

Predicting cardiovascular risk in the elderly in different European countries

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Aims The objective of this study was to develop risk functions for coronary heart disease and cardiovascular disease mortality for elderly men in different European countries.

Methods and Results The FINE Study is a prospective follow-up study of 2170 elderly men aged 65–84 years in Finland, Italy and The Netherlands. During 10 years of follow-up 289 men died from coronary heart disease and 545 men from cardiovascular disease. Risk functions were estimated using logistic regression analysis, in order to take competing causes of death into account. The results of the present study show that total cholesterol and smoking were the most important predictors of coronary heart disease mortality, and HDL cholesterol, systolic blood pressure and smoking of cardiovascular disease mortality. Left ventricular hypertrophy, being subject to coronary heart disease or cardiovascular disease in Finland and The Netherlands and use of antihypertensive medication in Italy, were also important predictors. For estimating the

absolute risk of coronary heart disease and cardiovascular disease mortality in the elderly it is necessary to take into account the European country in which they live.

Conclusion Total and HDL cholesterol, systolic blood pressure and smoking remain important predictors of coronary heart disease and/or cardiovascular disease mortality in elderly men, but also left ventricular hypertrophy, being subject to coronary heart disease, use of antihypertensive medication and country are predictive of coronary heart disease and cardiovascular disease risk.

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Introduction

Guidelines for prevention of coronary heart disease or cardiovascular disease are nowadays based on the absolute risk of coronary heart disease or cardiovascular disease, taking the total risk profile of an individual into account. In the elderly, absolute risks for coronary heart disease and cardiovascular disease are high and the

number of elderly people in Europe will increase in the years to come. Therefore, even a small decrease in risk causes a substantial reduction in the number of coronary heart disease and cardiovascular disease events. Estimation of absolute risk of coronary heart disease and cardiovascular disease in the elderly is needed for targeted preventive activities.

In middle-aged men and women, the Framingham risk function^[1] is widely used to estimate absolute risks of coronary heart disease and cardiovascular disease and this risk function has also been reasonably valid for northern European populations^[2]. Menotti *et al.*^[3] showed that in Italy in middle-aged men the Framingham risk function overestimates absolute coronary risk

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due to a lower incidence of coronary events. In the elderly it is not known whether the Framingham risk function is a valid tool for risk prediction. Due to weaker associations between risk factors and coronary heart disease and cardiovascular disease mortality in the elderly compared to middle-aged men^[4-6] it is necessary to develop separate risk functions for coronary heart disease and cardiovascular disease mortality in the elderly.

The aim of the present study is to develop risk functions for coronary heart disease and cardiovascular disease mortality for elderly men based on data collected in Finland, Italy and The Netherlands.

Methods

Study population

The FINE Study is an extension of the Seven Countries Study. Between 1958 and 1964, 16 cohorts of middle-aged men were examined according to a standardized protocol in seven countries^[7]. The survivors of the cohorts in Finland, Italy and The Netherlands were re-examined after 25 years. This examination was the baseline of the FINE Study, a prospective study in elderly men aged 65 to 84 years. The FINE Study includes the two Finnish cohorts (both rural) known as East Finland and West Finland (716 men in total), the Dutch cohort from the small town of Zutphen (887 men), and the two rural cohorts in Italy (682 men in total) from the villages of Crevalcore and Montegiorgio (in northern and central Italy, respectively). The response rate was 94% in Finland, 74% in The Netherlands and 76% in Italy.

Subjects with incomplete data for the risk factors included in the risk function (age, total and HDL cholesterol, systolic blood pressure, smoking, diabetes, ECG-left ventricular hypertrophy, use of anti-hypertensive medication and being a prevalent case of coronary heart disease or cardiovascular disease) were excluded (n=115).

Measurements

All men were examined according to the international protocol used in previous surveys of the Seven Countries Study^[7]. In Finland, fasting blood samples were taken and in The Netherlands and Italy non-fasting blood samples. In each country, total and HDL cholesterol determinations were carried out enzymatically in lipid laboratories standardized according to the criteria of the WHO Lipid Reference Laboratories in Prague, Czech Republic, or Atlanta, Georgia, U.S.A.^[8]. Blood pressure was measured twice on the right right arm in men in the supine position, using a standard sphygmomanometer in

Finland and Italy, and a random zero sphygmomanometer in The Netherlands. Systolic blood pressure was recorded at the first Korotkoff phase. Smoking was measured as current or non-smoking. Clinical diabetes mellitus was established by means of a standardized questionnaire. A 12-lead resting ECG was recorded. ECG-left ventricular hypertrophy was defined according to the Minnesota Code (codes 3.1 or 3.3, plus any code 4.1 to 4.3 or 5.1 to 5.3)^[9]. Use of anti-hypertensive medication was assessed with a standardized questionnaire.

Information on the history of coronary heart disease and cardiovascular disease was obtained from the Rose questionnaire^[9], combined with information from reported clinical records and additional questions from the examining physician. Coronary heart disease was considered to be present when either myocardial infarction (definite) or angina pectoris (definite) was diagnosed. Cardiovascular disease was considered to be present when either myocardial infarction (definite), angina pectoris (definite), intermittent claudication (definite), stroke (definite), TIA (definite) or heart failure (definite) was diagnosed.

Follow-up

Complete follow-up information after 10 years, obtained through official death certificates, was available in 99.7% of the subjects. In Finland, only information on causes of death was available. In The Netherlands and Italy, causes of death were in part validated through review of clinical records. Final causes of death were adjudicated by a single reviewer using the 9th revision of the WHO-ICD^[10] adopting a hierarchical order when multiple causes were given, as follows: violent causes, cancer, coronary heart disease, stroke and other. Coronary heart disease mortality was defined as ICD-9: 410-414 and cardiovascular disease mortality as ICD-9: 390-459.

Statistical analyses

Logistic regression analysis was used to calculate the 10-year probability of coronary heart disease and cardiovascular disease mortality. We did not use the Cox proportional hazards regression model or an accelerated failure time model as in the Framingham Study^[1,11] because these models calculate the risk of coronary heart disease or cardiovascular disease mortality in the absence of competing causes of death. As death by other causes becomes more important with increasing age, calculating the risk of coronary heart disease or cardiovascular disease mortality in the presence of competing causes of death, as is done by logistic regression, yields different results. As these equations are meant to be used by clinicians in order to predict the risk of individual patients, and such patients are subject to competing

Table 1 Mean, standard deviation and prevalence of risk factors included in the risk functions for coronary heart disease (CHD) and cardiovascular disease (CVD) mortality in men aged 65–84 years in the total population of the FINE Study, Finland, The Netherlands and Italy

	FINE	Finland	The Netherlands	Italy
Total number	2170	679	879	612
Number of CHD events	289	142	100	47
Number of CVD events	545	204	198	143
Age (years)	71.6 (5.1)	71.5 (5.2)	71.5 (5.3)	72.0 (4.5)
Total cholesterol (mmol . l ⁻¹)	6.05 (1.18)	6.17 (1.26)	6.10 (1.11)	5.85 (1.15)
HDL cholesterol (mmol . l ⁻¹)	1.20 (0.33)	1.23 (0.33)	1.12 (0.29)	1.29 (0.34)
Systolic blood pressure (mmHg)	156.5 (23.1)	153.9 (22.6)	151.1 (21.5)	167.1 (22.4)
Smoking (%)	25.5	18.6	30.4	26.3
Diabetes (%)	7.6	8.8	5.7	9.0
Left ventricular hypertrophy (%)	6.7	9.9	6.7	3.1
Use of anti-hypertensive medication (%)	21.2	20.8	12.9	33.5
History of CHD (%)	18.0	24.6	15.9	13.6
History of CVD (%)	31.0	39.3	24.9	30.4

causes of death, equations should give risk in the presence of competing causes of death, and thus logistic regression is better suited for the elderly. A disadvantage of logistic regression is that results apply only to the fixed follow-up time chosen for the analysis.

Risk factors included in the risk functions were: age, total and HDL cholesterol, systolic blood pressure, smoking, diabetes mellitus, ECG-left ventricular hypertrophy, use of antihypertensive medication and being subject to coronary heart disease or cardiovascular disease. Dummy variables for country were added to take into account differences in absolute risk between the countries. The maximum likelihood method was used to test if quadratic terms, log transformations of the continuous variables or interaction terms, should be added to the risk functions. A statistically significant interaction between the use of antihypertensive medication and Italy was included in the risk function for coronary heart disease and cardiovascular disease mortality and a statistically significant interaction between being subject to coronary heart disease or cardiovascular disease and Italy was also included in the risk functions.

The SAS computer package (version 6.12) was used for all statistical analyses (SAS Institute Inc., Cary, North Carolina, U.S.A., 1989).

Results

The mean levels of the risk factors included in the risk functions for coronary heart disease and cardiovascular disease mortality are given in Table 1. Total cholesterol ranged from 5.9 mmol . l⁻¹ in Italy to 6.2 mmol . l⁻¹ in Finland. HDL cholesterol ranged from 1.1 mmol . l⁻¹ in The Netherlands to 1.3 mmol . l⁻¹ in Italy. Systolic blood pressure was lowest in The Netherlands (151 mmHg) and highest in Italy (167 mmHg). The percentage of smokers was 19% in Finland, 26% in Italy

and 30% in The Netherlands. The prevalence of diabetes was highest in Italy and Finland (9%) and lowest in The Netherlands (6%). The prevalence of left ventricular hypertrophy was highest in Finland (10%) and lowest in Italy (3%). The use of antihypertensive medication varied from 13% in The Netherlands to 34% in Italy. A history of coronary heart disease (25%) and a history of cardiovascular disease (39%) were both most prevalent in Finland. During the 10 years of follow-up, 289 coronary heart disease events (13%) and 545 cardiovascular disease events (25%) occurred in 2170 men.

Table 2 shows the risk functions for coronary heart disease and cardiovascular disease mortality fitted on the FINE data. The Table presents the regression coefficients and the corresponding odds ratios (with 95% CI) for the risk factors. In appendix A the calculation of absolute risks based on those coefficients is described. In the risk function for coronary heart disease mortality, total cholesterol was a statistically significant predictor (OR=1.24; 95% Confidence Interval 1.11–1.38), but this was not the case in the risk function for cardiovascular disease mortality (OR=1.06; 95% CI 0.97–1.16). HDL cholesterol was statistically significantly associated with cardiovascular disease mortality (OR=0.69; 95% CI 0.49–0.96), but not with coronary heart disease mortality. Systolic blood pressure was only statistically significantly associated with cardiovascular disease mortality (OR=1.05; 95% CI 1.01–1.11). The effect of smoking on coronary heart disease and cardiovascular disease mortality was comparable, but was only statistically significant for cardiovascular disease mortality (OR=1.28; 95% CI 1.01–1.63).

In these elderly men, diabetes was not statistically significantly associated with coronary heart disease and cardiovascular disease mortality. The risk of coronary heart disease and cardiovascular disease mortality was twice as high in elderly men with left ventricular hypertrophy compared to men without left ventricular

Table 2 Regression coefficients and odds ratios (95% Confidence Intervals) for the risk factors and 10-year coronary heart disease (CHD) and cardiovascular disease (CVD) mortality in men aged 65–84 years

	CHD mortality		CVD mortality	
	Coefficient	OR (95% CI)	Coefficient	OR (95% CI)
Intercept	-7.9578	—	-9.0941	—
Age (years)	0.0682	1.07 (1.04–1.10)	0.0963	1.10 (1.08–1.12)
Total cholesterol (1 mmol . l ⁻¹)	0.2146	1.24 (1.11–1.38)	0.0584	1.06 (0.97–1.16)
HDL cholesterol (1 mmol . l ⁻¹)	-0.1842	0.83 (0.54–1.27)	-0.3773	0.69 (0.49–0.96)
Systolic blood pressure (10 mmHg)	0.0014	1.01 (0.94–1.07)	0.0523	1.05 (1.01–1.11)
Smoking (no/yes)	0.2140	1.24 (0.91–1.69)	0.2471	1.28 (1.01–1.63)
Diabetes (no/yes)	0.0765	1.08 (0.67–1.74)	0.2230	1.25 (0.87–1.80)
Left ventricular hypertrophy (no/yes)	0.6842	1.98 (1.30–3.02)	0.7042	2.02 (1.40–2.93)
Use of antihypertensive medication	-0.0515	0.95 (0.63–1.42)	0.2306	1.26 (0.91–1.75)
Antihypertensive medication * Italy	1.2741	3.58 (1.72–7.43)	0.4605	1.59 (0.96–2.62)
Prevalent case	1.4291	4.18 (3.05–5.71)	0.9378	2.55 (1.98–3.29)
Prevalent case * Italy	-1.1495	0.32 (0.13–0.77)	-0.6775	0.51 (0.31–0.82)
Dummy The Netherlands (no/yes)	-0.6264	0.53 (0.40–0.72)	-0.2858	0.75 (0.59–0.97)
Dummy Italy (no/yes)	-1.2469	0.29 (0.16–0.50)	-0.2846	0.75 (0.52–1.09)

hypertrophy. In Finland and The Netherlands, use of antihypertensive medication was not associated with coronary heart disease mortality. However, in Italy the odds ratio for the use of antihypertensive medication in the risk function for coronary heart disease mortality was 3.4 (0.95 × 3.58). Use of antihypertensive medication was not statistically significantly associated with cardiovascular disease mortality. Being subject to coronary heart disease or cardiovascular disease was associated with both coronary heart disease and cardiovascular disease mortality, especially in Finland and The Netherlands. In Italy, the effect of being subject to coronary heart disease and cardiovascular disease mortality was much lower, as shown by the lower ORs (OR=1.34 (0.32 × 4.18) for coronary heart disease mortality and 1.30 (0.51 × 2.55) for cardiovascular disease mortality).

The coefficients for the dummy variables for country showed that the risk of coronary heart disease mortality was significantly lower in both The Netherlands and Italy, with the lowest risk in Italy. The risk of cardiovascular disease mortality was highest in Finland. The Netherlands and Italy had comparable absolute risks of cardiovascular disease mortality, as shown by the comparable coefficients for the dummy variables of these countries.

Discussion

The results of the present study show that most classical risk factors for coronary heart disease and cardiovascular disease mortality remain predictive in the elderly, total cholesterol and smoking being the most important for coronary heart disease mortality, and HDL cholesterol, systolic blood pressure and smoking for cardiovascular disease mortality. Left ventricular hypertrophy was also an important risk factor for coronary heart disease and cardiovascular disease mortality in these

elderly men. Being subject to coronary heart disease or cardiovascular disease was an important risk factor in Finland and The Netherlands, but not in Italy. Using antihypertensive medication is a risk factor for coronary heart disease mortality in Italy. For estimating the absolute risk of coronary heart disease and cardiovascular disease mortality in the elderly it is necessary to take into account the European country in which they live.

In this study separate risk functions for coronary heart disease and cardiovascular disease mortality in the elderly were developed. It is important to have specific risk functions to predict absolute risks in the elderly instead of using the Framingham risk function, for several reasons. First, while the Framingham risk function is developed to estimate absolute risks in persons aged 30–74 years^[1], the number of elderly (>70 years) included is only 111 (4%) men and 163 (5%) women, leading to unreliable estimates for the elderly.

Second, the Framingham risk function is calculated with an accelerated failure time model in which the presence of competing causes of death is not taken into account. Especially in the elderly in whom dying of causes other than coronary heart disease and cardiovascular disease is frequent, it is important to take competing causes of death into account. This is because overall health in a population does not benefit from preventive action against cardiovascular disease in persons who will die from other causes. Therefore, we used logistic regression analysis in which absolute risks of coronary heart disease or cardiovascular disease mortality are calculated in the presence of competing causes of death.

Third, the relationship between cardiovascular disease risk factors and coronary heart disease or cardiovascular disease mortality is weaker in elderly compared to middle-aged men^[4–6]. In general, relative risks decrease with increasing age, but absolute risks increase. The relative risk found in the Seven Countries Study for the relationship between total cholesterol and coronary

heart disease mortality in middle-aged men using Cox proportional hazards regression was 1.25 (95% CI 1.19–1.35, per 1.00 mmol . l⁻¹ increase)^[12], while in the same elderly men in the FINE Study, we found a relative risk of 1.17 (95% CI 1.06–1.29)^[13]. This shows that also in this study population the predictive power of total cholesterol was lower in the elderly compared to that in middle-aged men.

In the present study, a non-significant odds ratio was found for the relationship between total cholesterol and cardiovascular disease mortality. Assuming that serum total cholesterol is not associated with stroke^[14], a weaker effect on cardiovascular disease mortality compared to the effect on coronary heart disease mortality is expected. HDL cholesterol was not significantly associated with coronary heart disease mortality in the present study. It is unclear whether HDL cholesterol is an important risk factor for coronary heart disease mortality in the elderly^[13]. However, there was a statistically significant inverse association between HDL cholesterol and cardiovascular disease mortality in the present study. This could be explained by the fact that several studies have found that a low HDL cholesterol level is a risk factor for stroke, even in the elderly^[15–17].

Systolic blood pressure was statistically significantly associated with cardiovascular disease mortality but not with coronary heart disease mortality in these elderly men. Van den Hoogen *et al.*^[18] found a significant relationship between systolic blood pressure and coronary heart disease mortality in middle-aged men in the Seven Countries Study (RR = 1.17; 95% CI 1.14–1.20 per 10 mmHg increase). The effect of systolic blood pressure on cardiovascular disease mortality in these middle-aged men was not estimated. It is assumed that systolic blood pressure is a risk factor for coronary heart disease and cardiovascular disease in elderly men until age 80, but the relative risks decrease with age^[6]. Our data do not support a relationship between systolic blood pressure and coronary heart disease mortality in the elderly.

There was an effect of smoking in both risk functions, but only for cardiovascular disease mortality was the odds ratio statistically significant. It has been reported that the effect of smoking on coronary heart disease mortality in the elderly is also attenuated compared to the effect in middle-aged men: a relative risk of 2.8 in men aged <65 years compared to a relative risk of 1.6 in men aged ≥65 years^[5].

There was a positive, non-significant, effect of diabetes on both coronary heart disease and cardiovascular disease mortality in this elderly population. The reason for the somewhat lower odds ratios for diabetes found in the present study compared with those found in other studies^[19,20] could be that we have adjusted for several variables associated with diabetes. If we calculate the crude odds ratio for diabetes in this study, it is indeed higher for both coronary heart disease and cardiovascular disease mortality (OR = 1.30; 95% CI 0.85–2.01 and OR = 1.59; 95% CI 1.13–2.23, respectively).

Left ventricular hypertrophy was positively associated with coronary heart disease and cardiovascular disease

mortality. It is known that left ventricular hypertrophy is an independent risk factor for coronary heart disease and cardiovascular disease mortality in the elderly^[21,22]. The odds ratio found in the present study was comparable with that found in the Framingham Study in men aged 65 years and older (OR = 2.1; 95% CI 1.3–3.5). In Italy, men using antihypertensive medication had a higher risk of coronary heart disease mortality compared to those not using this type of medication. In Finland and The Netherlands, prevalent cases had a statistically significant higher risk of dying of coronary heart disease and cardiovascular disease. An explanation could be that using antihypertensive medication in Italy and being a prevalent case in Finland and The Netherlands are both proxies for dying of coronary heart disease or cardiovascular disease in the future. To examine this hypothesis a 'disease variable' was included in the risk functions combining use of antihypertensive medication and/or being a prevalent case. The odds ratio for this 'disease variable' in the risk function for coronary heart disease mortality was 2.83 (95% CI 2.16–3.72) and in the risk function for cardiovascular disease mortality 2.25 (1.82–2.78) (data not shown). These odds ratios were not significantly different between the countries. This means that elderly men using antihypertensive medication and/or being a prevalent case have a higher risk of dying of coronary heart disease and cardiovascular disease, irrespective of the country in which they live.

The present study showed that, except for the intercept, the same risk functions for coronary heart disease and cardiovascular disease mortality could be used in Finland, The Netherlands and Italy. Earlier results of the FINE Study indeed showed comparable relative risks for the relationship between cholesterol levels and coronary heart disease mortality in the different European countries, but different absolute risks at the same cholesterol level in the elderly^[13]. Different absolute risks between the countries for men with the same risk factor profile were also found in the present study (see Appendix A). Therefore, dummy variables for country were added to the risk functions to take into account the differences in absolute risk between the countries. The negative coefficient in the risk function for the dummy variable for Italy means that a person in Italy with the same risk profile as a person in Finland has a lower absolute risk. This may be due to differences in e.g. dietary patterns between the countries. The Mediterranean diet is healthier than the Northern European diet, which might explain the lower absolute risk for coronary heart disease in Italy at the same blood pressure and cholesterol levels^[12,18]. The effect of the dummy variables for country on the prediction of the absolute risks is larger for the risk function for coronary heart disease compared to that for cardiovascular disease mortality, probably because diet has a larger impact on the absolute risks of coronary heart disease compared to cardiovascular disease.

We conclude that there is still an association between the risk factors total and HDL cholesterol, systolic

blood pressure and smoking and coronary heart disease and/or cardiovascular disease mortality in elderly men, although the associations are weaker than in middle-aged men. Left ventricular hypertrophy, being subject to coronary heart disease or cardiovascular disease in Finland and The Netherlands and using antihypertensive medication in Italy are also important risk factors. Besides this, it is necessary to take the European country into account when the absolute risk of coronary heart disease and cardiovascular disease mortality in the elderly men is calculated. The results of the present study have important implications for prevention in the elderly. A reduction in the absolute risk of dying from coronary heart disease or cardiovascular disease through lifestyle and dietary changes, in combination with proper clinical treatment, is necessary and will probably increase the quantity and quality of life in elderly men.

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Appendix A

In this appendix the method of calculating absolute risks is presented, using the regression coefficients given in Table 2. The 10-year probability of dying from a coronary heart disease event is computed using the following equation:

$$10\text{-year probability} = 1/1 + \exp(-L)$$

$$\begin{aligned} \text{where } L = & -7.9578 + 0.0682 * \text{age} \\ & + 0.2146 * \text{total cholesterol} \\ & - 0.1842 * \text{HDL cholesterol} \\ & + 0.0014 * \text{systolic blood pressure} \\ & + 0.2140 * \text{smoking} + 0.0765 * \text{diabetes} \\ & + 0.6842 * \text{left ventricular hypertrophy} \\ & - 0.0515 * \text{use of antihypertensive medication} \\ & + 1.2741 * (\text{antihypertensive medication} * \text{Italy}) \\ & + 1.4291 * \text{prevalent case} \\ & - 1.1495 * (\text{prevalent case} * \text{Italy}) \\ & - 0.6264 * \text{dummy The Netherlands} \\ & - 1.2469 * \text{dummy Italy.} \end{aligned}$$

Using the above mentioned equation, the 10-year probabilities of dying from a coronary heart disease event is estimated for two fictive persons. An *Italian man* aged 70 years without diabetes, who smokes, has no ventricular hypertrophy, no history of coronary heart

disease, does not use antihypertensive medication, has a total cholesterol level of $6.0 \text{ mmol} \cdot \text{l}^{-1}$, HDL cholesterol level of $1.3 \text{ mmol} \cdot \text{l}^{-1}$, and systolic blood pressure of 145 mmHg, has an L of $-7.9578 + 0.0682 * 70 + 0.2146 * 6.0 - 0.1842 * 1.3 + 0.0014 * 145 + 0.2140 * 1 - 1.2469 * 1 = -2.9656$ and thus a 10-year probability of dying from a coronary heart disease event of $1/1 + \exp(2.9656) = 0.05$. A *Finnish man* of the same age and with a similar risk profile has a 10-year probability of dying from a coronary heart disease event of 0.15. An *Italian man*

aged 80 years with diabetes, who smokes, has ventricular hypertrophy, a history of coronary heart disease, use anti-hypertensive medication, has a total cholesterol level of $6.5 \text{ mmol} \cdot \text{l}^{-1}$, HDL cholesterol level of $1.2 \text{ mmol} \cdot \text{l}^{-1}$, and systolic blood pressure of 150 mmHg, has a 10-year probability of dying from a coronary heart disease event of 0.47. A *Finnish man* of the same age and with a similar risk profile has a 10-year probability of dying from a coronary heart disease event of 0.74.