the probability of an MI in EpiDREAM. The probability of suffering an MI at 3.25 years is 0.12% for people classified in the lowest score tertile (IHMRS ≤ 4), 0.27% in the middle tertile (IHMRS: 5−9), and 0.68% in the highest score tertile (IHMRS ≥ 10). *Table 9* shows the 1- and 3.25-year probabilities of events by tertiles of the IHMRS. From the EpiDREAM validation cohort ROC curve shown in *Figure 3*, a risk score of ≥5 is associated with a sensitivity of 77.9% and a specificity of 49.5% for MI. In general, lower scores are associated with greater sensitivity and higher scores with higher specificity.

Figure 2 Calibration plot of the predicted vs. the observed event rate within the INTERHEART test set, as estimated by the INTERHEART Modifiable Risk Score. Larger circles imply higher densities of observations. The stippled line indicates the point of exact agreement between observed and predicted event rates.

Table 5 Internal validation of the INTERHEART Modifiable Risk Score in the INTERHEART test set, by ethnic group

Ethnicity	n	ROC c-statistic (95% CI)
European	1465	0.67 (0.64, 0.70)
Chinese	1863	0.70 (0.68, 0.73)
South Asian	965	0.74 (0.70, 0.77)
Other Asian	548	0.79 (0.75, 0.83)
Arab	812	0.73 (0.69, 0.76)
Latin American	733	0.76 (0.72, 0.80)
Black African	98	0.74 (0.63, 0.85)
Subsaharan African only	183	0.72 (0.65, 0.80)
Total[a]	6698	0.71 (0.70, 0.73)

[a]Data on 31 participants with ethnicity classified as 'other' are not shown separately, but are included in the total.

Discussion

Using data from a large international MI case−control study, we have created and validated a risk score which includes modifiable CHD risk factors. The final IHMRS contains variables relating to age and sex, smoking and second-hand smoke exposure, lipid levels, diabetes, and hypertension. A supplemental score describing the weights for other risk factor combinations is supplied, but the marginal increase in predictive ability of this 'full' score is outweighed by its complexity. The IHMRS as presented has demonstrated both internal validity, and good discrimination and calibration in a test sample. The external validity of the score is demonstrated by its prediction of both incident MI, and new angina and revascularization in an independent international prospective cohort study. In the external data set, a score of 10 and above (the highest tertile of the IHMRS) is associated with a

Table 6 Internal validation of the INTERHEART Modifiable Risk Model in the INTERHEART test set, by geographic region

Geographic region	n	ROC c-statistic (95% CI)
Western Europe	349	0.71 (0.65, 0.76)
Central/Eastern Europe	849	0.64 (0.60, 0.67)
Middle East/Egypt	930	0.72 (0.68, 0.75)
Africa	322	0.74 (0.68, 0.79)
South Asia	815	0.74 (0.71, 0.78)
China/Hong Kong	1,823	0.70 (0.68,0.73)
South East Asia/Japan	586	0.79 (0.76, 0.83)
Australia/New Zealand	173	0.68 (0.60, 0.76)
South America/Mexico	782	0.76 (0.73, 0.80)
North America	69	0.78 (0.67, 0.89)
Total	6698	0.71 (0.70, 0.73)

Table 7 Discrimination of the INTERHEART Modifiable Risk Score in population subgroups: receiver operating characteristic curve within the test set, with myocardial infarction as the reference variable, and the final score as the classification variable

| Population within the test set	n	ROC c-statistic (95% confidence interval)
For all subjects within the set	6698	0.71 (0.71, 0.73)
Men only	5168	0.71 (0.69, 0.72)
Women only	1530	0.74 (0.72, 0.77)
Young group (men <55 years and women <65 years)	3330	0.75 (0.73, 0.77)
Older group (men 55 years or older, and women 65 years and older)	3368	0.67 (0.65, 0.69)

markedly higher risk of adverse events, with an odds increase of 5.7 for MI, compared with an IHMRS score in the lowest tertile (score of 0−4). The predictive ability of this score is consistent across multiple ethnic groups and multiple geographic regions.

It is striking that despite the availability of multiple measures of 'lifestyle' risk factors, the most appropriate score derived presents a similar panel of risk factor variables to other commonly used risk scores.[6,7] This is in common with the findings of other groups, who have shown that despite hopes for novel CVD risk markers including common genetic polymorphisms,[28] such markers do not add to the discrimination of existing scores. An explanation is found in the current statistical understanding of the strength of association required between a risk factor and disease in order for that factor to be used as a screening test,[29] and even to make a meaningful impact on a predictive score for that disease.[30,31] Although the multiple modifiable risk factors demonstrated a statistically significant association with MI risk, they did not demonstrate the strength of association sufficient to impact on risk discrimination in such a score.
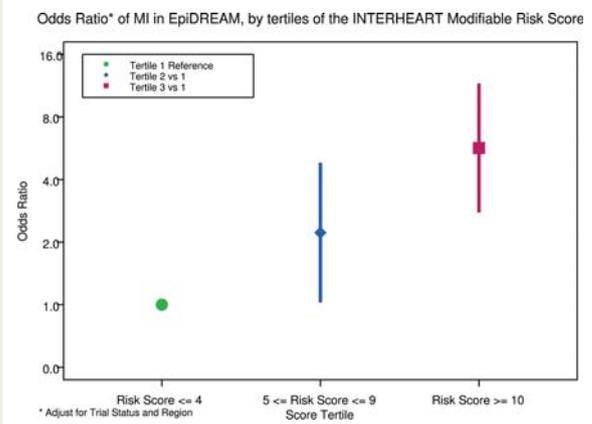
Table 8 The INTERHEART Modifiable Risk Score

Risk factors	Question		Point for the answer	Points for each section
Age	Are you a man 55 years or older OR woman 65 years or older?		2	Points:
	OR Are you a man younger than 55 years or woman younger than 65 years		0	
Apolipoprotein B:A1 ratio	Pick one only:	Q1: Less than 0.633	0	Points:
		Q2: 0.633−0.792	2	
		Q3: 0.792−0.983	3	
		Q4: Greater than or =0.984	7	
Smoking. Pick the description which matches you best:	I never smoked		0	Points:
	OR I am a former smoker (last smoked more than 12 months ago)		2	
	OR I am a current smoker or I smoked regularly in the last 12 months, and I smoke…	1−5 cigarettes/day	2	
		6−10 cigarettes/day	4	
		11−15 cigarettes/day	6	
		16−20 cigarettes/day	7	
		More than 20 cigarettes/day	10	
Second hand smoke	Over the past 12 months, what has been your typical exposure to other people's tobacco smoke?	Less than 1 h or exposure per week or no exposure	0	Points:
		OR one or more hours of second-hand smoke exposure per week	2	
Diabetes	Do you have diabetes mellitus?	Yes	6	Points:
		No or unsure	0	
High blood pressure	Do you have high blood pressure	Yes	5	Points:
		No or unsure	0	
				Total:

The categories of the risk factors are presented in the first column, and the specific questions to be asked in the middle columns. Only one answer is chosen for every question, and inserted into the 'points' column. All questions must be answered for the most accurate risk score estimate. Minimum score is 0 and maximum is 32.
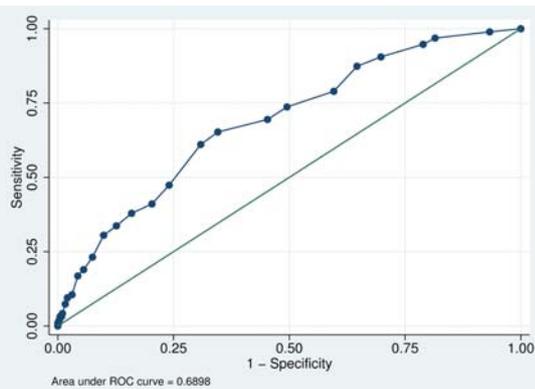
Figure 3 Receiver-operating characteristic curves for myocardial infarction, for the INTERHEART Modifiable Risk Score in the EpiDREAM Cohort Study. From the EpiDREAM validation cohort receiver-operating characteristic curve shown in *Figure 3*, a risk score of ≥5 is associated with a sensitivity of 77.9% and a specificity of 49.5% for myocardial infarction. In general, lower scores are associated with greater sensitivity and higher scores with higher specificity.

Figure 4 Odds ratio (adjusted for trial status and region) of myocardial infarction in EpiDREAM, by tertiles of the INTER-HEART Modifiable Risk Score.

A measure of apolipoproteins, in place of lipoproteins, is unique to the IHMRS. The apolipoprotein B:A1 ratio has been demonstrated to be a marker of coronary artery disease risk in large

Table 9 Risk of MI in EpiDREAM, by INTERHEART Modifiable Risk Score tertile

Tertiles of risk score	For the outcome of MI			
	1-year risk	3.25-year risk	Sensitivity	Specificity
0–4	0.04%	0.12%	93.7%	18.1%
5–9	0.09%	0.27%	77.9%	49.5%
≥10	0.23%	0.68%	42.1%	82.9%

prospective epidemiological studies[32,33] and has the advantage that it can be assayed from samples taken in the non-fasting state. The apolipoprotein B:A1 ratio was preferentially used in the IHMRS, as patients were not obliged to be in the fasting state at time of blood sampling, and previous work has suggested its superiority to lipoprotein measurements.[8] However, for settings where apolipoprotein assays may not be available, the 'non-laboratory-based' score may be used. Non-laboratory-based scores have an added advantage that they do not require lab testing facilities in order to estimate risk, making them ideal for the patient's first visit in primary care settings, for community worker use, and for use in resource-poor settings. Two other groups have created non-laboratory risk scores in recent years,[34,35] but neither score includes the wealth of modifiable risk factors available in INTERHEART. It is envisaged that the IHMRS might be used in clinical situations where risk factors are self-reported and the results are reviewed with a health-care worker.

Our score has a number of strengths. It is derived from a multi-ethnic study sample, from 52 countries of the world and every inhabited continent, with an even representation of men and women. It is generalizable across diverse ethnic populations and geographic regions, which is an advance over other risk scores which were developed and validated in white Caucasians primarily, and which have had variable predictability in non-white populations.[36] Our variables were chosen with both clinical and statistical utility in mind, and the data used were derived from standardized questionnaires and physical assessments. A central laboratory performed all the blood assays including those in the external validation studies. Patients have been shown to base their understanding of cardiovascular disease risk on personal experiences, rather than on population estimates.[37] The IHMRS provides a synthesis of patient-level modifiable risk factors, and risk level is described as tertiles of risk. This may well be an easier concept for patients to understand, rather than the more remote concept of a percentage risk of MI.

We have performed internal validity testing on the IHMRS, using a split-sample methodology. The final IHMRS model showed appropriate calibration in the test set within the separate deciles of predicted risk. The IHMRS had good calibration and discrimination, both in the entire test set and by the ethnic group, with ROC *c*-statistic values of >0.70 in all ethnic groups except the European and other ethnicity groups. Similarly good discrimination was seen in the women and in the younger participants in the test set. The cause of the deterioration in discrimination in the older

participants is not clear, but may be due to unmeasured factors affecting this age group which may affect CHD risk, such as concomitant illnesses. Risk factor levels may also be underestimated in this older age group, as more of these persons were on risk-modifying medications than in the younger group. The final IHMRS showed good discrimination (ROC *c*-statistic in the test set 0.72, 95% CI: 0.71, 0.73; and in the external validation set 0.67, 95% CI: 0.62, 0.73).

Prognostic models should be validated in an external sample, in order to demonstrate their generality and accuracy.[38] We have validated the IHMRS in the EpiDREAM cohort and shown that it is positively associated with an increase in the probability of MI in this cohort.[25] Further validity studies of the score in other external cohorts, in particular by ethnicity or geographic area, would be desirable. It can be argued that arbitrary 'cut-off levels' for continuous variables should be avoided[39]: dichotomizing a continuous variable can lead to loss of information and loss of power.[40] Nevertheless, since clinicians seek guidance and reference points with such scores, we have provided information on the score properties in the external cohort, by tertiles of IHMRS. In general, the lower IHMRS scores are associated with greater sensitivity and higher scores are associated with higher specificity.

There are some limitations of the IHMRS. First, it can be argued that case–control data is not the ideal data source to make such a score, and ideally, a prospective cohort should be used. Scores derived from case–control data cannot be considered 'predictive' of events in the same manner as those derived from cohort studies, and external validation to ascertain predictive ability in a cohort setting was an important step. However, case–control methodology permitted us to collect a large number of cases from different regions of the world to test the many variables which we felt were clinically important, without incurring penalties of overfitting.[41] To achieve a similar number of endpoints in a prospective cohort, especially in diverse settings, would require extremely large studies involving over a million individuals followed for at least 10 years. Furthermore, the case–control design enables large numbers of MI cases be obtained from diverse ethnic groups around the world, especially from resource-poor settings, and allowed inclusion of a large number of cases in younger subjects and in women, among whom the event rates are relatively low, and who are typically under-represented in cohort-based models. Variables ascertained in a case–control manner can be subject to recall bias. However, the study design also meant that our estimate of each participant's risk factor status was contemporaneous with the event. With regards in particular to lifestyle factors, these may well undergo changes over time, and thus, the estimated effects of such factors in a cohort setting may be biased due to regression to the mean. There was a missing data burden in the INTERHEART data, due primarily to a number of subjects who did not have apolipoprotein data. A sensitivity analysis with a missing data imputation procedure was undertaken, and it was shown that the missing data did not compromise the validity of the IHMRS estimates (see Supplementary material online, *Table S9*).

INTERHEART was matched by age (± 5 years) and sex. Despite this, we felt it was important to include an adjustment for age and sex, while accepting that their effects may be an underestimate, since they are important risk factors for CHD. Furthermore,

INTERHEART has been analysed using unconditional logistic regression[2] to minimize loss of data. However, creating an IHMRS using conditional logistic regression does not improve the discrimination of the score (see Supplementary material online, *Table S10*). This study only included those cases of acute MI who survived to hospital admission, although data were collected from family members for patients who were recruited to the study but who died before all study measures were collected. A subanalysis of all MI cases who died after recruitment but before discharge in INTER-HEART (3.2% of all cases, $n = 255$) showed that their mean IHMRS was marginally less than those who were alive at discharge (see Supplementary material online, *Table S11*). Therefore, the IHMRS was derived on both fatal and non-fatal hospitalized MI cases. Nevertheless, although it seems likely that the same risk factors described above may also predispose individuals to rapidly fatal MI in the pre-hospital setting, we cannot assume that this is so. Finally, a number of risk factors were determined by self-report (such as hypertension and diabetes). This historical recall may be considered inferior to direct measurement which was not possible in the acute MI setting. However, the prevalence of self-reported hypertension and diabetes has been found to approximate the known prevalence of disease in a number of studies.[42–44]

The study population in EpiDREAM consists of both individuals with normoglycaemia and with dysglycaemia, as subjects were preferentially screened if they were deemed to be at increased risk of dysglycaemia based on their family history, ethnicity, and anthropometric characteristics. Although this independent validation of the ability of the INTERHEART score to predict clinical events is reassuring, additional validation from prospective cohort studies, including those with population-based sampling and longer-term follow-up, would add to our understanding of the generalizability of the IHMRS.

Risk scores can be a useful educational and motivational tool for patients: educational in that they can understand their personal risk level, and motivational in that they can see their risk score decrease as their risk factors improve. Insofar as possible, such scores should aim for model parsimony. Inclusion of all statistically significant multiple modifiable risk factors made the score cumbersome and did not add to its predictive ability in the test set. The American Heart Association recommends using simple, consistent messages when educating patients about their risk factors,[45] and the European Society of Cardiology guidelines echo this concept in their simple 'telephone number' of targets for cardiovascular disease prevention.[4] However, the take-up of risk-scoring systems has not been uniform. Reasons for this include their complexity, the time required to input the data, the availability of the data required to complete some scores, and the perception some health-care providers may have that they are able to estimate risk without any such score.[46] Furthermore, there have been few studies documenting the efficacy of these tools in clinical practice. One systematic review identified four randomized controlled trials of such cardiovascular disease risk tools,[47] with only two trials showing an effect in terms of change in clinician prescribing in the risk estimation tool groups.[48,49] The IHMRS demonstrates clinical credibility, evidence of accuracy, and evidence of generality.[38] Impact studies testing the usefulness of the score in clinical practice are required.[50]

Conclusion

Using data from the INTERHEART case–control study, we have developed and validated a simple score for MI risk which is applicable to an international population.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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