

Cardiovascular risk assessment in Italy: the CUORE Project risk score and risk chart

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Abstract

Aim: Risk charts and risk score, based on the global absolute risk, are key tools for CVD risk assessment. When applied to the population from which they derive, they provide the best estimate of CVD risk. That is why the CUORE Project has among its objectives the assessment of the Italian population's cardiovascular risk, identifying the model for the prediction of coronary and cerebrovascular events in 10 years.

Methods: Data from different cohorts enrolled in the North, Centre and South of Italy between the 1980s and the 1990s were used. From the 7,056 men and 12,574 women aged 35-69 years, free of cardiovascular disease at base-line and followed up for a mean time of 10 years for total and cause-specific mortality and non fatal cerebrovascular and coronary events, 894 major cardiovascular events (596 coronary and 298 cerebrovascular) were identified and validated. To assess 10-year cardiovascular risk, the risk score and risk chart were developed for men and women separately, considering the first major coronary or cerebrovascular event as the endpoint.

Results: The risk score is applied to men and women aged 35-69 years and includes age, systolic blood pressure, total cholesterol, HDL-cholesterol, smoking habit, diabetes and hypertension treatment using continuous values when possible. The risk chart is applied to persons aged 40-69 years and includes the same risk factors as risk score, except for HDL-cholesterol and hypertension treatment, and uses categorical values for all variables.

Conclusions: The risk score and risk chart are easy-to-use tools which enable general practitioners and specialists to achieve an objective evaluation of the absolute global cardiovascular risk of middle-aged persons in primary prevention.

Key words: absolute cardiovascular risk, risk chart, risk score, risk equation, primary prevention.

Introduction

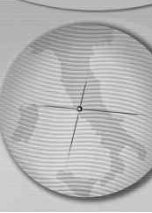
The identification of cardiovascular disease (CVD) risk is one of the main targets of primary prevention and the first step to reduce modifiable risk factors, from lifestyle changes to pharmacological treatments.

Risk charts and risk score, based on global absolute risk, are key tools for CVD risk assessment and determine the likelihood of developing the disease over the following years, provided that the value of several risk factors is known [1].

The global absolute risk is estimated through a risk equation using base-line risk factors and morbidity and mortality data from longitudinal studies follow-up. The risk equation includes: mean risk factors values of the population, risk

coefficients, which attribute an aetiological weight to single factors, and survival probability of the population without the disease. These three elements change according to different populations, particularly when different cultures or generational cohorts are compared (i.e. North American Countries and Mediterranean countries) as there may be different mean values of risk factors and different survival without the disease.

For this reason, the CUORE Project has developed a database of CVD risk factors collected in several longitudinal studies carried out between the mid 1980s and the mid 1990s which followed-up total and cause-specific mortality and CVD morbidity in order to assess global CVD risk for men and women separately [2-5].



Materials and methods

Twelve random samples of men and women aged 35–69 years were examined through baseline surveys from 1983 through to 1997: seven samples were drawn from general populations in Northern Italy, one factory-based sample in Northern Italy, three samples from general populations in Central Italy and one sample from Southern Italian women. Random sampling was based on population lists obtained from municipal electoral registers or the factory employee roll, stratified by age and gender. Participation rates were 64–78%. A more detail description of cohorts is reported in previous publications [2–5].

Baseline measurements

In all cohorts risk factors were assessed by using standardized procedures [6, 7]. Blood pressure (right arm) was measured twice (using a mercury sphygmomanometer), with the participant sitting after resting for 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded (first and fifth Korotkoff sounds); the first and second measurements were averaged for analyses. Serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL) were assayed by enzymatic colorimetry in three laboratories with external quality control and standardization program MONICA. Fasting plasma glucose was measured in 63% of the participants. Height and weight were measured with participants wearing light clothing without shoes. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared (kg/m^2).

Information was collected by questionnaire on cigarette smoking, personal history of myocardial infarction, stroke, diabetes mellitus, and hospitalization for major cardiovascular events as well as medication use for diabetes and hypertension.

Coronary and cerebrovascular events registration/validation

During follow-up (range 5–19 years, mean duration 10 years) which lasted until 2002, deaths were identified from vital statistics. Death certificates were coded using the International Classification of Diseases and Causes of Death, Ninth Revision (ICD-9) [8]. Vital status and death certificates were available for 99% of participants. Underlying causes of death ICD-9 codes 410–414 (ischemic heart disease), 798 (sudden death), 799 (other ill-defined and unknown causes of morbidity and mortality) as well as codes 250

(diabetes mellitus), 428 (heart failure), 440 (atherosclerosis) in association with 410–414 codes, were considered as suspected coronary deaths and further investigated for validation. Death ICD-9 codes 430–438 (cerebrovascular accidents) as well as codes 250 (diabetes mellitus), 401–405 (hypertension), 440 (atherosclerosis) in association with 430–438 codes, were considered as suspected stroke deaths and further investigated for validation.

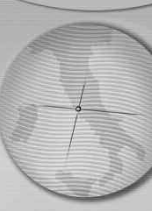
Non-fatal coronary events were ascertained through record linkage using hospital discharge diagnosis records with ICD-9 410–411 codes for suspected acute infarction (acute myocardial infarction, other acute and sub-acute forms of ischemic heart disease) and ICD-9-CM 36.0–36.9 codes for coronary surgery revascularization. Non-fatal stroke events were ascertained through record linkage using hospital discharge records with ICD-9 430 (subarachnoid hemorrhage), 431–432 (intracerebral hemorrhage), 434 (thrombosis) 436 (stroke) and ICD-9CM 38.12 for surgery revascularization. Fatal and non-fatal events were validated using MONICA diagnostic criteria for coronary events [9], based on symptoms (location and duration of pain), electrocardiograms, cardiac enzymes, history of ischemic heart disease, and available autopsy findings. MONICA diagnostic criteria for stroke, based on rapid development of focal signs (or global) or disturbance of cerebrovascular function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than vascular origin, were also used.

Statistical analysis

Attention focused on the incidence of first major coronary or cerebrovascular events in men and women aged 35–69 years who were free of previous coronary and cerebrovascular disease at baseline. With the inclusion of the women cohort from Southern Italy, the number of events occurred in women has become sufficient to perform analyses for men and women separately.

In order to identify the aetiological role of risk factors, considered singly and in combination, and to choose the *best model*, the statistical analysis was comprised of several steps: description of risk factors at baseline, correlation analysis among risk factors, univariate analysis, multivariate analysis and model effectiveness testing.

Univariate analyses were performed to study the relation of risk factors, considered singly, to the 10-year CVD risk. Cox regression hazard ratios, adjusted by age and samples and their statistical significance, were assessed for the following risk



factors: SBP, DBP, TC, HDL-C, TC-to-HDL-C ratio, non-HDL-C-to-HDL-C ratio, low-density lipoprotein cholesterol, triglycerides, BMI, BMI for smokers, BMI for non smokers, glycemia, smoking habit (never, former, or current smokers), dichotomic smoking habits (yes, current / no, never or former), number of cigarettes, waist and hip circumference, waist-to-hip ratio, diabetes (yes/no), hypertensive treatment (yes/no), family history of premature CVD (yes/no) and blood pressure levels categorized according to the National Heart, Lung and Blood Pressure Institute Guidelines [10].

To assess the relation of risk factors, considered together, to the 10-year CVD risk, multivariate analyses were performed. Starting from a basic Cox model that included age, SBP and dichotomic smoke habit, the other cardiovascular risk factor variables, when statistically significant in the univariate analyses and not presenting multicollinearity with the other variables in the model under study, were progressively included. The 10-year CVD individual risk score models were implemented including continuous values of risk factors when available.

All multivariate models were evaluated for accuracy (the degree to which predictions match outcomes) by assessing the area under the receiver operating characteristic (ROC) curve and performing Hosmer-Lemeshow test.

The *best model* for each gender was chosen taking into account the scientific literature, correlation analyses results, univariate analyses for each of the risk factors, statistical significance of the relation between risk factors and the 10-year CVD risk as assessed by the multivariate analysis, number of missing values, and model effectiveness tests.

To evaluate the generalizability of the *best model* (the ability to provide accurate predictions in different samples), internal validation, i.e. cross validation and bootstrapping methods, were assessed.

The equations for assessing global absolute CVD risk were estimated and then reapplied to the

population of the CUORE Project, which was subsequently subdivided into ten risk classes of the same size [11]. Incidences, evaluated by an exponential model based on observed incidence, in the first and last risk classes were compared by calculating the relative risk. All analyses were carried out using the SPSS statistical package (version 13.0).

Results

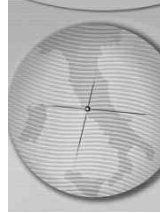
Considering the 12 cohorts, from the 7,520 men and the 13,127 women (Figure 1), 7,056 men and 12,574 women aged 35-69 years, free of previous cardiovascular events and with complete data on risk factors at baseline were used in the analysis; they developed 894 first major cardiovascular events (596 in men and 298 in women), 586 coronary events and 308 strokes during the follow-up period. The final *best models* for men and women, considered separately, take into account the following risk factors: age, SBP, TC, HDL-C, diabetes, smoking habit and the prescription of anti-hypertensive medications, using continuous values for age, SBP, TC and HDL-C. Survival after 10 years, calculated using the mean value of risk factors at baseline, was 0,953 for men and 0,989 for women. Mean values and standard deviations of risk factors and prevalence of high risk condition used in the prediction are reported in Table 1.

Table 2 shows the coefficients of risk factors included in the *best model* and hazard ratios with level 1 standard deviation higher and lower for continuous variables and yes versus no and no versus yes for categorical variables. Comparison between aetiological weight of single risk factors is thus enabled.

The individual risk score, derived from the *best model*, is available at The CUORE Project website www.cuore.iss.it. It can be applied on men and women aged 35-69 years and free from previous cardiovascular events. Provided that values for age, gender, smoking habit, systolic blood pressure, total

Table 1. Description of risk factors at baseline, men and women aged 35-69 free of previous cardiovascular disease at baseline. The CUORE Project samples.

Risk factors	Men (N=7.520)		Women (N=13.127)	
	mean	s.d.	mean	s.d.
Age, years	50.6	9.2	50.3	8.5
Systolic Blood Pressure, mmHg	138.7	20.5	135.9	22.0
Total Cholesterol, mg/dl	225.4	44.4	229.0	44.6
HDL-Cholesterol, mg/dl	50.4	14.0	60.0	15.4
	%		%	
Diabetes	5.9		3.8	
Hypertension medications	9.4		14.5	
Current smokers	40.1		25.9	



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Figure 1. Distribution of The CUORE Project cohorts, number of persons (N) and events for men and women aged 35-69 years free of previous cardiovascular disease at baseline. Follow-up refers to median duration in years.

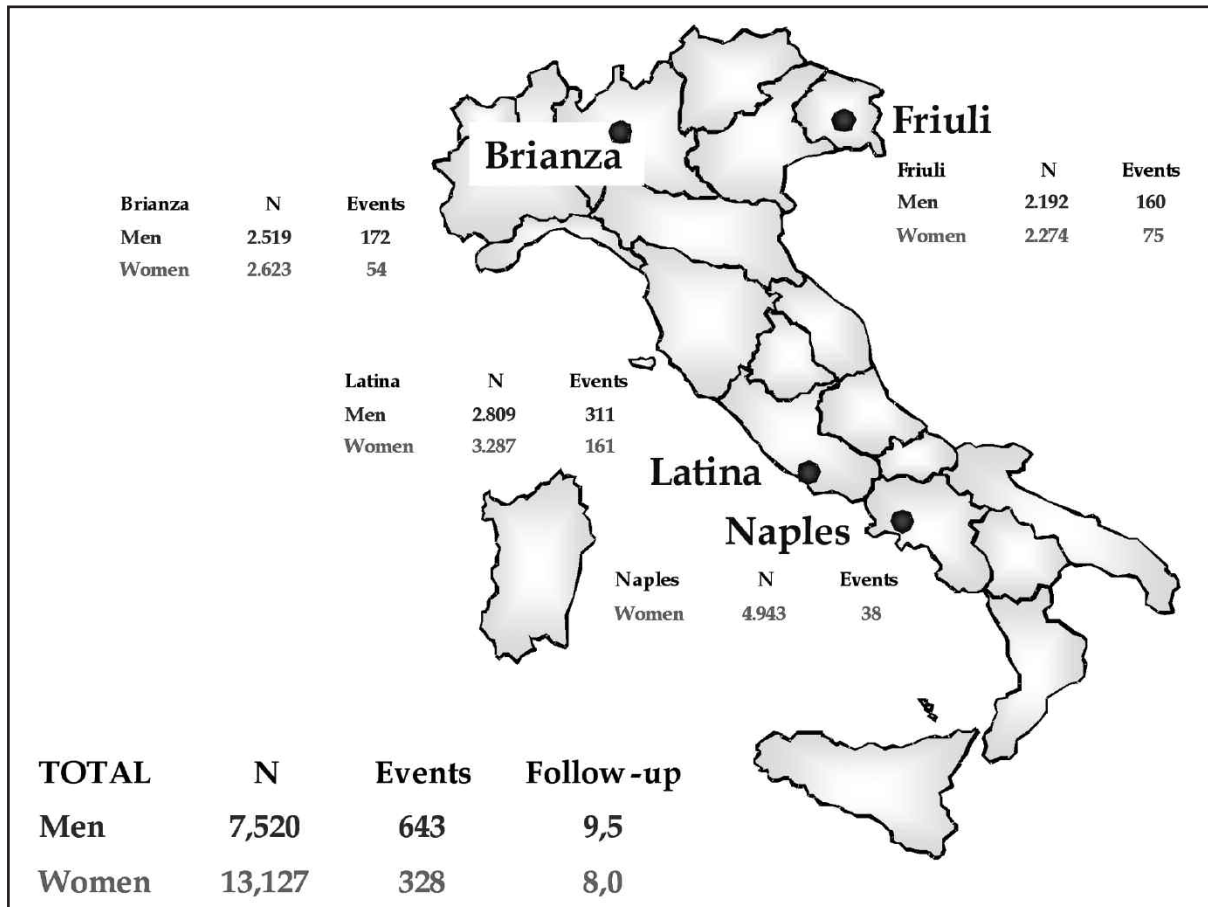


Table 2. Results of Cox regressions, best model for men and women aged 35-69 years free of previous cardiovascular disease at baseline. The CUORE Project samples.

	β	p-value	Men		Women				
			HR more adverse level*	HR more favourable level**	HR more adverse level*	HR more favourable level**			
Age, years	β_1	0.076	<0.0001	2.01	0.50	0.079	<0.0001	1.95	0.51
Systolic Blood Pressure, mmHg	β_2	0.013	<0.0001	1.31	0.76	0.016	<0.0001	1.41	0.71
Total Cholesterol, mg/dl	β_3	0.006	<0.0001	1.31	0.76	0.003	0.0362	1.14	0.88
HDL-Cholesterol, mg/dl	β_4	-0.013	<0.0001	1.60	0.60	-0.015	0.0002	1.26	0.80
Smoking habit, yes-no	β_5	0.508	<0.0001	1.66	0.60	0.773	<0.0001	2.17	0.46
Diabetes, yes-no	β_6	0.462	0.0005	1.59	0.63	0.339	0.0859	1.40	0.71
Hypertension treatment, yes-no	β_7	0.490	<0.0001	1.63	0.61	0.590	<0.0001	1.80	0.55
G (μ)		6.583				6.016			
Survival at baseline, S (t)		0.953				0.989			

β is Cox coefficient; HR is Hazard Ratio.

*For continuous variables, hazard ratio with level 1 standard deviation higher (see Table 1); for dichotomized variables, yes vs. no.

**For continuous variables, hazard ratio with level 1 standard deviation lower (see Table 1); for dichotomized variables, no vs. yes.

G (μ) is the linear combination of the risk factor averages or of the prevalence in each category for the corresponding β ; coefficients.

S (t) is 10-year survival evaluated at mean value of risk factors.

Risk equation is: $1 - [S(t)] \wedge \{EXP[\beta_1 \times \text{age} + \beta_2 \times \text{SBP} + \beta_3 \times \text{TC} + \beta_4 \times \text{HDL-C} + \beta_5 \text{ (if smoker)} + \beta_6 \text{ (if diabetic)} + \beta_7 \text{ (if under hypertension treatment)} - G(\mu)]\}$, where SBP is Systolic Blood Pressure, TC is Total Cholesterol, HDL-C is HDL-Cholesterol.

and HDL-cholesterol, diabetes, regular treatment for hypertension are known, it is possible to predict how many persons out of 100 with the same age and same characteristics will develop a major CVD

(fatal and non fatal myocardial infarction or stroke) over the following 10 years. For women, the diabetes coefficient was not statistically significant, probably because of the upper age limit of 69 years

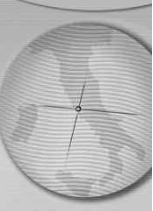
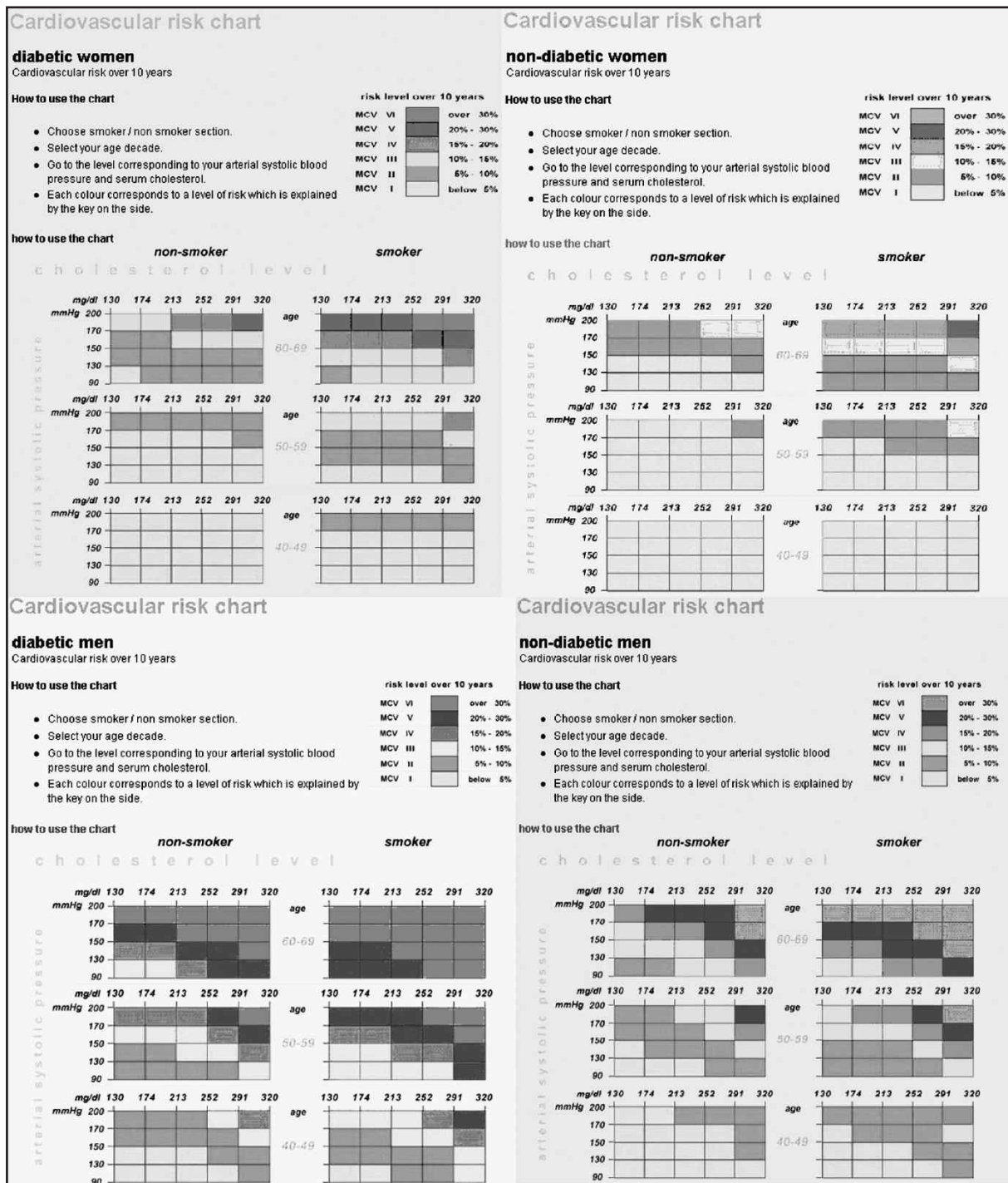


Figure 2. Cardiovascular risk chart of The CUORE Project from www.cuore.iss.it.



was too low to lead to the disclosure of this condition. However, the primary role of diabetes in cardiovascular prevention was assessed in the univariate analysis, where the diabetes coefficient was fairly significant for women also, hence the necessity to adjust the multivariate models for diabetes.

The risk chart, which represents the paper version of the risk score, was also developed. It can be applied to men and women aged 40-69

years who have not had previous cardiovascular events; it includes the same risk factors as risk score, except for HDL-cholesterol and hypertension treatment, and uses categorical values for all risk factors (Figure 2).

Figure 3 shows the results obtained by the reapplication of the risk score on participants of The CUORE Project. In the first risk class, 112 events occurred among 3,433 men and 80 among 9,331 women, while in the last class 17 occurred

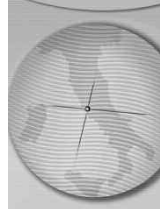
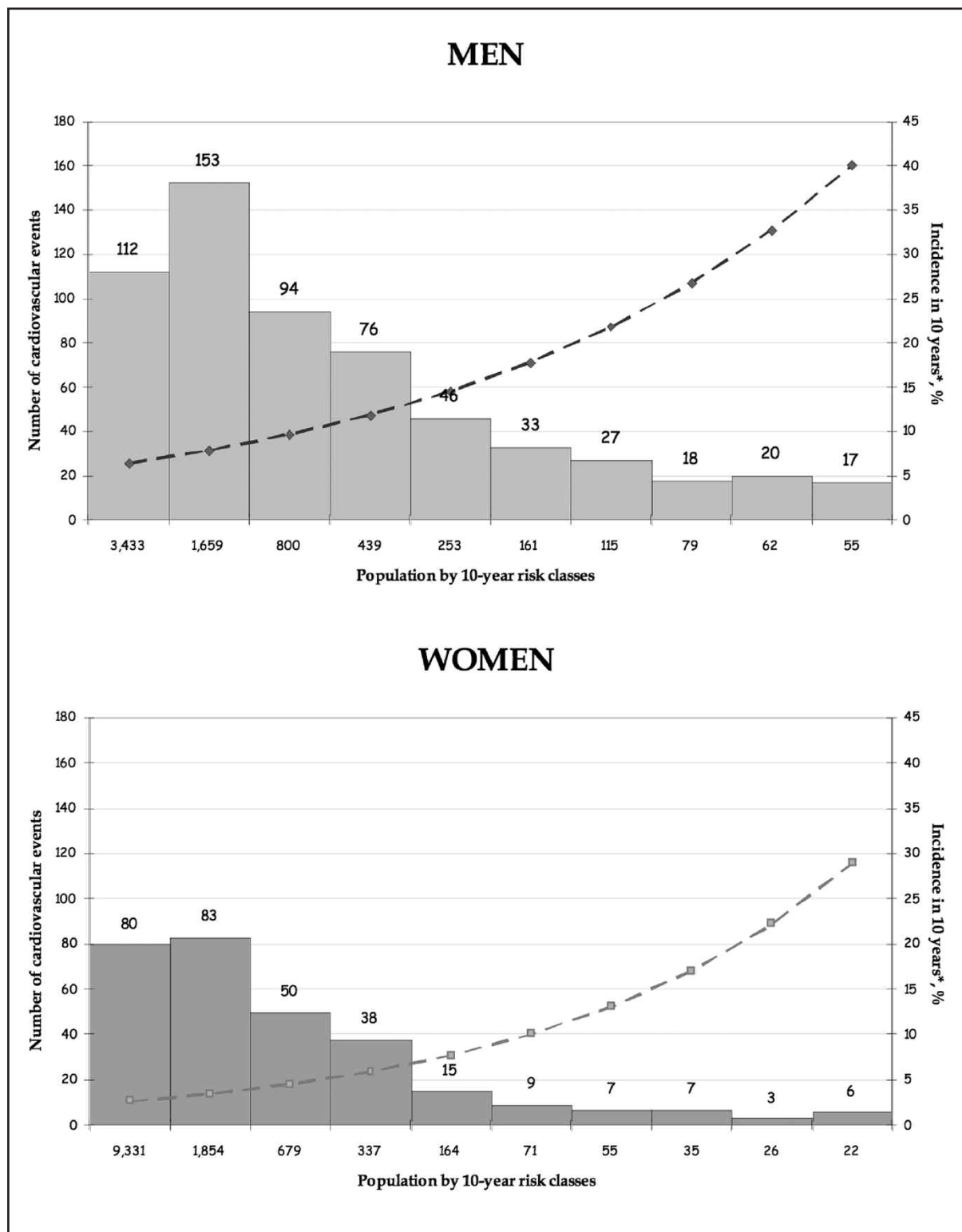


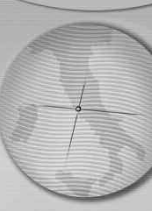
Figure 3. Cardiovascular disease event and 10-year incidence rate for men and women aged 35-69 years free of previous cardiovascular disease at baseline. The CUORE Project samples.



among 55 men and 6 among 22 women. Men belonging to the last class, where the observed risk is the highest, have a risk 9.4 times higher than those belonging to the first class; for women this ratio was 30.0.

Discussion

The global absolute CVD risk is the best way to assess CVD risk in persons who have no recognized clinical manifestations of atherosclerotic disease.



The use of this indicator takes into account the multifactorial aetiology of CVD and offers multiple treatment options to individuals at increased risk who might have treatment preferences, given that many of the high risk conditions are not accompanied by symptoms. Furthermore, the global absolute CVD risk makes the assessment more objective, accurate and comparable over time.

With respect to similar studies performed up to now in Italy, the advantage of The CUORE Project lies in the fact that the cohorts had a high numerosity, were enrolled in relatively recent time, included women, covered different geographical areas of the country and were followed-up for total and cause-specific mortality and non-fatal coronary as well as cerebrovascular events, which were validated using standardized methodology and following the same diagnostic criteria. The availability of only one measurement of risk factors and the progressive change of diagnostic criteria for event definition during follow-up are considered to be the main limitations of the Project. The recent use of biomarkers in the diagnosis of myocardial infarction as well as advanced technologies in the diagnosis of stroke have increased the quality of diagnosis.

With respect to risk charts and risk scores derived from the Framingham Study [12], the PROCAM (Munster) Study [13], the Seven Countries Study (Italia) [14, 15], and the SCORE project [16], major differences can be found in the availability of data on men and women and the different baseline risk factors, the choice of fatal and non-fatal events as end-points and the possibility to include or not to include stroke as an end-point. The PROCAM study and the Seven Countries Study did not have data on women; the former assessed event probability in women by dividing by four men's values. The SCORE study did not have data on diabetes and suggested to duplicate risk for diabetic men and quadruplicate it for diabetic women; in addition, it considered CVD mortality only as an end-point.

The individual risk score (available at The CUORE Project website www.cuore.iss.it) and the risk chart are simple tools for assessing the probability of developing a first major cardiovascular event in the coming years. They should be periodically updated through enrolment and follow-up of new cohorts in order to make it a widely usable preventive tool in public health.

The application of risk equation to the population of The CUORE Project has highlighted the fact that most events, in absolute terms, do not

occur in individuals at high risk of developing the disease but in those who have a lower risk. Paradoxically, the latter, being much more numerous than high risk individuals, develop a greater number of events in absolute terms. Prevention strategies, to be fully effective, should address the whole population and aim to increase as much as possible the number of low risk persons by reducing risk factors values in those individuals who are still not high risk and by keeping risk factors at a favourable level over lifetime in those at low risk.

The individual risk score, resulting from work carried out within The CUORE Project, which is financed by 1% of the National Health Fund, can be freely used by health professionals visiting the website www.cuore.iss.it; those unable to use computer may assess CVD risk by using the risk chart. These tools enable health professionals to make an objective assessment of a person's risk, share a common language with other specialists, and to monitor and evaluate, over time, the benefits of adopted preventive activities.

Acknowledgments

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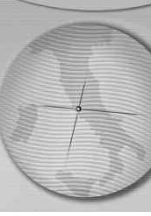
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