Predicting Onset of Coronary Heart Disease from Risk Factors Measured Once and Repeatedly. The Finnmark Study 1974-89

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Running head: RISK FACTORS MEASURED ONCE OR REPEATEDLY

PURPOSE: Changes in smoking behaviour or blood cholesterol level are considered to have at least some effects on disease prognosis. This study compares the influence upon disease outcome of potential risk factors that were measured once and repeatedly over time.

METHODS: We employed Cox's proportional hazards regression method for risk factors measured once or repeatedly, the repeated techniques were that of pooling repeated observations and that of the time-dependent covariates model. Measurements were taken on serum cholesterol, blood pressure, body mass, physical activity, smoking habits and familial history of heart disease a maximum of three times in 1974, 1977 and 1987 on 19,017 men and women aged 20 to 49 years in 1974. By the end of 1989, we had recorded 799 events of first myocardial infarction.

RESULTS: No systematic pattern as regards risk ratios being distinctly larger or smaller for any of the applications was observed, but the time-dependent model provided low values on subject age and also required tedious data programming and were intensive on computer resources. The results did not differ much either risk variables had been measured once or a maximum of three times.

CONCLUSIONS: Except for age, results from pooling data corresponded well with those of the time-dependent model, and only a modest impact was observed by including upgraded risk factor information.

KEY WORDS: Coronary Heart Disease, Cox Proportional Hazards Model, Prospective Studies, Repeated Measurements, Risk Factors, Software, Survival Analysis, Time-dependent Covariates.

INTRODUCTION

Prospective studies of risk factors for serious diseases have become increasingly popular during the few last decades. In the standard layout of such type of studies, information from healthy individuals taken at an initial examination is combined with the subsequently collected reports on specific disease outcome to assess the prognostic significance of relevant risk factors. A matter of concern, however, is the well-known instability of risk factor values over time (1). Examples of common changes are those from smoking to non-smoking and from sedentary to moderate physical activity. Major coronary heart disease risk factors of continuous nature such as serum total cholesterol and blood pressure are also subject to variation, either with subject age or lifestyle changes, or they may be liable to measurement errors. There are also potential risk factors, like the change of menopausal status known to take place in middle-aged women, which perhaps should be modelled to change during the course of follow-up even in instances where no new information on this characteristic has been collected directly (2). These examples represent changes that may affect the disease prognosis, especially in instances where follow-up lasts a decade or more.

Repeated measures on risk factors often are available from many of the ongoing and large-scaled health studies, and a few statistical techniques are available to utilise this additional information on changes (3, 4). A procedure of considering each screening and the subsequent follow-up until the next screening as a mini-study and then pool the repeated observations together, has been developed and frequently used in Framingham (3). Another plausible technique is to include risk factor measurements as so-called time-dependent covariates and to update these whenever new information becomes available (5). Although included in well known statistical program packages (6-8), this latter approach appears to be used infrequently.

The aim of this report is to compare different Cox models with covariates that were measured once or repeatedly. Rather than rigorous investigations of mathematical nature, we put focus on analysis results deriving from standard statistical software. A total of 19,017 healthy men and women were screened once, twice or three times during

a period of 13 years. Included were the major coronary heart disease risk factors total cholesterol, systolic blood pressure, the body mass index, physical activity, smoking and familial history of heart disease. After a maximum of 15 years of follow-up, 669 men and 130 women were clinically diagnosed with a first myocardial infarction.

METHODS

In Finnmark County, Northern Norway, all men and women aged 35 to 49 years as well as a subsample of those aged 20 to 34 years were invited to a first cardiovascular screening in 1974 and a total of 14,456 (83.1%) persons actually met (9). Those individuals who still lived within the county were invited to a subsequent screening in 1977, together with an additional subsample of men and women, and this time 17,181 (83.1%) persons met (10). In 1987, the men and women who were invited to the 1977 screening and still lived within the county were invited again, along with a new subsample of younger men and women (11).

Each examination included measurements of body height, body weight and blood pressure and collection of a non-fasting blood sample for analyses of serum lipids. In 1978, an enzymatic method was launched to determine serum cholesterol levels. Values from the 1974 and 1977 screenings were currently transformed to new method values through an expression derived from an extensive test program (10). In the 1974 and 1977 screenings, blood pressure was measured manually, and the lower of two readings was used. The 1987 blood pressure measurements were done automatically (Dinamap) and the mean of the second and third readings was used. We applied no transformation of blood pressure values due to the small difference between the new and old measurement method for systolic blood pressure (12). (Recalculation after having transformed blood pressure values according to a test program formula, changes in the risk ratios presented herein were less than 0.01.) A questionnaire was applied to collect information on physical activity at leisure (four categories describing activities as sedentary, moderate, active, or hard training), the daily smoking status at present (yes, no), and whether one or more parents or siblings had had a heart attack or angina

pectoris (yes, no, don't know). For the current analyses, the physical activity categories were numbered from 1 to 4 as listed above. We coded the answer "don't know" on the family history question as no.

A few values were missing for questionnaire (answers were checked) and measurements. However, there was a deficit of body height and weight measurements performed during the 1974 and 1977 screenings. We decided to utilise existing records from previous screenings in such instances (553 subjects in 1974 and 297 subjects in 1977).

The present analysis comprised subjects who were free from heart disease at the time of screening and also had available information on all included risk variables. The number of such men and women taking part in the screenings held either in 1974 or 1977, or both times, was 9902 and 9115, respectively. For 6055 men and 6290 women among these, risk factor information collected at the 1987 screening round was also used.

We followed the subjects from the date of the first attended screening for a first fatal or non-fatal myocardial infarction or sudden death. By December 31, 1989, a total of 669 male and 130 female events had been recorded. Subjects who died from other causes were treated as censored, and those who emigrated from Finnmark during the period of follow-up were traced (13).

STATISTICAL ANALYSIS

We employed Cox proportional hazards regression for all analyses (14). In accordance with the large majority of epidemiological reports to date, all analyses were sex specific and the results are presented in terms of risk ratios with corresponding 95% confidence intervals. We recorded dates to the exact day for examination, event of interest and censoring (death of other causes or end of study). Handling of data was done by the SAS statistical program package version 6.12 (15), and the Cox analyses were performed with PROC PHREG (7).

Single screening analysis

The data from a single screening with the subsequent follow-up throughout 1989 went into the model as fixed covariates, and no repeated measures thus were included. This standard single screening analysis was performed and results are presented with respect to each of the three screenings.

Pooling of repeated observations

Each screening and the associated follow-up outcome until the time of the subsequent screening were regarded as a mini study. For the 1987 screening, follow-up lasted to the end of the study, December 31, 1989. In the instances where a subject failed to attend the subsequent screening, the period of follow-up was expanded until the next round or the end of the study. The data from each such mini study then was pooled together. As an example, a woman who smoked in 1974, had quit smoking in 1977, smoked again in 1987 and developed a first myocardial infarction in 1989, thus contributed in the analysis with three observations: once as a smoking non-case, once as a non-smoking non-case, and finally, once as a smoking case. Each person therefore went into the analyses according to the number of screenings attended. Consequently, the amount of data was considerably larger compared with the single screening analysis, but the statistical calculations in themselves were of identical type.

Time-dependent covariate analysis

In the Cox model with time-dependent covariates (5), measures are allowed to change over time and the most recent risk factor values at all times go into the model. Commencing with the first attended screening, we updated risk factor information (covariates) from the point of time it became available from the subsequently attended screening for every risk variable. Each individual thus went into the model when attending a screening for the first time, and in instances where a later screening was visited, the deriving new risk factor values substituted the old ones. This technique

differs from that of the single screening analysis in that the covariate values may be changed repeatedly.

RESULTS

Summary statistics for the included risk variables are given in Table 1. The continuous variables are presented in terms of the 25th, 50th and 75th percentiles. For the other variables, we give the percentage response in the categories specified. As seen from the high cholesterol medians and the many daily smokers, the study participants in general had a rather unfavourable risk factor profile.

Table 2 displays the yearly number of reported fatal and non-fatal heart disease incidents among the subjects who participated in each screening. As expected, the number of events increased steadily over the years as study participants gradually became older. Also, the number of male events outnumbered the female events with a factor of approximately five.

To illustrate how risk factor values changed over time in the study subjects, we considered those men and women who attended all three screenings (Table 3). Although all subjects who went into the Cox models were not included, we expect this subsample to fairly well represent the general pattern of risk profile changes. Over time, particularly many men and women experienced increased blood pressure readings, whereas more subjects quit than took up smoking.

The results of the Cox analyses are presented in Table 4. The first three columns represent the risk ratios with 95% confidence intervals of the 1974, 1977 and 1987 single screening analyses, respectively. Pooling the 9902 study men who each contributed once, twice or three times, the number of observations became 21,987. The last column gives the results of the analyses with time-dependent covariates. As seen, subject age displayed statistically significant risk ratios in all instances, and the increased disease risk associated with an extra unit of serum cholesterol was estimated to vary between 23% and 39% in men and between 31% and 65% in women. However, the latter risk ratio was based upon the rather small number of 20 incident cases.

Systolic blood pressure and body mass index also proved to be significant risk factors, whereas risk decreased with increased physical activity in women. Risk ratios were also high for the dichotomous variables, especially daily smoking.

Comparing results across the various models, the estimated relative risks appeared to agree well with each other. We were unable to discern any systematic pattern such as all risk ratios being larger in one model than another. That the results varied more for women than men was probably due to the smaller number of female incident cases. Among the single screening analyses, that of the 1977 data provided the most similar results with those of the pooled and time-dependent models. The distinct low subject age risk ratios in the time-dependent model were notable. This model also provided the highest risk ratios for smoking, interestingly due to the previously reported very high risk associated with smoking in women (13). For the other variables, discrepancies were small and 0.03 or less between the pooled and time-dependent models. Finally, and except for the 1987 data with fewer cases, the width of the confidence intervals was very similar even although the number of pooled observations were much larger than the number of subjects who went into the other models. As expected, the more important factor on this point was the number of case events, and they were not pooled.

DISCUSSION

Much still remains unknown regarding the causal relationship between a given risk factor and cardiovascular disease. The disease risk may be related to the childhood value, the lifetime average value or the most current value. It is therefore not at all clear how results of prospective studies may be influenced by the length of the follow-up period. As the current investigation regards, it should be noted that from the point of time where risk factors were measured, the single screening analyses of the 1974 data, in particular, and also the 1977 data were based on a longer period of disease follow-up than the other analyses.

The time-dependent covariate model we fitted should not be mixed up with other Cox techniques at least partly described in the literature as time-dependent. The time-

scale variable has been referred to as the time-dependent variable and the application has been described as a time-dependent Cox analysis (16). Moreover, the analysis of pooled repeated observations has also been described in terms of a time-dependent covariate analysis (17), not incorrect in view of the definition of a time-dependent covariate as one whose value for a given individual may change over time (5). Finally, change of a risk variable value from baseline to a rescreening round has been analysed with the single screening approach with follow-up starting at the time of rescreening and been referred to as focusing on time-dependent covariates (18). None of these analyses, however, apparently has been performed using the Cox model with time-dependent covariates currently employed.

With the exception of subject age, the estimated relative risks were found to agree very well with each other across the models. The reason why the results of the 1977 single screening analyses were especially similar to the pooled and the time-dependent risk ratios may be due to the long period of time elapsed until the next screening. Thereby, approximately two thirds of the subject cases had their last measurements of risk variables in this particular screening.

Whereas the pooled and the time-dependent risk ratios for the continuous variables with the exception of subject age were very similar to those of the single screening analyses, those for the categorical variables were somewhat more distinct. This result may reflect that many study subjects changed smoking or physical activity behaviour during the maximum 15 years of follow-up and that these changes had some effect on the disease risk. One reason may also be that the relative change on categorical variables is larger than on continuous variables. As blood pressure regards and due to measurement error, a better estimate of a person's real value perhaps could be expected when two or three measurements were included. It was noteworthy, however, that risk ratios were no higher in those situations. In general, the impact on the risk ratios by utilising upgraded risk factor information was not very large. Perhaps this result can help throw some further light on the association between cardiovascular disease and its major risk factors.

The subject age variable plays a particular role as a covariate in Cox regression due to its constant rather than variable nature and the correlation with the time-scale variable (follow-up time). The effect of subject age therefore tends to be absorbed in the underlying hazard functions rather than to manifest itself in the coefficient estimate (3). It was therefore no surprise that the effect of attained age was somewhat lower in the time-dependent model. Rather than follow-up time, it has been argued that a more appropriate proportional hazards regression model would use subject age as the time-scale (19). We deliberately chose to use follow-up time as the time-scale due to the fact that this has been done in the large majority of presently published reports. However, recalculations with attained age as the time-scale variable provided results that were not very different. Except for the female 1987 screening data, the largest observed deviation was a smoking risk ratio increase from 2.15 (see Table 4) to 2.36 in men and from 3.58 to 4.05 in women for the pooled data. All other risk ratio changes were less than 0.20 and in most instances near zero, and a reduction with a factor of 0.11 and 0.07 in men and women, respectively, was observed for the high time-dependent smoking estimates.

Various options are available to deal with the situation where eligible subjects failed to attend every screening round. As the pooling technique regards, we expanded the follow-up period of the previous mini study until the next attended screening or the end of the study. Similarly, we kept covariate values in the time-dependent analysis until new information became available. For the pooled data, other relevant approaches would have been to exclude non-attending subjects from that mini study or to duplicate risk factor information from the most recent screening. This latter procedure of fabricating data has been followed in Framingham (20).

Some problems relate to the procedure of pooling repeated observations. First, particular care must be shown in instances where the examinations have not been repeated at regular intervals. This concern is perhaps less important for Cox's method than that of logistic regression, since the former technique does take into account relevant information regarding time. A second difficulty is that of including each

individual more than once. Such observations cannot be regarded as absolutely independent, especially in instances where the same individuals have been measured several times. The currently studied subjects contributed a maximum number of three times with individual follow-up times varying from approximately 2 to 15 years. These features sharply contrasted the Framingham analyses of data pooled from as many as 14 mini studies, all with a fixed two year follow-up period (20).

A problem with the time-dependent model was the tedious data programming required. We implemented the time-dependent covariates by specifying the values of the time-scale variable relevant for each screening. Others have pointed out that it is easy on this point to make mistakes without realising it (21). Another concern was the considerable amount of computer space and time consumed. In terms of CPU time elapsed, the time-dependent analyses required approximately 40 minutes whereas the other models used just a few seconds. On a smaller data set, this method has also been found to be many times more time intensive than logistic regression (3). The presently reported analyses were done on a standard PC (Pentium 133 MHz, 16 MB RAM) running under Microsoft Windows 95. We believe that such analyses were impossible on a PC until recently. However, with the rapid improvement of computer performances seen over the last few years and expected to continue still, the time and space difficulties would be overcome shortly. Furthermore, all results reported here were from SAS (7). All analyses currently reported should also be available on BMDP (6) and SPSS (8) (we ran some of the time-dependent analyses with identical results), as well as other software (22).

We conclude that although specific study designs may favour one approach over others, the time-dependent covariate model appears to have several promising features. However, health researchers may not expect radical risk ratios changes to take place by utilising interim risk factor measurements.

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TABLE 1. Summary statistics for study risk factor variables measured in 1974, 1977 and 1987. The Finnmark Study 1974-1989

	Men			Women		
Risk variable	1974 (20-49 years) (n = 7246)	1977 (20-52 years) (n = 8686)	1987[a] (30-62 years) (n = 6055)	1974 (20-49 years) (n = 6867)	1977 (20-52 years) (n = 8206)	1987[a] (30-62 years) (n = 6290)
Total cholesterol (mmol/L)						
25th percentile	5.72	5.54	5.83	5.54	5.36	5.82
50th percentile	6.57	6.38	6.62	6.33	6.12	6.71
75th percentile	7.50	7.28	7.45	7.23	7.04	7.65
Systolic blood pressure (mmHg)						
25th percentile	124	122	127	114	116	121
50th percentile	132	132	137	124	124	132
75th percentile	142	142	150	136	136	147
Body mass index (kg/m^2)						
25th percentile	22.8	22.9	23.8	21.6	21.5	22.9
50th percentile	24.5	24.8	25.7	23.6	23.6	25.3
75th percentile	26.5	26.9	27.9	26.6	26.6	28.5
Physical activity at leisure (%)						
Sedentary	21.5	23.1	24.7	27.9	23.2	26.4
Active or hard training	19.0	25.4	20.2	5.1	10.4	7.9
Daily smoking (%)						
Yes	64.6	57.2	51.3	49.4	46.3	43.5
Family history of heart disease (%)						
Yes	29.1	30.6	41.1	30.7	34.0	46.5

[a] Only men and women who also attended at least one of the screenings held in 1974 and 1977.

TABLE 2. Yearly number of first myocardial infarction events among healthy participants in 1974, 1977 and 1987. The Finnmark Study 1974-1989

	Men			Women		
Year	1974 (20-49 years) (n = 7246)	1977 (20-52 years) (n = 8686)	1987[a] (30-62 years) (n = 6055)	1974 (20-49 years) (n = 6867)	1977 (20-52 years) (n = 8206)	1987[a] (30-62 years) (n = 6290)
1974	3	-	-	0	-	-
1975	22	-	-	1	-	-
1976	18	-	-	3	-	-
1977	23	6	-	3	0	-
1978	29	27	-	5	4	-
1979	35	33	-	6	6	-
1980	32	36	-	6	6	-
1981	35	34	-	7	7	-
1982	21	24	-	4	5	-
1983	24	30	-	12	14	-
1984	49	50	-	9	9	-
1985	51	60	-	4	5	-
1986	59	57	-	11	13	-
1987	48	55	11	14	15	1
1988	59	67	47	13	16	9
1989	65	68	56	14	13	10
Total	573	547	114	112	113	20

[a] Only men and women who also attended at least one of the screenings held in 1974 and 1977.

TABLE 3. Percentage of the subjects participating all three times in 1974, 1977 and 1987 with change of risk factor values. The Finnmark Study 1974-1989

	Men, 20-49 years in 1974 (n = 4298)			Women, 20-49 years in 1974 (n = 4672)		
Risk variable	From 1974 to 1977	From 1977 to 1987	From 1974 to 1987	From 1974 to 1977	From 1977 to 1987	From 1974 to 1987
Total cholesterol						
Decrease ≥ 1 mmol/L	15.8	10.3	14.9	13.5	6.0	8.9
Increase ≥ 1 mmol/L	10.0	17.9	17.8	9.9	31.0	29.6
Systolic blood pressure						
Decrease ≥ 10 mmHg	19.8	13.0	13.3	17.6	9.7	9.0
Increase ≥ 10 mmHg	21.2	40.7	41.4	23.5	46.4	48.5
Body mass index						
Decrease ≥ 3 kg/m^2	0.8	1.3	1.3	3.8	3.1	3.2
Increase ≥ 3 kg/m^2	2.5	10.6	17.4	3.9	20.9	25.2
Physical activity at leisure						
Less active	19.4	27.2	24.8	14.1	23.0	18.2
More active	24.2	19.9	22.7	24.5	17.1	22.8
Daily smoking						
Quit	12.1	9.8	16.6	6.9	6.9	9.9
Taken up	3.4	6.3	4.4	3.0	5.2	4.3
Family history of heart disease						
From "no" to "yes"	7.5	15.0	17.1	9.2	16.8	20.7

TABLE 4. Risk ratios (with 95% confidence intervals) for variables included in various Cox models with first myocardial infarction as end point. The Finnmark Study 1974-1989

Risk variable	Screening in year followed throughout 1989			Pooled data from three screenings	Time-dependent covariates from three screenings
	1974	1977	1987		
Men					
No. of subjects/no. of cases	7246/573	8686/547	6055/114	21987 obs.[a]/669	9902/669
Age (10 years)	2.67 (2.27-3.13)	2.65 (2.29-3.07)	2.73 (1.97-3.77)	2.75 (2.44-3.08)	2.33 (2.06-2.64)
Total cholesterol (1 mmol/L)	1.23 (1.17-1.29)	1.39 (1.30-1.48)	1.31 (1.14-1.50)	1.32 (1.26-1.39)	1.34 (1.27-1.41)
Systolic blood pressure (10 mmHg)	1.14 (1.09-1.19)	1.13 (1.08-1.18)	1.08 (0.98-1.19)	1.12 (1.08-1.17)	1.12 (1.07-1.17)
Body mass index (3 kg/m^2)	1.13 (1.05-1.22)	1.14 (1.06-1.22)	1.07 (0.91-1.26)	1.13 (1.06-1.21)	1.12 (1.05-1.20)
Physical activity at leisure (1 unit)	1.07 (0.94-1.23)	1.00 (0.88-1.13)	0.86 (0.64-1.15)	1.03 (0.92-1.15)	1.02 (0.91-1.14)
Daily smoking (yes/no)	1.95 (1.60-2.37)	2.15 (1.77-2.60)	2.05 (1.38-3.06)	2.15 (1.81-2.56)	2.21 (1.86-2.63)
Family history of heart disease (yes/no)	1.63 (1.38-1.92)	1.55 (1.31-1.84)	1.59 (1.10-2.30)	1.66 (1.42-1.93)	1.63 (1.40-1.90)
Women					
No. of subjects/no. of cases	6867/112	8206/113	6290/20	21363 obs.[a]/130	9115/130
Age (10 years)	2.42 (1.64-3.56)	2.17 (1.54-3.05)	1.64 (0.74-3.61)	2.40 (1.79-3.23)	1.73 (1.29-2.32)
Total cholesterol (1 mmol/L)	1.31 (1.21-1.42)	1.38 (1.26-1.52)	1.65 (1.31-2.07)	1.43 (1.32-1.56)	1.45 (1.34-1.57)
Systolic blood pressure (10 mmHg)	1.30 (1.20-1.41)	1.22 (1.12-1.33)	1.12 (0.91-1.39)	1.22 (1.12-1.32)	1.22 (1.13-1.33)
Body mass index (3 kg/m^2)	1.11 (1.00-1.25)	1.12 (1.00-1.25)	1.06 (0.79-1.42)	1.12 (1.01-1.24)	1.12 (1.01-1.25)
Physical activity at leisure (1 unit)	1.11 (0.78-1.58)	0.78 (0.56-1.09)	1.02 (0.46-2.25)	0.70 (0.51-0.95)	0.69 (0.50-0.94)
Daily smoking (yes/no)	3.38 (2.21-5.17)	3.34 (2.20-5.07)	2.84 (1.10-7.35)	3.58 (2.41-5.33)	3.70 (2.49-5.50)
Family history of heart disease (yes/no)	1.26 (0.86-1.83)	1.37 (0.95-1.99)	0.68 (0.28-1.67)	1.51 (1.07-2.14)	1.49 (1.06-2.11)

[a] Observations: subjects were counted once (2115 men and 1539 women), twice (3489 men and 2904 women) or three times (4298 men and 4672 women) according to the number of screenings with subsequent follow-up they took part in.