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Long term survival in pre specified groups at risk in the Oslo Study 1972-3.

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Abstract

Aims In the Oslo study of 1972-3 we compared the mortality pattern up to 40 years in cardiovascular healthy groups at supposedly high and low risk and some groups having cardiovascular disease at screening.

Methods At screening 16203 (63 % of invited) men aged 40-49 years participated. Groups were identified by means of questionnaires regarding diseases, measurements of total cholesterol, triglycerides, glucose and blood pressure. Six groups were identified: very high cholesterol, very high blood pressure, very high glucose, non-smoking with non-elevated such risk factors, a randomized diet and antismoking trial, and a randomized drug treatment in mild to moderate hypertension.. Cox regression analysis with Kaplan-Meier graphs was used for statistical analyses.

Results The supposedly low risk group had total mortality of one third as compared to other groups such as men with hypertension, diabetes, hypercholesterolemia or those who participated in the two trials. Between these latter groups 2-5 years differences in median survival time were found, but their absolute risk stayed at rather high levels through all years with median remaining lifetime 3-8 years shorter than men free of known cardiovascular disease, diabetes or hypertension.

Conclusions The long term preventive effects on total mortality seems large if the levels of the classical risk factors blood pressure, total cholesterol and glucose can be adequately controlled concurrently with a non-smoking behavior. The study indicated that non-smoking and low total cholesterol were the most important contributors to extended survival.

Word count: 250

Keywords: long term mortality; risk factors; prevention

Introduction

In 1972-3 a cardiovascular study (CVD) in Oslo took place that was the first in a series of similar studies performed by the National Health Service in different counties of Norway [1]. Repeated screenings were performed by the years and the analyses of the collected data have provided much knowledge of CVD epidemiologic in the Norwegian population [2-9].

Since the second world war myocardial infarction (MI) incidence and mortality had increased at all years and had reached epidemic proportions, so prevention strategies were highly needed. Among several purposes of the Oslo study screening was the recruitment of participants to two randomized controlled trials among supposedly healthy men with a high risk of developing CVD. During the screening and two reexaminations to include men with no cardiovascular disease to the two trials, one diet and antismoking trial and one drug trial in mild hypertension [10-11], several other groups supposedly at both low and high risk were pre specified. These were participants with hypertension and hypercholesterolemia with levels above those selected for the trials, newly detected diabetics and a non-smoking group with simultaneously lower levels of the classical risk factors. Since then levels of classical risk factors have been drastically reduced, current smoking prevalence has decreased to less than a half, more effective drug treatment both for hypertension and hypercholesterolemia has been documented as well as better treatment and procedures in secondary prevention. At the same time large dietary changes have taken place with more sedentary behavior and a massive increase in body mass index. The prognosis of the pre specified groups from the Oslo study would therefore be hard to predict. Some men had also experienced a cardiovascular event or had diabetes at time of screening and their survivals have also remained unknown during these years.

Thus, the purpose of this study was to report the long-term survival results in the predefined subgroups as well as the diseased groups during an almost 40 year time period.

Material and methods

3

In 1972-3 all men born 1923-1932 in Oslo were invited to a screening examination for CVD. Eligible were 25915 men and 16203 participated (63 %) and they filled in a questionnaire about prevalent CVD and diabetes. Men without such diseases were called healthy in whom two reexaminations followed to include participants to the planned randomized trials [3]. In the mild hypertension trial men with blood pressure 150-179/95-109 mmHg were included whereas men with total cholesterol 6.4-8.9 mmol/L were included into the diet and antismoking trial provided they had a coronary risk score in the upper quartile in a risk score distribution based on the three classical risk factors systolic blood pressure, total cholesterol and cigarette smoking [3]. An assumed low risk group consisted of men with total cholesterol at screening (Liebermann Burchart method) <6.0 mmol/L, <6.0 mmol/L fasting at the first reexamination and with blood pressure <145/95 mmHg at both investigations and they should not have smoked cigarettes or be currently smoking pipe or cigar. Finally, fasting triglycerides should be <4.0 mmol/L and fasting blood sugar <9.5 mmol/L. The intention was to include 500 participants to this group, but ended up with 367 due to lower participation proportion than anticipated.

Men with a higher blood pressure than those included in the mild hypertension trial (high blood pressure group) were referred to specialized hypertension clinics, as were men with higher total cholesterol than those in the diet and antismoking trial (high cholesterol group). The same took place for those with a fasting glucose above 9.5 mmol/L (newly detected diabetes). The two randomized trials have been followed up with respect to morbidity and mortality up to 10 years for mild hypertension trial [12] and 20 years in the diet and antismoking trial [13]. Separate reports with mortality results by intervention/treatment group up to 40 years are planned for publication. Thus, there are 6 assumed healthy groups to be compared, one low risk group and 5 groups assumed to be at somewhat higher risk than the average screened population: the Mild hypertension trial, the Diet antismoking trial, the High blood pressure group, the High cholesterol group and the Newly detected diabetes group.

This follow up is extended to December 31th 2011 with respect to mortality. ICD code 410 was used for MI in version ICD8-9 and I21 in version ICD10. Statistics Norway added mortality data to the

4

Oslo study data file according to permissions given by the Data Inspectorate and tax authorities, Department of health and the project was approved by the regional ethics committee for medical research.

Statistical methods

Cox proportional hazards regression models were used and time to death or time to death at first MI was the dependent variable in some analyses and obtained age in others. Emigrated men were censored at date of emigration. The 6 risk group codes were exposure factors with the rest of men as reference , while adjustment factors were total cholesterol, systolic blood pressure, glucose and daily smoking (Yes,No). The reference group consists of all men except those in the 6 subgroups. They are a mixture of healthy and diseased men whose risk level in itself is not of interest in this study. When MI mortality was analyzed all other causes of death was used as a competing cause of death. The standard method used in STATA 13 was applied according to a method by Fine and Gray (14). A cumulative MI death incidence graph was also made by STATA 13 as were graphs of hazard functions by time. The cumulative incidence gives an approximation to the MI mortality probabilities. In our case with far more non-MI than MI deaths, the differences between competition adjusted or non-adjusted results will probably be rather great.

To compare predictive ability of risk factors on total mortality log likelihood statistics were used. This contains all statistical information given the model. A full model with the 6 groups and the 4 classical risk factors was estimated and its log likelihood was calculated. Then, one at a time, each of the 4 factors was removed from the model and rerun obtaining an updated log likelihood and the change for each factor was recorded. The factor with the greatest change would indicate the best predictive ability.

Results

Table I shows number of deaths among men with MI, angina pectoris, hypertension and diabetes found at screening. In most categories mortality risk was higher than in the healthy group, but some

5

subjects may have had several categories of disease. The absolute risk of death or death at first MI were high in those who had developed MI prior to screening or had diabetes as compared to not. **Figure I** displays unadjusted Kaplan Meier survival curves for the healthy men and for those with MI, diabetes, or drug treated for hypertension. All groups had markedly reduced median survival time as compared to the healthy one, that had 35 years of median survival time after screening. Men with hypertension had 26 years median survival whereas diabetics and men with MI had only 19 years median survival.

The low-risk group experienced an especially low risk of death at first MI with only 8 such deaths through 40 years of observation (**Table II**). Also total mortality was low as compared to other risk groups or the healthy subgroup, (**Figures I and II**). The low risk group had a median survival time of 88 years and a total mortality of one third as compared to other groups such as men with hypertension, diabetes, hypercholesterolemia or those who participated in the two trials. Between these latter groups 2-5 years differences in median survival time were found, but their absolute risk stayed at rather high levels through all years with median remaining lifetime 3-8 years shorter than men free of known cardiovascular disease, diabetes or hypertension. Between the 5 pre specified high risk groups there were only marginal total mortality risk differences, unadjusted for risk factors. This can also be seen from **Figure III** where smoothed hazard rates are displayed by time for each of the 6 risk groups. There is nothing to indicate that rates have developed differently by time, since an exponential increase seems to fit the data well in all groups.

Table III shows hazard ratios for the 6 groups at risk versus reference adjusted for the 4 classical risk factors at the end of the table. Despite statistical significant differences in mortality to the reference group, differences were small between the 6 groups internally, as displayed in **Figure IV (Online version).** This indicates that the sole difference in mortality risk between the low risk group and the 5 others was purely due to the measured differences in the 4 risk factor levels measured in 1972-73. These factors associated strongly to 40 year mortality, adjusted for each other.

A cumulative incidence function graph was made for death at first MI (**Figure V, Online version**), showing the unadjusted different survival patterns between the low and the other high-risk groups. In this curve non-MI deaths are treated as competing risks. After about 20 years of follow up there seems to be a break in the development of MI mortality risk, but since the model uses only one underlying hazard function, these changes seem to happen at the same time, which is probably not fully true. It should rather be interpreted that a shift in decline of MI mortality took place at some time during the 1990s. The poorest survival had the newly detected diabetes group. The low risk group still had the best survival, but differences to the other groups were moderate but still present. When adjustments were made for the 4 risk factors, there was no significant difference between any group as compared to reference (data not shown).

The log likelihood analysis showed that smoking was by far the most predictive risk factor among the 4 classical ones. When smoking was removed from the full model log likelihood was reduced by 621.7 units, whereas this reduction was 205.1 for systolic blood pressure, 83.8 for total cholesterol and 59.0 for glucose.

Discussion

This is the first report of the long term prognosis of 6 pre specified groups at risk in the Oslo study in 1972-73. The study validates the importance on mortality of classical risk factors measured at middle age through elderly and old age, despite drastic changes in risk factor distributions and treatment modalities introduced in Norway since that time.

There was a high excess mortality in prevalent MI men in this study with a relative risk of 3.3 (2.8-3.9), well known from previous studies among survivors from hospitalized acute MI patients [13], but is evidently also valid for patients with prevalent coronary heart disease. Due to the generally much better control of MI risk factors as well as a lower absolute risk to day together with improved treatment strategies of both acute MI as well as secondary prevention by potent drugs such as statins, it is not clear whether such findings will be valid in the future. Men with diabetes also had a clear excess mortality as compared to healthy men, HR= 2.9 (2.5-3.5) but treatment strategies have not

7

resulted in substantial risk reductions [15]. After 30 years of follow up 23 % were alive among the established diabetics, whereas this was 45 % for the newly detected ones. It could be that the latter group had had their diabetes for a shorter time resulting in somewhat longer survival.

The low-risk group had very few deaths at first MI. The concept of selecting non-smoking men without high levels of classical risk factors proved to give low mortality risk both of MI and totally. The group results indicate the great prevention potential even on total mortality if levels of classical risk factors can be kept fairly low while avoiding the habit of smoking. This happened despite the great changes in life style and advancements in treatment and intervention procedures during these years. The main factor to combat is smoking since that factor damages many organ systems and showed up in the prognostic analyses to be a better predictor for total mortality than the others. Also the other factors have been influential since adjustments for them closed the gap between risk groups with regard to survival.

In Norway massive reductions in total cholesterol (about 1 mmol/L in Norway), a more effective and metabolically neutral hypertension control and a more than 50 % reduction in smoking prevalence have together with more effective procedures and treatments of acute MI and better drugs in secondary prevention more or less eliminated coronary heart disease mortality at younger ages and substantially reduced it in the elderly. This has in all likelihood resulted considerably to the impressive fact that the average lifetime has increased by 1 year for every 5th running year during the latest 2-3 decades.

Conclusions

Large differences in long-term survival took place between groups in which classical risk factor levels differed. Today these are except for glucose regarded as causal by most researchers and the large reductions we have seen in cardiovascular and total mortality in the population as a whole during these 40 years are partly a result of the reduction on levels of these risk factors, mainly through life

style changes. At the same time modern drugs, such as metabolically neutral antihypertensive drugs and statins have been available to treat patients at high cardiovascular risk. Judging from Table3 and the observed large changes in smoking habits and total cholesterol in Norway the greatest risk reductions are probably due to the massive reduction in smoking and the changes in total cholesterol. The large increase in BMI and diabetes in the population has so far not transferred into increased mortality at the population level. However, there are observations in Sweden and Finland that the cholesterol level is again increasing slightly, probably due to the big wave of protein-rich and fatty diets promoted by some to reduce BMI levels in the overweight and obese (16,17). If this trend gets massive it may announce a less beneficial development in CVD mortality trends in the years to come.

Declaration of conflicting interests

The author declares that there is no conflict of interest.

References

[1] Leren P, Askevold EM, Foss OP et al. The Oslo Study. Cardiovascular disease in middle-aged and young Oslo men. Acta Medica Scandinavica. Suppl. 588: 1-38. 1975.

[2] Bjartveit K, Foss OP, Gjervig T et al. The cardiovascular disease study in Norwegian counties. Background and organization. Acta Medica Scandinavica. Suppl 634: 1-70. 1979.

[3] Lund-Larsen PG. ECG in Health and Disease. ECG findings in relation to CHD risk factors, constitutional variables and 16-year mortality in 2990 asymptomatic Oslo men aged 40-49 years in 1972. The Oslo Study. ISM monograph series no 30. 1994.

[4] Tverdal Å. A mortality follow-up of persons invited to a cardiovascular disease study in 5 areas in Norway (monograph). National Health Screening Service, Oslo. 1989.

[5] Thürmer H. Risk factors for, and 13-year mortality from cardiovascular disease by socioeconomic status: A study of 44690 men and 17540 women, ages 40-49. ISM Monograph series no 26. University of Tromsø, Norway. 1993.

[6] Holme I, Lund Håheim L, Hjermann I. Prediksjons funksjoner for 21 års utvikling av hjerteinfarkt fra Oslo undersøkelsen 1972/73. Tiddsskr Nor Lægeforen 2003; 123:1050-54.

[7] Holme I, Tonstad S. Risikofaktorer og dødelighets oppfølging av Oslo undersøkelsen 1972-73. Tidsskr Nor Lægeforen 2011; 131:456-60.

[8] Thelle DS, Førde OH. The Tromsø Heart Study. Methods and main results of the cross sectional study. Acta Med Scand 1976; 200:107-18.

[9] Førde OH, Thelle DS. The Tromsø Heart Study: risk factors for coronary heart disease related to the occurrence of myocardial infarction in first degree relatives. Am J Epidemiol 1977; 105:192-99.

[10] Hjermann I, Byre KV, Holme I et al. Effect of diet and smoking intervention on the incidence of coronary heart disease. Lancet 1981: 1303-10.

[11] Helgeland A. The Oslo Study. Treatment of mild hypertension: A 5-year controlled drug trial. Am J Med 1980; 69: 725-32.

[12] Leren P, Helgeland A. Coronary heart disease and treatment of hypertension. Am J Med 1986; 80 (suppl 2A): 3-6.

[13] Holme I, Håheim LL, Tonstad S et al. Effect of dietary and antismoking advice on the incidence of myocardial infarction: A 16-year follow-up of the Oslo Diet and antismoking study after its close. Nutr Met Cardiovasc Dis 2000; 16: 330-38.

[14] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999; 94: 496-509.

 [15] Dale AC, Vatten LJ, Nilsen TI et al. Secular decline in mortality from coronary heart disease in adults with diabetes mellitus: cohort study. Brit Med J 2008; 337: 236-9.

[16] Johansson I, Nilsson LM, Stegmayr B, Boman K, Hallmans G, Winkvist A. Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden. Nutrition Journal 2012; 11: 40. www.nutritionj.com/content/11/1/40 doi:10.1186/1475-2891-11-40.

[17] - Vartiainen E,Borodulin K, Sundvall J et al. Finriski-tutkimus: Väestön kolesterolitaso on vuosikymmenien laskun jälkeen kääntynyt nousuun (Cholesterol levels in Finnish population have increased after decades of decline). Soumen Lääkärilehti 2012;35:2364-8. Summary in English: http://www.laakarilehti.fi/e/summary.html?opcode=show/news_id=12400/type=4

Tabell 1 First myocardial infarction and total death risk through 40 years in Oslo study for groups with prevalent diseases.

Prevalent disease at screening	MI deaths/Number screened (%)	Total deaths (% of screened)
Myocardial infarction	60/164 (36.6)	148 (92.5)
Angina Pectoris	51/194 (26.3)	170 (87.6)
Other heart disease	21/191 (11.0)	141 (73.8)
AO	8/41 (19.5)	34 (82.9)
Stroke	6/36 (16.7)	36 (100.0)
Diabetes	29/153 (19.3)	141 (92.2)
Treatment of hypertension	82/446 (18.4)	370 (83.0)

Healthy (without acknowledged CV disease)	1250/15082 (8.3)	9379 (62.2)

MI= myocardial infarction; CI= confidence interval; AO= atherosclerosis obliterance; CV= cardiovascular.

Table 2 Death at first myocardial infarction and total death proportion through 40 years in assumed healthy CVD high risk groups defined after screening reexaminations.

Group	MI deaths/Number at risk (%)	Number of deaths (%)
Diet antismoking trial		
Intervention +	139/1232 (11.3)	880 (71.4)
Control		
Mild hypertension trial		
Drug Treatment +	102/785 (13.0)	683 (87.0)
Control		
Low risk	8/367 (2.2)	116 (31.6)
High BP	14/55 (25.5)	47 (85.5)
High TC	28/168 (16.7)	125 (74.4)
Newly detected diabetes	17/87 (19.5)	69 (79.3)

CVD= cardiovascular disease; MI= myocardial infarction; BP= blood pressure; TC= total cholesterol

Table 3 Hazard ratio of 40-year total mortality by 6 pre specified risk groups (vs all other participants) and classical risk factors based on 16195 men with complete data and 10222 deaths.

Group factor*	Hazard Ratio	95 % CI	P-value
Mild hypertension trial	0.84	0.76-0.92	<0.001
Diet antismoking trial	0.83	0.77-0.89	<0.001
Low risk group	0.75	0.62-0.91	0.003
High cholesterol group	0.74	0.55-1.00	0.047
High blood pressure group.	0.69	0.57-0.84	<0.001
Newly detected diabetes	0.91	0.70-1.19	0.500
Risk factors§			
Total serum cholesterol (per 1mmol/L)	2.59	2.24-3.00	<0.001
Systolic blood pressure (per 1 mmHg)	1.013	1.011-1.014	<0.001
Serum glucose (per 1 mmol/L)	1.99	1.72-2.29	<0.001
Daily smoking (Yes/No)	2.07	1.95-2.25	<0.001

*Adjusted for total serum cholesterol, systolic blood pressure, serum glucose and daily smoking.
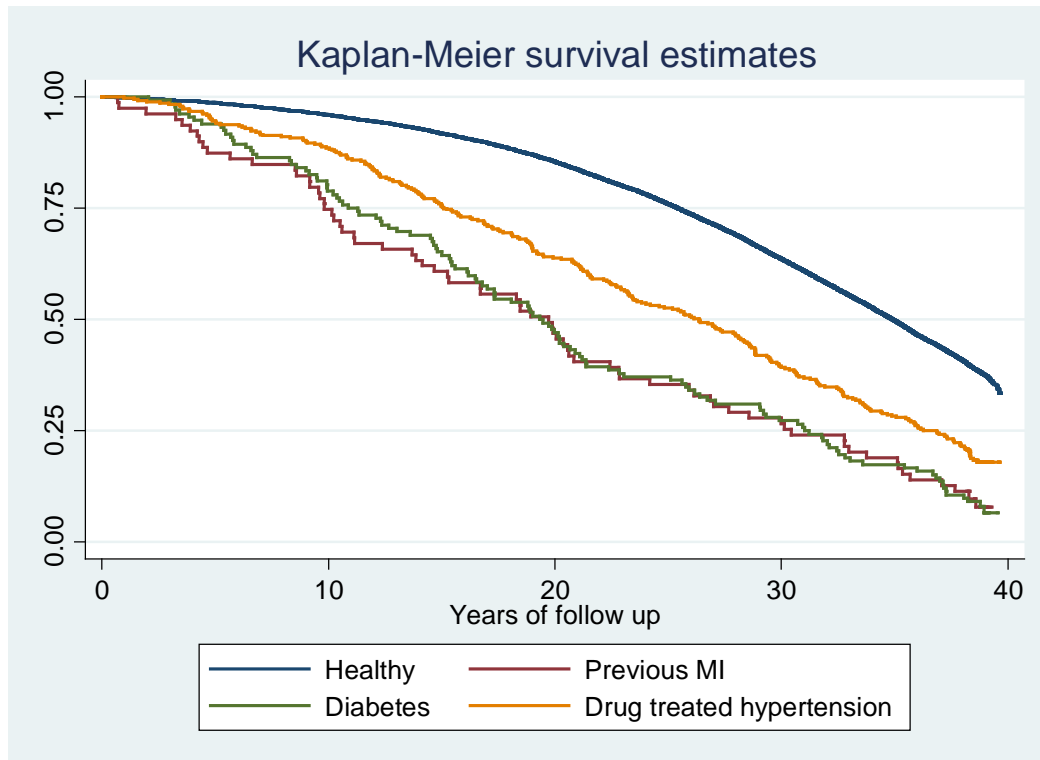
§ Adjusted for each other.

Figure 1 Kaplan Meier survival curves through 40 years for healthy men and men with prevalent myocardial infarction, diabetes and drug treated hypertension.
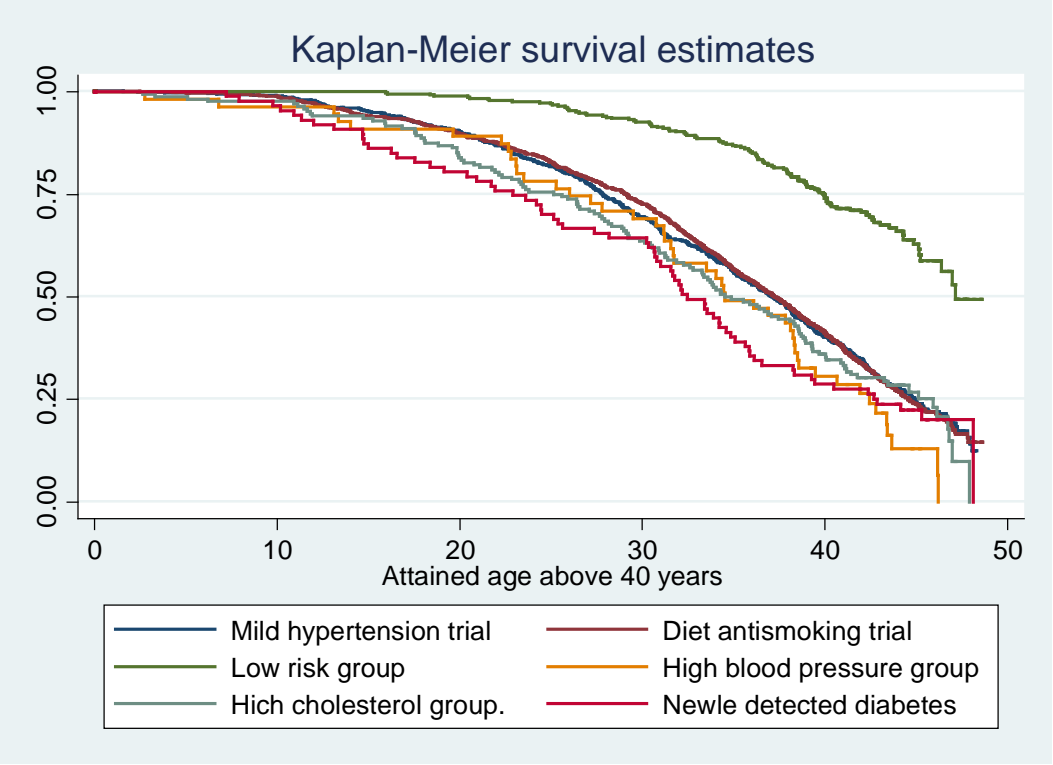
Kaplan-Meier survival estimates

17

Figure 2 Kaplan Meier survival curves for 6 groups defined after first and second screening reexamination.
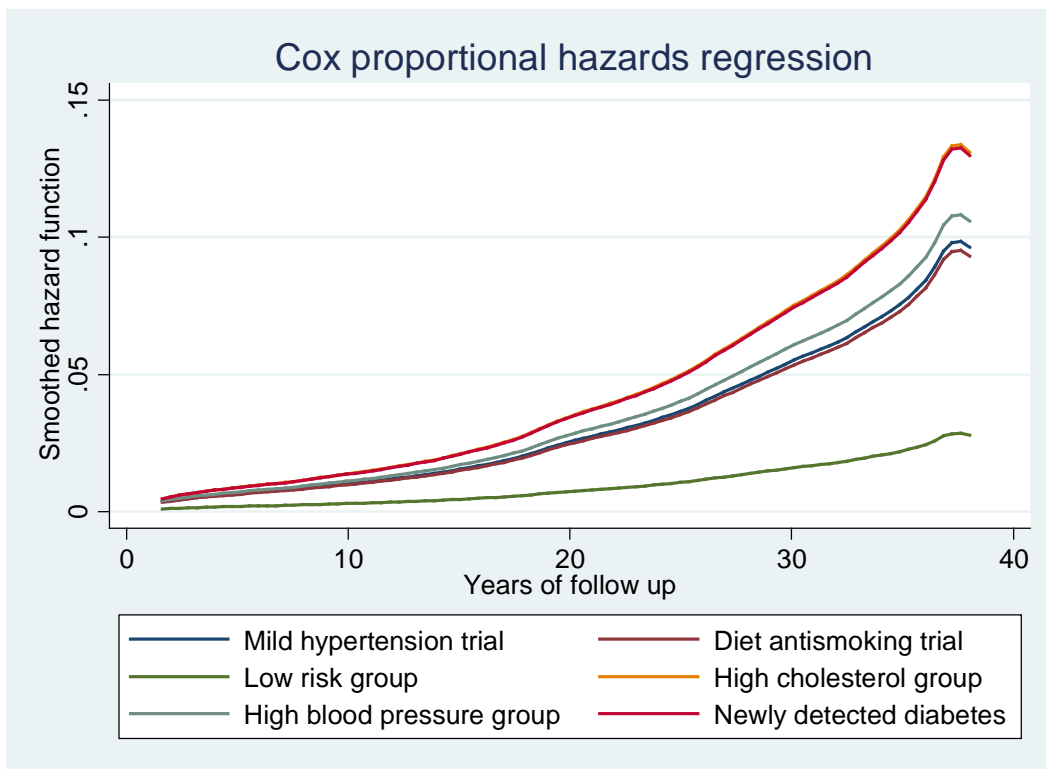

Figure 3 Smoothed hazard function of total mortality by risk groups and survival time.