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Cost-effectiveness of primary prevention of coronary heart disease through risk factor intervention in 60-year-old men from the county of Stockholm—a stochastic model of exercise and dietary advice

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Abstract

Background. Recent screenings show a high prevalence of cardiovascular risk factors in the county of Stockholm. Primary prevention may be a way to lower the risk burden of coronary heart disease, but we must establish that preventive programs are cost-effective.

Methods. Through the use of a stochastic Markov model, which predicts reduction in coronary heart disease events based on risk factor reductions, this study evaluates the results of a previous controlled trial in middle-aged men comparing dietary advice, exercise, and the combination of both applied to an observed cohort of 60-year-old men in the county of Stockholm.

Results. The model predicts lower costs and higher effectiveness for dietary advice compared to the alternatives. Assuming a declining effect of the intervention, dietary advice saves 0.0228 life-years compared to no intervention. If no decline is assumed, the corresponding figure is 0.0997 life-years. From the societal perspective, the added costs are 2,892 Swedish Kronor (SEK) and 14,106 SEK for the two modeling assumptions, resulting in a cost-effectiveness of 127,065 SEK per life-year gained (LYG) and 141,555 SEK/LYG. These figures are below what is generally thought of as cost-effective.

Conclusion. Based on the model, dietary advice appears to be the most cost-effective of the studied interventions.

Keywords: Primary prevention; Diet; Exercise; Cardiovascular disease; Economics, Medical

Introduction

Cardiovascular disease and particularly coronary heart disease (CHD) are the most common causes of death in Sweden, responsible for 49% of all deaths in 1996. Acute myocardial infraction contributed to one-fourth of the cardiovascular deaths [1]. To reduce the number of fatalities due to CHD, primary prevention may be a viable option. Prevention of CHD can be directed at several risk factors. These factors include smoking, high blood pressure, high cholesterol levels, overweight, physical inactivity, and others [2]. A recently performed screening of 60-year-old men and women in the county of Stockholm showed that large parts of the population are exposed to such risk factors and thus face a serious risk of suffering from CHD events [3]. Primary prevention may be a way to lower that risk.

When considering an intervention, it has become increasingly important to take into account the economic effects of the treatment as well as the efficacy [4]. The cost-effectiveness of a treatment is dependent on the cost of the treatment as well as on the risk in the treated group of individuals. Studies have shown that secondary prevention can be very cost-effective in certain risk groups. This has been shown, e.g., for cholesterol-lowering therapy in the 4S study [5,6]. In primary prevention, the effect is more uncertain, since the

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Table 1
Effect of intervention on some cardiovascular risk factors based on the diet and exercise study (mean reduction (SD))

Treatment group	Total cholesterol (mmol/L)		Diastolic blood pressure (mm Hg)	
	0–6 months	6–18 months	0–6 months	6–18 months
Diet	−0.19 (0.94)	−0.32 (0.69)	−6.07 (6.78)	−3.76 (7.95)
Exercise	−0.12 (0.71)	−0.22 (0.59)	−4.21 (7.23)	−3.0 (7.19)
Diet + exercise	−0.45 (0.99)	−0.15 (0.77)	−1.23 (7.36)	−2.87 (7.52)

risk is lower than in patients already suffering from CHD. Generally, results from studies on primary prevention in the larger population have been indecisive [7]. Hypertensive treatment has been shown to be reasonably cost-effective in middle-aged and older patients [8]. This implies that cost-effectiveness ratios may be favorable if the correct preventive measures are directed at the correct group. One way to identify target groups for preventive measures when cost-effectiveness constraints apply is through modeling. In a recent study by Johannesson [9], this was done to estimate at what total risk levels it is cost-effective to initiate cholesterol-lowering treatment. Many interventions affect more than one risk factor, which makes it necessary to use risk functions to model the risk.

The purpose of this project was to develop a general model to simulate costs and effects of various preventive measures among 60 year olds in Stockholm based on a recently performed screening. As an illustrative example we have evaluated the cost-effectiveness of dietary and/or exercise advice based on a study on risk factor reduction through these measures performed on a middle-aged group of healthy men in Stockholm in the early 1990s [10]. The long-term cost-effectiveness of exercise on cardiovascular disease in the United States has previously been studied by Hatziandreu et al. [11] and in Canada by Lowensteyn et al. [12]. Dietary advice (in Sweden) was included as a component in a study by Johannesson et al. [13]. None of these studies include costs in added years of life as a component, which recent health-economic research shows should be included if the full effects from a societal perspective are to be captured [14]. Since none of the previous studies uses stochastic techniques, no information about the distribution of their results is available, which also merits further research. This is also, according to our knowledge, the first study comparing dietary and exercise advice.

Material and methods

In order to determine the effects of primary prevention a stochastic Markov model has been constructed. It is used to evaluate the effects of intervention for people enrolled in the screening program fulfilling the inclusion criteria of the diet and exercise study.

The diet and exercise study

This study was performed in the county of Sollentuna, near Stockholm. A total of 160 men aged 35–60 were randomized to dietary advice (group D), exercise (group E), dietary advice and exercise (group DE), or a control group. The results have been reported elsewhere [10]. Inclusion criteria were no previous cardiovascular disease, diabetes, or other severe illnesses; no regular use of drugs; total cholesterol between 5.2 and 7.8 mmol/L; fasting triglycerides $<=5.6$ mmol/L; fasting blood glucose $<=6.7$ mmol/L, and diastolic blood pressure $<=100$ mm Hg. Patients underwent a first physical checkup during a visit to a physician. After randomization, they received advice on diet and/or exercise from the physician. Patients in the two groups receiving dietary advice also visited a dietitian who gave further individual advice. The dietitian also made a follow-up after 3 months to check compliance with the given advice. Patients in the exercise groups were asked to maintain a prepared activity log and were given the opportunity to join exercise groups. Patients were followed up at 6 and 18 months; the results on risk factors are shown in Table 1.

The 60-year-old cohort

Recently, the first phase of a screening program involving individuals living in the county of Stockholm and born between July 1, 1937, and June 30, 1938, i.e., individuals aged 60 at the time of the screening, has been concluded. In the program 5,460 men and women, or one-third of the 60-year-old population in the county of Stockholm, were invited to participate in medical examinations as well as to fill in extensive questionnaires on their perceived health, habits, socioeconomic situation, and more. A total of 78%, or 4,232 persons, chose to participate in the program. The cohort will be followed for several years, tracking cardiovascular events as well as changes in the risk profiles.

Analysis of the risk factors of the members of the cohort shows that 12% of the women and 21% of the men had cholesterol levels at ideal levels ($<=5.0$ mmol/L) and 19% of the women and 38% of the men suffered from elevated blood pressure (diastolic blood pressure >90 mm Hg). A total of 70% of the men and 60% of the women could be considered as suffering from overweight while as many as

Table 2
Risk factor profile of the 60-year-old male study population

Risk factor	
DBP (mm Hg)	84.1
Total cholesterol (mmol/L)	6.1
Current smoker (%)	19.9
LVH (%)	2.7
Glucose intolerance (%)	7.1

19 and 20%, respectively, could be considered obese with a body mass index (BMI) >=30 [3].

Diastolic blood pressure and cholesterol levels were measured in the screening and thus were directly available from the database, as was the smoking status of the individuals. ECGs were taken during the screening process and the occurrence of LVH according to the Minnesota code was evaluated independently. Plasma glucose levels were recorded during the screening process and patients with a plasma glucose level >6.1 mmol/L was labeled as suffering from diabetes mellitus.

From the screening database, those individuals without prior CHD have been extracted for analysis, in all 3,859 persons. Of these, 856 persons fulfilled the inclusion criteria of the previously performed diet and exercise study. Since a primary prevention program is currently being undertaken in the county of Sollentuna, individuals living there were excluded, leaving 813 persons for the economic evaluation. The risk factor profile of these individuals is shown in Table 2.

The model

The model is a stochastic Markov model. Markov models classify patients into a number of discrete states, each associated with certain costs and effects. The development of the disease is represented by transition probabilities between the states. The model is updated in fixed intervals of time called cycles [15]. In a stochastic Markov model, the probabilities and effects are varied according to their distributions. The current model has 10 states: 1 state for individuals without CHD (the starting state), 4 first-year states (one each for stable angina, unstable angina, recognized MI, and unrecognized MI), 4 states for the second and following years (one each for the diseases specified earlier), and finally 1 state for death.

The model uses yearly cycles (half cycle correction is applied). Each year, healthy individuals suffer a risk of having a CHD event, which means progression to one of the first-year states or to death if the event is sudden death (death within 1 of disease onset). Patients in a first-year state either die due to increased mortality during this year or move to the corresponding "second and following year" state. The maximum age allowed in the model is 109 years; after that all individuals are assumed to be dead. This model structure has previously been used when modeling the effects of hypertension [8,16], lipid lowering [6,9], and the effects of hormone replacement therapy [17,18].

The model is evaluated using second-order stochastic evaluation where inputs are varied stochastically according to their distributions (when available or reasonable assumptions could be made) and expected value calculations are performed for each of these variations. The model is run 6,000 times (the number of simulations needed to generate stable results).

Transition probabilities

Risk of cardiovascular events. The yearly risk of suffering a cardiovascular event, i.e., the yearly probability of transition from the healthy state to one of the states for the first year after an event, is given by a logistic risk function. The coefficients of the risk function are taken from the Framingham study [19] and include age, sex, total cholesterol, diastolic blood pressure (DBP), glucose intolerance, left ventricular hypertrophy (LVH), and smoking status (current smoker or not current smoker). In the stochastic evaluation, the parameter estimates in the Framingham model were varied according to their standard errors under an assumption of normality inherent in the model design.

Baseline risk factor characteristics were drawn from the distributions observed in the study population. Distributions were fitted using @ Risk 4.0 Best-fit. No changes in these risk factors (except from treatment effects) were assumed to occur over time.

The risk function used only specifies the risk of suffering an event. To determine what type of event has occurred (stable angina, unstable angina, sudden death, and recognized and unrecognized MI), the distribution of observed events from the Framingham study was used. These numbers were reported as absolute numbers, and they were therefore kept fixed in the simulation.

Mortality. Mortality in healthy individuals is assumed to be the same as for the general Swedish population for each age, corrected down by the fraction of deaths due to CHD. These data have been gathered from the Swedish population and causes of death registries [20,21]. The latest available figures, i.e., from 1996, have been used. The mortality during the first year after an event and for the following years is taken from the Framingham study [22]. The uncertainty of these estimates was not known, and they were therefore kept fixed during the evaluation.

The effects of intervention. The reduction in DBP and total cholesterol at 6 and 18 months is gathered from the diet and exercise study and is shown in Table 1. The risk factors are assumed to decrease linearly, which makes the 6- and 18-month observations good average estimates of the risk factor levels during the first and second years. Two alternative scenarios were explored for the period beyond the end of the study: in the first one the individuals are assumed to maintain the risk factor level achieved for the rest of their lives and in the second the risk factors are assumed to increase linearly back to the original levels during 2 years.

Health economic data

Three types of *costs* were used in the model: direct costs relating to direct health care expenditures as a result of the disease or intervention, indirect costs related to loss of production due to disease, and costs in added years of life defined as the difference in production and consumption due to extra survival [14]. Patient level direct and indirect costs related to cardiovascular disease were taken from a previous study by Zethraeus and colleagues [23] where costs of coronary events for patients admitted to the Södertälje Hospital in the county council of Stockholm were calculated. Direct costs included costs of in- and outpatient care and pharmaceuticals. Time and travel costs were not included. Indirect costs were assigned according to human-capital theory. The average direct costs for 1 year after the different events were 49,078 (recognized MI), 95,699 (unstable angina), and 47,634 Swedish Kronor (SEK) (angina pectoris). The corresponding indirect costs were 107,315, 96,535, and 76,010 SEK. When performing the stochastic evaluation, costs were drawn randomly (with replacement) from the observed patient-level data rather than drawing values from a fitted distribution, since the number of patients in the study was quite small. The Södertälje study did not include costs of unrecognized MI, nor did it include costs for the second and following years for the other events. Following assumptions made by Zethraeus [18], we assume that an unrecognized MI costs 3,500 SEK yearly in direct costs and 27,500 SEK in indirect costs and that the second and following year after all other events cost 7,000 SEK in direct costs and 55,000 SEK in indirect costs. We also assume that the standard deviation equals the mean in these cases, which is roughly the case for the figures from the Södertälje study. Costs in added years of life in Sweden have been calculated by Ekman [24]. No measure of spread was available for these figures, but a standard error of 8,000 SEK was used, assuming normality. All costs were in SEK adjusted to 2000 years value using the consumer price index (CPI).

Patients in all treatment groups made three visits to a physician (one at baseline and two follow-up visits) at a cost of 696 SEK. Patients in groups D and DE made one visit to a dietitian at a cost of 340 SEK, who also performed a follow-up by phone, estimated to half that cost based on the relation between the cost of a visit and advice by phone from a nurse (data on file, Stockholm County Council). We assumed that time and travel costs for making a visit equaled that of patients receiving hypertension treatment, i.e., 336 SEK at year 2000 value [8]. Patients in groups DE and E were given the opportunity to attend exercise groups, which 26% of group DE and 54% of group E accepted. The cost of running a group of 15 people is 7,500 SEK (personal communication, Korpen, Stockholm). Roughly 50% of members of both groups invested in new shoes, estimated to 700 SEK. No time cost was used for time spent on exercise during spare time, since such a figure is hard to estimate.

Table 3
Predicted survival based on the risk factor profile of the 60 year olds applied to different age groups

Sex and age	Statistics Sweden[a] (years)	Model prediction (years)
Man 50	29.11	26.76
Man 60	20.42	18.92
Man 65	16.45	15.08
Woman 50	33.23	30.65
Woman 60	24.18	22.14
Woman 65	19.92	17.89

[a] Source: [20].

Analysis was performed from two perspectives: that of the health-care payer (including only direct cost, which is reasonable since copayments are small in Sweden, and excluding time costs and out-of-pocket expenses) and that of society (including all costs). Number of life years gained (LYG) is used as the measure of *effectiveness* in the main analysis. Quality adjusted life-years (QALYs) are often used as a gold standard in economic evaluation. Due to lack of good data, particularly on distributions, of the reduction in quality of life due to cardiovascular events, QALYs were not included in the main analysis. However, they were included in a sensitivity analysis where the QALY loss was assumed to be 0.10 as was done in [25]. QALY weights for the healthy population have been taken from a study by Lundberg and colleagues [26]: 0.91 (60–64 years), 0.81 (65–74 years), 0.65 (75–84 years), and 0.60 (85+ years).

Cost-effectiveness is defined as

$$CE = \frac{\Delta C}{\Delta E} = \frac{C_i - C_n}{E_i - E_n}, \tag{1}$$

where C_i is the sum of all costs with intervention, C_n is the sum of all cost without intervention, E_i is the effect (number of life years or quality adjusted life years) with intervention, and E_n is the effect without intervention.

To adjust future costs and effects to net present value a *discount rate* of 3% has been applied to both costs and effects using continuously reinvested discounting (the discounting factor expressed as e^{-rt} where r is the discount rate and t is the time).

Validation

To validate the model, the survival years for an "average" Swedish patient aged 50, 60, and 65 were predicted and compared to life tables from Statistics Sweden [20].

As can be seen in Table 3, the model underestimates survival somewhat compared to Statistics Sweden. This may be due to the fact that the Framingham equation overestimates the risk somewhat in Swedish populations with normal risk [27]. Mortality rates after an event are also taken from the Framingham study, which may influence the

Table 4
Predicted mean (SD) costs and survival without intervention (base case) and with dietary advice, exercise, and dietary advice and exercise combined based on the two assumptions regarding the duration of intervention effect

	Direct costs (SEK)[a]	Direct costs (SEK), health care payer[b]	Indirect costs (SEK)[c]	Costs in added years of life (SEK)[d]	Total costs (SEK)[e]	Survival (years)
Base case	37,674	37,674	50,130	1,192,874	1,280,678	13.229
	(42,541)	(42,541)	(74,266)	(406,749)	(318,350)	(2.49)
Declining effect						
Diet + exercise	40,839	40,152	48,722	1,194,339	1,283,900	13.245
	(42,303)	(42,303)	(73,114)	(405,999)	(318,988)	(2.48)
Exercise	40,474	39,787	48,779	1,194,493	1,283,746	13.246
	(42,345)	(42,345)	(73,251)	(406,142)	(318,973)	(2.48)
Diet	40,258	39,921	48,209	1,195,103	1,283,570	13.252
	(42,237)	(42,237)	(72,723)	(405,808)	(319,183)	(2.48)
Remaining effect						
Diet + exercise	40,200	39,514	48,017	1,202,161	1,290,378	13.292
	(42,077)	(42,077)	(72,762)	(404,424)	(317,416)	(2.47)
Exercise	39,596	38,909	47,899	1,205,018	1,292,513	13.308
	(42,067)	(42,067)	(72,846)	(404,420)	(317,197)	(2.47)
Diet	39,170	38,834	47,286	1,208,328	1,294,784	13.329
	(41,901)	(41,901)	(72,426)	(404,130)	(317,325)	(2.47)

[a] Costs related to health care expenditures.
[b] Costs related to health care expenditures excluding patient copayments and out-of-pocket expenses.
[c] Costs related to work absence.
[d] The difference in production and consumption and production due to increased survival.
[e] The sum of a, c, and d.

results. However, the difference is not very large. The difference in survival decreases somewhat with age.

Results

The estimated (undiscounted) median survival for all individuals is 19.26 years. The model predicts a median of 0.085 first CHD events per person during the first 5 years and 0.47 first CHD events per person during the entire life span.

The predicted discounted mean survival along with costs from the societal perspective and the health care payer perspective can be found in Table 4.

The groups receiving dietary advice have the longest predicted survival regardless of assumptions about the long-term duration of effects. In fact, this alternative is a dominating strategy (either through lower costs or through extended domination) both from the societal and the health care payer perspective. The incremental cost and effect (life-years gained) and incremental cost-effectiveness can be found in Table 5. As can be seen in the table, an increased survival is predicted when no reduction is assumed. Cost-effectiveness ratios remain similar from the societal perspective, since the increase in survival is balanced by increased costs in added years of life. If considering only the cost for the health care payer, the incremental costs are cut in half, and hence the cost-effectiveness ratio is drastically reduced.

Sensitivity analysis

Table 6 shows the predicted number of QALYs. Dietary advice is still the better strategy, with an incremental effectiveness of 0.022 QALYs assuming declining effects of treatment and 0.086 QALYs if risk factors are kept constant after treatment. The corresponding cost-effectiveness ratios are 130,505 and 164,348 SEK/QALY gained (societal perspective) and 101,398 and 13,561 SEK/QALY gained (health care payer perspective).

Discussion

The predicted cost-effectiveness ratios are well within the limits of what is considered cost-effective, regardless of perspective and assumptions about the lasting effects on risk factors. As a comparison, the 4S trial on cholesterol lower-

Table 5
Cost-effectiveness of dietary advice compared to no intervention

	Incremental cost (SEK)	Life years gained (LYG)	ICER (SEK/LYG)[a]
Declining effect			
Societal perspective	2,892	0.0228	127,065
Payer perspective	2,247	0.0228	98,725
Remaining effect			
Societal perspective	14,106	0.0997	141,555
Payer perspective	1,164	0.0997	11,642

[a] Incremental cost-effectiveness ratio.

Table 6
Predicted mean (SD) QALYs without intervention (base case) and with dietary advice, exercise, and dietary advice and exercise combined based on the two assumptions regarding the duration of intervention effect

	QALYs[a]
Base case	10.242 (2.11)
Declining effect	
Diet + exercise	10.258 (2.10)
Exercise	10.258 (2.11)
Diet	10.264 (2.10)
Remaining effect	
Diet + exercise	10.297 (2.10)
Exercise	10.309 (2.10)
Diet	10.328 (2.09)

[a] Quality-adjusted life-years.

ing in secondary prevention showed a cost-effectiveness ratio of 56,400 SEK per LYG (from the health care payer perspective) [5]. It may seem surprising that an intervention with limited effect shows such a good cost-effectiveness ratio, but the costs related to dietary advice are also limited.

The results when using QALYs in a sensitivity analysis are equally good. It could perhaps be argued in some cases that changes in lifestyle could affect the quality of life of a person in a negative way. However, results from the diet and exercise study shows that this was not the case [28].

Most previously published studies on the cost-effectiveness of primary prevention have focused on pharmaceutical interventions. Exercise has, however, been found to be cost-effective [11,12]. In the economic evaluation of the CELL-study, a similar approach to the one applied here was used [13]. The study showed a cost-effectiveness of 223,000 SEK for intensive dietary advice versus no treatment, which is substantially higher than our findings (no cost in added years of life was used). The difference in results is explained by the fact that the diet and exercise trial showed a higher decrease in total cholesterol and also an effect on diastolic blood pressure.

These results show that dietary advice is preferable to exercise in this analysis. However, exercise is not a bad strategy as such. The ICER of exercise compared to no intervention is 180,470 SEK per LYG, which would likely be considered cost-effective in the absence of dietary advice as an alternative.

It is surprising that the groups receiving dietary advice and exercise in combination perform so poorly compared to the groups receiving dietary advice or exercise. A possible explanation is that it could be regarded as easier to focus on either diet or exercise when motivating oneself to changing habits. This view is also consistent with what was observed in the trial. Another possible explanation could be that this group contained outliers that had impact since the sample size was small. This is then reflected in the model.

The model uses data from the Framingham study to predict the risk of CHD events. This raises the question of the applicability of the Framingham risk score to the Stockholm population. Risk scores from the Framingham study has been shown to predict CHD risk reasonably well in men in the UK and Germany [29]. It has, however, been shown to overestimate the risks somewhat for patients with normal risk [27], which is consistent with what we find when comparing the model predictions to those from Statistics Sweden. The implications of this will be further explored in future work on the model by incorporating Swedish risk data. It should also be noted that the Framingham function only includes some risk factors that are affected by the interventions. Risk factors such as weight are not included. This implies that the cost-effectiveness ratios presented here are likely to be overestimated, which means that the intervention is even more cost-effective.

The standard deviations reported are probably too narrow, since no variation in the distribution between events and in mortality is captured in the model. There should be no effect on the mean values.

One of the most common ways to validate a model is to validate the results of a model by comparing them to the results of previously published models. The value of such a validation is limited, since it assumes that the comparator is valid. Another way of performing the validation is by using retrospective data, which often leaves the researcher to choose between using the available data to improve the model or for validation. When data are scarce, the former is perhaps the only possible alternative. The third alternative is to validate the model prospectively, which may be impossible for budget reasons or due to time constraints. The health situation of the 60 year olds will be followed over time and new cases of CHD will be recorded. This follow-up will give a unique opportunity to validate the short-term survival and observed number of events predicted by the model. The results from this validation will be reported as new data are collected.

The diet and exercise study included men aged 35 to 60 while the epidemiological cohort used in the prediction only included 60 year olds. It is possible that the studied interventions could have different effects in different age groups, but no such analysis was performed within the diet and exercise framework due to sample size considerations. It is therefore hard to estimate what effects this could have on the predictions made by the model.

Another aspect that should be taken into consideration is that the participants in the diet and exercise trial were those who volunteered to a prevention program and thus were likely to be motivated. This must be kept in mind when extrapolating the results to a broader population.

Conclusions

Based on the predictions of the model, dietary advice appears to be a cost-effective strategy among 60-year-old men in the county of Stockholm fitting the inclusion criteria of the diet and exercise study. This conclusion is valid regardless of whether the study perspective is the societal or the health care payers.

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