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Discriminative ability of a risk-prediction tool derived from the Framingham Heart Study compared with single risk factors

Richard Milne, Gregory Gamble, Gary Whitlock and Rodney Jackson

Abstract

Aim To compare the discriminative ability of a multivariate risk-prediction model with individual continuous cardiovascular risk factors in a free-living population.

Methods Standard cardiovascular risk factors were measured in 6354 participants (4638 men and 1716 women) aged 35 to 74 years with no history of cardiovascular disease either enrolled on Auckland general electoral rolls or employed by a New Zealand-wide multi-industry corporation, in 1992–3. The sensitivity and specificity of individual risk factors versus a five-year cardiovascular risk-prediction equation and the corresponding New Zealand risk charts in predicting hospitalisation and mortality from cardiovascular disease in the subsequent five-year period were estimated over a range of risk thresholds.

Results Discrimination between individuals who had or did not have subsequent cardiovascular events was poor for individual risk factors. Increasing age had significantly more discriminability than blood pressure or lipids and the Framingham Heart Study risk tool had better discriminability than any single risk factor.

Conclusions A Framingham risk equation and corresponding New Zealand risk charts discriminate between individuals who will or will not experience hospitalisation or death from cardiovascular events. Discriminability is only modest but it is better than that achieved using individual risk factors.

Screening for cardiovascular risk helps identify those individuals who are most likely to have a cardiovascular event, so that they can be treated or further investigated. Risk screening based on risk-prediction tools provides a relatively inexpensive method of improving on clinical judgement of risk based on single risk factors.[1–3]

The National Heart Foundation has produced coloured risk charts[4,5] based on a cardiovascular risk equation developed by the Framingham Heart Study collaborators.[6] The risk equation is designed to predict incident cardiovascular end points including angina pectoris, myocardial infarction, peripheral vascular disease, congestive heart failure, transient ischaemic attack and stroke. It was developed from US data collected in the 1970s and 1980s and has been validated in several populations.[7] We have shown that the equation predicts the age/sex-specific risk of first hospitalisation or fatal cardiovascular events at a population level for New Zealand men aged 35–74 and women aged 35–69 years,[8] but its ability to discriminate between individuals at high or low risk has not been characterised in a New Zealand population.

The objectives of this study were: (1) to compare the discriminative ability of a multivariate risk-prediction equation and corresponding risk charts with that of

continuous cardiovascular risk factors in a free-living population; (2) to provide information that could help policy makers and general practitioners set risk thresholds for further cardiological assessment and/or dietary or drug interventions.

Methods

Details of the study population, risk factors, case definitions and end points have been described elsewhere[8] and they are described briefly here.

Study population Study participants were recruited in 1992–93 from two sources: the workforce of a nationwide multi-industry corporation (Fletcher Challenge Limited, 72%) and the general electoral rolls of the Auckland metropolitan region (28%).[9,10] The cohort participants included in these analyses were 6354 individuals aged 35 to 74 years (4638 (73%) male and 1716 (27%) female, Table 1).

Table 1. Study participants

	Men	Women	Total
Workforce	3762	815	4577 (72%)
Electoral roll	876	901	1777 (28%)
Total	**4638 (73%)**	**1716 (27%)**	**6354**

Risk-factor data The methods used to collect baseline data on systolic and diastolic blood pressure, non-fasting blood total cholesterol and HDL (high-density lipoprotein) -cholesterol concentration, and cigarette smoking status have been reported elsewhere.[9–11] The ratio of serum total cholesterol to HDL-cholesterol (TC/HDL) can be measured accurately using a non-fasting sample.[12] Participants were classified as having diabetes mellitus if they reported having been told by a doctor that they have diabetes and/or if they were currently receiving treatment for diabetes. Treatment for hypertension was self-reported. HDL-cholesterol data were available for only the 28% of subjects taken from the electoral roll study; for the remaining 72% taken from the workforce study this parameter was allocated as the sex-specific population mean for the electoral roll study (1.1 for men and 1.4 for women, respectively). This parameter was insensitive to age.[8]

Case definitions and end points Participants were defined as cases if, within five years of their baseline risk assessment, they were admitted to a hospital in New Zealand and were subsequently discharged with a diagnosis of ischaemic heart disease (ICD-9: 410 to 414), cerebrovascular disease (ICD-9: 430 to 438), congestive heart failure (ICD-9: 428), peripheral vascular disease or intermittent claudication (ICD-9: 440 or 443) or 'sudden death, cause unknown' (ICD-9: 798), and/or if they died in New Zealand during this period and the recorded causes of death had an ICD-9 code in these ranges. All available discharge diagnoses for each episode of care were searched.

Hospital admissions for cardiovascular events and cardiovascular mortality were obtained from the New Zealand Health Information Service (NZHIS) and hospital discharge database, the 'National Minimum Dataset'. There is provision for up to nine hospital discharge codes for each patient, all of which were searched for the appropriate cardiovascular codes. Cardiovascular mortality was obtained from NZHIS mortality data.

Receiver operator characteristics (ROC) analysis The sensitivity and specificity of the Framingham risk equation, the risk charts and individual risk factors against observed cardiovascular events over a range of cut-off points were determined by establishing 2 x 2 contingency tables for true and false positives and negatives.[13] A point estimate of risk for each individual was calculated directly from the Framingham risk equation. ROC curves for the risk equation were developed by plotting 'sensitivity' against '1-specificity' from the contingency tables.[14]

To estimate sensitivity and specificity of the New Zealand risk charts, individuals were allocated to the closest coloured risk cell corresponding to their individual risk factors. For example, a participant aged 63, with systolic blood pressure (SBP) 143, diastolic blood pressure (DBP) 83, and TC/HDL 5.4 would be allocated the cell corresponding with age 60, BP 140/85, TC/HDL 5, giving a five-year risk of 5–10%. The point estimate of risk for each coloured cell was considered to be the mid point between the upper and lower bounds of the cell (eg, 15–20% would be taken as 17.5%). The area under the curve

(AUC) was estimated using a trapezoidal approach from logistic regression analysis modelling for the sensitivity/specificity of deciles of risk[15] and two or more AUCs were compared with a nonparametric approach.[16]

Results

Cohort and outcomes The 6354 individuals in this analysis comprised all individuals without previous self-reported cardiovascular events who had their risk profiles measured in 1992/3 and for whom five-year outcomes were available. Participant characteristics have been described previously.[8]

Over the five-year follow-up period there were 411 individuals who were recorded as having a first-ever cardiovascular event (325 male, 86 female). Of the cohort, 33 women and 84 men (1.8% of the total) had missing values of one or more risk factors and thus risk estimates for these people could not be made. Four of the men but none of the women with missing data experienced a first-ever cardiovascular event.

Discriminability of the risk equation and charts The ability of the risk equations to discriminate between individuals who will have subsequent cardiovascular events and those who will not have events can be determined using ROC analysis. The area under the ROC curve (AUC) ranges from 0.5 to 1.0, where 0.5 signifies correct classification in only 50% of chances, which is no better than chance, and an area of 1.0 signifies perfect classification.

Figure 1 shows the ROC curves for the risk equation, the National Heart Foundation risk charts and single risk factors, tested against 'any incident cardiovascular end point' for the cohort. Numbers shown on each graph represent selected risk cut-off points (thresholds) at which each paired value of sensitivity and specificity was determined. The New Zealand risk charts gave an ROC curve that was very similar to the risk equation (not shown).

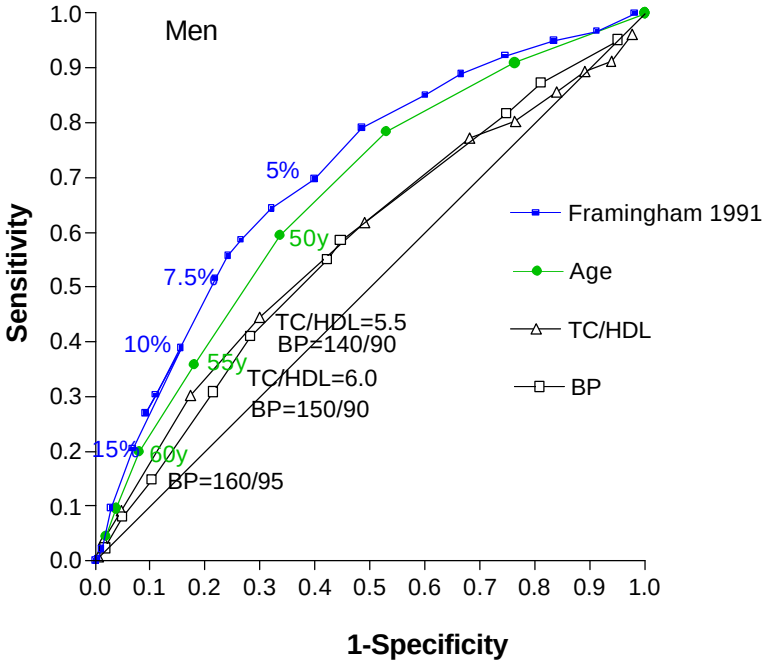
Table 2 shows that the area under the ROC curve is substantially higher for the risk chart and its corresponding risk equation than for the SBP or TC/HDL risk factors alone. Age is intermediate between the single risk factors and the risk equation. For men, the discriminability of the new risk equation for cardiovascular events is superior to that of SBP or TC/HDL alone. For women, our analysis could detect no significant difference in discriminability between the risk equation, risk charts or systolic blood pressure, probably because of the relatively low number of cardiovascular events.

Table 2. Area under receiver operator characteristics (ROC) curves

	Men			Women		
	Mean	**-CI**	**+CI**	**Mean**	**-CI**	**+CI**
Framingham risk equation 1991[6]	0.74	0.73	0.75	0.77	0.74	0.80
New Zealand risk charts	0.73	0.72	0.74	0.78	0.75	0.81
Age	0.71*	0.70	0.72	0.79	0.76	0.82
TC/HDL	0.63*	0.62	0.64	0.62*	0.59	0.65
SBP	0.63*	0.62	0.64	0.74	0.71	0.77

CI = 95% confidence interval; *different from the risk equation ($p < 0.05$)

Figure 1. Receiver operator characteristics (ROC) curves for men (a) and women (b) for the Framingham risk equation, blood pressure and cholesterol ratio (TC/HDL). The numbers beside the graphs indicate risk cut-off points for each risk factor or the risk equation.



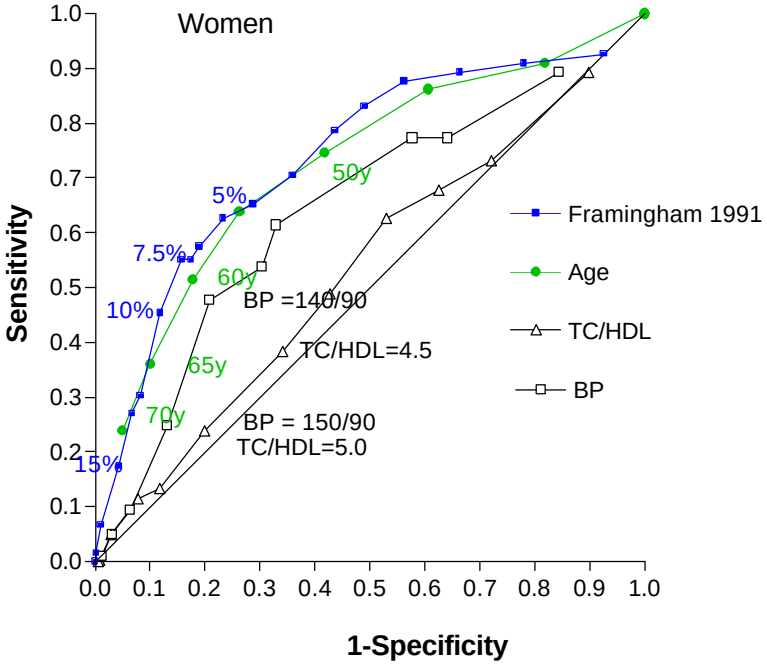
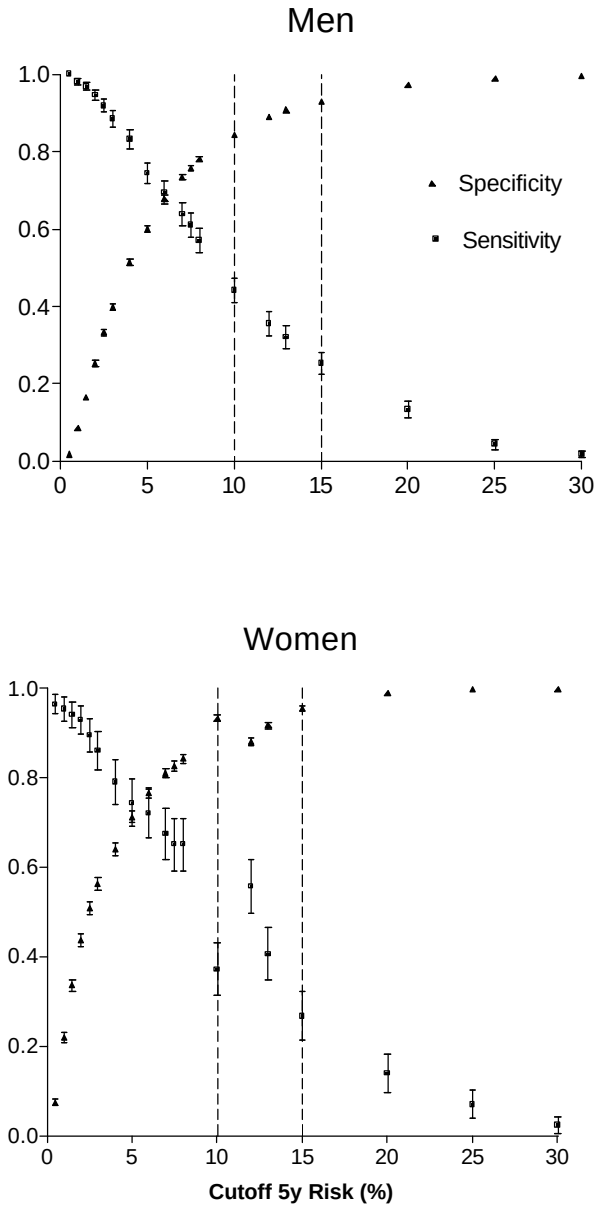


Figure 2. Sensitivity and specificity of the new risk equations as a function of risk cut-off (threshold). The broken lines indicate five-year risk thresholds of 10% and 15%.



Sensitivity, specificity and risk thresholds Figure 2 shows the sensitivity and specificity of the risk equation as a function of cut-off (risk threshold). At a 15% cut-off the specificity of the risk equation is over 90% for both men and women although the sensitivity is only 20% for men and 27% for women. At a lower threshold (eg, 10%) the sensitivity improves at the expense of specificity. Although these relationships cannot dictate an appropriate threshold, they do show that specificity becomes poor for thresholds less than 10% and that sensitivity is very poor above the 15% five-year risk cut-off point.

Discussion

This study shows that a Framingham Heart Study risk equation for 'any incident cardiovascular event,' and the corresponding New Zealand risk charts, provide similar sensitivity and specificity at clinically useful thresholds (eg, 10–15% five-year risk) for incident cardiovascular events, despite the approximations inherent in the risk charts. The equation appears to discriminate better than age in men but not in women, most likely because of inadequate sample size in women.

We have also shown that the risk equation and the charts have much better discriminability than the risk factors of either systolic blood pressure or lipid ratio (TC/HDL). HDL-cholesterol data were available for only 28% of our subjects and a population average was applied to the remainder. A recent UK study shows that inclusion of measured HDL-cholesterol instead of a population average in a risk assessment improves the discriminability of the British risk charts compared with the Framingham risk equation for coronary events[17] and a Canadian study emphasises the additional discriminability provided by HDL compared with cholesterol alone.[18] Our study may therefore underestimate the discriminability for lipids and also for the risk equation.

Smoking history and the presence of diabetes were included in the data set and presumably add to the overall discriminability of the risk equation. Because they take dichotomous values in the Framingham risk equation, it is not possible to plot individual ROC curves for them.

Although the risk equation accurately predicts the *proportions* of men and women who will have an event,[8] it has only modest ability to predict *which* individuals with risk greater than any specified threshold will have an event in a five-year period and therefore would benefit from an intervention such as blood-pressure or lipid-lowering therapy. Based on our findings, at a 15% risk cut-off, 80% of men who had an event in the five-year follow-up period would not be classified as high risk, although only 7% who would not benefit from treatment would receive it. Lower thresholds would improve sensitivity but compromise the specificity of risk stratification.

The overall discriminability (sensitivity and specificity over a range of cut-off points) of the Framingham risk equation for 'any cardiovascular event' is lower than reported for another Framingham risk equation for coronary deaths in the Lipids Research Clinics data set (AUC = 0.85).[18] There are several possible reasons for this difference: (1) poorer discrimination for a broad range of end points compared with coronary deaths;[3] (2) application of a risk equation based on 1970s and 1980s data to a 1990s New Zealand data set; (3) missing data in our cohort, including HDL-cholesterol. Neural network modelling could potentially improve on the accuracy of risk stratification, albeit with some loss of transparency and generalisability.[19]

We may have underestimated the discriminative ability of the risk equation and charts for several reasons. Non-hospitalised transient ischaemic attack and angina pectoris were not detected; however, these events are likely to lead to a hospitalised and/or fatal event that would be detected in national hospital or mortality registers. Information on 'ECG left ventricular hypertrophy' was unavailable; however, this risk factor is uncommon in individuals without known cardiovascular disease, it is not included in the current risk charts and it would be impractical to obtain measurements in general practice. Also, data on HDL-cholesterol concentrations were available for

only 28% of individuals in our cohort. Finally, lipid ratios were based on a single lipid test and there is evidence that discriminability can be improved by repeated measurement of risk factors such as serum lipids.[20]

ROC analysis alone cannot provide an evidence-based risk threshold for treatment or further assessment, largely because of resourcing issues. However, our findings show that a cut-off point of 15% five-year risk equates to the mean five-year risk for our cohort of New Zealand men aged 60–64 years and women aged about 70 years.[8] This cut-off point is considered by the National Heart Foundation of New Zealand as the lower border of 'high' risk and it is commonly used as the threshold at which general practitioners should advise drug therapy.[4] Although it is associated with good specificity it appears to have poor sensitivity (Figure 2). Lower thresholds improve sensitivity but they reduce specificity and thereby increase the cost of treating individuals who would not benefit much from therapy (false positives) (Figure 2).

It would be useful to develop a risk equation with higher discriminability than the Framingham equation based on a larger cohort, incorporating family history of cardiovascular disease and a range of putative novel risk factors such as C-reactive protein[21] in addition to standard risk factors including HDL-cholesterol. The next step is to base treatment decisions on the capacity to obtain lifetime benefits and on the cost effectiveness of therapy. Risk equations and other methods of risk stratification provide the foundation for such methodologies.

Author information: Richard J Milne, Associate Professor, Section of Epidemiology and Biostatistics, School of Population Health; Gregory D Gamble, Research Fellow, Division of Medicine; Gary Whitlock, Research Fellow, Clinical Trials Research Unit; Rodney T Jackson, Professor, Section of Epidemiology & Biostatistics, School of Population Health, University of Auckland, Auckland

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Correspondence: Dr Richard J Milne, Health Outcomes Associates Ltd, P O Box 60315, Titirangi, Auckland. Fax: (09) 817 2662; email: richard.milne@hoa.co.nz

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