Clinical research

Exercise testing of healthy men in a new perspective: from diagnosis to prognosis

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Aim It has recently been suggested that exercise testing may be more valuable prognostically than it is diagnostically in apparently healthy subjects. We wanted to compare the accuracy of CHD risk assessment based on classical risk factors with an assessment also based on multiple exercise test parameters.

Methods and results In 1972–75, 2014 apparently healthy men aged 40–60 had a symptom limited exercise test during a cardiovascular survey. Three hundred died from CHD during 26 years of follow-up. Compared to Cox regression models solely including classical risk factors (CRF), models also including multiple exercise test parameters (CRF+X) were clearly superior ($P < 0.0001$). Risk scores were computed based on the models. CRF and CRF+X risk scores often differed markedly; CRF+X scores were generally most reliable in both the high and low risk range. In smokers with cholesterol > 6.5 mmol/l ($n = 470$), the CRF and CRF+X models identified 67 vs. 110 men at the highest CHD risk level according to European guidelines (34.2% vs. 38.2% CHD mortality). Three in five CRF+X-identified smokers with cholesterol > 6.5 mmol/l had CHD mortality similar to the mean of all 2014 men.

Conclusion Integration of multiple exercise test parameters and conventional risk factors improved CHD risk assessment substantially – especially in smokers with high cholesterol.

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KEYWORDS
Exercise testing;
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Prediction;
Healthy men;
Follow-up studies

Introduction

Based on the worldwide epidemiological experience, the evaluation of cardiovascular risk, given in the recent European guidelines on cardiovascular disease prevention,¹ is based on four time-honoured classical coronary and cardiovascular disease (CHD and CVD) risk factors: age, serum cholesterol, resting systolic blood pressure and smoking status. Exercise testing – a valuable diagnostic tool in populations with established CHD – is not recommended in asymptomatic subjects due to both lacking evidence of its value and, especially, because false positive exercise ECGs are common.² However, this view is mainly based on the diagnostic value of exercise testing, and Ashley et al.³ recently suggested in their literature review that emphasis should be shifted from a diagnostic to a prognostic perspective. It is well known that several exercise test indices, besides ECG findings, such as exercise capacity,⁴ heart rate responses both during and after exercise⁵ and blood pressure responses,⁷ are strong predictors of cardiovascular events. However, few studies have explored the combined predictive abilities of such data, or tried to compare the
accuracy of CHD risk stratification, provided by a classical prediction model, with a model also including multiple exercise test parameters in apparently healthy subjects. The present report aims at providing such evidence.

Methods

Between 28 August 1972 and 30 March 1975, 2014 apparently healthy males aged 40–60 years participated in a cardiovascular survey at the University Hospital of Oslo, Norway. These were recruited from five Governmental agencies as described previously. Subjects with known or suspected CHD, other heart diseases, diabetes mellitus, treated hypertension, cancer, miscellaneous other chronic diseases, those unable to conduct a bicycle exercise test or were taking drugs regularly were excluded. Those with intercurrent febrile illnesses had to wait for at least 14 days before being examined. All were asked to fast for 12 h and abstain from smoking for at least 8 h.

Examination program

The examination program included height/weight and blood pressure measurements, a panel of blood tests, a case history (including smoking data obtained from a comprehensive questionnaire), clinical examination, resting ECG and a symptom limited exercise ECG test using an electrically braked Elema bicycle (Elema, Stockholm, Sweden). The starting load was 100 W, and the load was increased by 50 W every 6 min until exhaustion unless stopped earlier for safety reasons. Resting systolic blood pressure was measured three times with a mercury sphygmomanometer to the nearest 2 mmHg, after 5 min supine rest. The second reading almost always gave the lowest value, and was therefore chosen. Maximal heart rate was determined from the exercise ECG immediately prior to termination of exercise. ECGs were recorded at rest prior to the test, at 2, 4 and 6 min on all loads, at test termination, and at 1, 2, 3 and 5 min post exercise in the supine position. During the baseline survey (Survey 1), 105 men, suspected to have latent CHD based mainly on exercise ECG findings, underwent coronary angiography; 70 (67%) had a pathological angiogram. All participants and their physicians were informed about all survey findings.

A similar survey (Survey 2) was conducted during 1980–82; 1756 men (91% of all alive) participated, and among these 1428 (81%) remained healthy according to the baseline inclusion criteria. HDL cholesterol was measured in 95% of these men (but only in 8% during Survey 1). Data from Survey 2 have been used to validate results derived from Survey 1.

We defined two sets of predictors for CHD death:

- **Classical risk factors (CRF):** Age, total cholesterol, resting systolic blood pressure and smoking status (currently smoking/not smoking). These are included in the risk chart used in the European guidelines on cardiovascular disease prevention.

- **Exercise predictors (X):** Physical fitness (cumulative work during exercise divided by body weight), maximal heart rate, systolic blood pressure at the end of the first exercise load (100 W), and exercise ECG interpretation (ST-depression ≥1.0 mm 0.08 s after the J-point regardless of ST-segment morphology). Our choice of exercise predictors was based on standard knowledge in the literature supported by previous reports from our group.

Mortality and morbidity data

The Norwegian Data Inspectorate and the Norwegian Board of Health gave permission to obtain morbidity and mortality data. Mortality data were retrieved from the database of Statistics Norway covering all deaths in Norway, for our purposes complete up to 31 December 1999. Morbidity data, including data on diabetes, were obtained from one questionnaire survey taken in 1987, two additional clinical surveys taken in 1989–90 and 1995–96 and a nationwide search of all patient records from all Norwegian hospitals in 1995–96. Deaths caused by ischaemic heart disease and sudden, unexpected deaths were classified as coronary deaths. Cardiovascular deaths also include deaths caused by stroke and ruptured aortic aneurysms.

Statistical methods

Proportional hazards (Cox) models were used to (a) study associations between the selected predictors and time to death, and (b) to compute individual age, standardised CHD risk scores (estimated linear predicted values). Associations between the continuous variables and CHD mortality were all approximately linear. Diagnostic plots of log(S(t)) vs. log(t) indicate that the proportional hazards assumptions are acceptably fulfilled for all parameters used. Associations (a) are presented as relative risks (RRs) related to an increase of 1 SD for continuous variables and between group ratios for discrete variables.

We mainly studied two Cox models: a CRF model, which included the classical risk factors, and a CRF+X model, which included both the CRF and the exercise predictors. The covariates were age-standardised to obtain risk scores not dependent on age (b), with age set to 49.8 years (population mean) for all participants in analyses based on Survey 1, and to 56.6 years in analyses based on Survey 2. Resting systolic blood pressure, maximal heart rate, exercise blood pressure and physical fitness (after log transformation) were all an approximate linear function of age with the dispersions around the regression lines virtually independent of age. The age-standardised values were computed as the differences between the original values and the respective regression lines.

Proportional hazards models (Table 2) were compared using standard likelihood ratio statistics. All P-values are two-tailed, and a model parameter is described as significant if the corresponding P-value is below 0.05. To avoid that a subject’s risk score was affected by his own outcome, we used a cross validation procedure where each man’s risk score (b) was computed using a Cox model based on all participants except himself.

Subjects were classified into strata of increasing CRF and CRF+X risk. Differences in the abilities to discriminate risk, in relation to observed CHD mortality, were compared both across strata of equal sizes (quintiles) and across strata within defined risk levels. The CHD mortality in groups, defined according to estimated cross-validated risks (Tables 3–5), is presented as crude percentages (number of deaths divided by group size). As the CRF+X models identify non-CHD risk groups somewhat better than the CRF models (see below), these crude percentages provide modestly conservative estimates of CRF vs. CRF+X differences. In order to compare such differences across fixed risk strata we used the risk stratification scheme for cardiovascular death, as suggested by the European Guidelines based on the SCORE database. In order to obtain an approximately similar risk stratification for both CHD mortality
and cardiovascular mortality, the mean annual CHD mortality for the 26 years and the mean annual cardiovascular mortality for 10 years in the SCORE database was compared, with the assumption that 80% of all cardiovascular deaths were coronary. We have also included a brief reference (Table 4) to the concept of "CHD risk equivalence" as introduced in the recent report by the National Cholesterol Education Program Adult Treatment Panel III.

In order to study the effects of increasing pre-test CHD risk, we also analysed subgroups of individuals with one or more CRF above the defined levels associated with increased risk. These CRF included the habit of smoking, resting systolic blood pressure >140 mmHg, and serum cholesterol >6.5 mmol/l.

Results

Table 1 gives the relevant Survey 1 data of all 2014 men, and Survey 2 data of the 1428 men who remained healthy.

Table 2 demonstrates that all classical risk factors and exercise parameters are significant predictors of 26 years' CHD risk, both in separate and combined Cox models. Comparing the likelihood ratio statistics, it appears that the CRF+X model provides clear statistically significant improvement both compared to the CRF and the X model (P < 0.0001). In the following, we shall attempt to illustrate how this statistical improvement is reflected in risk discrimination.

Table 3 indicates steep and similar gradients in age-adjusted CHD mortality across risk quintiles based on the CRF and the X only model, but a steeper gradient for the CRF+X model. All models show a good correspondence between the predicted and the observed numbers of deaths. The CRF+X model was also able to better discriminate between high and low non-cardiovascular risk, compared to the CRF model (data not shown). Relative CRF vs. CRF+X differences were similar in the 40–50 and 50–60 years age range (data not shown).

In a substantial number of men there was a marked discrepancy between CRF and CRF+X risk classification. In these cases, mortality data mainly followed the CRF+X classification, clearly indicating that the CRF+X scores were the most accurate (data not shown).

Table 4 shows three examples of the CRF and the CRF+X model performance in a few selected subgroups:

Example 1 — total population

The CRF+X model identified twice as many men in the deep red risk zone1 ("very high risk") compared with the CRF model (157 vs. 79). The CRF model also identified a higher mortality (38.2% vs. 34.2%). CHD mortality among these CRF+X-identified men was also higher than the mortality observed in 70 men with a pathological baseline coronary angiogram (38.2% vs. 35.2%, see Methods section).

Example 2 — men with one defined CRF

Among smokers, substantial differences in favour of the CRF+X classification appear. The CRF and the CRF+X model identified 77 and 143 men (1/6 of all smokers) with very high risk, respectively, and 5.4% vs. 22.9% in the orange and yellow (low) risk zones. CRF vs. CRF+X differences for men with high cholesterol were also markedly in favour of the CRF+X model, however this was somewhat smaller than for smokers (70 vs. 123 men, n = 1024). There were 74 vs. 103 men with very high CRF vs. CRF+X risk among men with blood pressure >140 mmHg (n = 526).

Example 3 — men with combined CRFs

Among smokers with high cholesterol, the CRF model identified 67 men with very high risk, whereas the CRF+X model identified 110. Fig. 1(a) shows how the CRF and the CRF+X risk distributions differ. Fig. 1(b) demonstrates how these differences are reflected in terms of CHD mortality. Importantly, differences in mortality appear early during follow-up. The CRF model indicates that 4/5 have a clustering of mortality clearly above the mean of the total population of 2014 men. The CRF+X model, on the other hand, identifies one group with very high mortality and 3/5 with a mortality similar to the mean of the total population despite being smokers with high cholesterol.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Survey 1 (n = 2014)</th>
<th>Survey 2 (n = 1428)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Classical risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Systolic blood pressure at rest (mmHg)</td>
<td>130.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>43.8</td>
<td>32.8</td>
</tr>
<tr>
<td><strong>Exercise test data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical fitness (kJ/kg)</td>
<td>1.46</td>
<td>0.57</td>
</tr>
<tr>
<td>Exercise ECG interpretation (% positive)</td>
<td>10.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>162.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Systolic blood pressure at 100 W (mmHg)</td>
<td>181.5</td>
<td>24.3</td>
</tr>
</tbody>
</table>

Characteristics of all 2014 healthy men at the baseline examination in 1972–75, and of the 1428 men who were still healthy at the follow-up examination in 1980–82.
A Cox model, combining the CRF and exercise ECG interpretation as the only exercise predictor, identified 98 men with very high risk (mean CHD mortality 33.7%) compared to 79 men using the CRF model (see Table 4). Thus predictive abilities were improved, but only modestly compared to the improvement achieved by the CRF+X model. A similar model combining the CRF and physical fitness as the only exercise predictor identified 114 men with very high risk.

Increasing CRF+X risk, but not CRF, was strongly associated with increasing incidence of diabetes (Fig. 2). The CRF+X also appeared to enhance CHD risk assessment in men with fasting blood glucose in the upper normal range (details not shown).

The CRF vs. CRF+X differences, found when using new models based on Survey 2, were similar to the differences between models based on Survey 1 (Table 5). Despite the predicted CHD mortality being higher than the observed mortality, due to a marked sequential decline in CHD mortality during the observation period, the risk scores based on the "old" models from Survey 1 and the risk factor values from Survey 2, demonstrated similar CRF vs. CRF+X differences in predictive abilities.

**Discussion**

Previous attempts to integrate exercise testing in CHD risk assessment of asymptomatic subjects have been only modestly successful. Only one study has, to a limited extent, considered exercise predictors other than ECG interpretation. Our present paper is the first long-term follow-up study to compare a CHD risk assessment model, based on classical risk factors, with a model including both classical risk factors and multiple exercise test.
Table 4  Distribution of men and their 26 years CHD mortality within strata of increasing CHD risk according to the CRF and the CRF+X model

<table>
<thead>
<tr>
<th>CHD risk/ year (%)</th>
<th>All deaths/group size (%)</th>
<th>Smokers deaths/group size (%)</th>
<th>Smokers with cholesterol &gt; 6.5mmol/l deaths/group size (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRF model</td>
<td>CRF+X model</td>
<td>CRF model</td>
</tr>
<tr>
<td>&lt; 0.16</td>
<td>0/1 (6.2%)</td>
<td>3/48 (6.2%)</td>
<td>0</td>
</tr>
<tr>
<td>0.16-0.23</td>
<td>7/58 (12.1%)</td>
<td>7/209 (3.3%)</td>
<td>0</td>
</tr>
<tr>
<td>0.24-0.39</td>
<td>73/781 (9.6%)</td>
<td>71/718 (9.9%)</td>
<td>2/48 (4.2%)</td>
</tr>
<tr>
<td>0.40-0.79</td>
<td>125/837 (14.9%)</td>
<td>102/635 (16.1%)</td>
<td>78/501 (15.6%)</td>
</tr>
<tr>
<td>0.80-1.19</td>
<td>68/278 (24.5%)</td>
<td>57/247 (23.1%)</td>
<td>64/257 (23.9%)</td>
</tr>
<tr>
<td>&gt; 1.20</td>
<td>27/199 (34.2%)</td>
<td>60/157 (38.2%)</td>
<td>26/77 (33.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>300/2014 (14.9%)</td>
<td>300/2014 (14.9%)</td>
<td>170/883 (19.3%)</td>
</tr>
</tbody>
</table>

Coronary heart disease (CHD) mortality after 26 years among 2014 initially healthy men aged 40–60 years within strata of increasing age adjusted CHD risk, as indicated by two proportional hazards models. One model is based on classical risk factors only (CRF), and the other on classical risk factors plus multiple exercise test parameters (CRF+X). The definitions of risk levels and colour coding relate to the cardiovascular risk classification suggested by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice based on the SCORE database (see Methods section).

Assuming a mean ratio of 2.5 between incident “hard” CHD and CHD deaths.15–18
parameters. We have found the latter model to substantially improve the accuracy of CHD risk estimates.

**Improved predictive abilities**

For all comparisons investigated, the CRF + X model had superior predictive abilities compared to the CRF model, and absolute differences in favour of CRF + X increased with increasing pre-test CRF risk. The CRF + X model identified twice as many very high risk subjects as the CRF model (7.8% vs. 3.9%), and these CRF + X-identified men also had higher mortality—even exceeding that of men with a positive coronary angiogram at baseline. It is suggested that this finding is clinically relevant. Similarly, 90% of all CRF + X-identified subjects with very high risk were smokers, and almost one in four of smokers with high cholesterol had very high risk (Table 4).

**Levels of CHD risk (26 years):**

CRF quintiles: Q1: < 17.4%, Q2: 17.4% - 20.2%, Q3: 20.3% - 23.3%, Q4: 23.4% - 27.5%, Q5: > 27.5%

CRF+X quintiles: Q1*: < 13.2%, Q2*: 13.2% - 17.7%, Q3*: 17.8% - 23.2%, Q4*: 23.3% - 31.1%, Q5*: > 31.1%

Fig. 1 (a) Distributions of CHD risk according to the CRF vs. the CRF + X model among smokers with serum cholesterol > 6.5 mmol/l (n = 470). Histograms of the coronary heart disease (CHD) risk distributions according to the CRF and the CRF + X proportional hazards prediction models. "CRF" represents a model based on classical risk factors only, and "CRF + X" a model based on the CRF plus selected exercise test parameters. Data are based on data from the baseline examination in 1972–75 and 26 years of follow-up of 470 initially healthy men aged 40–60 years who were smokers and had serum cholesterol > 6.5 mmol/l. (b) Survival from CHD within quintiles of increasing CHD risk according to the CRF model vs. the CRF + X model among smokers with serum cholesterol > 6.5 mmol/l (n = 470). Kaplan–Meier plots of survival from coronary heart disease (CHD) within quintiles Q1–Q5 vs. Q1*–Q5* of increasing CHD risk according to CRF vs. CRF + X estimates. "CRF" represents a Cox proportional hazards model based on classical risk factors only, and "CRF + X" a Cox model based on the CRF plus selected exercise test parameters. Data are based on data from the baseline examination in 1972–75 and 26 years of follow-up of 470 initially healthy men aged 40–60 years who were smokers and had serum cholesterol > 6.5 mmol/l.
proved to have only average CHD mortality according to CRF, but not according to the CRF model (Fig. 1(b)). In other words, the CRF + X model identified a substantial number of men with high pre-test CRF risk with comparatively low long-term CHD mortality. Thus, healthy smokers with high cholesterol should represent one subgroup well-suited for exercise testing in which post-test data can be used as a guide to suggest primary preventive measures and/or indications for further investigations.

Information not provided by conventional CHD risk assessment

Numerous studies have explored the diagnostic value of exercise ECG testing in asymptomatic subjects. This issue was studied in the present cohort study during Survey 1. In other words, the CRF + X model identified a substantial number of men with high pre-test CRF risk with comparatively low long-term CHD mortality. Thus, healthy smokers with high cholesterol should represent one subgroup well-suited for exercise testing in which post-test data can be used as a guide to suggest primary preventive measures and/or indications for further investigations.

Table 5 Prediction of 19 years CHD mortality in Survey 2 population

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Comparison of the CRF and the CRF + X model derived from Survey 2 data</th>
<th>Comparison of the CRF and the CRF + X model derived from Survey 1 data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRF model</td>
<td>CRF + X model</td>
</tr>
<tr>
<td></td>
<td>Number of deaths</td>
<td>Number of deaths</td>
</tr>
<tr>
<td></td>
<td>Predicted</td>
<td>Observed</td>
</tr>
<tr>
<td>1</td>
<td>14.7</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>19.9</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>24.9</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>32.4</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>51.0</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td>142.9</td>
<td>143</td>
</tr>
</tbody>
</table>

Predicted and observed coronary heart disease (CHD) mortality within quintiles of increasing age adjusted CHD risk. The risk estimates on the left side are computed from CRF + X and CRF models based on Survey 2 data and 19 years of follow-up of 1428 men who remained healthy at Survey 2. The estimates on the right side are computed from CRF + X and CRF models based on Survey 1 data from 2014 healthy men and 19 years of follow-up, with insertion of Survey 2 data from 1428 men who remained healthy at Survey 2 (note that in the latter case predicted numbers of deaths are higher than observed numbers).

1. The CRF + X model was superior to the CRF model in discriminating between subjects at high and low non-cardiovascular risk.
2. There was a strong association between CRF + X risk and the incidence of diabetes, which was not seen when using the CRF model.
3. Men with fasting blood glucose levels in the high-normal range may also benefit from CRF + X screening, in concert with our previously reported increase in CHD mortality among men with high-normal fasting blood glucose. Considering the increasing incidence of diabetes, the role of exercise testing as a prognostic tool in subjects with at least high-normal fasting blood glucose should be studied further (see ACC/AHA Guidelines).

Prediction models are rarely tested for robustness in the presence of changes in outcome incidence, but such robustness should not be taken for granted. In this study, differences in risk-discriminating abilities were largely maintained despite a marked sequential decline in CHD mortality during the follow-up period; similar mortality...
declines have been seen in most developed countries. Moreover, the choice of CHD death, the hardest CHD end-point, may be important since its definition does not change like the definition of myocardial infarction for example.

In summary, our main findings should qualify as level 2b evidence according to the criteria of the NHS Research and Development Centre for Evidence Based Medicine.

**Other studies of asymptomatic populations**

Bruce et al. made the first attempt to add several exercise test parameters in a prognostic model when studying future CHD events. However, comparison with our study is of moderate value since follow-up was short, data were somewhat incomplete, and the analyses were mainly based on categorical data. Moreover, the low number of deaths necessitated inclusion of soft CHD end points, further making comparison difficult.

In the AHA/ACC Guidelines on exercise testing, seven additional studies are listed in which exercise testing has been introduced for prognostic purposes in asymptomatic subjects. However, besides having relatively short observation times, these studies cannot be compared to ours as they are based on exercise ECG interpretation only. As clearly shown by us, the inclusion of exercise ECG interpretation alone improved the predictive abilities only modestly.

**Contribution of classical risk factors vs. exercise predictors to CHD risk estimates**

It is unsettled how the exercise parameters add prognostic information to the classical risk factors. In an attempt to elucidate this important consideration we also compared risk scores based on the CRF model with scores based only on the exercise predictors (X-model; Table 3). Interestingly, both models had comparable total high/low risk discriminatory properties, but the models identified different subjects to a large extent. Although epidemiological data can never prove causation, these observations suggest that the CRF and the exercise predictors contribute to risk assessments through different mechanisms. The classical risk factors probably operate through their basic influence on atheromatosis development. The exercise predictors, on the other hand, possibly add most of their prognostic information by unveiling the presence of asymptomatic CHD. Silent ischaemia may thus be indicated by ST-depressions and/or poor fitness in some cases; CHD-related disturbances in autonomic regulation by the attenuation of maximal heart rate and impaired arterial compliance by an early, excessive rise in exercise blood pressure. Incidentally, in this study an exaggerated blood pressure response was a strong predictor of CHD mortality even among the most fit (details not shown).

If accepted as coherent, these considerations would suggest that CRF risk assessments might maintain their value in all age groups. CRF+X risk assessment should possibly only be advocated among middle aged and old subjects, among whom sub-clinical CHD is increasingly prevalent, and they might serve as an impetus for considering further examinations and/or initiating aggressive primary preventive measures when exercise test data indicate adverse prognosis.

**Introduction of other predictors**

We have tried to refine our CRF+X model further by including other exercise parameters, such as post-exercise heart rate recovery, but with only modest success. Combination of several inter-correlated variables however, such as heart rates at different stages of an exercise test should be considered with caution, especially from a statistical point of view. Substitution e.g., of maximal heart rate with heart rate increase during exercise principally gave the same results. Addition of other CHD risk factors like fasting blood glucose, erythrocyte sedimentation rate, CHD inheritance (first degree relative developing CHD before age 60) and HDL data from Survey 2 improved predictive abilities minimally (data not shown).

**Study limitations**

Although we have used a statistical cross validation procedure and shown that the results based on Survey 1 hold true even when data from Survey 2 are introduced, our results have still to be fully validated. Although being apparently healthy at baseline, our study population recruited in the mid 1970s had a high CHD mortality compared to the risk levels at which primary preventive intervention is indicated according to recent recommendations. Besides, risk-factor levels and risk-factor interactions may vary from one population to another, and our analyses should be repeated by others.

Our data may have been biased by the participants receiving advice on how to change their lifestyle (e.g., exercise, quit smoking, etc.) when appropriate, and the study findings (including coronary angiograms of 105 men) also being reported to their physicians. Such bias probably led to an underestimation, rather than an overestimation, of the prognostic significance of exercise testing. The significance may also have been underestimated by our very long term follow-up, since CRF vs. CRF+X differences appeared to be even larger in analyses based on shorter follow-up (e.g., 15 years, data not shown). This is not surprising considering, after 26 years, a large proportion of the survivors were in their 80s.

The relation between pre-test CRF risk and the prognostic significance of exercise test data may be biased by our choice of CRF cut-off levels. However, when analysing the data by sliding these levels up or down similar general patterns consistently emerged (details not shown).

We have only examined healthy men aged 40–60 years, and it is probably unwise to extrapolate to women, beyond these age limits, or to subjects with clinical symptoms or signs of heart disease.
Exercise test data in combination with conventional risk factors improved, in many instances substantially, CHD risk assessment in apparently healthy, middle-aged men, both in the high and low risk range. When conventional screening suggests high risk, exercise testing can probably be advocated as a means to decide further actions, particularly among smokers with high cholesterol.

### References


