The assessment of cardiovascular risk for primary prevention in the Italian adult population

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**THE ASSESSMENT OF CARDIOVASCULAR RISK
FOR PRIMARY PREVENTION
IN THE ITALIAN ADULT POPULATION**

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Thesis Maastricht University

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The Doctor's Visit, 1658-1662. Wellington Museum, London.

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THE ASSESSMENT OF CARDIOVASCULAR RISK FOR PRIMARY PREVENTION IN THE ITALIAN ADULT POPULATION

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht
op gezag van de Rector Magnificus,
Prof. Dr. L. L. G. Soete,
Volgens het besluit van het College van Decanen,
In het openbaar te verdedigen op
Donderdag 28 Februari 2013 om 10.00 uur
door

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The research described in this thesis is mainly part of the CUORE Project, launched in 1998, financed by 1% of the Italian National Health Fund and is coordinated by the Italian National Institute of Health.

To Prof. Jeremiah Stamler,

who honours me

with his illuminated teachings

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1. Planning of this thesis

Noncommunicable diseases, mainly cardiovascular diseases (CVD), cancers, diabetes and chronic respiratory diseases, represent a leading threat to human health and development. These four diseases are the world's biggest killers, causing an estimated 35 million deaths each year [World Health Organization, 2008]. These diseases are preventable. Up to 80% of heart disease, stroke, and type 2 diabetes and over a third of cancers could be prevented by eliminating shared risk factors, mainly tobacco use, unhealthy diet, physical inactivity and the harmful use of alcohol [World Health Organization, 2008]. Unless addressed, the mortality and disease burden from these health problems will continue to increase.

The management of patients with cardiovascular risk factors changed over the past decade. The focus on single risk factors has given way to an approach that accounts for the multifactorial origin of CVD and the requirement for a comprehensive management of patients at high risk. In primary prevention a step by step approach, starting from the assessment of CVD risk in individuals, is recommended with the aim to maintain the risk factors at favourable level or modify adverse risk factors before any forms of cardiovascular symptoms appear.

The aim of the present thesis is to investigate theoretical and practical aspects of *the cardiovascular risk assessment for primary prevention in the Italian adult population*. Most of results shown in this thesis are carried out within the CUORE Project using a database of risk factors measured during several longitudinal

studies, started in the mid 1980s, and with the follow-up of cardiovascular mortality and morbidity. The CUORE Project was launched in 1998 and financed by 1% of the Italian National Health Fund and is coordinated by the Italian National Institute of Health (ISS).

The identification of individual CVD risk is one of the main targets of primary prevention and the first step towards reducing modifiable risk factors. Assessment of CVD absolute risk is commonly based on risk prediction equations derived from the experience of the Framingham Heart Study in U.S.A. [Circulation, 1998]. However, differences in population risk levels and survival compromise the external validity of these risk equations. Accordingly, longitudinal studies were conducted in other populations with the aim of defining appropriate factors that calibrate absolute risk predictions to local population levels of CVD risk. The first objective of the thesis is to assess for the Italian adult population the predictive roles of several cardiovascular risk factors for first fatal and non-fatal coronary and cerebrovascular events. The first two papers included in this thesis show findings on twelve Italian population samples of the CUORE Project about favorable cardiovascular risk profile and 10-year fatal and non-fatal stroke [**references A**] and coronary heart disease (CHD) [**reference B**] incidence in adult women and men. The focus on both analyses is on protective effects of favorable levels of all readily measured modifiable major stroke and CHD risk factors. On the basis of what arise from these first two analyses, the Italian risk charts and risk score are developed using risk equations based on the CUORE Project database [**reference C**]. Attention focused on the incidence of first non-fatal and fatal major coronary or

cerebrovascular events in men and women aged 35-69 years who were free of previous CVD at baseline. Risk charts and score are simple and objective tools of assessing the likelihood of experiencing a first major cardiovascular event (CHD or stroke) over the following 10 years in middle aged men and women, when the values of the following risk factors are known: gender, history of diabetes, smoking, age, systolic blood pressure (SBP), HDL cholesterol (HDL-C), total cholesterol (TC) and presence of hypertension treatment.

Many available risk factors were excluded from those included in the Italian risk charts and score despite their known relation with CVD risk, e.g., overweight and obesity, family history of CVD, physical activities, education. Thus, some of these risk factors were evaluated in depth performing further analyses. The relation between body mass index (BMI) and CVD risk were studied to evaluate the influence of BMI on incidence of major cardiovascular events through their role on the levels of classical risk factors for the Italian population, which constitute the elements of the national risk charts and scores [**reference D**]. These analyses in the Italian cohorts of the CUORE Project indicate that BMI is positively and strongly related to the major cardiovascular risk factors, results consistent with such data from other prospective investigations.

Also social factors were excluded from Italian risk charts and score despite they could offer useful information for planning prevention strategy for CVD. A further statistical analyses were performed using CUORE Project data to explore the relationship between education, marital status and major cardiovascular risk factors and to evaluate the role of social status indicators in predicting

cardiovascular events and deaths in several Italian cohorts [**reference E**].

Comparisons of the Italian assessment of cardiovascular diseases with other countries risk assessment could be interesting but it is not easy because different risk factors, end-point and methodologies were usually used. Since Italy is considered a country at low risk for CVD, Italian results were compared with the SCORE Projects charts [Eur Heart J, 2003] for European countries at low risk [**reference F**]. The use of comparable end-points and statistical methods was possible thanks to a collaboration with the SCORE research group. Since the end point used in the SCORE risk chart are only fatal stroke and coronary events, CUORE Project risk charts for the assessment of cardiovascular mortality were first developed.

In addition to risk charts and scores an other tool is being widely used by clinicians as a tool for CVD risk assessment: the metabolic syndrome (MetS). The MetS is recognized as a cluster of cardiovascular risk factors that frequently coincide with insulin resistance and hyperglycemia. In recent years, many studies have demonstrated that MetS is a strong predictor of type 2 diabetes, and have investigated the association between the MetS and incident CVD. Nevertheless many analyses pointed to the uncertainty exists about the clinical and public health importance of the MetS: imprecisely defined, lack of certainty regarding its pathogenesis and doubt regarding its value as a CVD risk marker. Using CUORE Project data a statistical analysis was performed to study multiple aspects of the MetS that remain problematic and to evaluate its utility for the CVD risk assessment in the Italian adult

population in particular in comparison with other tools such as CVD risk charts and scores [**reference G**].

The CUORE Project risk charts and scores are nowadays recommended by the Italian Ministry of Health for cardiovascular risk assessment of the general adult Italian population in primary prevention. In spite of this, Italy still lacked a valid national system of surveillance to track CVD risk. The last part of this thesis has the aim to evaluate the use of tools for the assessment of CVD risk in the Italian population for primary prevention in clinical practice. A pilot project was implemented in Italy from the January 2006 with the main aim of evaluating the feasibility of a surveillance network of general practitioners (GPs) for CVD and obesity evaluation [**reference H**]. From 2006 the Observatory of Cardiovascular Risk (OCR), coordinated by the Italian National Institute of Health, pools data collected by GPs through a free of charge software useful to automatically calculate the CUORE Project risk score, supports GPs with quality control, and disseminates results for monitoring risk score and risk factors by genders, age and geographical area, evaluating the efficacy of prevention action in primary care. Preliminary data of the OCR conclude this thesis [**reference I**].

2. Part I - Assessment of CVD risk in the Italian population

Reference A

FAVORABLE CARDIOVASCULAR RISK PROFILE (LOW RISK) AND 10-YEAR STROKE INCIDENCE IN WOMEN AND MEN: FINDINGS ON TWELVE ITALIAN POPULATION SAMPLES

Simona Giampaoli, Luigi Palmieri, Salvatore Panico, Diego Vanuzzo, Marco Ferrario, Paolo Chiodini, Lorenza Pilotto, Chiara Donfrancesco, Giancarlo Cesana, Roberto Segà and Jeremiah Stamler.

American Journal of Epidemiology, 2006; 163: 893-902.

Reference B

FAVORABLE CARDIOVASCULAR RISK PROFILE AND 10-YEAR CORONARY HEART DISEASE INCIDENCE IN WOMEN AND MEN: RESULTS FROM THE PROGETTO CUORE

Luigi Palmieri, Chiara Donfrancesco, Simona Giampaoli, Michela Trojani, Salvatore Panico, Diego Vanuzzo, Lorenza Pilotto, Giancarlo Cesana, Marco Ferrario, Paolo Chiodini, Roberto Segà, and Jeremiah Stamler.

European Journal of Cardiovascular Prevention and Rehabilitation,
2006; 13: 562–570.

Reference C

CARDIOVASCULAR RISK ASSESSMENT IN ITALY: THE CUORE PROJECT RISK SCORE AND RISK CHART

Simona Giampaoli, Luigi Palmieri, Chiara Donfrancesco, Salvatore Panico, Diego Vanuzzo, Lorenza Pilotto, Marco Ferrario, Giancarlo Cesana, Amalia Mattiello, on behalf of The CUORE Project Research Group.

Italian Journal of Public Health, 2007; Year 5, Vol. 4, N. 2: 102-109.

Reference D

PREVENTIVE POTENTIAL OF BODY MASS REDUCTION TO LOWER CARDIOVASCULAR RISK: THE ITALIAN PROGETTO CUORE STUDY

Salvatore Panico, Luigi Palmieri, Chiara Donfrancesco, Diego Vanuzzo, Paolo Chiodini, Giancarlo Cesana, Marco Ferrario, Amalia Mattiello, Lorenza Pilotto, Roberto Segà, Simona Giampaoli, Jeremiah Stamler.

Preventive Medicine, 2008; 47: 53-60.

Reference E

SOCIAL STATUS AND CARDIOVASCULAR DISEASE: A MEDITERRANEAN CASE. RESULTS FROM THE ITALIAN PROGETTO CUORE COHORT STUDY

Carla Fornari, Chiara Donfrancesco, Michele A Riva, Luigi Palmieri, Salvatore Panico, Diego Vanuzzo, Marco M Ferrario, Lorenza Pilotto, Simona Giampaoli, Giancarlo Cesana.

BMC Public Health, 2010; Sep 24;10:574.

Reference F

ITALIAN CARDIOVASCULAR MORTALITY CHARTS OF THE CUORE PROJECT: ARE THEY COMPARABLE WITH THE SCORE CHARTS?

Chiara Donfrancesco, Luigi Palmieri, Marie-Therese Cooney, Diego Vanuzzo, Salvatore Panico, Giancarlo Cesana, Marco Ferrario, Lorenza Pilotto, Ian M. Graham and Simona Giampaoli.

European Journal of Cardiovascular Prevention and Rehabilitation, 2010; Aug;17(4):403-9.

Reference G

THE METABOLIC SYNDROME: A CRITICAL APPRAISAL BASED ON THE CUORE EPIDEMIOLOGIC STUDY

Simona Giampaoli, Jeremiah Stamler, Chiara Donfrancesco, Salvatore Panico, Diego Vanuzzo, Giancarlo Cesana, Giuseppe Mancina, Lorenza Pilotto, Amalia Mattiello, Paolo Chiodini and Luigi Palmieri¹ for the Progetto CUORE Research Group

Preventive Medicine, 2009; June 48(6):525-31.

3. Part II - Use of the CVD risk assessment in the Italian primary prevention

Reference H

ITALIAN NETWORK FOR OBESITY AND CARDIOVASCULAR DISEASE SURVEILLANCE: A PILOT PROJECT.

Chiara Donfrancesco, Cinzia Lo Noce, Ovidio Brignoli, Gabriele Riccardi, Paola Ciccarelli, Francesco Dima, Luigi Palmieri and Simona Giampaoli

BMC Family Practice, 2008; 9:53; doi:10.1186/1471-2296-9-53.

Reference I

CUORE PROJECT EXPERIENCE: CAN THE 10-YEAR CARDIOVASCULAR RISK SCORE ASSESSMENT BE IMPLEMENTED IN PRIMARY CARE?

Luigi Palmieri, Rita Rielli, Luca Demattè, Chiara Donfrancesco,
Paola Cicarelli, Patrizia De Sanctis Caiola, Francesco Dima, Cinzia
Lo Noce, Ovidio Brignoli, Alfredo Cuffari, and Simona Giampaoli.

European Journal of Cardiovascular Prevention and Rehabilitation,
2011; Aug;18(4):642-9.

4. Discussion and conclusions

Atherosclerotic CVD is the most common cause of death worldwide. Usually atherosclerosis is caused by the combined effects of multiple risk factors. For this reason, most guidelines on the prevention of CVD stress the assessment of global absolute risk of CVD. To assist the clinician in calculating the effects of these multiple interacting risk factors, a number of risk estimation systems have been developed.

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. These last 15 years witnessed the implementation of large-scale longitudinal studies providing data on extremely numerous population samples, with a follow up of mortality, fatal and non-fatal cardiovascular events and cancer. The relevant data, stored in large databases and including biological samples preserved at very low temperatures, allowed an in-depth processing, in particular the realization of risk assessment at national level.

Assessment of CVD risk in the Italian population

The CUORE Project has developed a database of CVD risk factors collected in several Italian 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 absolute risk of CVD for men and women separately. 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 sample size, 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. Thanks to this longitudinal studies, Italy is one of the few countries to have developed own tools, such as risk charts and score, for the assessment of CVD risk in the general adult population.

With respect to risk charts and risk scores derived from the Framingham Study [Circulation, 1998], the PROCAM Study [Circulation, 2002], the Seven Countries Study [Eur Heart J, 2000; Ann Ital Med Int, 2002], and the SCORE project [Eur Heart J, 2003], major differences can be found in the availability of data on men and women, 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. All these risk charts and scores, as of course also the Italian ones, 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.

Risk charts and the individual risk score, resulting from work carried out within the CUORE Project enable Italian health professionals to make an objective assessment of a person's risk, to share a common language with other specialists, and to monitor and evaluate, over time, the benefits of adopted preventive activities. The risk charts consist of global absolute risk classes calculated for risk factors categories (age, gender, diabetes,

smoking, SBP and TC). The individual risk score provides an even more accurate assessment as it takes into account continuous values for some risk factors such as age, TC and HDL-C and SBP; anti-hypertensive therapy is also included in the assessment, taking into account that the SBP level is influenced by specific drug effects. Anti-hypertensive therapy is also an indicator of longstanding hypertension. Risk charts and individual risk score can be applied to men and women ages 40-69 and ages 35-69 respectively, free from previous cardiovascular events. Risk charts and the individual risk score predict 10-year risk of fatal and non-fatal coronary and cerebrovascular events. A separate analysis was done to build CUORE Project risk charts for the assessment of 10-years cardiovascular mortality and to compare them with those developed by the SCORE Project for low risk European countries. Risk factors considered, as for SCORE, were age, SBP, smoking habit, TC or TC/HDL-C ratio. The CUORE Project charts with TC/HDL-C yielded similar results to the corresponding charts of SCORE Project for low risk European countries. For men, 81% of cardiovascular risk categories (<1%, 1-4%, 5-9%, $\geq 10\%$) agree between CUORE and SCORE charts: 79% and 82% for non-smoking men and smoking men respectively, with tendency of non-smoking men CUORE chart to a lower risk than the SCORE one and the opposite for smoking men chart. For women, 91% of cardiovascular risk categories agree between CUORE and SCORE charts: 96% for non-smoking women and 86% for smoking women. This could represent a proof of reliability of both populations of reference and methodologies and may lead to the inclusion of the CUORE Project data in the ten-year risk SCORE update for CVD in low risk regions of Europe. Given the importance

of estimating risk of non-fatal events, especially in those regions at low risk of cardiovascular mortality where non-fatal coronary heart disease and stroke are the main cause of morbidity, the inclusion of non-fatal events in the updated version could also be considered.

Following the principle of parsimony, many risk factors were excluded from final CUORE Project equations, as well as, from many CVD risk equations from other countries, despite their known relation with CVD risk, e.g., overweight and obesity, family history of CVD, physical activities, education. Within the CUORE Project many additional analyses were done to assess the relation among some risk factors not included in the final risk equations and CVD risk, as well assessment of a particular combination of them (MetS).

The analysis to evaluate the relation between BMI and CVD risk in the Italian adult population rose that the positive association between BMI and some risk factors (SBP, TC, HDL, diabetes) is sizable, statistically significant, and consistent across models, univariate and multivariate. The great and positive association between BMI, CVD risk factors and CVD risk resulted consistent with such data from other prospective investigations, e.g., Chicago Heart Association Study, the Framingham Offspring Study, the Greek EPIC Study, and the REGICOR Study. Our estimates of potential decrease in disease risk due to improvement in major risk factors with reduced BMI support the importance of overweight/obesity prevention and control for CVD prevention.

From the analysis to evaluate the role of social status indicators (education and marital status) in predicting cardiovascular events and deaths in the Italian adult population resulted that there was

an inverse relationship between educational level and major CVD risk factors (such as blood pressure, triglycerides, BMI, diabetes) in both genders, according to the results of studies conducted in other Western countries [Diabetes Care, 1999]. Significant higher major cardiovascular risk factors were detected in married or cohabitating women, with the exception of smoking. Cardiovascular risk score was lower in married or cohabitating men and cardiovascular case-fatality was significantly higher in men not married and not cohabitating. In the Mediterranean culture, the percentage of married or cohabitating men is higher than the percentage in women, and, due to the elevated consideration of family ties, remaining single and living alone is usually not a choice, but probably indicates isolation and the lack of social support. No relationship between incidence of coronary events and the two social status indicators was observed. Higher cardiovascular risk observed in low educated people deserves careful attention even if, during the follow up it did not seem to determine an increase of coronary events.

Studying the role of MetS in the prediction of CVD risk in the Italian adult population resulted that MetS was no better than the sum of its parts in predicting CVD, important information was lost due to omission of TC and smoking, and from considering MetS traits as yes/no variables, according with other prospective epidemiologic studies. In addition CVD risk prediction by MetS was less strong for men and no stronger for women than by classical risk factors (blood pressure, diabetes, serum cholesterol, smoking, overweight/obesity).

Use of the CVD risk assessment in the Italian primary prevention

Prevention, whose main aim is to keep the risk factors' level under control, is still the best weapon in the fight against CVD, which comes suddenly and unexpectedly, thus the victim often does not receive adequate aid as the event normally occurs outside the hospital. The risk factors for CVD are numerous and heterogeneous. Some factors are non-modifiable, such as age, gender and family history of CVD. Other important factors are defined as 'modifiable' to highlight the fact that can be controlled through external interventions, thus reducing the likelihood of falling ill. This category includes behavioural habits related to peculiar lifestyles, such as cigarette smoking, low level of physical activity and an unhealthy diet. The last two can lead to obesity, diabetes and a high blood cholesterol level, which, together with high blood pressure, represent the main biological risk factors. Risk charts and individual risk score carried out from the CUORE Project were recommended by the Italian Ministry of Health for cardiovascular risk assessment of the general adult population in primary prevention as the first step to reduce CVD risk or keep it at favourable level by changing or reducing modifiable risk factors through healthy lifestyle. The use of risk charts and individual risk score to assess cardiovascular risk is highly recommended at least: every six months in people at high cardiovascular risk (equal to or greater than 20%), every year in people at cardiovascular risk to be kept under control through an healthy lifestyle (equal to or greater than 5% and lower than 20%), every five years in people at low cardiovascular risk (lower than 5%).

Starting from 2005 in Italy, beside population-based interventions implemented by the Italian Ministry of Health, in collaboration with the ISS, has launched a national training plan aimed at increasing GPs' awareness about the key role of cardiovascular prevention, in order to implement an Italian national surveillance system. A software called cuore.exe, downloadable free of charge from the website of the CUORE Project, helps GPs to set up a data archive, to monitor cardiovascular risk and risk factors trends in patients over time through the CUORE Project score.

Studies were implemented to evaluate the introduction of the CVD risk assessment in clinical practice. A pilot project implemented in Italy for two years starting from January 2006 with the main aim of evaluating the feasibility of a GPs surveillance network for CVD and obesity in men and women aged 35–74 years. At the end of the study, the completeness of information collected through cuore.exe was considered satisfactory. The CUORE Project individual risk was assessed by GPs on 45% of those patients considered eligible for application of the CUORE Project risk function and for the remaining 55% individual risk was assessed within the statistical analysis thanks to the availability of risk factors collected by GPs. These results demonstrate the feasibility of a GPs surveillance network for CVD in Italy. Also preliminary results of the Italian OCR until 2011, that pools data collected by GPs through the cuore.exe, underlined the importance of CVD risk assessment in clinical practice and demonstrate the feasibility to implement a risk factors and CVD risk surveillance system involving GPs after an appropriate training programme. Although data are derived from a non-representative sample of 1,032 GPs, it appears evident that risk can be reduced and maintained low

despite age increase and counselling advices may be well received. Among men and women followed-up by GPs, statistically significant reductions of systolic and diastolic blood pressure, total cholesterol, and prevalence of smokers have been registered; moreover, results suggest an improvement in hypertension and hypercholesterolaemia control, according with some studies that demonstrated how a physician-implemented CVD risk evaluation/communication programme improves patients' modifiable risk factor profile and lowers predicted risk compared with usual care, and give evidence for the efficacy of an intervention addressing multiple risk factors for primary prevention at 1 year using risk scores and counselling or treatment interventions [Int J Clin Pract 2008; BMC Med 2010; CMAJ 2007; Med Decis Making 2000]. On the other side, some puzzlements rise on the use of CVD risk scores for primary prevention; doubts are more related to accuracy of tools in predicting CVD risk than to efficacy in using risk assessment and consequently in therapeutic and lifestyle interventions [Heart 2006]. Discussion is still open. The last step of the national training plan on the use and application of cardiovascular risk charts foresees discussion of OCR results with health operators at regional, sanitary district, and/or GPs' association levels. The discussion of the collected data, already started in some regions, may play a major role in the identification of strengths and weaknesses of preventive action and represents the first step to improve good clinical practice standards.

5. Summary

The aim of this thesis was to investigate theoretical and practical aspects of the cardiovascular risk assessment for primary prevention in the Italian adult population.

Crucial issues have been discussed:

- **Why should global absolute risk of CVD be assessed?**

The use of the global absolute risk of CVD is consistent with the multifactorial aetiology of CVD; it allows multiple choices in treating high-risk individuals or monitoring low risk over lifetime taking into account a person's possible preferences (e.g., stop smoking versus starting treatment for hypercholesterolemia) and the fact that most of the identified high-risk conditions are clinically silent. In addition, the global absolute risk of CVD calculation allows clinicians to perform a more objective and careful evaluation of their patients, comparable with subsequent evaluations, to show that risk increase with age and to evaluate the cost/benefit ratio of preventive actions.

- **Why should total CVD risk assessment for Italian general population be estimated using Italian longitudinal data?**

The risk equation for the assessment of CVD risk 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. The validity of using these risk functions is based on the characteristics of the population generating them and the individuals to whom they are applied. Therefore to avoid misclassification, due to underestimation or overestimation of CVD risk, own risk functions are recommended for each country or at least for countries with similar CVD risk.

- **Which risk factors are important in order to predict 10-year risk of fatal and non-fatal stroke and coronary events for the Italian adult population?**

Choice of the best models then used to build Italian risk charts and scores took into account scientific literature, correlation analyses results, statistical significance of hazard ratios assessed by the univariate and multivariate analyses, use of the variables with the least number of missing values, and model effectiveness tests

under the statistical principle of parsimony. The following risk factors are considered, among those available, as the best set of CVD risk predictors for Italian adult population: age, gender, SBP, TC, HDL-C, history of diabetes, presence of hypertension treatment and smoking habit. Many available risk factors were excluded from final risk equations despite their known relation with CVD risk, e.g., overweight and obesity, family history of CVD, physical activities, education. They resulted as having a predictive role only when considered alone or were considered as having a lower predictive role than those included in final equations. A separately analyses were also be done for some of them.

- **Which is the role of MetS as a tool for CVD risk assessment for the Italian adult population?**

Several studies, including the CUORE Project data, demonstrated that MetS use for CVD risk prediction has important limitations, particularly if there is concurrent inattention to the independent impact on risk of TC and smoking, and quantitative levels of MetS traits, also if there is neglect of persons with only one or only two metabolic syndrome traits. MetS as a CVD risk predictor is no better than the sum of its parts. The clinical use of MetS for CVD risk assessment is of questionable value and needs critical reconsideration, taking into account availability of other approaches with strengths beyond the MetS.

- **CVD risk assessment implications for practice and policy in Italy**

In accordance with that Geoffrey Rose wrote many years ago, the application of the CUORE Project risk charts and scores to the population 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.

Starting from 2005 in Italy, beside population-based interventions implemented by the Italian Ministry of Health, in collaboration with the ISS, has launched a national training plan aimed at increasing GPs awareness about the key role of CVD prevention, in order to introduce lifestyle changes among individuals at high risk and general population, to reduce the frequency of risk conditions and in the mean level of single risk factors. According to the European guidelines on CVD prevention, the 10-year CVD risk assessment was indicated as the first step for the implementation of preventive actions in clinical practice and recommended for evaluate statins reimbursement in primary prevention when there are no indication for family history as laid down in Italian Drugs Agency (AIFA) Note 13 (2007). The active role of GPs in the process of prevention represents a potential key to success. GPs have the primary and

complete responsibility toward their patients, contribute to the development of individual assistance plan and recommend specialist visits when necessary.

6. Selected Publications

- A. Giampaoli S, Palmieri L, Panico S, Vanuzzo D, Ferrario M, Chiodini P, Pilotto L, **Donfrancesco C**, Cesana G, Segà R and Stamler J. Favorable cardiovascular risk profile (low risk) and 10-year stroke incidence in women and men: findings on twelve Italian population samples. *American Journal of Epidemiology*, 2006; 163: 893-902.
- B. Palmieri L, **Donfrancesco C**, Giampaoli S, Trojani M, Panico S, Vanuzzo D, Pilotto L, Cesana G, Ferrario M, Chiodini P, Segà R, and Stamler J. Favorable cardiovascular risk profile and 10-year coronary heart disease incidence in women and men: results from the Progetto CUORE. *European Journal of Cardiovascular Prevention and Rehabilitation*, 2006; 13: 562–570.
- C. Giampaoli S, Palmieri L, **Donfrancesco C**, Panico S, Vanuzzo D, Pilotto L, Ferrario M, Cesana G, Mattiello A, on behalf of The CUORE Project Research Group. Cardiovascular risk assessment in Italy: the CUORE Project risk score and risk chart. *Italian Journal of Public Health*, 2007; Year 5, Vol. 4, N. 2: 102-109.
- D. Panico S, Palmieri L, **Donfrancesco C**, Vanuzzo D, Chiodini P, Cesana G, Ferrario M, Mattiello A, Pilotto L, Segà R, Giampaoli S, Stamler J. Preventive potential of body mass reduction to lower cardiovascular risk: the Italian Progetto CUORE Study. *Preventive Medicine*, 2008; 47: 53-60.

- E.** Fornari C, **Donfrancesco C**, Riva M A, Palmieri L, Panico S, Vanuzzo D, Ferrario M, Pilotto L, Giampaoli S, Cesana G. Social status and cardiovascular disease: a Mediterranean case. Results from the Italian Progetto CUORE cohort study. BMC Public Health, 2010; Sep 24;10:574.
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- G.** Giampaoli S, Stamler J, **Donfrancesco C**, Panico S, Vanuzzo D, Cesana G, Mancina G, Pilotto L, Mattiello A, Chiodini P, and Palmieri L for the Progetto CUORE Research Group. The metabolic syndrome: A critical appraisal based on the CUORE epidemiologic study; Preventive Medicine, 2009; June 48(6):525-31.
- H.** **Donfrancesco C**, Lo Noce C, Brignoli O, Riccardi G, Ciccarelli P, Dima F, Palmieri L, Giampaoli S, and Obesity Project Research Group (oprg). Italian network for obesity and cardiovascular disease surveillance: a pilot project. BMC Family Practice, 2008, 9:53; doi:10.1186/1471-2296-9-53.

- I.** Palmieri L, Rielli R, Demattè L, **Donfrancesco C**, Ciccarelli P, De Sanctis Caiola P, Dima F, Lo Noce C, Brignoli O, Cuffari A, and Giampaoli S. CUORE Project experience: implementation of the 10 year risk score. *European Journal of Cardiovascular Prevention and Rehabilitation*, 2011; Aug 18(4):642-9.

7. Curriculum Vitae

Chiara Donfrancesco was born in Rome (RM), Italy, on 24th of October, 1979.

Education

She attended the Statistic Science Faculty (University La Sapienza, Rome), and in 2003 discussed a thesis in the field of statistical inference (Title: *Procedures for error control in multiple tests: a comparative analysis*).

In 2005, she obtained qualification to practice a profession of statistician through qualifying examination at the University La Sapienza of Rome.

On 2004 she attended the course "Statistic methods in Epidemiology and Clinical Medicine" organized by Statistic Science Faculty of University of Rome" La Sapienza", Italy.

On 2004 she attended the course "Epidemiology specific topics. 3 units. Epidemiology and Prevention of Cardiovascular Disease; Global Absolute Cardiovascular Risk Assessment" organized by ISS, in Rome, Italy.

On 2006 she was selected to participate and attended the course "Ten-Day International Teaching Seminar on Cardiovascular Disease Epidemiology and Prevention", organized by The Council on Epidemiology and Prevention of the World Heart Federation in Brisbane, Australia.

On 2006 she was selected to participate and attended the course "WHO/IDF Cambridge Seminar on the Epidemiology and Public

Health Aspects of Diabetes Mellitus" organize by WHO/IDF, in Cambridge, United Kingdom.

On 2007 she attended the postgraduate course "The Cardiometabolic Syndrome. An update on pathophysiology, clinical aspects and therapeutic strategies" patronized by University of Rome La Sapienza, Italian Society of Diabetology, Italian Society of Endocrinology, Italian Society of Arterial Hypertension, Italian Society of Internal Medicine, Italian Society for the study of Atherosclerosis, in Rome, Italy.

On 2010 she attended the course "1st European Health Examination Survey Training Seminar" organized by the National Institute for Health and Welfare (THL) Department of Chronic Disease Prevention Chronic Disease Epidemiology and Prevention Unit at the National Institute of Health, in Rome, Italy.

On 2010 she attended the course "2nd European Health Examination Survey Training Seminar" organized by the National Institute for Health and Welfare (THL) Department of Chronic Disease Prevention Chronic Disease Epidemiology and Prevention Unit at National Institute for Health and Welfare (THL), in Helsinki, Finland.

On 2012 she attended the course "Introduction to software R" organized by Statistic Science Faculty of University of Rome" La Sapienza", Italy.

Scientific activities

In 2004 she worked as statistician at the Demographic Department of University La Sapienza and at the Umberto I General Hospital, Rome, Italy.

Since 2005, she is researcher at the Unit of Epidemiology of Cerebro and Cardiovascular Diseases (coordinated by Simona Giampaoli), National Centre of Epidemiology, Surveillance and Health Promotion of the Italian National Institute of Health (ISS) in Rome, Italy.

Principal aims of Dr. Chiara Donfrancesco are to implement epidemiological studies in order to assess cardiovascular risk factor distribution and life style habits in the Italian general population and their trends over different period of time and different geographical areas, to assess aetiology of classical and new risk factors for the prediction of coronary and cerebrovascular risk in the Italian general population, to support national preventive programmes and actions.

Her main scientific roles have been:

- Responsible of the ISS Operative Unit for the Project "Buone pratiche sull'alimentazione: valutazione del contenuto di sodio, potassio e iodio nella dieta degli italiani" - MINISAL-GIRCSI (2009-2011 - Coordinator of the Project: Pasquale Strazzullo);
- Responsible of urine samples collected within the Osservatorio Epidemiologico Cardiovascolare/MINISAL-GIRCSI and stored in the biological bank of the National

- Centre for Epidemiology, Surveillance and Health Promotion of the ISS;
- Principal investigator of the Italian cohort of the FINE Study (Finland, Italy, Netherlands, Elderly);
 - Investigator of EMERGING RISK FACTORS COLLABORATION;
 - Member of the research group of the CUORE Project - Epidemiology and Prevention of Ischaemic Heart Disease of the Italian Ministry of Health (Responsables: Simona Giampaoli, Luigi Palmieri, Diego Vanuzzo, Salvatore Panico, Marco Ferrario, Giancarlo Cesana, Licia Iacoviello);
 - Member of the research group of the Osservatorio Epidemiologico Cardiovascolare/Health Examination Survey (Coordinators: Simona Giampaoli e Diego Vanuzzo);
 - Member of the research group of the EUROCISS project (Cardiovascular Indicators Surveillance Set) (Responsible: Simona Giampaoli, Mette Madsen, Andrzej Pajak, Paola Primatesta, Susana Sans);
 - Member of the scientific committee of the biological bank of the National Centre for Epidemiology, Surveillance and Health Promotion of the ISS;
 - Participation to the Italian HUB of population biological banks as responsible of biological samples;
 - Cooperation as researcher to MORGAM (Monica Risk Genetics Archiving and Monograph);
 - Associate editor of BMC Cardiovascular Disorders from 2012.

Invited speaker at scientific meetings

L'obesità aumenta il rischio cardiovascolare?. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Rome, Italy, May 2005.

Uso e applicazione della carta del rischio cardiovascolare, Scuola di Specializzazione in Igiene e Medicina Preventiva, Facoltà di Medicina e Chirurgia, University of Rome "La Sapienza", Rome, Italy, May 2006.

Sorveglianza sugli eventi cardio e cerebrovascolari. International Conference organized by Italian Ministry of Health, Centre for diseases prevention and control. Rome, Italy, April 2007.

An Italian general practitioners network survey on obesity. 5th International Conference on Behavioral Risk Factor Surveillance, Rome, Italy, October 2007.

Progetto pilota per una rete di sorveglianza sulle malattie cardiovascolari e sull'obesità. 25° National Conference SIMG. Florence, Italy, November 2008.

Sale, ipertensione e rischio cardiovascolare: il Progetto MINISAL-GIRCS". Convegno "Abuso di sale, obesità e ipertensione. Meno sale, più salute: vicini alla soluzione?", Rome, Italy, June 2010.

L'aggiornamento della carta del rischio cardiovascolare,. IX National Conference of Società Italiana per la Prevenzione Cardiovascolare (SIPREC). Genova, Italy, April 2011

Il consumo di sale in Italia, 42° National Conference of Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), Florence, Italy, May 2011.

Il monitoraggio del consumo di sale in Italia, II WORKSHOP 2011 for coordinators of PASSI surveillance system, Rome, Italy, May 2011.

Le malattie cardio e cerebrovascolari nella popolazione adulta italiana, Conference "La salute degli italiani nei dati del CNESPS", Rome, Italy, June 2011.

Studio MINISAL-GIRCSI: consumo di sodio e potassio, sovrappeso e obesità in una popolazione generale in Italia, XXVIII National Conference of Società Italiana dell'Ipertensione Arteriosa e della Lega Italiana contro l'Ipertensione Arteriosa, Rome, Italy, October 2011.

Malattie cardiovascolari e tumori, Congresso di Ricognizione sulle Attività dell'ISS nell'Area dei Tumori: Prospettive di Interazione e Sviluppo, Rome, Italy, December 2011.

Can we estimate CVD risk in those over 70 and is it worthwhile? Europrevent 2013, organized by the European Association for Cardiovascular Prevention and Rehabilitation (EACPR) from 18-20 April 2013 in Rome, Italy.

Presenter at scientific meetings

Obesity and cardiovascular disease risk. European Society of Cardiology Congress September, Stockholm, Sweden, 2005.

The Metabolic Syndrome: Mix Of Traits And Utility For Cardiovascular Disease Risk Prediction -- Population- Based Data From The Cuore Project. 47th Cardiovascular Disease Epidemiology and Prevention Conference of the American Heart Association (AHA), Orlando, Florida, USA, February 2007.

An Italian general practitioners network survey on obesity. 48th Cardiovascular Disease Epidemiology and Prevention Conference, and Nutrition, Physical Activity and Metabolism Conference of the American Heart Association (AHA), Colorado Springs, Colorado, USA, March 2008.

The Metabolic Syndrome: utility for cardiovascular risk prediction - - the Italian population-based CUORE Project. EUROPREVENT Congress 2008; Paris, France, May 2008.

An Italian general practitioners network survey on obesity. EUROPREVENT Congress 2008; Paris, France, May 2008.

Socioeconomic status and cardiovascular disease: the Mediterranean case. Results from the Italian Progetto CUORE populations. 49th Cardiovascular Disease Epidemiology and Prevention Annual Conference, and Nutrition, Physical Activity and

Metabolism Conference of the American Heart Association (AHA), Palm Harbor, Florida, USA, March 2009.

Impact of favorable cardiovascular risk profile on total and cardiovascular mortality: results from the CUORE Project. 49th Cardiovascular Disease Epidemiology and Prevention Annual Conference, and Nutrition, Physical Activity and Metabolism Conference of the American Heart Association (AHA), Palm Harbor, Florida, USA, March 2009.

Italian cardiovascular mortality charts of the CUORE Project: are they comparable with the European SCORE charts?. 49th Cardiovascular Disease Epidemiology and Prevention Annual Conference, and Nutrition, Physical Activity and Metabolism Conference of the American Heart Association (AHA), Palm Harbor, Florida, USA, March 2009.

The Italian Health Examination Survey: Time Trends of CVD Risk Factors. 50th Annual Conference on Cardiovascular Disease Epidemiology and Prevention in association with the Council of Nutrition, Physical Activity, and Metabolism of the American Heart Association. San Francisco, California, USA, March 2010.

The CUORE Project: Preliminary Analyses for the Updating of the Italian Cardiovascular Risk Charts. 51st Annual Conference on Cardiovascular Disease Epidemiology and Prevention in association with the Council of Nutrition, Physical Activity, and Metabolism of the American Heart Association, Atlanta, Georgia, USA, March 2011.

Sodium and Potassium Dietary Intake in the Italian Adult Population: Preliminary Results of the Minisal-Gircsi Study. 51st Annual Conference on Cardiovascular Disease Epidemiology and Prevention in association with the Council of Nutrition, Physical Activity, and Metabolism of the American Heart Association, Atlanta, Georgia, USA, March 2011.

Time Trend of Cardiovascular Diseases Prevalence in The Italian Adult Population: The Italian Health Examination Survey. 52nd Cardiovascular Disease Epidemiology and Prevention Annual Conference, and Nutrition, Physical Activity and Metabolism Conference of the American Heart Association (AHA). San Diego, California, USA, March 13-16, 2012.

Sodium and Potassium 24 Hours Excretion in The Italian Adult Population: Preliminary Results of The MINISAL-GIRCSI Study. 52nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention in association with the Council of Nutrition, Physical Activity, and Metabolism of the American Heart Association (AHA) 2012. San Diego, California, USA, March 13-16, 2012.

8. Publications

1. THE EMERGING RISK FACTORS COLLABORATION. C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction. *N Engl J Med* 2012; 367:1310-1320.
2. Palmieri L, Rossi S, **Donfrancesco C**, Pannozzo F, Busco S, Caiola De Sanctis P, Capocaccia R, Giampaoli S. Malattie cardiovascolari e tumori: una prevenzione unica?. In Belardelli F, Moretti F (Ed.). *Attività e impegno dell'Istituto Superiore di Sanità nella lotta contro il cancro*. Roma: Istituto Superiore di Sanità; 2012 (Rapporti ISTISAN 12/37): 257-263.
3. **Donfrancesco C**, Palmieri L, Vannucchi S e Giampaoli S. Quanto pesa il sovrappeso sul rischio cardiovascolare?. 10 October 2012. <http://www.epicentro.iss.it/problemi/obesita/ObesityDay2012Cardio.asp>.
4. **Donfrancesco C**, Ippolito R, Lo Noce C, Palmieri L, Iacone R, Russo O, Vanuzzo D, Galletti F, Galeone D, Giampaoli S, Strazzullo P on behalf of the MINISAL-GIRCSI Program Study Group. Excess dietary sodium and inadequate potassium intake in Italy: Results of the MINISAL study. *Nutr Metab Cardiovasc Dis*. 2012 Jul 24.
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6. Palmieri L, Rielli R, Donfrancesco C, Dematte L, Giampaoli S. Il rischio cardiovascolare globale assoluto e l'Osservatorio del rischio cardiovascolare (Orc). 2012 <http://www.epicentro.iss.it/focus/cardiovascolare/ORC2012.asp>.
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- Donfrancesco C**, Kee F, Mancia G, Cesana G, Kuulasmaa K, Susana S. Impact of age on the importance of systolic and diastolic blood pressure for stroke risk. The MORGAM project. Hypertension. 2012 Sep 24. [Epub ahead of print].
8. The EMERGING RISK FACTORS COLLABORATION. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. *Int J Epidemiol*. 2012 Jul 23.
 9. Collaborazione to 'Geoffrey Rose e la strategia della medicina preventiva'. Seconda edizione italiana, Il Pensiero Scientifico Editore, gennaio 2012: 115 pp.
 10. Giampaoli S, Vannucchi S, Palmieri L, **Donfrancesco C** Prevenzione, valutazione e gestione integrata dell'ictus. Una guida per la Medicina Generale ad integrazione del testo 'G-PAC – Guida informativa per la Prevenzione secondaria degli Accidenti Cerebrovascolari'. Il Pensiero Scientifico Editore, marzo 2012: 100 pp.
 11. Palmieri L, **Donfrancesco C**, Lo Noce C, Dima F, Vanuzzo D, Pilotto L, Giampaoli S. Livello di educazione e andamento temporale dei fattori di rischio cardiovascolari tra il 1998 e il 2008 nella popolazione adulta italiana. *Notiziario dell'Istituto Superiore di Sanità* 2011;24(10):i-ii.
 12. Palmieri L, **Donfrancesco C**, Giampaoli S. Trend dell'obesità nella popolazione adulta italiana. Istituto Superiore di Sanità 2011. Rapporti ISTISAN 11/42.
 13. Palmieri L e Donfrancesco C. Trend della prevalenza delle malattie coronariche e cerebrovascolari nella popolazione adulta italiana. *Epidemiol Prev* 2011. 35 (5-6):94-95.

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15. De Nicola L , **Donfrancesco C**, Minutolo R, Lo Noce C, De Curtis A, Palmieri L, Iacoviello L, Conte G, Chiodini P, Sorrentino F, Coppo R, Vanuzzo D, Scherillo M, Giampaoli S. Epidemiologia della malattia renale cronica in italia: stato dell'arte e contributo dello studio CARHES. G Ital Nefrol 2011. 28 (4): 401-407.
16. Palmieri L , , **Donfrancesco C** Giampaoli S. 2008 vs 1988: andamento temporale dei fattori di rischio cardiovascolare in Italia. Supplemento a CardiLink Scientific News n. 4 - Ottobre-Dicembre 2010 - Anno XIV.
17. **Donfrancesco C**, Palmieri L, Culotta C. Aggiorniamo le carte! Strumenti per la valutazione del rischio cardiovascolare in Italia. Diabelink - Supplemento a Cardiolink Scientific News n. 2 - Aprile- Giugno 2011 - Anno XV.
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25. Triglyceride Coronary Disease Genetics Consortium and EMERGING RISK FACTORS COLLABORATION. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010. 375: 1634-1639.
26. **Donfrancesco C**, Palmieri L a nome del Gruppo di Ricerca del Progetto CUORE. Aspetti metodologici nell'analisi dei dati italiani del Progetto CUORE: sindrome metabolica e rischio cardiovascolare. Sindrome metabolica e malattie cardiovascolari, Vol. 3, Numero 1 - marzo 2010.
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28. **Donfrancesco C**, Palmieri L, Giampaoli S, Vanuzzo D, Pilotto L, Panico S, Ferrario MM, Cesana G, Mattiello A, Chiodini P, a nome del Gruppo di Ricerca del Progetto CUORE. Impatto sul rischio cardiovascolare delle diverse componenti che definiscono la sindrome metabolica. *G Ital Cardiol* 2010. 11 - Suppl 3 al n. 5: 37-42.
29. Palmieri L, Lo Noce C, Vanuzzo D, Dima F, **Donfrancesco C**, Pilotto L, Ciccarelli P, Giannelli AM, Vannucchi S, Laurendi G, Giampaoli S, a nome del Gruppo di Ricerca dell'Osservatorio Epidemiologico Cardiovascolare. Osservatorio Epidemiologico Cardiovascolare: andamento temporale dei fattori di rischio cardiovascolare. *G Ital Cardiol* 2010. 11 - Suppl 3 al n. 5: 31-36.

30. Panico S, Palmieri L, **Donfrancesco C**, Vanuzzo D, Chiodini P, Cesana G, Ferrario MM, Mattiello A, Pilotto L, Sega R, Giampaoli S, a nome del Gruppo di Ricerca del Progetto CUORE. Il potenziale preventivo della riduzione dell'indice di massa corporea per ridurre il rischio cardiovascolare: il Progetto CUORE. *G Ital Cardiol* 2010. 11 - Suppl 3 al n. 5: 43-47.
31. **Donfrancesco C**, Palmieri L, Vanuzzo D, Panico S, Ferrario MM, Cesana G, Pilotto L, Chiodini P, Mattiello A, Lo Noce C, Dima F, De Sanctis Caiola P, Vannucchi S, Giampaoli S, a nome del Gruppo di Ricerca del Progetto CUORE - Epidemiologia e Prevenzione delle Malattie Cerebro e Cardiovascolari e del Gruppo di Ricerca dell'Osservatorio Epidemiologico Cardiovascolare. Il Progetto CUORE: analisi preliminari per l'aggiornamento delle carte del rischio e del punteggio individuale. *G Ital Cardiol* 2010. 11 - Suppl 3 al n. 5: 20-24.
32. Palmieri L, Rielli R, Demattè L, **Donfrancesco C**, La Terza G, De Sanctis Caiola P, Dima F, Lo Noce C, Giannelli A, Brignoli O, Cuffari A, De Rosa M, Addis A, Laurendi G, e Giampaoli S. Osservatorio del Rischio Cardiovascolare: Primi Risultati. *G Ital Cardiol* 2010. 11: 154-161.
33. **Donfrancesco C**, Palmieri L, Vanuzzo D, Panico S, Cesana G, Ferrario M, Pilotto L, e Giampaoli S a nome del gruppo di ricerca del Progetto CUORE. Omogeneità delle carte del rischio del Progetto CUORE per la valutazione della mortalità cardiovascolare e le carte del Progetto SCORE. *G Ital Cardiol* 2010. 11: 148-153.
34. **Donfrancesco C**, Palmieri L, Cooney M-T, Vanuzzo D, Panico S, Cesana G, Ferrario M, Pilotto L, Graham I M, and Giampaoli

- S. Italian cardiovascular mortality charts of the CUORE Project: are they comparable with the SCORE charts? *Eur J Cardiovasc Prev Rehabil.* 2010 Mar 25.
35. The EMERGING RISK FACTORS COLLABORATION. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *The Lancet*, Volume 375, Issue 9709, Pages 132 - 140, 9 January 2010.
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- epidemiologic study. Preventive Medicine, June 2009. 48(6):525-31.
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 42. Panico S, Palmieri L, **Donfrancesco C**, Vanuzzo D, Chiodini P, Cesana G, Ferrario M, Mattiello A, Pilotto L, Segà R, Giampaoli S, Stamler J. Preventive potential of body mass reduction to lower cardiovascular risk: the Italian Progetto CUORE Study. Preventive Medicine 2008. 47: 53-60.
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