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*European Journal of Cardiovascular Prevention & Rehabilitation* 2010 17: 403

DOI: 10.1097/HJR.0b013e328334ea70

The online version of this article can be found at:

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## Original Scientific Paper

# Italian cardiovascular mortality charts of the CUORE project: are they comparable with the SCORE charts?

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Received 5 February 2009 Accepted 3 November 2009

**Background** The aim of this study was to build risk charts for the assessment of cardiovascular mortality of the CUORE project, an Italian longitudinal study, and to compare them with the systematic coronary risk evaluation (SCORE) project charts for low risk European countries.

**Design** Random population samples enrolled in the 1980s and 1990s in Italy were included in the analysis: 7520 men and 13 127 women aged 35–69 years without previous cardiovascular events and with a mean follow-up period of 10 years for cardiovascular disease. ICD-9 codes of death certificates similar to those of the SCORE project were considered when they appear as first cause of death.

**Methods** Sex-stratified Cox proportional hazard model including age, systolic blood pressure, ratio between total and HDL cholesterol, and smoking habit as risk factors was used to assess cardiovascular mortality.

**Results** Analysis showed that all risk factors included in the model were statistically significant. The corresponding area under the receiver operating characteristic curve was 0.825 (95% confidence interval: 0.803–0.846) for men and 0.850 (0.823–0.877) for women. The CUORE project charts yielded similar results to the corresponding charts of the SCORE project: Lin's coefficient was 0.929 for men and 0.935 for women.

**Conclusion** The comparison between CUORE and SCORE mortality risk charts shows that SCORE charts reflect quite well the Italian cardiovascular mortality and, correspondingly, Italian cohorts of the CUORE project are quite representative of European countries at low risk for cardiovascular mortality. *Eur J Cardiovasc Prev Rehabil* 17:403–409 © 2010 The European Society of Cardiology

European Journal of Cardiovascular Prevention and Rehabilitation 2010, 17:403–409

Keywords: cardiovascular mortality, longitudinal studies, primary prevention, risk prediction

## Introduction

Global risk assessment has become an accepted component of clinical guidelines and recommendations for cardiovascular prevention [1–3]. In Europe, systematic coronary risk evaluation (SCORE) risk charts are recommended in clinical practice as a valid tool to estimate

cardiovascular risk. They were built using data from the SCORE study, a pooling project of several European longitudinal studies, with base-line examination conducted from 1967 to 1991. Different charts for high and low risk European populations were published by Conroy *et al.* in 2003 [4].

In Italy, the CUORE project, funded by the Italian Ministry of Health, was launched at the end of 1990s, with the aim of building a database of cardiovascular risk

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factors collected within longitudinal studies started in the 1980s and 1990s using standardized procedures and methods and implementing the follow-up of cardiovascular mortality and morbidity for assessing cardiovascular risk in the adult Italian population [5–8].

The aims of the analysis presented here are to build CUORE project risk charts for the assessment of cardiovascular mortality and to compare them with those developed by SCORE for low risk European countries. This may lead to a possible collaboration with the SCORE project and, eventually, to the inclusion of the CUORE project data in the 10-year risk SCORE update for cardiovascular disease (CVD) in low risk regions of Europe.

## Materials and methods

### Population samples

The CUORE project pooled standardized data from random population samples in Northern, Central, and Southern Italy: 20 647 (7520 men and 13 127 women) aged 35–69 years without previous cardiovascular events were included in the analysis and followed-up until 2002 (10-year mean period) for CVD. As women usually develop less CVD events than men, more women than men were involved in the study. Data collection procedures and methods were standardized and are comparable with those of the MONICA project [9–11]. Participation rates were 64–78% except for one cohort (MATISS 1987 with 40%). A detailed description of these cohorts has already been published [12–15] and is available on the CUORE project web site ([www.cuore.iss.it](http://www.cuore.iss.it)).

### Baseline measurements

Risk factors were assessed by standardized procedures [9–11]. Blood pressure (right arm) was measured twice with a mercury sphygmomanometer, participant sitting, after 5 min of rest; systolic blood pressure (SBP) or diastolic blood pressure were recorded (first and fifth phase of Korotkoff sounds); the first and second measurements were averaged for analyses. Total cholesterol and HDL cholesterol (TC, HDL-C) were assayed on serum in four different laboratories under the quality control of reference laboratories and measurements were carried out using the colorimetric enzymatic method. Information was collected by questionnaire on cigarette smoking, personal history of myocardial infarction, stroke, diabetes mellitus, hospitalization for cardiovascular events, and medication.

### Cardiovascular events registration/validation

Standardized methods were used to identify and validate suspected events. Major cardiovascular events, in particular myocardial infarction, stroke, revascularization treatment (bypass or angioplasty), and sudden death, were identified through record linkage between mortality and hospital discharge registers over December 2002 [14,15].

In this analysis, only cardiovascular mortality was considered using the following ICD-9 codes when they appear as first cause of death: ICD-9 codes 401–414 and 426–443, with the exception of the 430.0 ICD-9 code for definitely nonatherosclerotic causes of death. Instantaneous death (ICD-9, 798.1) and death within 24 h of symptoms onset (ICD-9, 798.2) were also classified as cardiovascular deaths. Similar codes were considered for the SCORE analysis [4].

### Statistical analysis

Cox proportional hazard models were used to estimate 10-year risk score of cardiovascular mortality and corresponding areas under the receiver operating characteristic (ROC) curve were calculated. Risk factors included, as for SCORE, were age, SBP, smoking habit, TC or TC/HDL-C ratio. Sex-stratified models were performed to consider the whole dataset for the estimation of risk factor coefficients assuming that risk factors do not significantly vary in their effect from men to women. Cohort-adjustment and interactions between risk factors were studied.

To compare CUORE and SCORE charts, Lin's concordance coefficients were calculated between each cell of the CUORE risk charts and the corresponding one of the SCORE risk charts for low risk European countries. Agreement between frequency in the cardiovascular risk categories (<1%, 1–4%, 5–9%, ≥10%) according to CUORE and SCORE charts was assessed by sex and smoking habit.

Results associated to a  $P$  value  $\leq 0.05$  were considered statistically significant. Statistical analyses were performed using SAS software, release 8.1 (SAS Institute Inc., Cary, North Carolina, USA).

## Results

Among 7520 men and 13 127 women free of CVD at baseline, 308 and 181 cardiovascular deaths were identified, respectively (99 385 and 144 797 individuals years). Sex-stratified model with only TC was considered not statistically significant to allow a consistent assessment of 10-year risk of fatal CVD necessary to build the corresponding charts. Only charts referring to TC/HDL-C ratio were shown.

### Cardiovascular risk chart considering total cholesterol

The Cox model of CUORE project is reported in Table 1 as model 1. Age, SBP, and smoking habit were statistically significant risk factors whereas total cholesterol was not.

### Cardiovascular risk chart considering total cholesterol/HDL-cholesterol ratio

Cohort-adjustment did not result in improvement of risk prediction. Interaction between age and smoking was

**Table 1 Cox proportional hazard models, CUORE project cohorts, men and women aged 35–69 years free of earlier CVD at baseline**

Variable	Stratified by men and women											
	Model 1					Model 2						
	Coefficient	STD ER	HR	95% CI	P value	Coefficient	STD ER	HR	95% CI	P value		
Age, years	0.133	0.007	1.14	1.13	1.16	<0.001	0.146	0.010	1.16	1.14	1.18	<0.001
Systolic blood pressure (mmHg)	0.019	0.002	1.02	1.02	1.02	<0.001	0.019	0.002	1.02	1.02	1.02	<0.001
Total cholesterol (mg/dl)	0.0005	0.001	1.00	1.00	1.00	NS						
Total cholesterol/HDL-cholesterol							0.104	0.026	1.11	1.06	1.17	<0.001
Smoking (yes, no)	0.424	0.104	1.53	1.25	1.87	<0.001	2.315	0.854	10.13	1.90	53.97	<0.01
Age and smoking interaction							-0.032	0.014	0.97	0.94	1.00	<0.05
Men		S (10)=0.987		G ( $\mu$ )=9.631				S (10)=0.987		G ( $\mu$ )=10.803		
Women		S (10)=0.996		G ( $\mu$ )=9.473				S (10)=0.996		G ( $\mu$ )=10.539		

S (10) = 10-year survival evaluated at mean value of risk factors. G ( $\mu$ ) is the linear combination of the risk factor averages or of the prevalence in each category for the corresponding coefficients. CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NS, not significant; STD ER, standard error.

found and included in the final model. All risk factors included in the cardiovascular mortality Cox model of the CUORE project were statistically significant (Table 1, model 2). The corresponding area under the ROC curve was 0.825 (95% confidence interval: 0.803–0.846) for men and 0.850 (0.823–0.877) for women.

The CUORE project charts yielded similar results to the corresponding charts of the SCORE project for low risk European countries (Figs 1 and 2). In the CUORE chart, the risk range for men was 0–20% and 0–25% for non-smoking and smoking men, respectively (0–15% and 0–28% for the SCORE chart); the risk range for women was 0–9% and 0–11% (0–8% and 0–15% for the SCORE chart). Lin's coefficient was 0.929 for men and 0.935 for women. For men, 81% of cardiovascular risk categories (<1%, 1–4%, 5–9%,  $\geq$ 10%) showed agreement between CUORE and SCORE charts: 79 and 82% for non-smoking and smoking men, respectively, with a tendency for the non-smoking men's CUORE chart to predict a lower risk than the SCORE chart and the opposite for the charts for men who smoked. For women, 91% of cardiovascular risk categories agreed between the CUORE and SCORE charts: 96% for non-smoking women and 86% for smoking women.

## Discussion

The CUORE project used standardized data collection methods and validated and classified cerebrovascular and coronary fatal and nonfatal events using the MONICA project diagnostic criteria [9–11]. These characteristics allowed comparison between the CUORE charts for 10-year risk assessment of cardiovascular mortality and the SCORE project charts for low risk European countries.

Within the CUORE project, national risk charts were developed in 2004 to assess the probability of developing major fatal and nonfatal cardiovascular events [5–7] and are nowadays recommended by the Italian Ministry of Health for cardiovascular risk assessment of the

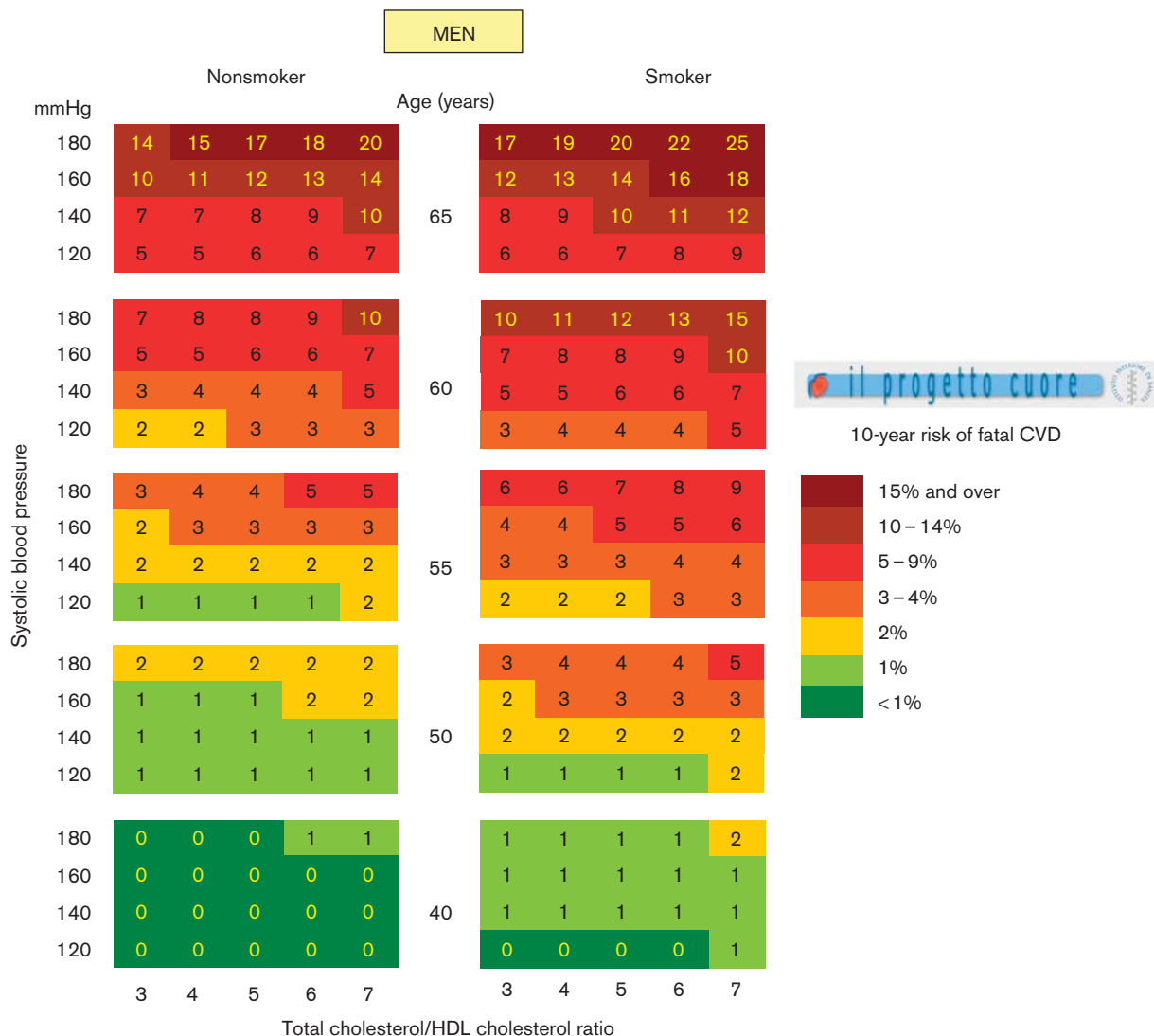
general adult Italian population in primary prevention [8]. In the light of this, the aim of the present analysis is not to introduce other charts in Italian clinical practice or evaluate which model, CUORE or SCORE, yields the better assessment of Italian CVD mortality risk, but to test homogeneity of CUORE and SCORE results for the assessment of cardiovascular mortality in low risk regions of Europe. This is the main reason for the interest in comparing risk charts and not models accuracy.

The sex-stratified model with TC was considered not statistically significant to allow a consistent assessment of 10-year risk of fatal CVD necessary to build the corresponding charts. This was probably because of the low impact of total cholesterol for CVD risk in Italian women compared with other CVD risk factors, as shown in earlier CUORE project analyses [14,15], in combination with the low number of cardiovascular deaths that occurred among women during the follow-up. With future inclusion of new cohorts, similar analyses may be successfully performed.

Considering the sex-stratified model with TC/HDL ratio, all risk factors were statistically significant and a good level area under the ROC curve was found. The comparison between CUORE and SCORE charts yielded homogeneous results: a very high association between estimated risks was found for corresponding charts, as well as an high agreement between the frequency of cardiovascular risk categories.

Not surprisingly, CUORE and SCORE charts are homogeneous: Italy is one of the low risk European countries and some CUORE project cohorts enrolled in the 1980s and considered in this analysis are those previously included in the RIFLE study, which represented the dataset for Italy used to build SCORE charts for low risk European countries [16,17]. Nevertheless, the contribution in terms of number of individuals involved in both studies (2065 men and 2448 women) is quite low: 2% of

Fig. 1



Ten-year risk of fatal cardiovascular disease. Chart based on results in men from Cox model with total cholesterol/HDL-cholesterol ratio stratified by sex. CUORE project cohorts, 35–69 aged, free of earlier cardiovascular disease (CVD).

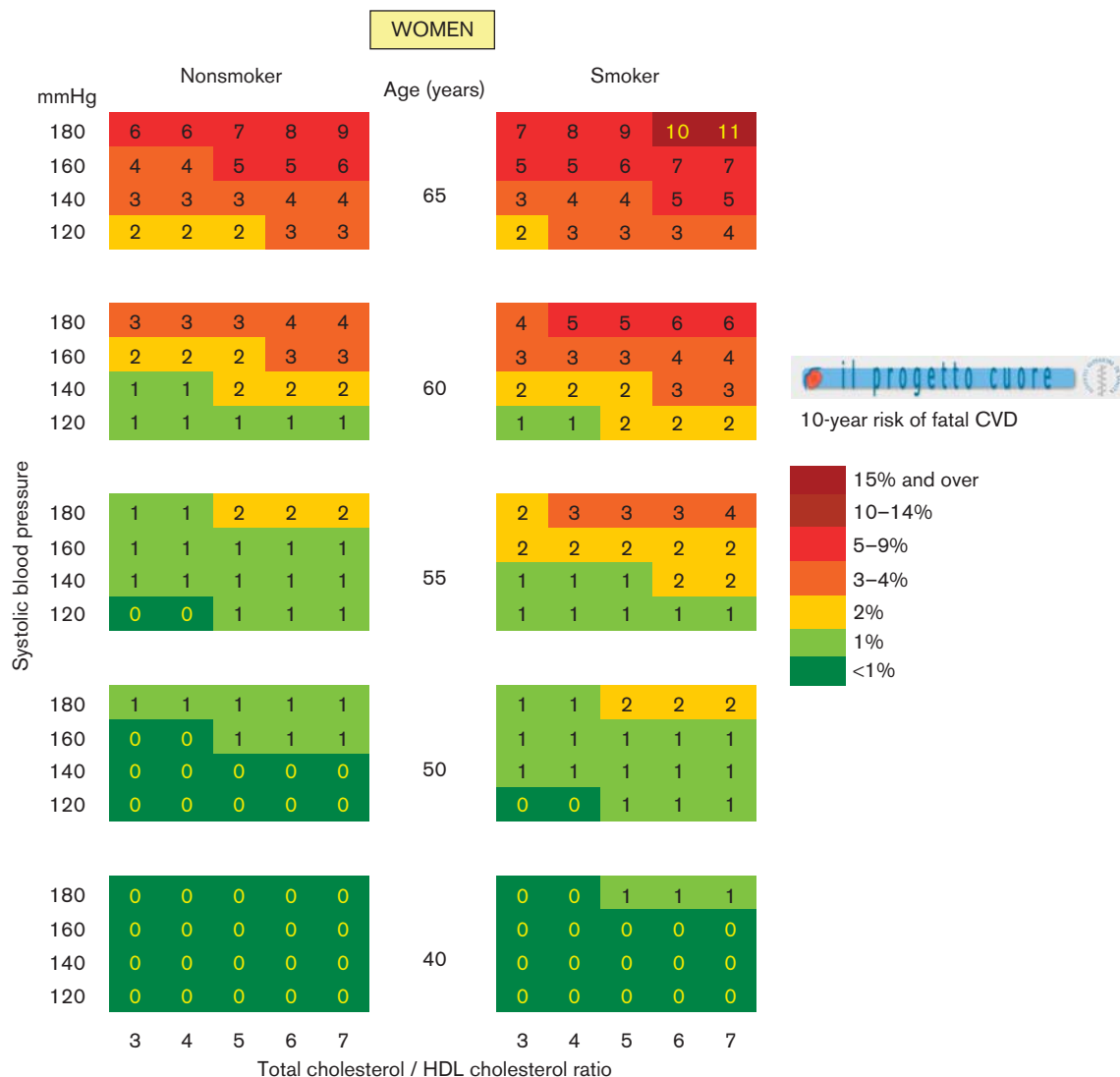
the individuals used for risk factor coefficients assessment in SCORE charts (205 178 men and women from high and low risk European countries) and 6 and 8% of men and women, respectively, used for low risk baseline survival function assessment in SCORE charts (37 183 men and 31 598 women from low risk European countries). In addition, mortality follow-up of the RIFLE study used for SCORE charts lasted 6 years, while the follow-up considered in the CUORE project was 10 years.

More discrepancies were found among non-smoking men/women compared to smoking men/women. Small differences are probably because of the differences in risk factors level and CVD death rate between cohorts used in this analysis and those used for SCORE charts: the first are only Italian cohorts, while the second

included Italy, Belgium, and Spain [4,18]. In addition, to have a sufficient number of individuals and fatal events and to consider the same age range used in earlier CUORE studies [5–7,14,15], CUORE analysis included individuals aged 35–69 years, instead of individuals aged 40–65 years as in SCORE, which may cause small differences in risk estimation among younger and older age classes.

Main differences in risk charts are in the very high-risk levels, well above the threshold of 5% recommended by the European guidelines [3]. Discrepancies at these risk levels are much less important than discrepancies closer to the threshold (e.g. 3–7%), as the individual is already classified as high risk and treatment decisions will not be affected beyond this point.

Fig. 2



Ten-year risk of fatal cardiovascular disease. Chart based on results in women from Cox model with total cholesterol/HDL-cholesterol ratio stratified by sex. CUORE project cohorts, 35-69 aged, free of earlier cardiovascular disease (CVD).

Some differences between the CUORE and SCORE methods used to build risk charts are worth discussing. The choice of applying the Cox proportional hazard model, instead of the Weibull models used by SCORE, is because of the fact that it was also used in earlier CUORE analyses [5-7,14,15]. SCORE charts were cross checked by comparison with Cox models, thus the use of Cox regression models in this analysis should not compromise comparisons.

In the CUORE analysis, the hazard functions were based on person's time under observation rather than on person's age as in the SCORE functions. The approach used to build CUORE charts is commonly used in many epidemiological analyses, where it is not useful to estimate

survival for a follow-up time longer than study's follow-up period, and prevents the effect of splitting time on risk into two different variables: age at screening and time since screening.

To reach a sufficient number of fatal events allowing a consistent assessment of 10-year risk of fatal CVD, CUORE charts were calculated in one single step using CVD mortality as end-point instead of combining two separate risk estimations (coronary heart disease and all noncoronary atherosclerotic CVD) as for SCORE. SCORE models were cross-checked by examined models in which total cardiovascular risk was calculated in one single step, thus the use of this method should not compromise comparisons.

The assessment of absolute risk represents the first step for a correct and useful primary prevention at population level. Ideally, each country should have its own risk function but, because of the lack of data from prospective studies in every European country, the development of the SCORE general European risk function, which can be applied to areas with approximately similar CVD incidence rates, proved to be a more practical approach. As country variations have been observed in cardiovascular mortality [19–21], SCORE charts were developed for high-risk and low-risk regions of Europe. Recalibration methods have been recommended as they seem to work effectively in different settings [22–24]. Some European countries developed a score system to assess CVD risk in their own country using recalibration methods starting from Framingham or SCORE models [25,26]; others provided a validation of developed tools [27]; others developed a function based on cohorts enrolled in their countries [5–7,28,29]. The lack of recent studies involving a sufficiently large population, an array of risk factors information and a follow-up of cardiovascular events collected using standardized procedures, in particular, in low risk populations, where large sample sizes are required to produce a sufficient number of events, are the main reasons for the interest in testing the homogeneity of CUORE and SCORE data to study a possible inclusion of the CUORE project data in the 10-year risk SCORE update for CVD in low-risk regions of Europe.

## Conclusion

Some considerations arise from the results of the CUORE project presented here: the comparison between CUORE and SCORE mortality risk charts shows that SCORE charts reflect Italian cardiovascular mortality quite well and, correspondingly, Italian cohorts of the CUORE project are quite representative of low risk European countries cardiovascular mortality. This could represent a proof of reliability of both populations of reference and methodologies and suggest inclusion of CUORE project cohorts in SCORE chart update for use in low-risk regions of Europe. Given the importance of estimating risk of nonfatal events, especially in those regions at low risk of cardiovascular mortality where nonfatal coronary heart disease and stroke are the main cause of morbidity, the inclusion of nonfatal events in the updated version could also be considered. The updated risk charts could include cohorts tested in this analysis and those with more recent baseline enrolled between 1998 and 2002 (Osservatorio Epidemiologico Cardiovascolare) [30].

## Acknowledgements

The CUORE project is funded by grants from the Italian Ministry of Health, supported by the Italian National Centre for Prevention and Disease Control (CCM), coordinated by the Istituto Superiore di Sanità, Rome, Italy.

The Progetto CUORE Research Group. S Giampaoli, L Palmieri, F Dima, C Lo Noce, C Donfrancesco, P Caiola De Sanctis, P Ciccarelli, A Giannelli, Istituto Superiore di Sanità, Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Rome, Italy. G Cesana, R Segal, S Sarman, C Fornari, G Corrao, L Bolognesi, Centro Studi di Sanità Pubblica, Università degli Studi Milano-Bicocca, Monza (Mi), Italy. M Ferrario, Dipartimento di Scienze Cliniche e Biologiche, Università degli Studi dell'Insubria, Varese, Italy. D Vanuzzo, L Pilotto, R. Mirolo, L. Zanier, F Mattiussi, G Picco, M Martini E Zanin, Centro di Prevenzione Cardiovascolare, ASS 4 'Medio Friuli' e Agenzia Regionale della Sanità del Friuli-Venezia Giulia, Udine, Italy. S Panico, E Celentano, A Mattiello, R Galasso, M Del Pezzo, M Santucci de Magistris, P Chiodini, Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi Federico II, Naples, Italy. The CUORE Project is funded by grants from the Italian Ministry of Health, coordinated by the Istituto Superiore di Sanità, Rome, Italy.

Potential conflicts of interest: none declared.

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