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Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project

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KEYWORDS
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Aims The SCORE project was initiated to develop a risk scoring system for use in the clinical management of cardiovascular risk in European clinical practice.
Methods and results The project assembled a pool of datasets from 12 European cohort studies, mainly carried out in general population settings. There were 205 178 persons (88 080 women and 117 098 men) representing 2.7 million person years of follow-up. There were 7934 cardiovascular deaths, of which 5652 were deaths from coronary heart disease. Ten-year risk of fatal cardiovascular disease was calculated using a Weibull model in which age was used as a measure of exposure time to risk rather than as a risk factor. Separate estimation equations were calculated for coronary heart disease and for non-coronary cardiovascular disease. These were calculated for high-risk and low-risk regions of Europe. Two parallel estimation models were developed, one based on total cholesterol and the other on total

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cholesterol/HDL cholesterol ratio. The risk estimations are displayed graphically in simple risk charts. Predictive value of the risk charts was examined by applying them to persons aged 45–64; areas under ROC curves ranged from 0.71 to 0.84.
Conclusions The SCORE risk estimation system offers direct estimation of total fatal cardiovascular risk in a format suited to the constraints of clinical practice.

Introduction

Current recommendations on the prevention of coronary heart disease in clinical practice stress the need to base intervention on an assessment of the individual's total burden of risk rather than on the level of any particular risk factor.[1–7] This is because most people who develop atherosclerotic cardiovascular disease have several risk factors which interact to produce their total risk. It follows that there is a need for clinicians to be able to estimate total risk of cardiovascular disease.

The guidelines for risk factor management issued by the First Joint Task Force of the European Societies on Coronary Prevention[1] used a simple risk chart based on a risk function published by the Framingham investigators.[8] The chart displayed risk of any coronary heart disease event, fatal or non-fatal based on categories of age, sex, smoking status, total cholesterol and systolic blood pressure. It built on the pioneering work of Jackson and his colleagues, who introduced simple graphical displays of risk as a basis for treatment decisions.[9] A 10-year absolute risk of 20% or more was arbitrarily recommended as a threshold for intensified risk factor intervention. The chart, in a modified form, was also used by the Second Joint Task Force.[6] However, the Task Forces had a number of concerns about using this chart as a basis for clinical intervention. These included

(1) The applicability of a risk function derived from US data to European populations: while there is some evidence that risk estimates based on Framingham data generalise well to other populations at similar levels of risk both in the US[10] and in Europe[11] it appeared likely that the risk chart overestimated absolute risk in populations with lower coronary heart disease rates.[10,12] This was, in fact, demonstrated in a comparison of the Framingham risk function-based risk chart with a risk function derived from an Italian population study.[13]

Moreover, recent studies applying Framingham risk function to data from Danish and German prospective studies have demonstrated that the Framingham risk function clearly overestimates coronary heart disease risk also in these populations[14,15].

(2) The definition of nonfatal end-points used in the Framingham Study[16] differs from definitions used in most other cohort studies, and from end-points used in clinical trials. It includes, in addition to non-fatal myocardial infarction, new onset angina and 'coronary insufficiency' (unstable angina), making it difficult to validate the function with data from other cohort studies, and difficult to relate to the results of therapeutic trials. The ratio of new onset angina to 'hard' acute coronary heart disease events (coronary death and nonfatal myocardial infarction) is not known for the model used in the Task Force chart, but in a more recent publication from the Framingham group[17] new angina accounted for 41% of all events in men and 56% in women. There appeared to be no straightforward way of converting 'Framingham risk' to other definitions. A re-analysis of the European data from the Seven Countries Study by Menotti and his colleagues demonstrated, however, that using strict criteria the ratios between various coronary heart disease end-point components (mortality, 'hard criteria' events and 'soft criteria' events) were similar in northern and southern European cohorts.[18]

(3) The difficulty in using local data to adjust the model for use in individual European countries.

Accordingly, the European Society of Cardiology and the Second Joint Task Force instigated the development of a risk estimation system based on a large pool of representative European data sets that would capture the regional variation in risk. This led to the establishment of the SCORE (Systematic COronary Risk Evaluation) project as a European Concerted Action project funded under the European Union BIOMED programme.

The aim of the SCORE project is to develop a system of risk estimation for clinical practice in Europe, in liaison with the Third Joint Task Force. This is being done in three phases: first, the development of simple paper-based risk charts for high-risk and low-risk European populations; second, the development of methods for creating national or regional risk charts based on published mortality data, and, finally, the integration of risk estimation into a computer-based risk factor management application. In this paper we present risk charts

for high and low risk regions of Europe, based on total cholesterol and on total cholesterol/HDL cholesterol (cholesterol/HDL cholesterol) ratio.

Subjects and methods

The SCORE project assembled a pooled dataset of cohort studies from 12 European countries. The participating studies[19–33] are listed in Table 1. Most cohorts were population-based, though some occupational cohorts were included to increase representation of regions of lower risk. Subjects were excluded from the development of the risk chart if they had a previous history of heart attack.

Definition of end-points

Cardiovascular mortality was defined as ICD-9 codes 401 through 414 and 426 through 443, with the exception of the following ICD-9 codes for definitely non-atherosclerotic causes of death: 426.7, 429.0, 430.0, 432.1, 437.3, 437.4, and 437.5. We also classified 798.1 (instantaneous death) and 798.2 (death within 24 h of symptom onset) as cardiovascular deaths.

Statistical methods

Data were analysed using Stata Release 7. The risk functions underlying the risk charts were calculated using a Weibull proportional hazards model. The model has two parts: one part models the shape of the baseline survival function and the other calculates the relative risks associated with the risk factors. The model was stratified on cohort and sex — that is, separate hazard functions were calculated for men and women in each of the component cohorts, but risk factor coefficients were calculated from the whole dataset. This approach assumes that risk factors do not vary in their effect from country to country and are the same in men and women.

The use of the Weibull model has the advantage that the risk estimation equation can be written as a formula. However, all model predictions were cross checked by comparison with Cox regression models, to ensure that the assumptions made by Weibull regression about the shape of the survival function did not compromise the performance of the risk chart.

Unlike many epidemiological analyses, we constructed the hazard function based on the person's age, rather than on their time under observation. The more usual approach, in which age is modelled as a risk factor and the hazard function is based on time-on-study, has been criticised for making inefficient use of the available data by splitting the effect of time on risk into two different variables: age at screening and time since screening.[34] While the traditional approach probably results in negligible bias in the estimation of cardiovascular risk factor effects, if has the disadvantage that survival cannot be estimated for follow-up times greater than the length of the study's follow-up period. Using age as the time variable, however, allows us to make estimations for the entire range of age observed in the study. Ten-year risk calculations are based on the conditional probability of cardiovascular mortality in the ensuing ten years, given that one has survived to the index age.

Risk of cardiovascular death was calculated by combining two separate risk estimations: a model for coronary heart disease (ICD 410-414) and a model for all non-coronary atherosclerotic cardiovascular disease. This was done partly in recognition that the weights assigned to different risk factors and the shape of the lifetime hazard function may be different for the two different components of total cardiovascular mortality, but also because this allows the calculation of the two components of underlying risk separately. This will allow the risk function to be implemented on computer so that the person's total risk can be broken down into its coronary and non-coronary components. It also allows the model to be used to calculate the likely reduction in end-points of different types resulting from treatment of risk factors. Again, we examined models in which total cardiovascular risk was calculated in a single step to verify that the two-step procedure did not affect the performance of the risk estimation function.

Areas under ROC curves were used to assess the discrimination of models. Diagnostic performance was assessed by examining the positive clinical likelihood ratios for various thresholds of risk. The clinical likelihood ratio is often simply called the likelihood ratio, causing confusion with the statistical term. It is a measure of the information content of a test. Its simplest definition is the change in the odds of disease when a person is revealed to have a positive test result. More accurately, it expresses the power of a positive test result to augment an estimate of disease probability independent of the pre-test risk of disease in a given population.[35] This independence represents a distinct advantage over the more commonly-used positive predictive value, which varies with the absolute risk. Lin's concordance coefficient was used to measure concordance between risks estimated using cholesterol and those using cholesterol/HDL cholesterol ratio.[36,37]

Table 1 Participating projects in the SCORE partnership

Country	Study [Key reference]	Recruitment*	Component cohorts pooled	Participants	Age range	Years recruited	Participation rate
Finland	The FINRISK Study[19]	RS(a) SRS-M(b)/P	4	37 296	24–64	1972/1977(a) 1982/1987(b)	80%
Russia	Collaborative US-USSR study on the prevalence of dyslipoproteinemias and ischemic heart disease in American and Soviet populations[20]	RS/MO		3325	37–62	1975–77	70%
Norway	Norwegian Counties Study[21,22]	CP	3	48 425	35–49	1974–78	88%
UK (BRHS)	British Regional Heart Study[23]	CS/GP/MO		7292	38–61	1978–80	78%
UK (Scotland)	Scottish Heart Health and Scottish MONICA cohort follow-up studies[24]	CS/GP		12 285	25–66	1984–87	64%
Denmark	The Glostrup Population Studies[25]	RS/BC/P	7	9945	29–80	1977–91	74%
Sweden	The Primary Prevention Study in Göteborg (Gothenburg)[26]	RS/MO		7435	47–56	1970–73	75%
Belgium	Belgian Interuniversity Research on Nutrition and Health (BIRNH)[27]	SRS		10 641	25–75	1980–84	36%
Germany	The MONICA Augsburg cohort study[28]	SRS-M		3968	25–65	1984–85	79%
Italy	Risk Factors and Life Expectancy (RIFLE) pooling project[29]	P	52	53 439	19–80	See reference	See reference
France	Paris Prospective Study[30]	OCC/MO		7337	43–53	1967–72	80%
Spain	Catalonia Cohort Study (1), Barcelona Multifactorial Trial (2), Factory Heart Study (3)[31–33]	RS(1) OCC(2,3) MO(2,3)	3	4701	25–68	1986–88(1) 1974–77(2) 1980–82(3)	75%(1) 77%(2) 83%(3)

*RS=Random Sample; SRS=Stratified Random Sample; SRS-M=Stratified Sample using MONICA protocol; CS=Cluster Sample; CP=Complete Population; P=Pooling project; BC=Birth Cohort; OCC=Occupational Cohort; MO=Men only.

The baseline survival functions for the cohorts from Denmark, Finland, and Norway, combined with the risk factor coefficients derived from the whole dataset, were used to develop the high risk model, while the baseline survival function for the cohorts from Belgium, Italy and Spain were used similarly to develop the low-risk region model. These cohorts were selected as typifying high- and low-risk populations based on examination of cardiovascular death rates standardised for risk factor levels in study cohorts, but also taking into account age-standardised death rates in national mortality statistics[38], as well as cohort sizes and availability of data for both men and women.

We calculated risk for two different risk charts: one based on total cholesterol and the other on cholesterol/HDL cholesterol ratio. In each case, the remaining risk factors entered into the model were sex, smoking and systolic blood pressure (age was used to define the hazard function, as explained above).

Model fit was checked extensively within the risk factor range displayed in the risk charts by calculating observed and expected event rates for each of the 400 risk factor combinations shown on the chart and identifying areas of adjacent cells where residuals were large, or all of a similar sign.

Results

Table 1 describes the design features of the cohorts which were pooled to calculate and evaluate the risk charts. Three of the studies were of men only. The predominant design was population-based cohort study, but occupational data from France, Italy and Spain was also included to increase representation of lower risk regions. Table 2 gives descriptive information on risk factors and death rates in the cohorts. There were 205 178 persons (88 080 women and 117 098 men) representing 2.7 million person years of follow-up. There were 7934 cardiovascular deaths, of which 5652 were deaths from coronary heart disease. To facilitate comparison between cohorts, the table shows the cumulative lifetime risk to age 65, calculated using Kaplan–Meier estimation, using the age-as-exposure-time method described above. In addition to the evident differences between cohorts in absolute risk of both cardiovascular disease and coronary heart disease, there is considerable variation in the ratio of coronary heart disease to total cardiovascular disease. In countries with low absolute risk of cardiovascular disease, coronary heart disease accounts for a smaller percentage of all cardiovascular events (Kendall's tau-b correlation 0.453 between cardiovascular disease death rate and proportion of cardiovascular disease accounted for by coronary heart disease).

Having examined the variation in relative risks between men and women and between the component cohorts of the study, we could find no evidence of systematic regional or sex variation in risk factor effects. In particular, regional variation in the risk factor coefficients was uncorrelated with regional mortality rates from cardiovascular disease.

Figs. 1–4 show the 10-year risk of a fatal cardiovascular disease event for 400 combinations of risk factors for high and low risk regions. There are two pairs of charts, one which shows cholesterol (Figs. 1 and 2), and one cholesterol/HDL cholesterol ratio. Risk is read by rounding the person's age to the nearest age shown on the chart, their cholesterol or cholesterol/HDL ratio to the nearest whole unit, and their blood pressure to the nearest multiple of 20 mmHg. The model coefficients and method of calculation are detailed in Appendix A.

To examine variation in the predictive ability of the risk function, we calculated estimated risk within each component cohort of the SCORE database, using the male and female baseline survival function from the individual cohorts to adjust the model to the correct absolute risk. Since age is a major determinant of coronary risk and the age ranges of the cohorts are rather heterogeneous, we limited calculation of model fit to the age group 45 to 64.

Table 3 shows the performance of the risk functions for high risk regions, and Table 4 shows the same information for the charts for low risk regions. The performance of the cholesterol-based and cholesterol/HDL cholesterol ratio-based charts is very similar; certainly there is no consistent indication of the superiority of one format over the other. We examined the risk estimations made by both charts to see if cholesterol/HDL ratio identified individuals who would not be recognised as high risk on the basis of cholesterol alone. There was no evidence of this; 79.0% of persons in all cohorts had the same estimated risk using both methods when the chart for high risk areas was used, and 98.2% had a risk that differed by no more than 1%. The low risk area charts for cholesterol and cholesterol/HDL ratio gave the same risk classification to 89.9% of persons and a classification that differed by at most 1% to 99.9% of persons. Concordance coefficients were 0.99 for both high and low risk charts, indicating that the two methods yield virtually interchangeable results.

Table 2 Risk factors and death rates in the component cohorts

	Country	Number	Smoking (%)	Mean cholesterol (mmol/L)	Mean HDL cholesterol (mmol/L)	Mean SBP	95th centile of follow-up (years)	Cumulative CVD death rate by age 65*	Cumulative CHD death rate by age 65*	CHD as % of all CVD by age 65
Men	Finland	18 083	44%	6.5	1.26	142	23.8	12.80%	10.81%	84%
	Russia	3325	51%	5.7	1.34	133	19	11.91%	8.45%	71%
	Norway	24 438	54%	6.4		136	18.5	7.91%	6.11%	77%
	UK (BRHS)	7292	51%	6.3	1.15	145	17.8	7.11%	5.72%	80%
	UK (Scotland)	6000	52%	6.3	1.37	134	13.8	6.49%	5.37%	83%
	Denmark	4932	57%	6.1		129	15.6	6.44%	4.89%	76%
	Sweden	7435	49%	6.4		149	24.3	4.80%	4.07%	85%
	Belgium	5507	50%	6.0		136	10.1	4.79%	2.25%	47%
	Germany	1978	39%	6.1	1.32	133	11.2	4.72%	3.65%	77%
	Italy	28 261	46%	5.6	1.27	135	13.7	4.01%	3.10%	77%
	France	7337	68%	5.8		138	26.1	3.20%	1.66%	52%
	Spain	3415	54%	5.7	1.19	132	10.1	2.81%	1.99%	71%
	Total	117 098								
Women	Finland	19213	15%	6.4	1.51	140	23.8	2.66%	1.65%	62%
	Denmark	5013	47%	6.1	1.61	124	15.7	2.37%	1.48%	62%
	UK (Scotland)	6285	38%	6.5	1.68	131	13.8	2.33%	1.56%	67%
	Norway	23 987	37%	6.2		131	18.5	1.95%	1.24%	64%
	Belgium	5134	17%	6.1	1.54	132	10.1	1.60%	0.60%	38%
	Germany	1990	22%	5.9	1.65	126	11.2	1.15%	0.74%	64%
	Italy	25 178	22%	5.5	1.45	133	13.7	0.96%	0.67%	70%
	Spain	1286	12%	5.6	1.41	120	10.6	0.94%	0.64%	68%
	Total	88 080								

*Death rates are calculated as Kaplan-Meier estimates. Countries are shown in order of cumulative risk of CVD for each sex.

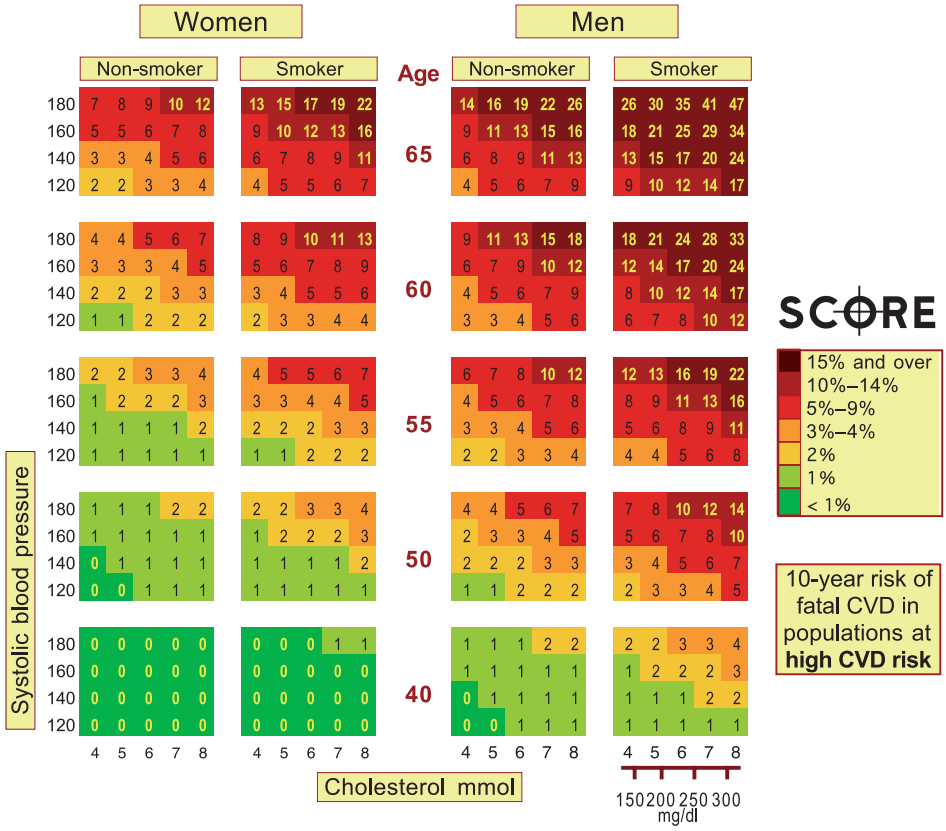

Fig. 1 Ten-year risk of fatal cardiovascular disease in populations at high cardiovascular disease risk. Chart based on total cholesterol.

Discussion

There have been numerous papers over the years presenting methods of calculating risk of coronary heart disease and stroke, and it is worthwhile to review our motives in adding yet another.

Total cardiovascular risk rather than coronary heart disease risk

First and most fundamentally, the method we describe is aimed at estimation of total cardiovascular risk rather than risk of coronary heart disease. This represents a shift from the traditional epidemiological concern with the causes of specific diseases to a public health perspective which focuses on the consequences of risk factors. By calculating total cardiovascular risk, we hope to give a better estimate of risk to the person, and also a better reflection of the health service implications of cardiovascular risk factors. Non-coronary cardiovascular disease is important because it represents a greater proportion of all cardiovascular risk in European regions with low rates of coronary heart disease (see Table 2). The method we adopted calculates total risk in two parts, the coronary heart disease component and the non-coronary component, allowing calculations to be made on the consequences of treatment. As a spin off to this, the function can therefore be used to calculate the risk of each type of end-point separately, though we would stress that total risk is to be preferred when making treatment decisions or carrying out patient education.

Why fatal events only?

Why did the SCORE project shift the emphasis in risk estimation to fatal cardiovascular disease events only instead of combined fatal and non-fatal events? There is no doubt that both patients and physicians are as interested in non-fatal as in fatal cardiovascular disease events, and furthermore morbidity and incapacity caused by non-fatal cardiovascular disease events is the major economic burden for the health care system and the society. Non-fatal cardiovascular disease events pose, however, a number of problems for the development of

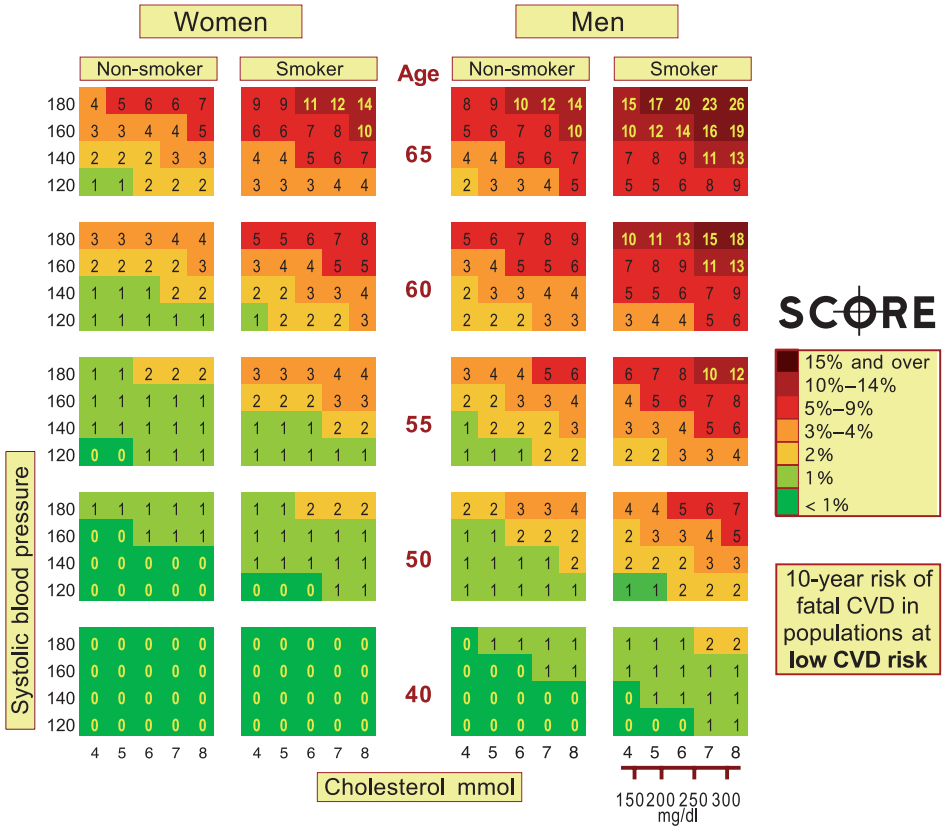

Fig. 2 Ten-year risk of fatal cardiovascular disease in populations at low cardiovascular disease risk. Chart based on total cholesterol.

risk estimation systems, because they are critically dependent on definitions and methods used in their ascertainment. The Framingham Study[16,17,39,40], on which the risk charts of the Joint Task Forces of the European Societies and many other risk estimation systems are based, included into non-fatal coronary heart disease end-points, in addition to non-fatal myocardial infarction (clinically verified infarctions and 'silent' infarctions identified on the basis of ECG changes), the onset of angina of effort and 'coronary insufficiency' (unstable angina), and ascertained the occurrence of these events at re-examinations conducted at 2-year intervals. Therefore it has been difficult or even impossible to replicate the Framingham study end-point ascertainment in other cohort studies. Furthermore, as pointed out in the 1999 statement for health care professionals from the American Heart Association and the American College of Cardiology[41], the Framingham definition of non-fatal coronary heart disease does not correspond to the end-points used in clinical trials. Evidently for these reasons, the Framingham investigators have in their most recent publication[17] used a risk function based on 'hard' coronary heart disease end-points, coronary death and non-fatal myocardial infarction, and the Framingham risk scoring recommended for the assessment of 10-year coronary heart disease risk in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III Report[42] is based on this end-point definition.

The SCORE project considered the use of 'hard' coronary heart disease end-points (coronary death and non-fatal myocardial infarction) and 'hard' cardiovascular disease end-points (cardiovascular death and non-fatal cardiovascular disease events). Data on incident non-fatal myocardial infarctions were available from six studies, most of them from high-risk populations. Even fewer studies had collected data on nonfatal strokes and none of them had collected data on nonfatal atherosclerotic cardiovascular disease events other than coronary heart disease and stroke events. Considering the limitations in the availability of the nonfatal end-point data and possible non-uniformity in their definition, fatal atherosclerotic cardiovascular disease was selected as the end-point. An important reason for this decision was also that the ultimate aim of the SCORE project is to develop cardiovascular disease risk estimation systems applicable at

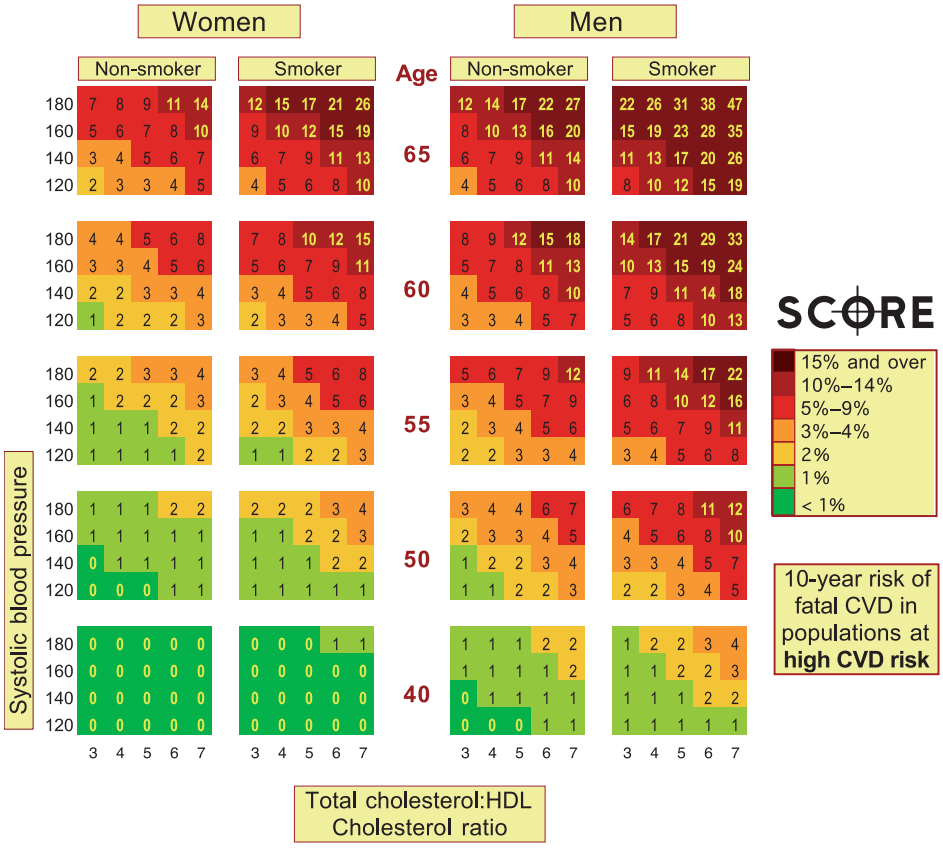

Fig. 3 Ten-year risk of fatal cardiovascular disease in populations at high cardiovascular disease risk. Chart based on total cholesterol. HDL cholesterol ratio.

national level in different European countries representing different rates of cardiovascular disease and different mixes of coronary and non-coronary cardiovascular disease. Many European countries do not have cohort studies of cardiovascular disease, but all countries have national cause-specific mortality data. These data can be used to estimate the baseline risk of the population. With this as a starting point, it is possible to estimate risk at different levels of risk factors. Thus, for countries which have no cohort data it will be possible to produce national cardiovascular risk charts using national cardiovascular mortality data and SCORE risk functions with appropriate adjustments. The next task of the SCORE project group will be to describe methods needed for the production of such national risk charts.

Changing thresholds for high risk

A shift in the risk estimation from the risk of any coronary heart disease event to the risk of fatal cardiovascular disease will also mean a redefinition of the threshold for the 10-year absolute risk considered to signal the need for intensified risk modification efforts. Such decisions have to be made by international and national expert bodies formulating recommendations on cardiovascular disease prevention on the basis of scientific evidence and considering constraints related to practical and economic factors. The First and Second Joint Task Force of the European Societies[1,6] recommended as a threshold for intensified risk factor intervention a 10-year absolute risk of 20% or more of developing any manifestation of coronary heart disease based on the risk chart derived using the Framingham risk function. This recommendation focused the attention on the importance of absolute risk as the basis of multi-factorial assessment of cardiovascular disease risk, but oversimplified a complex issue. In addition to pointing out the problems in the application of the Framingham risk function to low risk European populations, the arbitrarily chosen absolute coronary heart disease risk threshold of 20% or more has been criticised, because it leads to a very high prevalence of high-risk individuals in

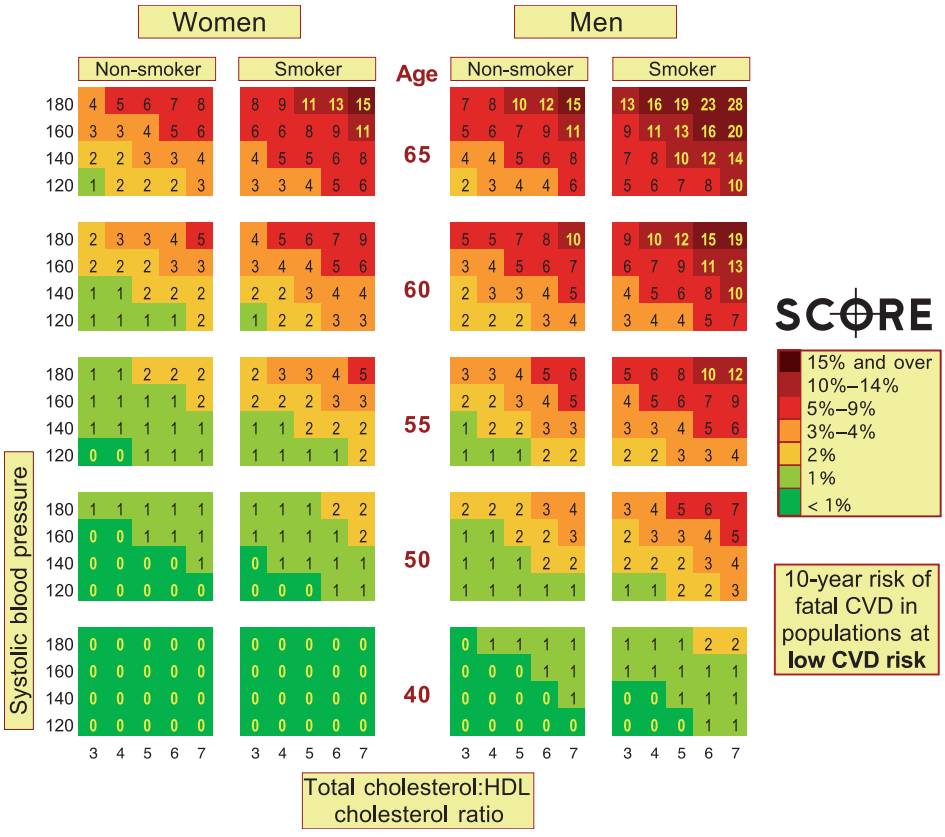

Fig. 4 Ten-year risk of fatal cardiovascular disease in populations at low cardiovascular disease risk. Chart based on total cholesterol. HDL cholesterol ratio.

older age groups, particularly among men, and may lead to a false impression about the long-term risk in young people with high risk factor levels. Dutch[43] and British[3] national expert groups have, in fact, recommended somewhat different thresholds for high-risk, using Framingham risk function-based risk charts, based on the limitations of national resources for intervention. In this context it is important to note that the recent definition of the high coronary heart disease risk in asymptomatic people based on the last version of the Framingham risk function, adopted by the NCEP Adult Treatment Panel III[42], greater than 20% 10-year risk of developing 'hard' coronary heart disease (coronary death or non-fatal myocardial infarction), in fact means a substantially higher level of risk than the definition of 20% or greater 10-year risk of any coronary heart disease recommended by the First and Second Joint European Task Forces.[1,6]

Thus, even without the SCORE project, the concept of definition of high risk when applied to prevention in asymptomatic people needs a thorough reconsideration. To stimulate discussions on this issue and to emphasise that there is no single level of absolute risk that defines an optimal threshold for risk factor intervention, regardless of the persons age, sex or nationality, the SCORE risk charts display the 10-year risk of cardiovascular death both as figures as well as categories. Health economic research has suggested that the risk threshold for cost effectiveness of risk factor interventions, such as cholesterol lowering drug therapy, is not a simple function of absolute risk but also varies with age and sex.[44] The recent work of Marshall and Rouse, in addition, suggests that a stepwise approach to risk calculation may make better use of staff time than routine assessment of all adults, even where a fixed threshold for intervention is being used.[45]

Prospective epidemiological studies have suggested that the relationships of the major risk factors with the risk of cardiovascular death are largely similar to their relationships with a combined end-point comprising both fatal and non-fatal events, but most of this information concerns the risk of coronary heart disease. Further research is needed to compare the performance of the SCORE risk estimation system using fatal cardiovascular

Table 3 Performance of the high-risk region risk chart in persons aged 45-64 in the derivation cohort and other high-risk cohorts

	Cholesterol chart				Cholesterol:HDL ratio chart			
	Sensitivity	Specificity	LR (95%CI)	ROC area (95%CI)	Sensitivity	Specificity	LR (95%CI)	ROC area (95%CI)
Cohort								
Threshold								
Derivation								
3%	87	59	2.1 (2.1, 2.2)	0.81	88	53	1.9 (1.8, 1.9)	0.80
5%	66	79	3.1 (3.0, 3.3)	(0.80, 0.82)	74	72	2.7 (2.5, 2.8)	(0.78, 0.82)
7%	49	88	4.1 (3.8, 4.3)		61	82	3.5 (3.2, 3.8)	
10%	34	94	5.7 (5.2, 6.2)		44	90	4.5 (3.9, 5.1)	
Russia								
3%	90	40	1.5 (1.4, 1.6)	0.72	87	45	1.6 (1.5, 1.7)	0.71
5%	59	73	2.0 (1.8, 2.5)	(0.67, 0.75)	52	75	2.0 (1.7, 2.4)	(0.67, 0.75)
7%	32	86	2.3 (1.7, 3.0)		39	87	3.1 (2.4, 3.9)	
10%	20	95	3.6 (2.4, 5.4)		19	95	3.6 (2.4, 5.4)	
Scotland								
3%	82	52	1.7 (1.6, 1.8)	0.72	80	58	1.9 (1.8, 2.0)	0.77
5%	66	73	2.4 (2.2, 2.7)	(0.67, 0.76)	62	77	2.7 (2.4, 3.1)	(0.73, 0.80)
7%	51	84	3.2 (2.8, 3.7)		45	87	3.4 (2.9, 4.0)	
10%	33	92	4.3 (3.5, 5.2)		24	94	3.8 (2.9, 4.9)	
Sweden								
3%	97	15	1.1 (1.1, 1.2)	0.71	No HDL data available			
5%	84	47	1.6 (1.5, 1.7)	(0.70, 0.75)				
7%	61	68	1.9 (1.7, 2.2)					
10%	40	85	2.7 (2.3, 3.3)					
UK								
3%	94	20	1.2 (1.1, 1.2)	0.70	96	19	1.2 (1.2, 1.2)	0.71
5%	83	46	1.5 (1.4, 1.6)	(0.67, 0.73)	85	43	1.5 (1.4, 1.6)	(0.68, 0.74)
7%	66	64	1.9 (1.7, 2.0)		71	61	1.8 (1.7, 2.0)	
10%	45	82	2.5 (2.1, 2.9)		51	78	2.3 (2.0, 2.6)	

Table 4 Performance of the low-risk region risk chart in persons aged 45-64 in the derivation cohort and other low-risk cohorts

	Cholesterol chart				Cholesterol:HDL ratio chart			
	Sensitivity	Specificity	LR (95%CI)	ROC area (95%CI)	Sensitivity	Specificity	LR (95%CI)	ROC area (95%CI)
Cohort								
Threshold								
Derivation								
3%	65	71	2.2 (2.1, 2.4)	0.74	67	70	2.2 (2.1, 2.4)	0.75
5%	35	88	2.9 (2.6, 3.3)	(0.72, 0.76)	40	87	3.0 (2.7, 3.3)	(0.73, 0.77)
France								
3%	51	82	2.8 (2.2, 3.6)	0.71	No HDL data available			
5%	20	96	5.5 (3.2, 9.2)	(0.65, 0.78)				
Germany								
3%	81	74	3.1 (2.6, 3.5)	0.84	83	74	3.1 (2.7, 3.6)	0.82
5%	43	90	4.2 (3.0, 5.8)	(0.79, 0.88)	53	87	4.2 (3.2, 5.5)	(0.78, 0.88)

disease as end-point with risk estimation systems using 'hard' coronary heart disease as end-point. Furthermore, because the computerised SCORE risk function will allow a breakdown of the person's total risk of cardiovascular death into its coronary and non-coronary components, it will be important to examine that application in prospective study data from populations known to have different proportions of coronary and non-coronary cardiovascular mortality.

Other aspects of the SCORE risk charts

Versions for total cholesterol and cholesterol/HDL ratio

Persons with multiple risk factors tend to have lower HDL cholesterol levels and there is therefore

a concern that failing to take HDL cholesterol into account will underestimate risk in those most at risk[46,47]. A number of clinicians therefore, have expressed interest in a risk estimation system based on cholesterol/HDL ratio. Accordingly, we developed two parallel systems. After extensive evaluation, we have concluded that the two systems have remarkably similar properties, and classify persons to very similar levels of risk. Cholesterol/HDL ratio has therefore, no advantage over cholesterol alone as a single index of lipid level. We stress that models which include multiple lipid measures may well be statistically superior and can be used in computerised risk estimation systems. They will, however include too many dimensions to be used to generate visually displayable risk charts.

Change in the ages for which the risk is displayed

In the SCORE risk charts we are providing more detail in the age group 50 to 65, which is the period during which risk changes most rapidly. Risk for age 30 has been suppressed. Persons aged 30 are essentially risk free within the next 10 years, and in many of the SCORE datasets there were no events in this age group. As was pointed out earlier, showing the 10-year risks for them would give a wrong message about the long-term risk of the young people with high risk factor levels.

SCORE risk charts are for primary prevention

The SCORE risk charts are intended for risk stratification in the primary prevention of cardiovascular disease. We have not provided risk estimates for persons with established coronary heart disease, as there is now a widely accepted consensus that all persons with clinically established coronary heart disease or other atherosclerotic disease should be treated as high risk cases, recognising, however, that the same major risk factors which are important in primary prevention remain important also in secondary prevention.[3,6,48,49] Life expectancy model analyses suggest that the relative benefits of risk factor modification are almost similar for both low-risk and high-risk groups of patients with cardiovascular disease.[50]

Why not separate risk charts for persons with diabetes?

Diabetes is known to be associated with a marked increase in the risk of cardiovascular disease; among persons with clinically established type 2 diabetes the increase in cardiovascular disease risk is at least 2-fold in men and even higher, as much as 4-fold, in women.[6] The 'conventional' major risk factors are known to have almost similar relationship with cardiovascular disease risk in diabetic and non-diabetic persons but at every level of a risk factor or at any combination of risk factors the absolute risk is increased in diabetic persons.[51,52] This excess risk of diabetic persons is in part explained by 'diabetes-related' factors, such as type and duration of diabetes, glycaemic control, and presence of retinopathy or microalbuminuria or proteinuria.[53]

In the recommendations of the Second Joint Task Force of the European Societies[6] separate risk charts were given for persons with diabetes based on the Framingham risk function, to emphasise their particularly high risk. This was done realising the statistical and other limitations of the Framingham risk function in this respect. The main limitations of the Framingham Study algorithm are that it is based on a small number of diabetic people in the original cohort-237 subjects (4%) with diabetes in the cohort of 5573 people – and that the study used its own definition of diabetes based on a random blood glucose concentration >9 mmol/l or the use of antidiabetic treatment. Separate Framingham risk function-based risk charts for diabetic people have also been given by the New Zealand[54] and British[3] expert groups. Framingham equations with a dichotomous diabetes variable have also been used in computer programs for the management of cardiovascular risk factors[55], although their validity for diabetic persons has been questioned.[56]

Data on diabetes had not been collected uniformly in SCORE study cohorts. In the majority of the cohorts the diagnosis of diabetes was based only on a self report (sometimes with corroborative evidence from a family doctor) and in some study cohorts information on diabetes was not available. Thus, we could not apply to the SCORE data set the current criteria for diabetes diagnosis given by the American Diabetes Association[57] or by the World Health Organization.[58] We did not exclude people with diabetes diagnosis from the SCORE data base used for the development of risk functions. However, we decided, because of non-uniformity in the ascertainment of diabetes, not to include a dichotomous diabetes variable into the risk function and not to produce separate risk score system for persons with diabetes. As recently concluded by the investigators of the World Health Organization Multinational Study Group on Vascular Disease in Diabetes[59], future developments in the assessment of cardiovascular disease risk in diabetes must include' diabetes-related' variables, as well as the 'conventional' risk factors. Such risk estimation

systems have, however, to be based on large representative groups of diabetic subjects with uniform baseline data collection. Following these principles, the United Kingdom Prospective Diabetes Study group has already developed mathematical models for the estimation of absolute risk of coronary heart disease and stroke risk in men and women with newly diagnosed type 2 diabetes.[53,60] SCORE risk charts may, however, be used for a rough assessment of cardiovascular risk in diabetic persons, because the relationship of the 'conventional' major risk factors with cardiovascular disease is almost parallel in diabetic and non-diabetic subjects, although the risk of diabetic subjects is at much higher level. Thus, the instruction for the use of SCORE risk charts will say that at every risk factor combination the risk will be at least twice as high in diabetic men and up to four times higher in diabetic women compared with that given by the charts.

Limitations

The charts presented here have limitations which we should point out. The underlying risk functions are based on single risk factor measurements, not on the persons 'usual' levels. We examined the effects of regression dilution bias on the risk estimates, and found that it was only those at very low or very high risk who were significantly affected. For persons whose risk falls in the 2% to 5% category, the effects of using 'usual' rather than single risk factor levels is negligible. The charts also consider only the principal risk factors. In practice, the impact of other risk factors modulating disease risk needs to be considered also. These factors include a strong family history of early-onset cardiovascular disease, milder degrees of impaired glucose regulation, triglycerides, and fibrinogen. Future risk estimation systems may incorporate at least some of these factors. However, as yet their impact on the overall accuracy of risk estimation is uncertain, as a statistically significant association is no guarantee of a material gain in predictive power.

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Appendix A

Calculating 10-year risk estimates for fatal cardiovascular disease.

Step 1
Calculate the underlying risks for coronary heart disease and for non-coronary cardiovascular disease separately for the person's age now and for their age in ten years time, using the values for alpha and p shown in table A. The underlying survival probability, S_0,is given by:

$$S_0(age) = \exp\{-(\exp(\alpha))(age-20)^p\}$$
$$S_0(age+10) = \exp\{-(\exp(\alpha))(age-10)^p\}^* \quad (1)$$

Step 2
Using the coefficients in table B, calculate the weighted sum, *w*, of the risk factors cholesterol, smoking and systolic blood pressure. Two weighted sums will have to be calculated, one for coronary heart disease and one for non-coronary cardiovascular disease.

Smoking is coded as 1 for current and 0 for non-smoker, so no value for smoking has to be entered if the person is a non-smoker. Cholesterol is measured in mmol/L and SBP is measured in mmHg. The weighting for each risk factor is denoted by beta.

$$w = \beta_{chol}(cholesterol-6) + \beta_{SBP}(SBP-120) + \beta_{smoker}(current) \quad (2)$$

Step 3
Combine the underlying risks for coronary heart disease and for non-coronary cardiovascular disease, at the person's age and at their age ten years from now (four calculations) which were calculated in step 1 with the weighted sum of a person's risk factors from step 2 for the two end-points,

* The Weibull model is traditionally expressed in terms of $\lambda = \exp(\alpha)$

coronary heart disease and non-coronary cardiovascular disease to get the probability of survival at each age for each cause.

$$S(age)=\{S_0(age)\}^{\exp(w)}$$
$$S(age+10)=\{S_0(age+10)\}^{\exp(w)} \quad (3)$$

Step 4
For each cause, calculate the 10-year survival probability based on the survival probability for the person's current age and their age in 10 years time:

$$S_{10}(age)=S(age+10)/S(age) \quad (4)$$

Step 5
Calculate the 10 year risk for each end-point as

$$Risk_{10}=1-S_{10}(age) \quad (5)$$

Step 6
Combine the risks for coronary heart disease and non-coronary cardiovascular disease by adding them:

$$CVDRisk_{10}(age)=[CHDRisk(age)]+[Non\text{-}CHDRisk(age)] \quad (6)$$

Table A Coefficients for Eq. (1)

		CHD		Non-CHD CVD	
		α	p	α	p
Low risk	Men	−22.1	4.71	−26.7	5.64
	Women	−29.8	6.36	−31.0	6.62
High risk	Men	−21.0	4.62	−25.7	5.47
	Women	−28.7	6.23	−30.0	6.42

Table B Coefficients for Eq. (2)

	CHD	Non-CHD CVD
Current smoker	0.71	0.63
Cholesterol (mmol/L)	0.24	0.02
Systolic BP (mmHg)	0.018	0.022

Appendix B

Project Structure and Organisation

In 1994, when the recommendations of the First Joint Task Force of European Societies on coronary heart disease prevention were published, the Working Group on Epidemiology and Prevention of the European Society of Cardiology (ESC) proposed to the Board of the ESC that a research project for the development of risk prediction system based on data from European cohort studies should be developed. This initiative was reinforced by the Second Joint Task Force of European and other Societies and as the outcome the Systematic COronary Risk Evaluation (SCORE) project was instigated and carried out under the auspices of the ESC. The project received funding from the European Union as a three-year European Concerted Action project under the BIOMED-2 programme between 1998 and 2001.

The structure of the administrative organisation of the SCORE project is described below followed by the list of participating studies, centres and investigators.

Steering Committee: Kalevi Pyörälä (Kuopio, Finland, *Chairman*), Ronán M. Conroy (Dublin, Ireland), Ian M. Graham (Dublin, Ireland), Ulrich Keil (Münster, Germany), Alessandro Menotti (Rome, Italy), Troels F. Thomsen (Glostrup, Denmark), Hans Wedel (Gothenburg, Sweden), Lars Wilhelmsen (Gothenburg, Sweden), David Wood (London, UK).

Co-ordinating and Data Management and Analysis Centre: Department of Epidemiology and Public Health Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland: Ian M. Graham (*Project leader*), Ronán M. Conroy (*Principal investigator*), Anthony P. Fitzgerald (*Statistician*).

Participating studies, investigators and centres/institutions by countries: Belgium (Belgian Interuniversity Research on Nutrition and Health (BIRNH): Guy De Backer, Dirk De Bacquer, Department of Public Health, Ghent University, Ghent; Marcel Kornitzer, Laboratory of Epidemiology and Social Medicine, School of Public Health, Free University of Brussels, Brussels; Denmark (The Glostrup Population Studies): Knut Borch-Johnsen, Michael Davidsen, H.I. Torben Jorgensen, Troels F. Thomsen, Centre for Preventive Medicine, Medical Department M, Glostrup University Hospital, Glostrup; Finland (The FINRISK Study): Anne Juolevi, Pekka Jousilahti, Jaakko Tuomilehto, Erkki Vartiainen, Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki; France (Paris Prospective Study): Dominique Courbon, Pierre Ducimetiere, National Institute of Health and Medical Research (INSERM), Unit 258, Villejuif; Germany (The MONICA Augsburg cohort study 1984-1995): Ulrich Keil, Angela Liese, Institute of Epidemiology and Social Medicine, University of Münster, Münster; Hannelore Löwel, GSF-Institute of Epidemiology, Neuherberg; Italy (Risk Factors and Life Expectancy (RIFLE) Pooling

Project): Mariapaola Lanti, Alessandro Menotti, Association for Cardiac Research, Rome; Norway (Norwegian Counties Study): Inge Njølstad, Institute of Community Medicine, University of Tromsø, Tromsø; Randi Selmer, Aage Tverdal, Norwegian Institute of Public Health, Oslo; Russia (Collaborative US-USSR study on the prevalence of dyslipoproteinemias and ischemic heart disease in American and Soviet populations): David Neberiedze, Rafael G. Oganov, George S. Zhukovsky, National Research Center of Preventive Medicine, Russian Ministry of Health, Moscow; Spain ([1]Catalonia cohort study, [2]Barcelona Multifactorial Trial, [3]Factory Heart Study): Susana Sans[1,2,3], Institute of Health Studies, Barcelona; Ignacio Balaguer-Vintró[1,2,3], David Monterede[1,2,3], Luis Tomás [2,3], Saint Pau Hospital Research Insitute, Barcelona; Sweden (The Primary Prevention Study in Göteborg [Gothenburg]): Georg Lappas, Lars Wilhelmsen, Hans Wedel, Section of Preventive Cardiology, Göteborg University, Göteborg; UK (British Regional Heart Study): S. Goya Wannamethee, Mary Walker, Peter H. Whincup, Andrew Thomson, Department of Public Health Sciences, St. George's Hospital Medical School, London; (Follow-up studies of the Scottish Heart Health and Scottish MONICA cohorts): Richard A'Brook, Hugh Tunstall-Pedoe, Cardiovascular Epidemiology Unit, University of Dundee, Ninewells Hospital and Medical School, Dundee.

The investigators of the component cohorts of the Italian RIFLE Pooling Project were: P. Alessandrini (Venice), G.B. Ambrosio (Venice), F. Angelico (Rome), R. Antonini (Rome), A. Attili (Rome), G. Avellone (Palermo), G. Bittolo-Bon (Venice), A. Bucci (Rome), G.P. Buzzelli (Florenece), G. DePretis (Udine), G. Dobrilla (Bolzano), A. Dormi (Bologna), E. Farinaro (Naples), M. Ferrario (Monza-Milano), A. Gaddi (Bologna), M. Giachi (Siena), S. Giampaoli (Rome), M. Mancini (Naples), G. Marenco (Pietra Ligure), G. Misciagna (Castellana Grotte), Se. Muntoni (Cagliari), Sa. Muntoni (Cagliari), L. Ockoliczanyi (Parma), G. Palasciano (Bari), G. Ricci (Rome), G.F. Salvioli (Modena), A. Spagnolo (Rome), M.T. Tenconi (Pavia), G.C. Urbinati (Rome), D. Vanuzzo (Udine).

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