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Framingham Heart Study risk equation predicts first cardiovascular event rates in New Zealanders at the population level

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Abstract

Aim To establish the population-level predictive validity of the Framingham Heart Study risk equation used to derive cardiovascular disease risk-prediction charts for New Zealand management guidelines on raised blood pressure and dyslipidaemia.

Methods During 1992–3, standard cardiovascular risk factors were measured in a cohort of 6354 people (4638 men and 1716 women) aged 35–74 years with no history of cardiovascular disease, who were either enrolled on Auckland general electoral rolls or employed by a nationwide multi-industry corporation. Five-year cardiovascular event rates were predicted for the cohort using a Framingham risk equation and were compared with observed five-year cardiovascular event rates for hospitalisation and mortality.

Results Incident cardiovascular hospitalisations or death were reported for 411 cohort participants (325 men and 86 women) during five years of follow up. There was good agreement between observed and predicted five-year cardiovascular event rates in all five-year age/sex categories up to 69 years. The risk equation tended to underestimate risk slightly in men and overestimate risk slightly in women up to 69 years, while in 70- to 74-year-olds it was accurate for men. Its accuracy in older women is uncertain.

Conclusion A Framingham Heart Study risk equation used to estimate incident cardiovascular events in individuals without previous cardiovascular disease accurately predicts five-year risk of hospitalisation or death from a first cardiovascular event in New Zealand men aged 35–74 and women aged 35–69 years at the population level.

Cardiovascular disease risk charts, based on a risk-prediction equation developed by the Framingham Heart Study collaborators,[1] are integral to New Zealand guidelines on the management of dyslipidaemia and raised blood pressure.[2,3] This risk equation was designed to predict incident cardiovascular end points and was developed from biennial medical examinations of a cohort of mainly white Americans living in the town of Framingham, Massachusetts in the 1970s and 1980s.[1] Although the risk charts have been used in New Zealand since 1992 and various Framingham risk equations and associated risk scores have been validated in several populations and ethnic groups internationally,[4,5] it is not known how well the equations predict population risk in New Zealand.

The objective of this study was to establish the accuracy of the Framingham risk equation at a population level, by applying the equation to a New Zealand cohort and comparing predicted event rates with observed event rates by five-year age groups in men and women.

Methods

Study population The Fletcher Challenge–University of Auckland Heart and Health Study is a cohort study designed to investigate causes of common disease and injury in a large population of New Zealand men and women.[6] 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.[6,7]

The cohort participants included in these analyses were 6354 individuals aged 35 to 74 years (4638 (73%) male and 1716 (27%) female) without previous self-reported cardiovascular events (angina, hospitalisation for coronary heart disease, transient ischaemic attack or stroke).

At baseline, 10% of participants were Maori, 5% were Pacific people, and 85% were European or other ethnicity. All participants provided signed consent to take part in this study, which was approved by the University of Auckland Human Subjects Ethics Committee.

Risk factors measured at baseline The methods used to collect baseline data on systolic and diastolic blood pressure, non-fasting blood cholesterol and HDL (high-density lipoprotein) -cholesterol concentration have been reported elsewhere.[6–8] Participants were classified as cigarette smokers if they reported smoking daily or had given up in the last 12 months, and 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. HDL-cholesterol data were available only for those individuals in the electoral roll cohort. The sex-specific population mean HDL-cholesterol levels (1.1 for men and 1.4 for women, respectively) were allocated to all members of the workforce cohort; this parameter was age insensitive in the electoral roll cohort. It was assumed that none of the participants had ECG-determined left ventricular hypertrophy, a variable included in the Framingham risk-prediction equation.

Outcome assessment Data on cardiovascular disease death or hospitalisation were obtained from the National Register of Births, Deaths and Marriages and the New Zealand Health Information Service (NZHIS) and hospital discharge database, the 'National Minimum Dataset'.

Individual records in the National Minimum Dataset were identified using probabilistic record linkage software (MatchWare Technologies, 1992). There is provision for up to 20 hospital discharge codes for each patient, all of which were searched for the appropriate cardiovascular codes.

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 diagnostic codes for each episode of care were searched.

Risk prediction 'Predicted' cardiovascular events were estimated for each individual in the cohort using a risk equation derived from a cohort of 5573 members of the Framingham Heart Study and Framingham Offspring Study cohorts, age 30 to 74 years, using four to 12 years of follow up from a baseline established between 1968 and 1975.[1] The Framingham risk equation is based on a Weibull accelerated failure time model,[1,9,10] with a time frame set to five years in our study. This equation incorporates any incident cardiovascular end point including angina pectoris, myocardial infarction, peripheral vascular disease, congestive heart failure, transient ischaemic attack and stroke. The equation includes the following risk factors: age, sex, systolic blood pressure, total cholesterol, HDL-cholesterol, diabetic status (yes/no), tobacco smoking status (yes/no or quit at least 12 months previously) and evidence of left ventricular hypertrophy on resting electrocardiogram (yes/no).

Analyses The accuracy of the risk equation at a population level was determined by comparing the age/sex-specific incidence of first-ever cardiovascular events (ICD-9: 410–4, 430–8, 428, 440, 443, 798) in the study cohort with cardiovascular events predicted by the risk equation for 'any incident cardiovascular event'[1] based on individual risk profiles. A chi-square test was used to compare observed with predicted events.

Results

Table 1 gives the distribution of risk factors for the cohort by age group and sex. The larger numbers of participants in the younger age groups, particularly for men, are due

to the predominance of younger men in the Fletcher Challenge cohort. In both men and women, systolic blood pressure and the prevalence of diabetes tended to increase with age, while smoking prevalence decreased with age. There are no clear age-related trends in levels of diastolic blood pressure or lipids. Blood pressure levels were higher in men than women and HDL-cholesterol levels higher in women than men.

Table 1. Population risk factor profiles by age and sex

Age (years)	n	SBP	sd	DBP	sd	TC	sd	HDLc	sd	Sm	Diab
Men											
35–39	1039	123.1	12.8	78.4	10.1	5.3	1.07	1.10	0.07	30.5%	0.9%
40–44	1046	124.3	13.7	79.6	10.4	5.5	1.12	1.10	0.10	23.0%	1.5%
45–49	889	126.8	14.3	81.5	10.3	5.7	1.09	1.10	0.10	23.6%	2.8%
50–54	753	129.4	16.3	82.0	10.8	5.7	1.09	1.10	0.096	21.8%	2.8%
55–59	487	133.1	16.8	81.7	11.0	5.7	1.08	1.11	0.14	18.3%	4.5%
60–64	214	138.3	17.3	79.2	11.4	5.7	1.08	1.13	0.25	18.7%	5.6%
65–69	103	145.6	18.3	77.1	11.1	5.6	1.00	1.13	0.34	8.7%	7.8%
70–74	107	148.4	21.8	74.1	11.8	5.6	0.86	1.10	0.33	11.2%	5.6%
Total	**4638**										
Women											
35–39	300	113.2	12.7	70.8	10.7	5.1	1.01	1.32	0.19	25.3%	2.3%
40–44	346	116.6	15.0	73.4	11.2	5.2	0.93	1.31	0.17	18.8%	1.4%
45–49	318	120.3	13.8	75.1	9.5	5.4	0.93	1.35	0.23	17.6%	1.9%
50–54	260	126.9	17.0	77.4	10.3	5.8	1.11	1.35	0.26	13.8%	1.9%
55–59	149	129.6	17.9	74.7	11.0	6.1	1.15	1.38	0.3	16.8%	2.7%
60–64	140	137.6	19.8	74.6	11.1	6.2	1.09	1.40	0.41	13.6%	5.7%
65–69	92	140.1	18.3	74.0	10.7	6.3	1.01	1.41	0.38	8.7%	2.2%
70–74	111	146.9	18.4	75.3	12.4	6.3	1.13	1.38	0.34	8.1%	4.5%
Total	**1716**										

DBP = diastolic blood pressure; Diab = diabetes; HDLc = HDL-cholesterol; SBP = systolic blood pressure; sd = standard deviation; Sm = tobacco smokers; TC = total cholesterol

Table 2 shows the distribution of cardiovascular end points, by Australian ICD-9 disease codes, which were identified from hospital discharge statistics or death certificates. Only the first event or set of events is included for each individual. As we used all discharge diagnoses, some of these definitions are not mutually exclusive and the number of diagnoses in Table 2 is higher than the number of individuals who had an event. For example, if a man were discharged with ICD-9 codes for both unstable angina and myocardial infarction, he would be entered twice in Table 2 but counted only once in the analysis.

There were 411 individuals who were recorded as having a first-ever cardiovascular event in five years (325 men, 86 women) including 30 fatalities (7.3% of these individuals, or 4.7 per 1000 of the cohort). None of the deaths were coded as ‘sudden death’, possibly because New Zealand coding of deaths that occur out of hospital does not correspond exactly to the Framingham definition of ‘sudden death’.

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.

Table 2. First cardiovascular events identified from hospital discharge data or death certificates over the five-year period 1992/3 to 1996/7

ICD-9 code	Description	Incident events*		Cardiovascular deaths†	
		Men	Women	Men	Women
410	Acute myocardial infarction	84	11	8	0
411	Other acute and sub-acute forms of ischaemic heart disease including unstable angina, acute coronary insufficiency, impending infarction, coronary occlusion without infarction	79	15	0	1
412	Old myocardial infarction	2	0		
413	Angina pectoris	43	11		
414	Other forms of chronic ischaemic heart disease	88	26	12	2
428	Congestive heart failure	32	14		
430	Subarachnoid haemorrhage	6	4	3	2
431	Intracerebral haemorrhage	2	0		
432	Unspecified intracranial haemorrhage	1	0		
433	Occlusion and stenosis of prevertebral arteries	3	2		
434	Occlusion of cerebral arteries	13	2	0	1
435	Transient cerebral ischaemia	17	7		
436	Acute but ill-defined cerebrovascular disease	9	3	1	0
437	Other and ill-defined cerebrovascular disease	4	2		
438	Late effects of cerebrovascular disease	1	0		
440	Intermittent claudication	8	2		
443	Peripheral vascular disease	9	7		
798	Sudden death	0	0		
Total number of incident events‡		**401**	**106**	**24**	**6**
Total number of individuals with incident events‡		**325**	**86**	**24**	**6**

*fatal or non fatal; †deaths from incident or recurrent events; ‡about one quarter of individuals received more than one cardiovascular discharge code on a single admission, so the number of coded events (401 + 106 = 507) is higher than the number of individuals with events (325 + 86 = 411), each individual was counted only once

Figure 1 and Table 3 show the distribution of observed incident cardiovascular events and predicted cardiovascular risk across risk categories. Only a small fraction of the population was at 'high' risk according to the Framingham risk equation (8.1% of men and 5.4% of women had a predicted risk greater than 15% in five years), but accounted for approximately one quarter of all events. However, the large proportion of the population at low risk (about 60% of men and 70% of women had a predicted risk of less than 5%) also accounted for about one quarter of the events.

Figure 1. Distribution of observed events (a) and of individuals in the cohort (b) across five-year bands of cardiovascular risk[1] by age and sex

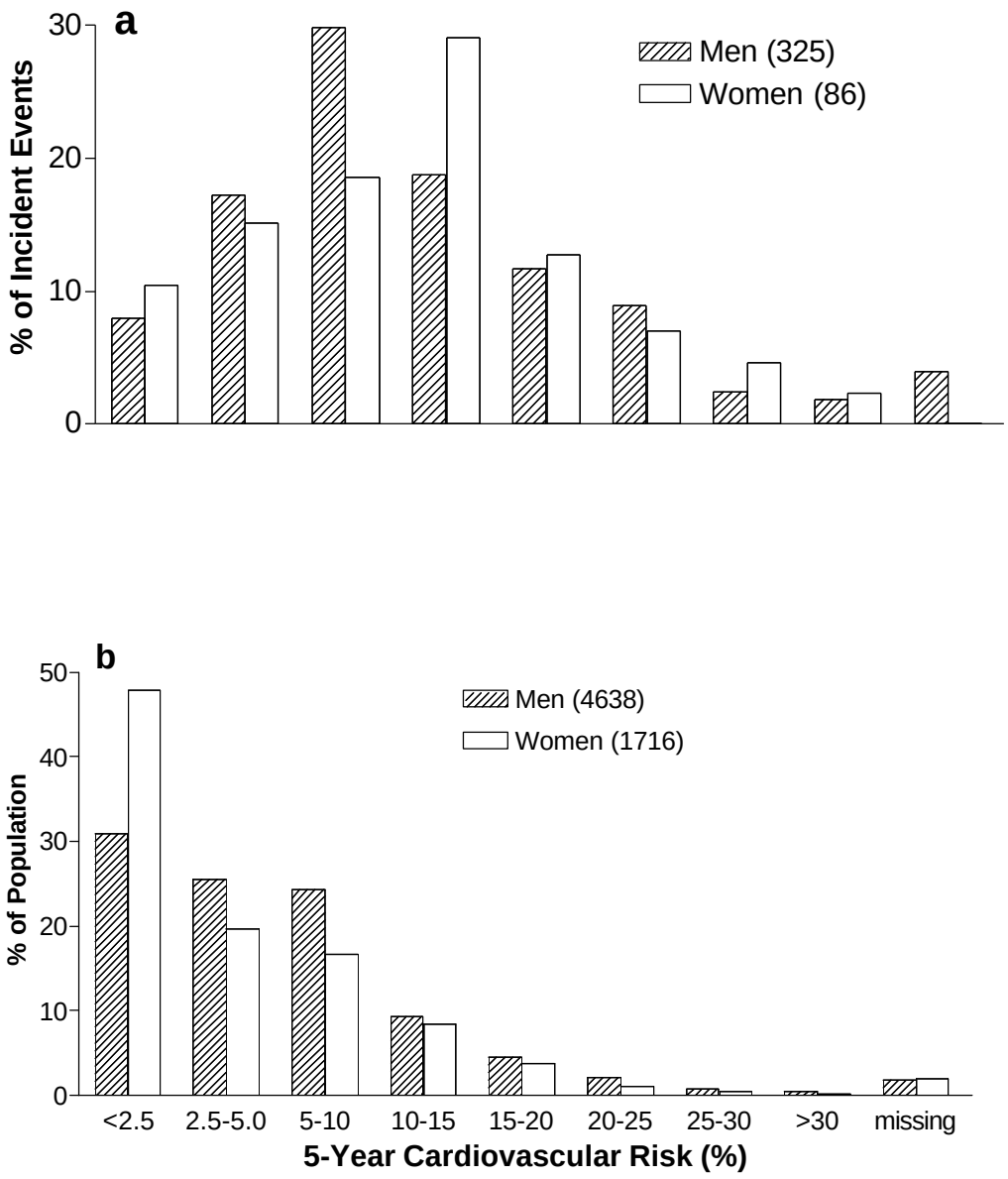


Figure 2 shows the age/sex-specific five-year incidence of first-ever cardiovascular events observed in the cohort and predicted by the risk equation. The predicted risk (based on the Framingham risk equation) tended to underestimate risk slightly for men but not for women up to 69 years of age. The risk equation underestimated risk substantially for women aged 70–74 years; however, the high event rate in this group is likely to be a chance finding (see Discussion).

Table 3. Proportions of individuals in study population with five-year risk above specified risk thresholds, and observed incident events over five years in these people

Proportion of events in study population	Men (%)	Women (%)
Risk >5%		
Predicted	41.6	30.5
Observed	73.5	74.4
Risk >10%		
Predicted	17.4	13.9
Observed	43.7	55.8
Risk >15%		
Predicted	8.1	5.4
Observed	24.9	26.7
Risk >20%		
Predicted	3.5	1.7
Observed	13.2	14.0

Figure 2. Observed versus predicted cardiovascular events by age and sex (mean ± 95% CI; *p <0.05; c^2 test)

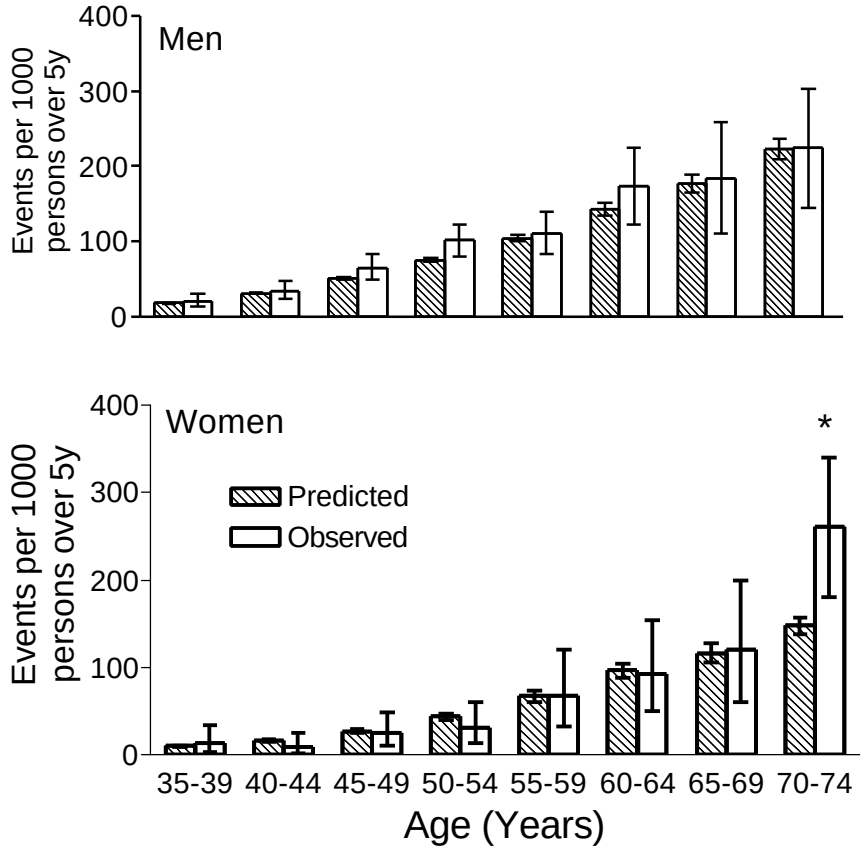
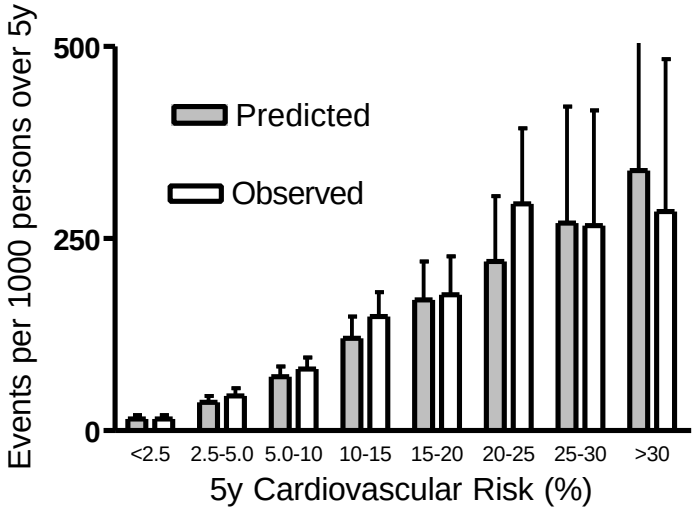


Figure 3 shows that the risk equation appears to maintain accuracy over a wide range of risk. Its accuracy is less certain for very-high-risk individuals (risk >20%) because they represented a very small fraction of the cohort (Figure 1).

Figure 3. Observed versus predicted cardiovascular events across five-year bands of cardiovascular risk for men and women combined (mean ± 95% CI)



Discussion

The Framingham Heart Study cardiovascular risk-prediction equation used to develop New Zealand cardiovascular risk charts[1] predicted the five-year age-specific incidence of hospital discharges and mortality from cardiovascular disease in a cohort of New Zealand men aged 35–74 years and women aged 35–69 years at the population level. This is the first formal validation of the Framingham Heart Study risk equation in a New Zealand population. These findings provide indirect support for the decision to base New Zealand cardiovascular risk charts on a Framingham Heart Study risk equation.[2,3]

Although it is accurate at a population level, the Framingham risk equation has only modest accuracy at the individual level. For example, an ‘at risk’ threshold of 10% five-year cardiovascular risk or above would have identified approximately 15% of this cohort but accounted for only about half of all events occurring in the subsequent five-year period.

This study was based on a heterogeneous population, combining a representative population sample from electoral rolls and a large working population of men and women. Although the latter sample was obtained from a single corporation, the company included all occupational groups and all major ethnic groups (including 10% Maori and 5% Pacific), over a wide range of age and geographic sites throughout New Zealand. The risk equation should be used with caution in non-European ethnic groups because the numbers were too small to validate separately.

While baseline ECG data to determine left ventricular hypertrophy (LVH) were not available, this is unlikely to have a significant impact on risk prediction as ECG-diagnosed LVH is very rare in the general population without cardiovascular disease. HDL-cholesterol data were available only for the electoral roll cohort (28% of all participants) and this may have reduced the predictive validity of the Framingham equation.

The Framingham risk equation used to predict risk was based on fatal and non-fatal, and hospitalised and non-hospitalised, cardiovascular events, whereas in our study only hospitalised and fatal events were included. However, it is likely that many individuals whose first cardiovascular event did not require hospitalisation, were subsequently hospitalised or would have died of cardiovascular disease during the follow-up period and therefore would have been captured in the national outcomes data set we used. The five-year cardiovascular mortality rate was low (4.7 per 1000) because the cohort was free of cardiovascular disease and elderly individuals were under-represented as the Fletcher Challenge cohort was a working population (eg, there were fivefold fewer men aged 65–69 than aged 55–59 years).

Risk prediction appeared to be reasonably accurate in all age/sex groups except in women aged 70–74 years. While others have found that standard risk factors do not predict risk in older women as well as in older men,[4] the high event rate in older women in our study is likely to be a chance finding because routine morbidity and mortality statistics do not show the sudden upswing in events in older women observed in our study.

Risk prediction is reasonably accurate at least up to 20% five-year risk but its accuracy could not be confirmed for very-high-risk men and women (Figure 3). However, risk estimation is less important for these individuals because they are likely to have multiple risk factors and their requirement for treatment is obvious.

We cannot be certain that we have captured all events because some individuals may suffer events outside the New Zealand health system and exclusion of those individuals with a self-reported cardiovascular history could lead to under- or over-estimation of results. However, such effects are likely to be small.

We report the accuracy of risk prediction at the individual level separately.[11] There is a pressing need for large local studies to provide valid risk assessment in Maori, Pacific and Asian peoples. It is somewhat surprising that the best tools available to assess the risk of the world's most common cause of death and disability remain inadequately evaluated and are based only on a study of about 5000 people from a town in the north-east of the United States.

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References:

1. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991;121:293–8.
2. 1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. Dyslipidaemia Advisory Group on behalf of the scientific committee of the National Heart Foundation of New Zealand. NZ Med J 1996;109:224–31.
3. Guidelines for the management of mildly raised blood pressure in New Zealand. Wellington: Core Services Committee, Ministry of Health; 1995.
4. Grundy SM, D'Agostino Sr RB, Mosca L, et al. Cardiovascular risk assessment based on US cohort studies: findings from a National Heart, Lung, and Blood institute workshop. Circulation 2001;104:491–6.
5. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–7.
6. MacMahon S, Norton R, Jackson R, et al. Fletcher Challenge-University of Auckland Heart & Health Study: design and baseline findings. NZ Med J 1995;108:499–502.
7. Jackson R, Yee RL, Priest P, et al. Trends in coronary heart disease risk factors in Auckland 1982-94. NZ Med J 1995;108:451–4.
8. Whitlock G, MacMahon S, Vander Hoorn S, et al. Socioeconomic distribution of smoking in a population of 10,529 New Zealanders. NZ Med J 1997;110:327–30.
9. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation 1991;83:356–62.
10. Anderson KM. A nonproportional hazards Weibull accelerated failure time regression model. Biometrics 1991;47:281–8.
11. Milne RJ, Gamble GD, Whitlock G, Jackson RT. Discriminative ability of a risk-prediction tool derived from the Framingham Heart Study compared with single risk factors. NZ Med J 2003;116(1185). URL: http://www.nzma.org.nz/journal/116-1185/663/