



Competing risks and lifetime coronary heart disease incidence during 50 years of follow-up



Paolo Emilio Puddu^{a,*}, Paolo Piras^a, Alessandro Menotti^b

^a Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, Sapienza University of Rome, Rome, Italy

^b Association for Cardiac Research, Rome, Italy

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ABSTRACT

Objectives: To study coronary heart disease (CHD) incidence versus other cause of death using the cumulative incidence function and the competing risks procedures to disentangle the differential role of risk factors for different end-points.

Material and methods: We compared standard Cox and Fine-Gray models among 1677 middle aged men of an Italian population study of cardiovascular diseases that reached 50 years of follow-up with the quasi extinction of the population. The incidence of either fatal or non-fatal cases in 50 years was used as primary event, while deaths from any other cause, mutually exclusive from the primary events, were considered as secondary events. We considered 10 selected risk factors.

Results: The main result was that cholesterol was significantly and positively related to incidence of CHD contrasted with deaths from any other cause. On the other hand, when the primary events were deaths from any other cause and the competing events were CHD, cholesterol was inversely and age positively related. This outcome did not exclude the predictive role of other risk factors, such as age, cigarettes, arm circumference (protective), systolic blood pressure, vital capacity (protective), cholesterol, corneal arcus and diabetes, documented by the Cox model, that had common roles for both end-points.

Conclusions: Fine-Gray model, initially proposed to handle adequately cumulative incidence function may thus prevent overestimation of risks related to the Kaplan–Meier based methods such as Cox model and identify the specific risk factors for defined end-points.

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1. Introduction

Some population studies of long duration, started in the last century, have reached the stage of extinction or quasi-extinction of the populations themselves. This allows, under some circumstances, to estimate morbid events during lifetime [1–7]. The evaluation of rates, risk and predictors (determinants, risk factors) in this situation may produce difficulties in handling and interpretation of data and findings. In fact, it is well known that the simple Kaplan–Meier survival curves are distorting reality since they tend to overestimate the risk and reduce survival mainly when the follow-up is very long. Intriguing interpretations may arise from these findings when dealing with standard multivariable predictive models as they do not take into account the role of the so-called competing risks, that is the effect of morbid and/or fatal conditions that are alternative (and in competition) with the basic studied condition [8–11].

* Corresponding author at: Laboratory of Biotechnologies Applied to Cardiovascular Medicine, Department of Cardiovascular, Respiratory, Nephrological, Anesthesiological and Geriatric Sciences, Sapienza University of Rome, Viale del Policlinico, 155, Roma 00161, Italy.

E-mail address: paoloemilio.puddu@uniroma1.it (P.E. Puddu).

Although special procedures were proposed to estimate survival correctly and to make prediction by appropriate models [9,10], these were rarely applied since investigations that reached the extinction or the quasi-extinction of the study populations are rare. We thus attempted to use these novel approaches in an Italian population study of cardiovascular diseases that reached 50 years of follow-up with the quasi extinction of the population. The incidence of coronary heart disease (CHD) was used as primary event, while deaths from any other cause, mutually exclusive from the primary events, were considered as secondary events.

2. Material and methods

The two Italian Rural Areas (IRA) of the Seven Countries Study (SCS) of Cardiovascular Diseases were considered for this analysis. They were enrolled and first examined in 1960 and made by a total of 1712 men aged 40–59 representing 98.5% of defined samples [7].

2.1. Risk factors

A selected group of risk factors were considered as follows: a) age (years) approximated to the nearest birthday; b) cigarette smoking

(n/day) derived from a standard questionnaire; c) body mass index (units) computed from height and weight, measured following the technique described in the World Health Organization (WHO) Cardiovascular Survey Methods Manual [12] (WHO Manual); d) arm circumference (mm) measured at right arm following the technique described in the WHO Manual [12] and mathematically cleaned from the bicipital skinfold thickness; e) systolic blood pressure (mm Hg) measured at right arm, in supine position following the technique described in the WHO Manual [12] using the average of two measurements; f) heart rate (beats/min) derived from a resting ECG tracing; g) vital capacity (l/m^2) following the technique described in the WHO Manual [12] and using the best of three attempts; h) serum cholesterol (mmol/L) measured on casual blood sample following the technique of Anderson and Keys [13]; i) corneal arcus (present-absent) as judged by a physician; l) diabetes (present-absent) derived from history, possible specific treatment and urine glucose measurement.

2.2. End-points

Incidence of CHD in 50 years of follow-up was considered the primary end-point and was measured exploiting all possible information collected at baseline, at periodical re-examinations, at special search at hospitals, clinics and general practitioners, interviews with relatives and data from causes of death as described in detail elsewhere [14,15]. Diagnoses were based on history, physical examination, ECG tracings, occasionally reported diagnoses, and causes of death. CHD were cases manifested as sudden death (when other causes could be reasonably excluded), fatal and non-fatal myocardial infarction, and other fatal and non-fatal acute ischemic syndromes. Heart disease manifested only as heart failure, severe chronic arrhythmia, heart blocks, documented diagnoses of hypertensive heart disease or “chronic CHD” were not classified as CHD for reasons given elsewhere [14,15]. In previous analyses these cases were classified as Atypical CHD or Heart Disease of Uncertain Etiology since they had not relationship with serum cholesterol. In the present analyses these cases are incorporated into the group of death from other causes or of survivors.

Incidence cases were associated with a date corresponding to the first event occurred in 50 years. There were 35 cases of definite or possible CHD cases at entry examination and these prevalent cases were excluded from analysis.

Cases of death from any other cause in 50 years among those who remained free from CHD were considered as secondary (competing) end-point (OTHER DEATHS). Collection of mortality data along 50 years was complete and, beyond the availability of death certificates, it was largely based on a procedure that anticipated in principle and content of the so-called WHO Verbal Autopsy [16]. Causes of death, accompanied by the respective date, were coded by the WHO ICD-8 [17] and based on defined criteria.

Baseline data were collected before the era of the Helsinki declaration. Subsequently verbal consent was obtained in view of collecting and using follow-up information.

2.3. Statistical analysis

The denominator was of 1677 units. Each individual could suffer none, one or more CHD events but only the first event (either fatal or non-fatal) with its date of occurrence was used for analysis. Kaplan–Meier survival curves related to CHD or death from any other cause were computed. Mean values of risk factors at entry examination were computed. Cox proportional hazards models were solved with 50-year CHD incidence as end-points and the risk factors measured at entry as predictors. In this case those surviving or dying from other cause in 50 years were considered a censored. Another Cox model was solved using as end-point the combination of CHD event and OTHER DEATHS.

Similar models were solved for OTHER DEATHS playing the role of competing risks versus CHD incidence in 50 years, and vice-versa by

using Fine–Gray model elaborated for proportional hazards with the subdistribution of a competing risk [9] using the R package as described by Gray [10]. Therefore CHD events and OTHER DEATHS were alternatively the principal event and the competing event. Another end-point was made by the combination of CHD events plus OTHER DEATHS and was called Combined Events (COMB).

3. Results

In 50 years, among the 1677 men CHD-free at entry examination, there were 451 CHD events, 1190 OTHER DEATHS and 36 survivors.

The average values of all 10 covariates measured at baseline among the 1677 men are illustrated in Table 1 according to the distribution in Survivors, CHD events and OTHER DEATHS. There were some differences among the 3 groups. Significantly different levels were found for 7 risk factors comparing Survivors with CHD incidence; for 5 risk factors comparing Survivors with OTHER DEATHS; and for 4 risk factors comparing CHD incidence with OTHER DEATHS.

Fig. 1 illustrates the Kaplan–Meier survival curves of CHD incident cases and OTHER DEATHS during 50 years of follow-up. The survival for both end-points was very small confirming that the Kaplan–Meier approach tends to overestimate the risk.

Table 2 shows the solutions of Cox and Fine–Gray models. In the first Cox model, risk factors significantly predicting events were age, serum cholesterol, cigarette smoking, corneal arcus, and systolic blood pressure, while vital capacity was not far from significant levels confirming notions already documented elsewhere. In the Cox model with combined events (COMB) as end-point 8 of 10 covariates were significantly related to the end-point: age, cigarettes, arm circumference (protective), systolic blood pressure, vital capacity (protective), cholesterol, corneal arcus and diabetes.

The Fine–Gray models were characterized by a single end-point, i.e. COMB including 2 types of events (CHD and OTHER DEATHS), treated alternatively as principal or competing event. Therefore, the solutions were different depending on whether CHD was the primary or competing event. Serum cholesterol was the only risk factor significantly and positively related to CHD as primary event, when OTHER DEATHS

Table 1

Mean covariates values for the categories described in the text.

Panel A	Survivors		CHD incidence		OTHER DEATHS	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	42.92	2.45	48.77	4.98	49.33	5.06
Cigarettes (n/day)	4.53	7.93	9.08	9.49	8.79	9.56
Body Mass Index (units)	24.76	2.61	25.66	.63	25.05	3.72
Arm circumference (mm)	274.2	19.24	270.83	22.73	267.68	23.86
Systolic blood pressure (mm Hg)	130.22	11.52	143.63	20.00	143.19	20.48
Heart rate (beats/min)	66.47	9.05	71.22	12.73	71.28	12.84
Vital capacity (l/m^2)	1.81	0.18	1.65	0.25	1.64	0.24
Cholesterol (mmol/l)	4.87	0.94	5.37	1.07	5.16	1.04
Corneal arcus (%)	0.028	0.167	0.149	0.356	0.136	0.343
Diabetes (%)	0	–	0.049	0.216	0.047	0.212

Panel B	Survivors versus CHD	Survivors versus OTHER DEATHS	CHD versus OTHER DEATHS
	p	p	p
Age (years)	0.0001	<0.0001	0.0402
Cigarettes (n/day)	0.0053	0.0083	0.5826
Body Mass Index (units)	0.1457	0.6426	0.0029
Arm circumference (mm)	0.3875	0.1048	0.0158
Systolic blood pressure (mm Hg)	0.0001	0.0002	0.6958
Heart rate (beats/min)	0.0287	0.0259	0.9325
Vital capacity (l/m^2)	0.0002	<0.0001	0.4585
Cholesterol (mmol/l)	0.0068	0.0987	0.0003
Corneal arcus (%)	0.0446	0.0756	0.3347
Diabetes (%)	0.4070	0.3014	0.8785

SD: standard deviation.

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