Original articles
First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study

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Coronary heart disease; Epidemiology; Risk factors; Prediction.

Background. **The Gubbio study is an Italian population study which measures the risk factors and incidence of major cardiovascular diseases. This analysis produces multivariate models for the prediction of cardiovascular end-points.**

Methods. **A population sample of 2963 men and women aged 35-74, free from major cardiovascular diseases, was examined in 1983 with risk factor measurement, and a 6-year incidence was computed for coronary heart disease and all cardiovascular (atherosclerotic) events. Proportional hazards models were solved for the prediction of these events.**

Results. **Over a 6-year period, 74 hard criteria, and 126 any criterion coronary heart disease and 174 cardiovascular events were recorded. Multivariate models showed the predictive power of sex (relative risk ranging 1.63 to 2.60), age (relative risk for 5-year difference ranging 1.38 to 1.48), systolic blood pressure (relative risk for 20 mmHg difference ranging 1.17 to 1.27), HDL cholesterol (relative risk for a difference of 10 mg/dl ranging 0.73 to 0.81), non-HDL cholesterol (relative risk for 40 mg/dl difference ranging 1.15 to 1.27), cigarette smoking (relative risk for 10 cigarette difference ranging 1.21 to 1.28), and body mass index (relative risk for 3 units ranging 0.99 to 1.02). All coefficients were statistically significant except that for body mass index, they were larger for hard criteria coronary heart disease, and their magnitude was similar to that found in previous Italian population studies.**

Conclusions. **Traditional cardiovascular risk factors predict coronary and cardiovascular events in another Italian population study confirming previous findings and similar predictive models.**

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Introduction

The medical profession has recently shown a mounting interest in the prediction of cardiovascular diseases exploiting risk functions derived from population studies in view of the present possibility of starting preventive action. Risk charts for the prediction of coronary heart disease (CHD) events have been proposed within guidelines but most of them derive from studies conducted in the United States or elsewhere in Europe[1,2]. On the other hand, evidence has shown that risk prediction is accurate only if risk functions derive from the community where one is operating[3].

Italian risk functions for cardiovascular diseases were mainly produced using data from the Seven Countries Study[4-6], and marginally from a few other studies[7-10]. The availability of new risk functions based on more recent data are likely to be useful in order to confirm previous information and to widen the population basis to produce risk charts or other tools for prediction.

The Gubbio Population Study is a prospective epidemiologic investigation which started in 1983[11]. The main aim of the study was to investigate, in a population setting, the mean values and distribution of sodium-lithium countertransport and its relationship with blood pressure levels, hypertension, other personal characteristics and the development of hypertension during several years of follow-up. Major findings on this specific aim have been reported elsewhere[12-16]. At the same time a monitoring system to identify new fatal and non-fatal cardiovascular events

has been set up and a follow-up examination was carried out on survivors about 6 years after the first one.

The aim of this report was to produce new Italian risk models for the prediction of coronary and more generally cardiovascular disease incidence in a free-living population setting as a function of traditional risk factors.

Methods

Gubbio is a small town located in central Italy. All subjects living or working within the medieval walls and their closer relatives living outside, aged 5 or older, were invited to participate in the baseline examination. A total of 5831 subjects were invited and 5376 participated in the entry examination held between 1983 and 1985, with a participation rate of 92.2%. A second examination started about 6 years later and was carried out between 1988 and 1992 on survivors. Oral consent was obtained from the participants in compliance with the Helsinki declaration.

On both occasions detailed questionnaires on general individual characteristics, lifestyle, and medical history were administered; anthropometric, biochemical, biophysical, and medical measurements were taken.

For the purpose of this analysis a few risk factors measured at entry examination were considered as possible predictors of cardiovascular events. They were:

• sex (coded as 0 and 1 for female and male, respectively);

• age in years; for the purpose of this analysis only subjects aged 35 to 74 years were considered;

• systolic blood pressure in mmHg, measured by trained personnel, in a sitting position after 5 min rest, on the right arm, by mercury sphygmomanometer, with the use of appropriate sized cuffs; three measurements were taken following the procedure described by the WHO Cardiovascular Survey Methods[17] (from now on called WHO Manual) and the average of the second and third measurement was used for analysis; the fifth phase of the Korotkoff sounds was recorded as diastolic blood pressure but not used for this analysis;

• smoking habits were elicited from a standard questionnaire and the average number of cigarettes currently smoked per day was recorded;

• serum total cholesterol was measured using an enzymatic method as well as HDL cholesterol[18,19]; the laboratory involved in these analyses was under quality control of the WHO Lipid Reference Center of Prague (Czech Republic); for the purpose of this analysis we used HDL cholesterol and non-HDL cholesterol, the latter obtained by simple difference from total minus HDL cholesterol, as an approximation of LDL cholesterol;

• body mass index (weight in kg/height in m^2) was derived from the measurement of height and weight according to the procedures suggested by the WHO Manual[17].

The end-point for predictive analysis was made up of the fatal and non-fatal cardiovascular events which occurred during the first 6 years of follow-up.

Mortality data were obtained from the local registry office and coded by an independent reviewer using the 9th Revision of the WHO-ICD[20]. Before coding, data were reviewed for completeness and consistency. In the case of death due to multiple causes a hierarchical system was adopted giving preference to violent causes, cancer in advanced stages, CHD, stroke, and other causes.

Information on non-fatal events was elicited from several sources, i.e.:

• the London School of Hygiene standard questionnaires on angina pectoris, myocardial infarction (with additional questions) and intermittent claudication[17], administered during the second examination;

• history of hospitalization and review of diagnoses for coherence with the reported data;

• an ECG at rest taken during the second examination and read by the Minnesota Code, 1968 edition[17];

• telephone questionnaire for those who did not attend the second examination and subsequent check of hospital records, if necessary.

The available information was used to apply the following criteria for cardiovascular diseases of probable arteriosclerotic origin:

1. CHD, subdivided into the following manifestations:

1.1. CHD deaths. They included any fatal event classified as code 410-414 or code 428.0-1 according to the WHO-ICD-9;

1.2. definite myocardial infarction. This was diagnosed on the basis of a hospital discharge diagnosis of myocardial infarction or documented by typical symptoms, enzyme elevation and ECG changes; or by definite ECG abnormalities found at the second examination (large Q waves, Minnesota Code 1.1; or intermediate Q waves plus negative T waves, Minnesota Code 1.2 plus 5.1 or 5.2; or by the combination of definite symptoms accompanied by any Minnesota Code 1.2, 1.3, 5.1, 5.2, 6.1, 6.2, 7.1, 7.2, 7.4, 8.3);

1.3. possible myocardial infarction. This was diagnosed on the basis of symptoms not confirmed by hospital discharge diagnosis; or isolated findings of ECG abnormalities of intermediate Q waves alone (Minnesota Code 1.2); or lesser Q waves plus negative T waves (Minnesota Code 1.3 + 5.1 or 5.2);

1.4. angina pectoris. This was defined by the London School of Hygiene questionnaire and rules or by a documented hospital discharge diagnosis of angina pectoris; the latter also included cases of unstable angina;

1.5. chronic heart disease of possible coronary origin (atypical CHD). This was diagnosed in cases with signs and symptoms plus hospital admission for heart failure or major chronic arrhythmia not attributable to any specific cause, such as atrial fibrillation or third degree heart block; or in cases where an artificial pacemaker had been implanted;

1.6. coronary bypass surgery. This was recorded as doc-

umented by hospital discharge diagnosis;
1.7. coronary angioplasty. This was recorded as documented by hospital discharge diagnosis;
2. cerebrovascular disease, subdivided into the following manifestations:
2.1. cerebrovascular deaths. This included any fatal event coded as 430-438 according to the WHO-ICD-9;
2.2. definite non-fatal stroke. This was defined by a history and hospital discharge diagnosis of paralysis, paresis, hemiparesis, aphasia or other serious disturbances of the central nervous system, attributed to circulatory problems and which lasted more than 24 hours; segregation of hemorrhagic from thrombotic strokes was almost always impossible;
2.3. transient ischemic attack. This was diagnosed on the basis of the same signs, symptoms and history as stroke, but with a duration shorter than 24 hours; it also included cases where the diagnosis of stroke was uncertain;
2.4. any documented surgical procedure on carotid arteries;
3. peripheral arterial disease, subdivided into the following manifestations:
3.1. intermittent claudication. The diagnosis was based on the London School of Hygiene questionnaire and criteria; or a documented hospital discharge diagnosis of peripheral arterial disease;
3.2. aortic aneurysm. The diagnosis was based on a documented hospital discharge diagnosis of aortic aneurysm;
3.3. arterial surgical procedures. They comprised any surgical procedure on the aorta, subclavian arteries, iliac and leg arteries, including bypass, prosthetic substitution or amputation of lower extremities.

Three groups of incidence cases were considered for this analysis:
A. CHD-hard criteria (CHD-H), including only manifestations (1.1) or (1.2);
B. CHD-any criterion (CHD-A) including any manifestation from (1.1) through (1.7);
C. cardiovascular diseases-all criteria, including any manifestation from (1.1) through (3.3).

A few subjects who presented with any of the above conditions at baseline were excluded from the analysis.

Cox proportional hazards models were run for each end-point for a follow-up of 6 years. Covariates were sex, age, systolic blood pressure, HDL cholesterol, non-HDL cholesterol, cigarette smoking, and body mass index.

Results

Altogether 2963 individuals of both sexes and aged 35-74 years were available for analysis (1333 males, and 1630 females). Baseline risk factor levels are reported in table I and reflect the average level rather common in Italy in the 1980's.

Table II reports the distribution of disease manifestations classified as first events for each of the three groups considered in the analysis, i.e. CHD-H, CHD-A and cardiovascular diseases. Within each group the first manifestation which occurred at follow-up was selected to identify the distance between risk factor measurements and the disease. Among first CHD-H there was an almost even share of fatal and non-fatal events. Among first CHD-A a large contribution was also given by cases of angina pectoris. Among first cardiovascular diseases, CHD contributed 70% of total events, cerebrovascular diseases 23%, and peripheral artery diseases 7%.

Table III reports proportional hazards solutions, for each end-point, together with relative risks, expressed as hazard ratios, as a function of arbitrarily chosen differences in risk factor levels. The chosen differences roughly correspond to one standard deviation for each variable. Solutions have been tested for proportionality that represents a condition for a legitimate use of the Cox proportional hazards model. No significant deviation from proportionality assumptions was identified for the risk factors tested in this way.

Table I. Mean levels of cardiovascular risk factors used for the analysis.

Risk factor	Males	Females
Age (years)	53.66 ± 11.15	54.73 ± 10.96
Systolic blood pressure (mmHg)	135.52 ± 21.32	138.95 ± 24.01
HDL cholesterol (mg/dl)	43.41 ± 11.23	50.64 ± 12.16
Non-HDL cholesterol (mg/dl)	176.08 ± 42.70	170.71 ± 42.40
Cigarettes (n/day)	7.7 ± 10.9	2.46 ± 5.63
Body mass index (kg/m^2)	27.15 ± 3.61	27.50 ± 4.66

Data are expressed as mean ± SD.

Table II. Diagnostic composition of numerators of the predictive functions. Subjects with more than one event during the follow-up period are allocated to the first one occurring in time.

First clinical manifestation	CHD hard events	CHD all events	CVD all events
Non-fatal angina pectoris	–	23	23
Non-fatal possible myocardial infarction	–	15	15
Non-fatal definite myocardial infarction	33	33	31
Non-fatal atypical CHD	–	11	11
Surgical procedures for CHD	–	2	2
Fatal myocardial infarction	33	33	32
Fatal atypical CHD	8	9	8
Non-fatal TIA	–	–	16
Non-fatal stroke	–	–	11
Fatal stroke	–	–	13
Non-fatal peripheral arterial disease	–	–	12

CHD = coronary heart disease; CVD = cardiovascular disease; TIA = transient ischemic attack.

Table III. Solutions of the proportional hazards models for the prediction of CHD-hard criteria, CHD-any criterion, and all CVD events, as a function of seven risk factors.

End-points and risk factors	Coefficient	T test	Delta for estimating hazard ratios	Hazard ratios and 95% CI
CHD-hard criteria (n=74, 52M/22F)				
Sex	0.9539	3.48	Male/female	2.60 (1.52-4.44)
Age	0.0797	5.66	5 years	1.48 (1.30-1.71)
Systolic blood pressure	0.0123	2.37	20 mmHg	1.27 (1.04-1.57)
HDL cholesterol	-0.0316	-2.60	10 mg/dl	0.73 (0.57-0.92)
Non-HDL cholesterol	0.0060	2.53	40 mg/dl	1.27 (1.05-1.53)
Cigarettes	0.0249	2.45	10 cigarettes/day	1.28 (1.05-1.56)
Body mass index	-0.0046	-0.15	3 units	0.99 (0.82-1.18)
CHD-any criterion (n=126, 75M/51F)				
Sex	0.5028	2.54	Male/female	1.65 (1.12-2.44)
Age	0.0646	6.22	5 years	1.38 (1.25-1.53)
Systolic blood pressure	0.0081	1.99	20 mmHg	1.18 (1.00-1.38)
HDL cholesterol	-0.0237	-2.67	10 mg/dl	0.79 (0.66-0.94)
Non-HDL cholesterol	0.0035	1.73	40 mg/dl	1.15 (0.98-1.35)
Cigarettes	0.0189	2.09	10 cigarettes/day	1.21 (1.01-1.44)
Body mass index	0.0075	0.33	3 units	1.02 (0.89-1.17)
CVD-all criteria (n=174, 102M/72F)				
Sex	0.4868	2.90	Male/female	1.63 (1.17-2.26)
Age	0.0651	7.37	5 years	1.38 (1.27-1.51)
Systolic blood pressure	0.0079	2.26	20 mmHg	1.17 (1.02-1.34)
HDL cholesterol	-0.0213	-2.85	10 mg/dl	0.81 (0.70-0.94)
Non-HDL cholesterol	0.0043	2.55	40 mg/dl	1.19 (1.04-1.36)
Cigarettes	0.0203	2.68	10 cigarettes/day	1.22 (1.06-1.42)
Body mass index	0.0042	0.22	3 units	1.01 (0.90-1.13)

CI = confidence interval. Other abbreviations as in table II.

The coefficient for sex, transformed into exponential, suggested the relative risk for men compared to women. This approach was legitimate since no significant interaction terms were found between sex and each risk factor. For CHD-H, the ratio male/female was about 2.60, but it became definitely smaller when considering CHD-A and all cardiovascular events. All factors were highly predictive of new CHD-H except body mass index that produced a negative non-significant coefficient. The protective role of HDL cholesterol was suggested by the negative sign of the coefficient and its statistical significance.

The solution for CHD-A showed a similar picture but the discriminating power of each coefficient was less strong, with non-HDL cholesterol slightly below the statistical critical threshold. The model for cardiovascular diseases showed, again, strong associations between risk factor levels and the occurrence of the first event, and all coefficients were statistically significant except that of body mass index.

The hazard ratios provided a practical guide in interpreting the role of differences in risk factor levels in relation to risk for the specified events. Relatively small differences in risk factor levels were associated with relatively large differences in incidence risk. By multiplying hazard ratios of different risk factors an approximated estimate can be obtained of the combined effect for the specified differences. For example the effects of a 20 mmHg difference in systolic blood pressure and that of 40 mg/dl of non-HDL cholesterol is roughly given by 1.17 * 1.19 = 1.39, representing a 39% excess risk for a first cardiovascular event in the next 6 years.

Discussion

These preliminary risk functions derived from the Gubbio study suggest the important predictive role of some risk factors already seen in other populations, both Italian and international. Age, sex, blood pressure, HDL and non-HDL cholesterol, and cigarette smoking, all are strong predictors of CHD or cardiovascular events. The uncertainties of the predictive role of body mass index reported by other studies were also confirmed[21].

As expected slightly smaller coefficients, compared to those for CHD events, were found in the prediction of all cardiovascular events. They included also minor or less specific conditions, but their statistical significance was as strong as for CHD-H events thanks to the

greater numerator involved. The group of cardiovascular events included also stroke whose number was too small to produce independent models.

Risk functions for the prediction of CHD or cardiovascular events have been produced by many studies. A summary of data from some major international studies appeared a few years ago[21]. All of them have confirmed the universal short- and long-term predictive role of personal characteristics known as coronary or cardiovascular risk factors, although direct comparisons are usually difficult.

A systematic review of the risk functions for CHD computed by many different investigations using the multiple logistic function, reached the conclusion that the magnitude of coefficients is rather similar across the studies[22]. Similar findings were reported by a direct comparison of the cohort known as MRFIT primary screenees and the Italian RIFLE Pooling Project[10] where the end-point was made by CHD deaths over a 6-year period. Again, almost equal coefficients for risk factors predicting CHD deaths were found by an analysis of the Seven Countries Study during a 25-year follow-up in 8 nations. No heterogeneity was found comparing coefficients for five factors in cultures largely different in cardiovascular risk factor levels and CHD death rates[22]. Another indication about the similarity in the predictive power of traditional risk factors has recently been provided by a literature review made within the MONICA Project[24]. All this suggests that, at an international level, the strength of the relative risk of major risk factors is similar among populations, whereas the absolute risk can be largely different due to other unmeasured or unknown factors.

Population studies producing coronary risk functions in Italy are few[3-10] and only three before the Gubbio study dealt with incidence, i.e. a combination of fatal and non-fatal events[3-8]. In those studies the same factors tested here were predictive of CHD incidence, CHD mortality and cardiovascular mortality. Among the many risk functions for CHD that were produced by the Italian section of the Seven Countries Study, some can tentatively be compared with those presented here, although in the Seven Countries Study they did not include women, and HDL cholesterol was not available. For example a 10-year solution for major CHD events in the Seven Countries Study solved by the Cox model[5] could be compared with the present Gubbio solution for the same end-point. No statistically significant differences were found comparing coefficients for age, cigarette smoking, systolic blood pressure and body mass index, nor was any difference found when comparing the coefficient for non-HDL cholesterol in the Gubbio study with that for total cholesterol in the Seven Countries data. The impression is that the magnitude of the coefficient for non-HDL cholesterol is similar to the one for total cholesterol and that HDL cholesterol simply adds an extra contribution to predictivity, as in another Italian study[9].

In conclusion, this analysis on the Gubbio data shows that another Italian population group exhibits the same relationship of risk factors to CHD or cardiovascular events. The interest of the Gubbio study is bound to the fact that it is the most recent available in the country and that it is one of the few providing information on both fatal and non-fatal events, in both sexes. This background, dealing with the predictive role of the "classical" risk factors in another population study, poses the basis for testing other risk factors, not available in previous studies, but available in the Gubbio study, whose analysis is in due course.

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