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Abstract

This research is aimed to develop a 10-year risk prediction model and identify key contributing Cardiovascular Disease (CVD) risk factors. A Cox proportional hazard regression method was adopted to design and develop the risk model. We used Framingham Original Cohort dataset of 5079 men and women aged 30 - 62 years, who had no overt symptoms of CVD at the baseline. Out of them, 3189 (62.78%) had an actual CVD event. A 10-year CVD risk model based on multiple risk factors (such as age, sex, body mass index (BMI), hypertension, systolic blood pressure, cigarettes per day, pulse rate, and diabetes) was developed in which heart rate was identified as one of the novel contributing risk factors. We validated the model via statistical and empirical validation methods. The proposed model achieved an acceptable discrimination and calibration with C-index (receiver operating characteristic (ROC)) being 0.71 from the validation dataset.

1. Introduction

Many cardiovascular-related morbidities and mortalities are preventable by effective health management and employing effective diet plans, lifestyle interventions, and drug administration. For example, by assessing cardiovascular disease (CVD) risk factors regularly and introducing lifestyle adjustments or clinical treatments, the CVD can be prevented (Bansilal, Castellano, & Fuster, 2015). The CVD occurs due to variety of conditions and ultimately affect the heart and blood circulation system. Due to the high rate of disease morbidity, CVD has become a leading cause of mortality around the world. In New Zealand, statistics on CVD mortality in 2017 suggests that the percentage of deaths caused by CVD is 33% for the New Zealanders (Bannink, Wells, Broad, Riddell, & Jackson, 2006). However, challenges and issues regarding the development of CVD risk assessment models still exist (Crowson et al., 2017; Panaite, Salomon, Jin, & Rottenberg, 2015). CVD risk models based on single risk factor cannot realize the influence of multiple factors simultaneously. Risk assessment models using statistical regression methods prefer to use classic risk factors such as age, smoking, diabetes, sex, high blood pressure and total cholesterol to estimate the risk score (D'agostino et al., 2008). Studies applying data mining or machine learning techniques for the CVD risk estimations cannot provide an absolute risk assessment for the next certain years, although some of these models tried to incorporate novel predictors in the risk models. This research aims to identify novel risk factors for CVD by employing conventional predictors and then enhancing the risk estimation by developing a multi-variable-based risk prediction model that targets 5-year and 10-year CVD events (Zhao, Liu, Xie, & Qi, 2015).

2. Methods
2.1.　　　Framingham Original Cohort study dataset
The study uses the Framingham Original Cohort study dataset (Fernandez et al., 2009). The data was obtained after a successful ethics approval from NHLBI and the Auckland University of Technology Ethics Committee (AUTEC) (Ref: 17/385 Early detection and self-management of cardiovascular disease using Artificial Intelligence-based Model).

The dataset includes a cohort with a total of 5079 men and women aged 30-74 years free of CVD at the baseline, out of them, 3189 had CVD events eventually. Details of the CVD events distribution in male and female among the study population are summarized in Table 1.

	Count	CVD Events	Age Range
Male	2294	1560	30 - 74
Female	2785	1629	30 - 74
Total	5079	3189	30 - 74

Table 1: CVD Event Distribution in Male and Female

2.2. Data Preparation
There are 32 exams in the Framingham Original Cohort study dataset (D'agostino et al., 2008), data frame collected in the first exam "Exam1" was chosen to develop the CVD prediction model because it has the maximum number of samples from 5209 subjects. Data from 130 subjects were removed because of the ethics protection. A total of 20 risk factors was used for creating the risk model, including age, sex, body mass index, hypertension, heart related diseases, heart beats, blood pressure, smoking, diabetes and other long-term conditions (Fernandez et al., 2009).

2.3. Statistical Analysis
Cox proportional hazard regression analysis was undertaken for creating the risk model (Cox, 1972). The prediction model included multiple parameters to estimate the probability of developing CVD for an individual. There are mainly three statistical approaches in survival analysis, i.e. non-parametric, semi-parametric, and parametric approaches (Collett, 2015). The non-parametric approaches can only do univariate analysis with single predictor and are not suitable for the study of continuous variables. Both parametric and semi-parametric approaches can do multiple parameters analysis (Goldstein, Navar, Pencina, & Ioannidis, 2017). They all assume that the predictors and the log hazard rate should have a linear relationship. However, the Cox Proportional Hazard model (the most popular method belonging to the semi-parametric statistical method) has an advantage that only the rank orderings of the failure and censoring times are used to estimate and test the regression coefficients (Lu, Cai, Wang, Tong, & Xiang, 2018).

Statistical analyses were performed in R Studio platform. Missing values for candidate risk factors were imputed using multiple imputation. Continuous and categorical variables were transformed and imputed using algorithms modified from Maximum Generalized Variance (MGV) in the SAS PRINQUAL procedure. R function 'Function.transcan' creates R functions to transform variables using transformations created by 'transcan' inside the "Hmisc" package was used. For candidate predictors we performed two steps of variables selection from the list. The first step was conducted in a "Forward Selection" manner, i.e. the univariate Cox analysis was applied to multiple variables one by one, and then insignificant predictors were filtered based on a significance level p-value

>0.05. In the second step, all selected variables from the univariate analysis were entered into the multivariate Cox regression analysis.

In the validation stage, two approaches were undertaken to assess the predictive ability of our fitted model, statistical validation and empirical validation. The statistical validation was performed with respect to both discrimination and calibration. The empirical validation was defined as an empirical comparison with a general CVD risk prediction model (the Framingham office-based risk equation) in a horizontal and longitudinal perspective. The horizontal comparison was conducted by comparing with the Framingham prognostic model using data collected from multiple samples at the same time-point. The longitudinal comparison was conducted by comparing with the Framingham prognostic model using data collected from specific examples at different time-points (fixed time intervals follow-up) and see the risk trend for an individual over time.

3. Development of the Risk Model
3.1. Derivation of a 10-year Risk Score for CVD

Risk factors included in the risk model are age, sex, body mass index (BMI), hypertension, systolic blood pressure (SBP), cigarettes per day, pulse rate, the status of diabetes. Characteristics of risk factors were listed in Table 2. Statistics of "Min.", "1st Qu." (1st quarter), "Median", "Mean", "3rd Qu." (3RD Quarter), and "Max." of these risk factors are summarized.

Predictors	Variables	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
AGE	age	28	37	44	44.15	51	74
SEX	sex	1	1	2	1.548	2	2
BMI	bmi	14.12	22.66	25.17	25.61	27.92	56.68
HYPERTENSION	hyp	0	0	0	0.147	0	1
BLOOD PRESSURE SYSTOLIC	bps	84	122	136	138.6	150	270
CIGARETTES PER DAY	cgrpd	0	5	20	16.26	20	60
PULSE RATE	pr	37	67	75	75.61	83	170
DIABETES	dia	0	0	0	0.0197	0	1

Table 2: Summary Statistics for Risk Factors Used in Risk Model

The regression coefficients, hazard ratios, and their corresponding upper and lower 95% confidence intervals (CI) were estimated, as presented in Table 3. Values of the baseline hazard rate where the time point is ten years were estimated as well, shown in Table 4. The 10-year baseline hazard rate is 0.1023354 at mean values of all covariates, 0.001863652 at all covariates equal to zero. The survival probability (exp(basehaz)) is 0.9027267 at mean values and 0.9981381 at all covariates equal to zero.

Predictors	Variables	coef*	Hazard Ratio	lower .95	upper .95
AGE	log of age	2.083643	8.033686	6.4082	10.0716
SEX	sex	-0.469719	0.625178	0.5787	0.6754
BMI	log of bmi	0.608864	1.838342	1.4368	2.3521
HYPERTENSION	hyp	0.241461	1.273108	1.1342	1.429
BLOOD PRESSURE SYSTOLIC	log of bps	1.682571	5.37937	3.7938	7.6277
CIGARETTES PER DAY	cgrpd	0.009669	1.009716	1.0065	1.013
PULSE RATE	log of pr	-0.30209	0.739271	0.5879	0.9297
DIABETES	dia	1.087501	2.96685	2.3244	3.7869
*Estimated regression coefficient					

Table 3: Regression Coefficients and Hazard Ratios in Risk Model

	Covariates at mean value	Covariates equal to zero
Baseline hazard estimate	0.1023354	0.001863652
Baseline survival estimate	0.9027267	0.9981381

Table 4: Baseline Hazard and Survival at 10 Years

As the Cox model (Cox, 1972) defines by Equation 1, where t represents the time that the event occurs; $\lambda(t)$ is the hazard function for a subject at time t, determined by a set of m covariates (X_1, X_2, ..., X_k); $\beta_1, \beta_2, ... \beta_k$ are the regression coefficients that measure the effect size of covariates; exp is the exponential function (exp(X)= ex); $\lambda_0(t)$ is the baseline hazard rate, an arbitrary (unknown) function, corresponds to the value of the hazard when all X_i equal to zero (Lin & Wei, 1989).

$$\lambda(t) = \lambda_0(t)exp(\beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k) \qquad (1)$$

So, the Cox model can be written as a survival function:

$$S(t) = \left[S_0(t) \right]^{exp(\sum_{i=1}^{k} \beta_i X_i)} \qquad (2)$$

A general formula for computing risk estimates has the form:

$$\hat{H(t)} = 1 - S_0(t)^{exp(\sum_{i=1}^{k} \beta_i X_i - \sum_{i=1}^{k} \beta_i \bar{X}_i)} \qquad (3)$$

Where, H(t) is the CVD risk estimated for an individual; S0(t) is baseline survival rate at follow-up time t, where t = 10 years, see Table 4, βi is the regression coefficient, see Table 3, X_i is the value of the i_{th} risk factor (if is continuous it is the log-transformed value), $\bar{X}_i$ is the corresponding mean, and k denotes the number of risk factors. The CVD risk function could be derived from Equation 3, using regression coefficients from Table 2 and the baseline hazard rates from Table 3, hence, we

computed the probability of developing any type of CVD for an individual.

3.2. Nomograms

A nomogram is a two-dimensional diagram to represent a mathematical function involving several predictors. It is a simple graphical illustration to approximately predict a particular event based on conventional statistical regression methods such as Cox proportional hazards model for survival analysis (Cox, 1972; Lin & Wei, 1989). A nomogram is accomplishing the estimation of individual survivals in 10 years and the median survival time by years was depicted in Figure 1.

In Figure 1, each predictor has a set of n scales, and there is a mapping between each scale and the "Points" scale. The bottoms are the corresponding 10-year survival estimates, and the median survival time (years). By accumulating the total points corresponding to the specific configuration of covariates for a patient, a clinician can then manually obtain the predicted value of the event for that patient.
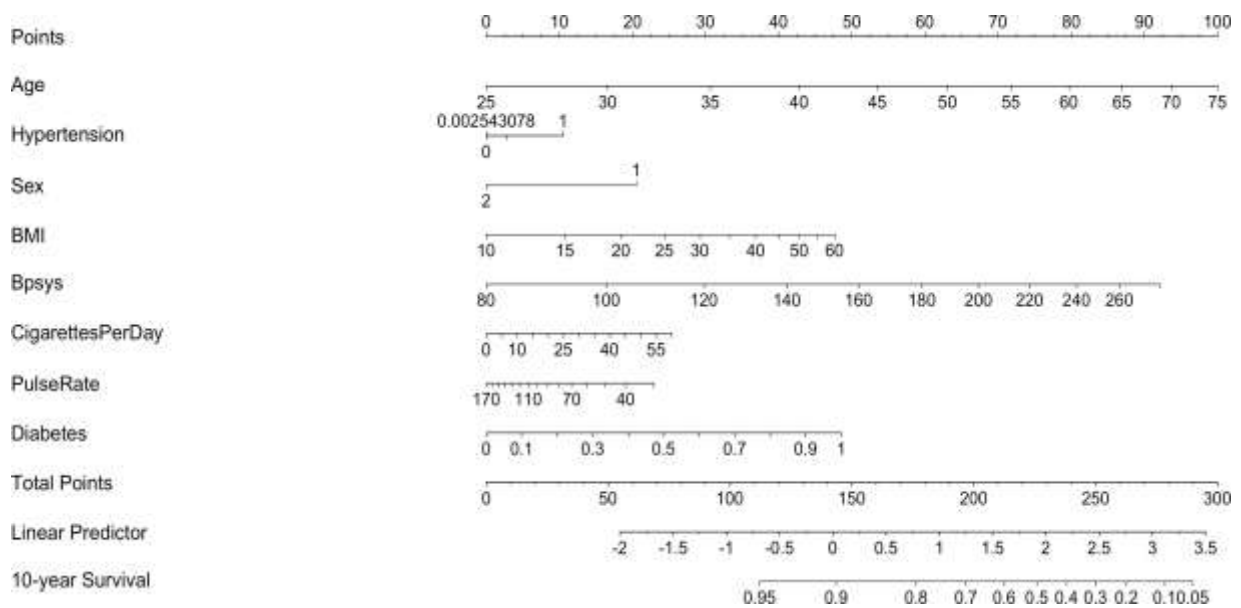

Figure 1: Nomogram for Predicting Overall Survival in 10-year

4. Results and Validation

First, the validation of our predictive risk model was performed using traditional statistics. The C-index (also called receiver operating characteristic (ROC) area) was used to assess the goodness of the risk model based on a bootstrap internal resampling validation (Collins, Ogundimu, & Altman, 2016). From the statistical validation analysis, a C-index (area under the receiver operator curve [AUROC]) of 0.71 was achieved indicating the moderately good ability of discrimination. Secondly, we performed an empirical validation by comparing our risk assessment model with the Framingham Heart Study model in an external dataset horizontally and longitudinally over time. In the horizontal validation process, there were 2786 samples in the external dataset (Fernandez et al., 2009), and 1693 samples with a CVD event. Risk scores using The Framingham Heart Study (FHS) model (D'agostino et al., 2008) and the proposed risk model were computed separately. Statistics of min (lower whisker), 1st quartile (the lower hinge), median, 3rd quartile (the upper hinge), and max (the extreme of the upper whisker) of

estimated risks for all samples are depicted in Figure 2.

The box-whisker graph in Figure 2 shows that the risks assessed by our Cox model are higher than the risk calculated by the Framingham model, but the error for five statistics (min, 1st Qu, median, mean, 3rd Qu., max) is within 0.02. For example, the median values of the FHS model and the Cox model are 0.1429475 and 0.1661985 respectively. For individuals with a CVD event, the Cox model is much more accurate than the FHS model whereas, for individuals without CVD, the Cox risk model overestimates the risk. Overall, the risk scale of the Cox model is consistent and is par with the Framingham model (D'agostino et al., 2008).
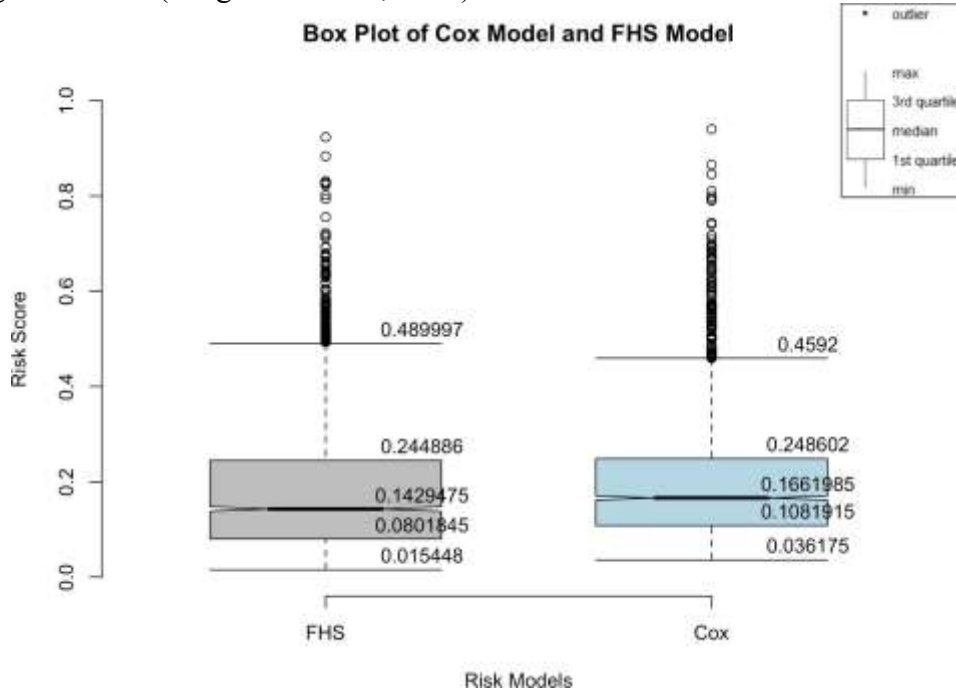

Figure 2: Horizontal Comparison between Cox Model and FHS Model

In the longitudinal validation process, we selected four sex-specific subjects with or without CVD from the end of the Framingham Study. A summary of these four subjects is listed in Table 5 to confirm the longitudinal validation of the predicted CVD event.

Samples	Gender	CVD	Diabetes
Sample 1	Male	✗	✗
Sample 2	Male	✓	✓
Sample 3	Female	✗	✗
Sample 4	Female	✓	✓

Table 5: Data Summary for Samples in the Longitudinal Validation

For each sample, data with fixed time intervals (approximately two years) from longitudinal time follow-up are extracted. The risk of developing CVD in 10 years related to the selected five exams data are separately computed using the Cox model and the Framingham model. Figure 3 shows the trend of risk over the years with 5% error and the trend of risks of these two models are consistent and risks for a specific sample increase over-time, the dotted trend lines

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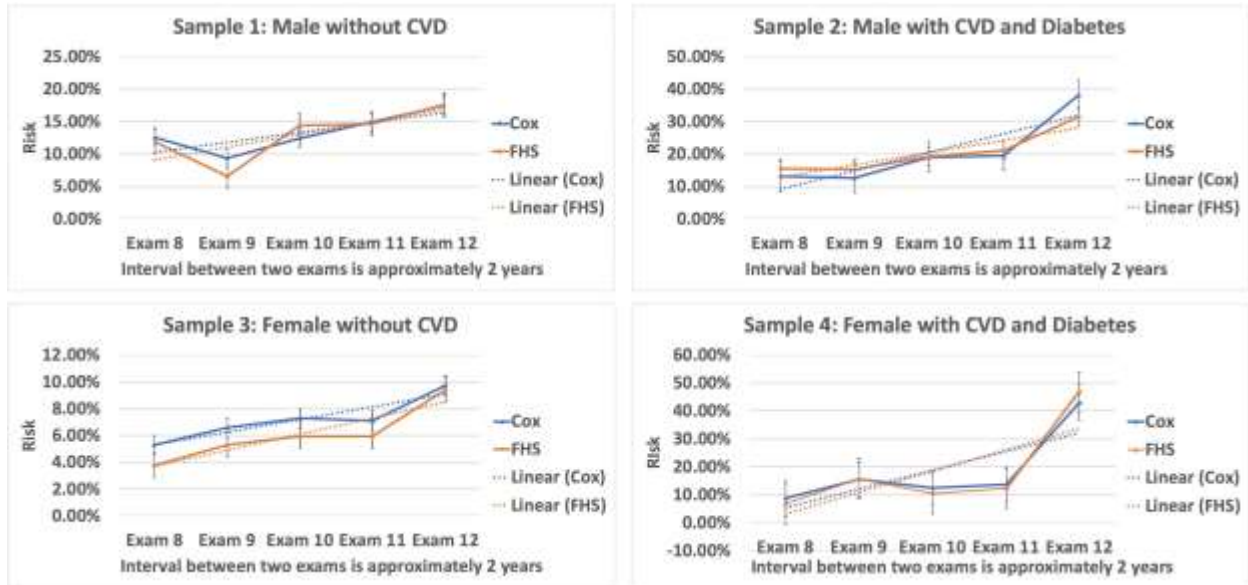
in each graph represents the increase in the CVD risk over-time. Also, samples (both male and female) with diabetes that developed CVD will have a higher risk than the ones with no developed CVD.

Figure 3: Longitudinal Validation

5. Discussion

It is widely accepted that CVD has become one of the significant public health problems globally and in New Zealand and continues producing immense burdens on the healthcare system (Desai, Bartz, Gottdiener, Lloyd-Jones, & Gardin, 2016; Fernández-Ruiz, 2017; Wells et al., 2018). Previous studies have noted the importance of identifying associated risk factors and the early detection and intervention of CVDs and also investigated regarding reducing the risk of developing CVD in early stages. Consequently, CVD risk prediction tools based on a single variable or multiple variables have been devised to yield estimates of the CVD risk (McClelland et al., 2015).

Motivated by the objective of early detection and risk estimation of CVD, the present study was designed to identify novel CVD risk factors, determine the effect of these factors, and then develop a risk prediction model based on the identified factors (Weng, Reps, Kai, Garibaldi, & Qureshi, 2017). Although risk factors could vary from one specific CVD component to another, there is sufficient evidence that different types of CVD have commonalities of risk factors. Concerning the aim of this research, we derived and validated a new 10-year risk equation for general CVDs based on time follow-up data rigorously measured by the Framingham Heart Study (D'agostino et al., 2008).

This investigation extends the number of risk factors by the previous general CVD risk formulations, incorporating heart rate to estimate absolute CVD risk. The approach used in this research is based on advanced statistical techniques that allow reducing the bias in the assessment of true CVD risk. The whole process of data analysis strictly follows the guideline of regression modelling strategies and survival analysis.

We use continuous variables (age, BMI, SBP, pulse rate) to generate the model that performs better than other similar models developed using categorical variables. Compared with simpler approaches that try to make inferences of 5-year and 10-year risk models such as the model

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based on logistic regression analysis and the CVD risk model using Kaplan-Meier and log-rank test, the proposed Cox risk model is more adequate and will avoid severe errors of underestimation or overestimation (Arts et al., 2016). Moreover, this model was developed based on a more substantial number of samples and events, suggesting a valid estimation of the real risk (Bansilal et al., 2015; Collett, 2015; Fernandez et al., 2009; McClelland et al., 2015).

6. Conclusion

The old version of the Framingham general CVD risk function is useful for identifying individuals at high risk of CVD, but it was based on a limited number of risk factors (serum cholesterol, SBP, smoking history, electrocardiogram, and glucose intolerance) (Garg et al., 2017). The new Framingham laboratory-test-based formula included HDL cholesterol in the risk function. The QRISK study investigators incorporated family history as a novel risk factor by the Framingham's general guidelines. Although researchers have published risk scores for predicting general CVDs, these functions did not include heart rate in the risk model (Stevens, Stevens, Hobbs, & Lasserson, 2015).

Risk models formulated by using machine learning or data mining techniques have incorporated heart rate as a risk factor but tools that can predict CVD absolute risk are fewer. For example, a prediction tool focuses on the classification of CVD event by employing the ANN and the Bayesian classifier based on heart rate variability. The diagnosis CVD model categorizes the CVD risk as different levels, but an absolute risk score cannot be obtained. Even though a supportive tool will generate the estimate of a risk score, but the user can not know how many years the score is targeting.

Some equations only focused on specific CVD outcomes. The Europe SCORE project equations were developed for the fatal cardiovascular event (Bitik et al., 2016). These risk estimation tools are just for coronary heart disease. Also, there are some risk models aiming stroke. Compared with these disease-specific models to estimate the risk of developing specific CVD outcomes, the present study generated a general CVD risk tool that could predict a global CVD risk as well as the risk of developing individual components.

Moreover, compared with the laboratory-based algorithms, the present research proposed a more straightforward way to estimate 10-year CVD risk based on risk factors without requiring clinical or laboratory tests such as the HDL measurement or blood test. In today's connected word, an individual's CVD risk could be assessed my many simple ways, such as using wearable sensors (Bitik et al., 2016; Wu, Zhang, Pirbhulal, Mukhopadhyay, & Zhang, 2015) or internet of things (IoT) devices (Kaappa et al., 2017; Raja, Saravanan, Anitha, Priya, & Subhashini, 2017; Pascoli, & Iannaccone, 2016) or self-monitoring applications (Baig, GholamHosseini, & Connolly, 2016; Baig, GholamHosseini, Moqeem, Mirza, & Lindén, 2017; Baig, Hosseini, & Lindén, 2016; GholamHosseini, Menthes, Baig, & Linden, 2016).

The proposed study devised a risk prediction model based on office-based multivariable predictors. A novel risk factor 'heart rate' was incorporated into this risk equation by conventional risk factors. A satisfying predictive ability with C-index (AUROC) being 0.71 was obtained, which ensures the accuracy of estimating risk scores. Compared with studies focusing on specific diseases, this algorithm can be applied to both general CVDs and specific CVD components such as the stroke, heart failure, and diabetes. Moreover, this risk model is much more convenient compared to models based on laboratory test predictors. Practitioners can perform this equation to quantify risk during a patient visit and identify high-risk individuals for further preventive health care.

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