

## Original Research

# Statistical Modelling of 10-Year Fatal Cardiovascular Disease Risk in Greece: The HellenicSCORE (a Calibration of the ESC SCORE Project)

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Key words:  
Cardiovascular  
disease, risk, models.

Manuscript received:  
October 26, 2006;  
Accepted:  
January 23, 2007.

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**Introduction:** Interest in the development of functions that estimate the likelihood of an individual suffering a future cardiovascular disease (CVD) event has increased in recent times (e.g. Framingham sheets, SCORE-Systematic COronary Risk Estimation, PROCAM, etc.). However, the estimates of absolute risk may show substantial variations between different populations, because of geographical, cultural, social, behavioural and genetic differences, as well as various methodological issues related to the predictive models employed. We sought to calibrate the SCORE equations to the Greek population.

**Methods:** We used the SCORE system that offers an estimation of total fatal CVD risk in "high" and "low" CVD risk European countries. The project pulls together a pool of datasets from 12 European countries and 2.7 million person-years of observation. A mathematical procedure to adjust the risk estimates for individual countries was applied, based on local mortality and risk factor prevalence data from the ATTICA epidemiological study, which enrolled 3042 men and women (18+ years old), from the Attica region of Greece.

**Results:** We present the calibration of the HellenicSCORE (equations, charts) by age group and sex, based on mortality data, as reported by the National Statistical Services, and prevalence data regarding smoking, total cholesterol and blood pressure levels, as reported by the ATTICA study.

**Conclusion:** The proposed HellenicSCORE will hopefully result in better estimation of the risk of CVD death in Greece and enhance handling of CVD risk factors in the referent population.

**W**hile diseases caused by dietary deficiency or infection may have a single cause, the combined effects of multiple environmental and genetic factors cause most chronic diseases. The mathematical prediction of future cardiovascular events has received increased attention in recent years. The main purpose of these models is to estimate individuals' risk for a cardiac event in order to facilitate preventive efforts. Based on these models, risk charts have been developed and incorporated into guidelines for the prevention

of cardiovascular disease.<sup>1</sup> The best-known predictive risk charts in cardiovascular disease (CVD) prevention are the Framingham Heart Study Sheets. The Framingham Heart Study<sup>2</sup> was one of the most important epidemiological studies and was designed as a prospective, single-centre, community-based cohort. The coronary prediction algorithm developed provides estimates of developing angina pectoris, or myocardial infarction, or coronary artery disease death, over the course of 10 years. The study's investigators stated clearly that the risk esti-

mating score sheets were only for persons without known heart disease, that the algorithm encompasses only coronary heart disease, and that the population was almost all Caucasian and, therefore, might not correspond to other populations.<sup>2</sup> Since the first publication of these risk sheets many physicians and public health policy makers have used them in daily clinical practice and research. In 1994 the European recommendations on coronary heart disease prevention adopted the 10-year Framingham heart study equations. These equations were presented in a form of a Coronary Risk Chart.<sup>3</sup> However, some investigators advocate that the effort of risk prediction has so far not been very successful,<sup>1</sup> although the set of risk factors associated with CVD is consistent between studies.<sup>4-8</sup> A potential explanation was attributed to several geographical, cultural, social, behavioural and genetic peculiarities that differed between the populations investigated.<sup>5-9</sup>

Understanding the difficulties faced in this area of cardiovascular risk prediction and the importance of developing local epidemiological studies, the Working Group on Epidemiology and Prevention of the European Society of Cardiology published in 2003 a research project for the development of risk prediction charts based on data from 12 European cohort studies (the SCORE project: Systematic COronary Risk Estimation).<sup>10</sup> Cardiovascular mortality was the investigated outcome among 205,000 persons. During 2.7 million years of follow up, 5,652 deaths from coronary heart disease were observed. Age- and sex-specific risk charts were developed based on cholesterol and systolic blood pressure levels, separately for high and low risk European populations. The separation of the European countries into high and low risk was an advance, in that it reflected the widely varying cardiovascular mortality rates in different European countries. However, the inclusion of only 12 cohorts may raise several concerns about the applicability of the developed risk charts to estimate risk in all European populations.

So far in Greece there has been only one study that attempted to predict CVD risk through mathematical modelling: the CARDIO2000 epidemiological study.<sup>11-13</sup> However, CARDIO2000 was a matched case-control study; therefore, it could not accurately estimate the risk for an event, but only the relative odds of having an event. Thus, in order to compensate for this gap in CVD risk prediction, we present the HellenicSCORE project. It is a statistical model that predicts the 10-year risk for fatal CVD events in a Greek population, based on sex, age, smoking habits, total cholesterol and sys-

tolic blood pressure levels. This model is a mathematical calibration of the ESC SCORE project, based on local mortality and prevalence data from the National Statistical Services<sup>14</sup> and the ATTICA epidemiological study, which was conducted in the Athens metropolitan area during 2001-02.<sup>15</sup>

## Methods

### *Mortality data*

Annual rates were obtained from the World Health Organization mortality database for 2002.<sup>14</sup> The data available on this web site comprise deaths reported and coded in the Hellenic vital registration system (Hellenic Statistical Services). Underlying causes of death are defined as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury”, in accordance with the rules of the International Classification of Diseases.<sup>14</sup>

### *Study Population*

Current Greek risk factor prevalence was obtained from the “ATTICA” study.<sup>15,16</sup> This epidemiological study was carried out in the province of Attica (Athens metropolitan area), which includes 78% urban and 22% rural areas. From May 2001 to December 2002, 4056 inhabitants from the above region were randomly selected and asked to enroll into the study. Of these, 3042 agreed to participate (75% participation rate). All participants were without any clinical history of chronic diseases and were interviewed by trained personnel (cardiologists, general practitioners, dieticians and nurses) who used standard questionnaires that evaluated lifestyle habits and various socio-demographic, clinical and biological characteristics.

### *Measurements*

Age was defined in whole years and classified into decades for the purposes of the present project. Current smokers were defined as those who smoked at least one cigarette per day; former smokers were defined as those who had stopped smoking for at least one year, and the rest of the participants were considered as non-smokers. Occasional smokers (less than 7 cigarettes per week) were recorded and combined with current smokers because of their small number. Arterial blood pressure was measured three times (in mmHg), at the end

of the physical examination with the subject in a sitting position after at least 30 minutes of rest. Blood samples were collected from the antecubital vein between 8 and 10 am, with the subject in a sitting position after 12 hours of fasting and avoidance of alcohol. Total cholesterol was measured in mg/dl using the chromatographic enzymic method with a Technicon automatic analyser RA-1000 (Dade Behring, Marburg, Germany). The intra and inter-assay coefficients of variation of cholesterol levels did not exceed 4%. Table 1 illustrates the characteristics of the participants by gender and age group.

### Recalibration methods

Recalibration combines information from national mortality statistics and empirical risk factor distributions with SCORE estimates of the relative risk factor effect in order to produce individual 10-year estimates of the risk of fatal CVD, given age, sex, smoking status and levels of systolic blood pressure and total cholesterol. We used the recalibration method recommended by D'Agostino et al.<sup>16</sup> Given the expected sex differences in mortality rates and risk factor levels, all statistical analyses and modelling were performed for men and women separately.

If we associate the risk of fatal CVD in the population with the average risk factor levels in the same population, we expect that an individual with an unfavourable risk factor profile will have a higher 10-year CVD mortality risk than the “usual” population-based CVD mortality risk, given his/her age and gender. Here, the

term “unfavourable” intrinsically refers to the concept of comparing an individual's risk factor profile with the average risk factor profile in the population. Finally, the risk excess for an individual compared to the population's average risk can be calculated if we know how a deviation from the population average risk factor profile would influence the probability of fatal CVD over 10 years or, in other words, how the relation between risk factor differences and CVD mortality is quantified.

### Step-by-step description of recalibration

#### Step 1

We predicted the average age and sex-specific levels of systolic blood pressure, total cholesterol and smoking prevalence using data from the ATTICA study. Risk factor levels were modelled as quadratic functions of age (Table 2), with separate models for men and women. Quadratic terms were included to capture the significant non-linear associations with age. This was particularly evident for total cholesterol, where the rate of increase declined with age, and for smoking prevalence, where the rates declined more rapidly with increasing age.

#### Step 2

Using the WHO mortality data for 2002,<sup>14</sup> we calculated the average annual CVD mortality for men and women by 5-year age-group. Annual rates were modelled using an age-specific Poisson model with age in-

**Table 1.** Summary of risk factor levels in the ATTICA study.

Sex	Age (years), n	Systolic blood pressure (mmHg)	Total cholesterol (mg/dl)	Smoking (%)
Men	>75 (n=42)	138 ± 19	197 ± 35	7
	65–75 (n=97)	136 ± 19	207 ± 41	29
	55–65 (n=231)	134 ± 18	205 ± 44	41
	45–55 (n=434)	128 ± 16	204 ± 39	50
	35–45 (n=387)	121 ± 15	196 ± 39	55
	< 35 (n=323)	119 ± 14	174 ± 41	49
Women	>75 (n=37)	146 ± 18	218 ± 37	5
	65–75 (n=126)	135 ± 19	216 ± 36	21
	55–65 (n=208)	133 ± 20	211 ± 39	34
	45–55 (n=376)	121 ± 18	206 ± 40	42
	35–45 (n=398)	113 ± 14	183 ± 35	46
	< 35 (n=383)	107 ± 13	166 ± 34	43

Data are expressed as mean ± standard deviation or relative frequencies.

**Table 2.** Estimated average risk factor levels based on an analysis of data from the ATTICA study.

Sex	Age (years)	SBP (mmHg)	Total cholesterol (mg/dl)	Smoking (%)
Men	65	134.7	207.2	34
	60	132.7	208	41
	55	130.5	207	46
	50	128.4	205	50
	40	123.9	195	54
Women	65	134.4	215	27
	60	130.2	215	33
	55	126.1	208	37
	50	122.3	202	41
	40	115.1	189	45

cluded as a piecewise function that joined the mid-points of each age-interval.

### Step 3

The cumulative survival rates were calculated using standard results for continuous survival data:<sup>17</sup>

$$S(t) = \exp \left( - \int_0^t \lambda(u) du \right)$$

where  $\lambda(u)$  is the age-specific mortality rate estimated in step 2. The cumulative survival rates were used to estimate the 10-year CVD mortality rates.

### Step 4

The 10-year CVD mortality rate for an individual with particular levels of systolic blood pressure, total cholesterol and smoking status was calculated by comparing risk factor levels to the age- and sex-specific mean levels, and then allowing for the impact of deviation from the average using the SCORE derived hazard ratios.

To estimate the hazard ratios and develop the corresponding risk chart we considered two options: (a) first we used the hazard ratios that were based on an analysis of the entire SCORE database, and (b) we then used the hazard ratios based only on the low CVD risk cohorts (i.e. Spain, Italy and Belgium). The estimated hazard ratios are presented in Table 3. Results are based on a Cox proportional hazards analysis stratified by sex and cohort. Unlike the original SCORE analysis, we modelled the risk CVD mortality directly, without dividing it into coronary heart disease and non-CHD. With this type of epidemiological data it seemed more appropriate, given the fact that it is difficult to get an accurate classification of cause of

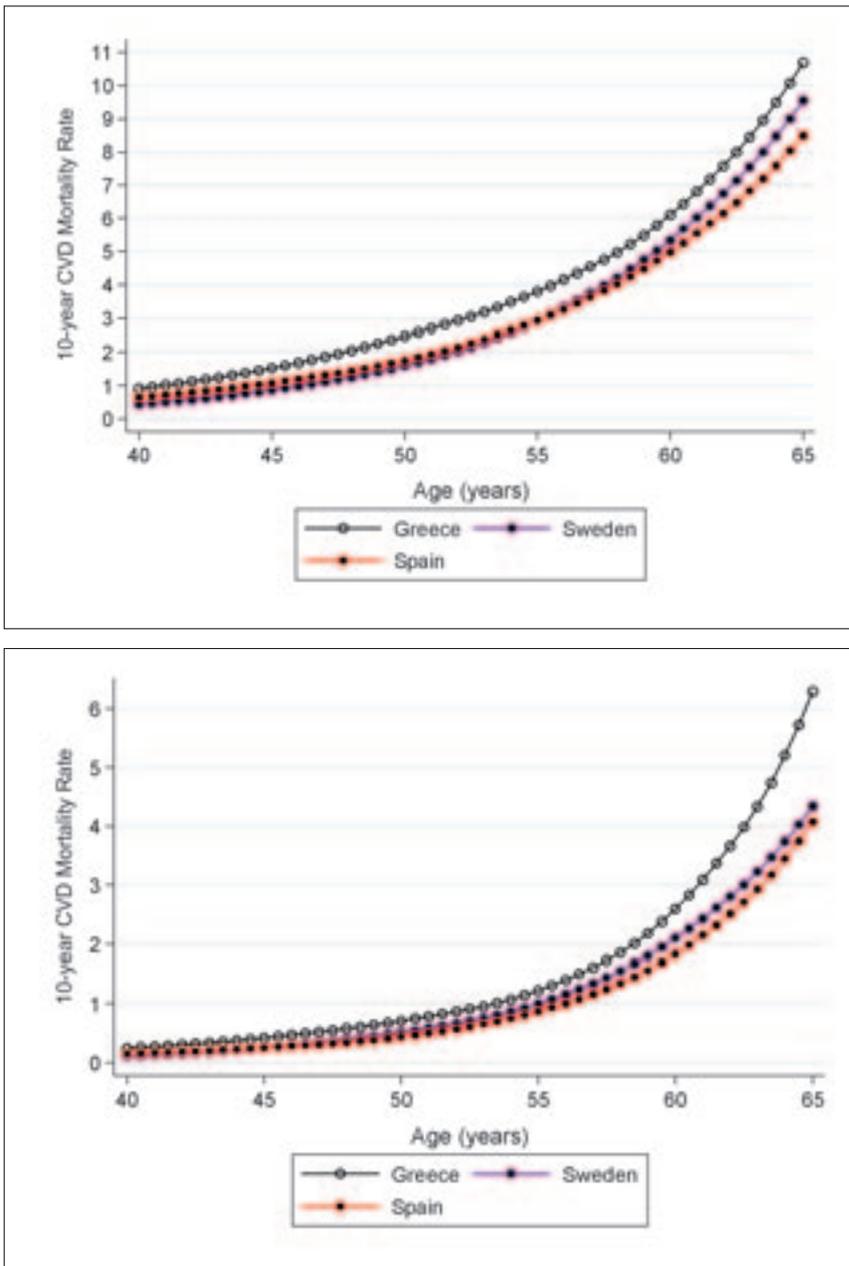
death. As we can see, there were differences in the risk estimates for the effect of smoking and total cholesterol when we compared the “all cohorts” and the “low-risk cohorts” approach.

## Application

### The Hellenic risk charts

Figure 1 illustrates the 10-year CVD mortality rates in men and women from Greece, Sweden and Spain. As we can see, the national rate is higher in Greece than that in Sweden and Spain. Figure 2 (a and b) illustrates the absolute ten-year risks of fatal CVD events, according to both approaches and based on risk factor categories, separately for men and women. In addition, the predicted effects of risk factor levels based on the supplied formula are presented in Table 3. It should be noted that the resulting risk chart is clearly sensitive to the hazard ratios (relative risks) derived from SCORE.

To give an example of this process, let us consider the results for a man aged 60. According to the ATTICA study the average systolic blood pressure, cholesterol and smoking prevalence are 132.6 mmHg, 208 mg/dl, and 41%, respectively (Table 2). Based on national annual rates, the 10-year CVD mortality rate is 0.061, thus the corresponding 10-year survival rate is  $1 - 0.061 = 0.939$ . According to the original estimation procedure presented by Conroy et al,<sup>10</sup> if we want to calculate the CVD risk for a 60-year-old man, who is a current smoker, with a systolic blood pressure of 160 mmHg, and total cholesterol 270 mg/dl, we have to do the following calculations using the logarithmically transformed hazard ratios, based on an analysis of all cohorts (Table 3).



**Figure 1.** Ten-year cardiovascular disease (CVD) mortality rates in women (above) and men (below) for selected countries.

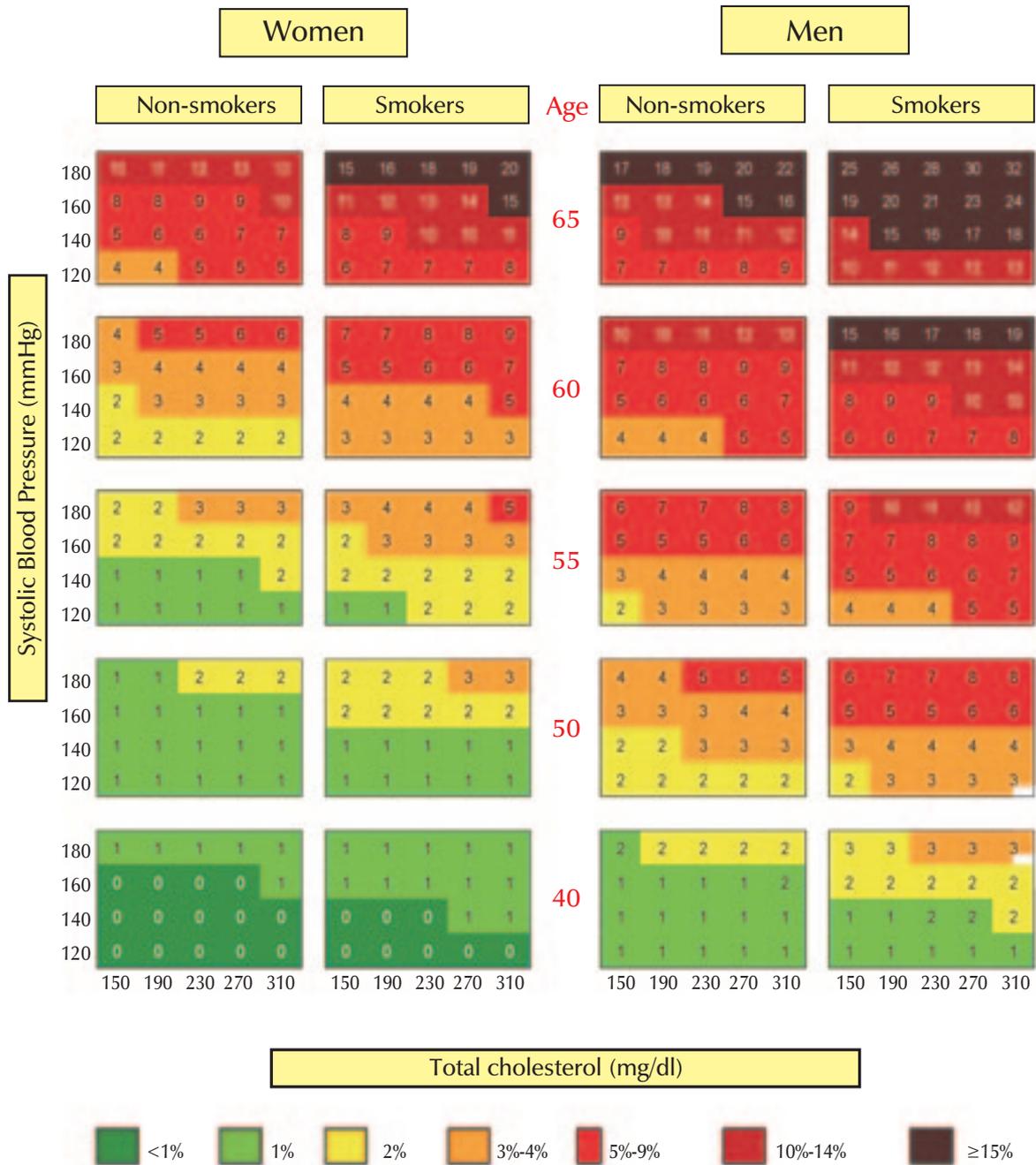
Calculation of  $k_1$ ,  $k_2$  and  $k_3$ :

1.  $k_1 = 0.01856 \times (160 - 132.7) + 0.17768 \times \frac{(270 - 208)}{38.6} + 0.72136 \times (1 - 0.41) = 1.217$
2.  $k_2 = e^{k_1} = 3.37$
3.  $k_3 = 0.939^{k_2} = 0.808$

So, the 10-year risk of CVD mortality for the above mentioned man is  $1 - k_3 = 1 - 0.808 = 0.192$  (or 19%). At this point it should be noted that the beta-coefficients correspond to the log(hazard ratios) for results based on all cohorts.

### Discussion

It is now widely accepted that risk prediction of chronic diseases is a useful tool at the individual level in daily clinical practice, as well as for the development of fu-



**Figure 2a.** Ten-year risk of fatal cardiovascular disease in Greece (the calibration is based on the “low-risk” cohorts’ beta coefficients).

ture public health strategies to address the burden of the diseases.<sup>18</sup> In this paper, we present the formulas and the charts that estimate the 10-year risk for fatal CVD events in Greece. These charts are based on the SCORE project and were calibrated for the Greek population using national mortality data and informa-

tion about age, gender, smoking habits, total cholesterol and systolic blood pressure levels, from the ATTICA epidemiological study.<sup>15</sup>

In spite of the wide use of risk charts, like the Framingham sheets or SCORE, ethnic, genetic, social, cultural and risk factor variability could lead to substan-

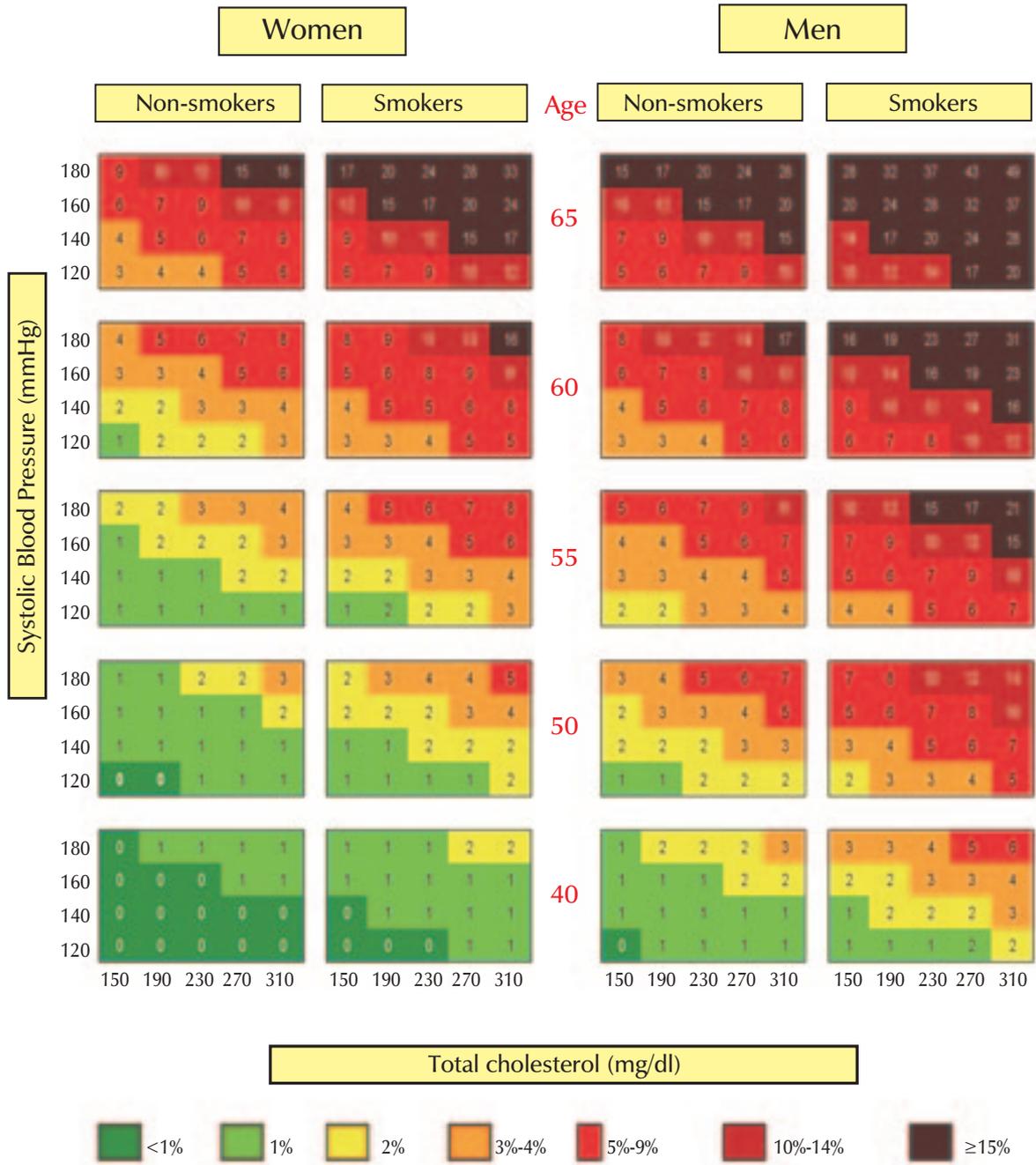


Figure 2b. Ten-year risk of fatal cardiovascular disease in Greece (the calibration is based on all cohorts' beta coefficients)

tial variability in the prediction of cardiovascular events. It has already been reported that the Framingham Heart Study score sheets, or the predictive risk models from northern European countries, overestimate the risk in several southern European populations.<sup>4-7</sup> It is interesting that these differences in the absolute risk were not attributed to differences in the incidence of the various manifestations of CVD (i.e. fatal,

myocardial infarction, and unstable angina). Moreover, homogeneity analysis showed that the differences were not due to the baseline risk factor levels.<sup>6,7</sup> Furthermore, based on the 10-year follow up of the BRHS the investigators concluded that the recommended risk scoring proposed by the Framingham Heart study scoring significantly overestimated the absolute coronary risk assigned to northern European individuals, too.<sup>19,20</sup>

**Table 3.** Relative effect of systolic blood pressure, total cholesterol and smoking on cardiovascular disease mortality, based on a Cox proportional hazards analysis.

Risk factor	Hazard ratio, HR (95% CI of HR)	
	Using all cohorts for calibration	Using low risk cohorts (Italy, Belgium, Spain) for calibration
Systolic blood pressure (per 1 mmHg)	1.02 (1.01 to 1.02) logHR = 0.018560	1.01 (1.01 to 1.02) logHR = 0.016550
Total cholesterol (per 1 mg/dl)	1.19 (1.17 – 1.21) logHR = 0.17768	1.07 (1.02 – 1.13) logHR = 0.06765
Smokers vs. non smokers	2.06 (1.96 – 2.16) logHR = 0.72136	1.54 (1.34 – 1.77) logHR = 0.431782

logHR were used in the formula for the calculation of  $k_1$ .

Some investigators have suggested that the inaccuracy of risk prediction could be attributed to the differences in the incidence of CVD between populations. In particular, the link between hazard ratios derived from Cox proportional hazards models and estimation of absolute risk is dependent on some form of “reference” level of risk (i.e. average CVD free survival of the population from which the model was derived). Thus, if this average survival varies between populations, then the prediction of absolute risk will also vary. In order to resolve this problem, recalibration of the models has been suggested.<sup>7</sup> However, for that to be done the incidence in each population and the prevalence of risk factors must be known through local epidemiological studies.

In this paper we present the risk charts that estimate 10-year risk for fatal CVD events in Greece, based on a recalibration of the SCORE project. We followed two approaches for the calibration. The first approach was to use as a basis the models derived from all cohorts of the SCORE project, and the second approach was to use the models derived from the “low-risk” cohorts. Average levels of systolic blood pressure, total cholesterol and smoking prevalence by age group and sex were incorporated into the development of the HellenicSCORE model. Using the first approach, the absolute risk estimates were higher compared to the second approach (Figures 3a and 3b). This raises the question as to which chart would provide the most accurate estimation of risk to guide preventive advice in today’s Greece. Overall CVD mortality has decreased in Greece in recent years.<sup>15</sup> It could be speculated that overall CVD risk has been

underestimated in Greece, since stroke may be a proportionately greater contributor to CVD mortality in apparently low risk countries. Without a systematic examination, it is not possible to be certain of the accuracy of death certification; for example, if stroke were a favoured diagnosis in uncertain cases, CVD mortality estimations might be inflated.

At first glance, if one looks at the extremes of the risk estimates we have presented in this work (i.e. top right hand in the charts), both charts seem to give risk estimates that are higher than the generic low and high-risk European charts. However, at the extremes, numbers will be small and confidence limits wide. Management decisions will be made at around the 5% level, arbitrarily defined by the Joint European Guidelines as “high risk”. At this level differences are much smaller; indeed, the charts based on the entire data set may assign slightly fewer subjects to the “high risk” category than the generic European high-risk charts. On this basis, we suggest that chart presented in Figure 3b, derived from the entire SCORE data set, may be appropriate for the estimation of risk of cardiovascular death and consequent risk management advice in Greece. This approach is in line with the approach used in other European countries to date.

### Limitations

The charts presented here have some limitations. Firstly, the SCORE calculates only mortality and not morbidity; thus the calibration of the HellenicSCORE can also only estimate mortality. Secondly, the sample used

for the calibration procedure (i.e. the ATTICA study database) may not be representative of the whole Greek population. However, it should be underlined that roughly the half of the Greek population lives in the surveyed area, and the Attica area consists of 78% urban and 22% rural population. Moreover, the underlying risk functions are based on single risk factor measurements, not on the person's "usual" values. The charts also consider only the principal risk factors. In practice, the impact of other risk factors modulating disease risk, such as diet and psychological factors, should also be considered. In addition, family history of CVD was not taken into account in the original SCORE project and consequently was not included in the calibrated HellenicSCORE. Future risk estimations should incorporate at least some of these factors. Finally, the accuracy of reported causes of death in the death certificates used to ascertain CVD deaths is more than dubious.

### Concluding remarks

We have presented the risk charts for the Greek population (HellenicSCORE project), based on age, sex, smoking habits, systolic blood pressure and total cholesterol levels. We give two options, based on different calibrations of the SCORE project. As to which option is more appropriate, only a prospective study conducted in Greece could give the answer. Nevertheless, we have made a tentative recommendation to adopt a chart based on recalibration utilising the entire SCORE data set. Estimation of the risk of future CVD events is an attractive and dynamic field in epidemiological research and prevention, and has the potential to stimulate more effective preventive strategies.

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