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Lifetime competing risks between coronary heart disease mortality and other causes of death during 50 years of follow-up

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ABSTRACT

Objectives: To study coronary heart disease (CHD) death versus 11 other causes of death using the cumulative incidence function (CIF) and the competing risks procedures to disentangle the differential role of risk factors for different end-points.
Material and methods: Standard Cox and Fine-Gray models among 1712 middle-aged men were compared during 50 years of follow-up. CHD death was the primary event, while deaths from 11 selected causes, mutually exclusive from the primary end-point, were considered as secondary events. Reverse solutions were also performed. We considered 10 selected risk factors.
Results: CHD death risk was the second highest among 12 mostly specific causes of death. Some risk factors were specific: serum cholesterol for CHD death whereas, systolic blood pressure, cigarette smoking and age may have a differential role in other causes of death. Application of the Fine-Gray model based on CIF enabled to dissect, at least in part, the respective role that baseline covariates may have to segregate the probabilities of two types of death in contrast from each other. They also point to the absence of contributing significance for some of the selected risk factors and this calls for a parsimonious approach in predictions.
Conclusions: The relative rarity of competing risk challenges when defining the risk factors role at long-term needs now be corrected since we have clearly shown, with Fine-Gray model, at direct or reverse use, that comparing different end-points heavily influences the risk factor predictive capacity.

1. Introduction

The concept of competing risk derives from the possibility that a morbid or fatal event may enter in competition, and therefore being influenced in its appearance, with other events, as a consequence of chance or delay due to prevention or sharing common risk factors. The competition may avoid or delay the principal event under consideration [1]. The evaluation of mortality rates, risk and predictors (determinants, risk factors) in this situation may produce difficulties in handling and interpretation of data and findings [2]. Analytical procedures, such as the Kaplan–Meier survival curves and predictive models derived from the similar principles like the Cox model may distort reality since they tend to overestimate the risk and reduce survival estimates [3,4]. This is probably more common when the follow-up is very long and interpretations of findings may prove complex and uncertain when dealing with traditional multivariable predictive models as they do not take into account the role of these competing risks and the effects of morbid and/or fatal conditions that are alternative (and thus in competition) with the basic studied condition [3,4]. A procedure called "cumulative incidence" has been proposed to overcome the excess estimates of survival that Kaplan–Meier and derived modeling entail [2,5–7]. Then, a variant of the Cox proportional hazards model that integrates the cumulative incidence function, known as Fine-Gray model, represents a tool that determines a sub-distribution in a correct way of the role of risk factors, thus taking into account the competition between pairs of events [5,6].

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 to estimate fatal events during lifetime [4,8–17]. Despite the availability of the special procedures mentioned above [6,7], these were rarely applied since investigations that reached the extinction or the quasi-extinction of the study populations are rare. Even for studies of shorter duration the use of those statistical approaches appears in very few contributions to the literature [3,4,18,19].

In an Italian population study of cardiovascular diseases that reached 50 years of follow-up with the quasi-extinction of the population we attempted to use the cumulative incidence function and the Fine-Gray variant of the Cox model. Going ahead a previous approach where

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incidence of both fatal and non-fatal coronary heart disease (CHD) events versus all other causes of death was studied [4], the possible competition of mortality from CHD was selected here as primary event, while deaths from any other cause, mutually exclusive from the primary events, and taken altogether or subdivided into 11 other groups, were considered as secondary events. The reverse condition was also investigated and the common Cox model results were provided for comparative and discussing purposes, adapted in a way that CHD were coded 1 and all individual causes were coded 0 whereas the few survivors were excluded.

2. Material and methods

Data of the Italian Rural Areas (IRA) of the Seven Countries Study (SCS) of Cardiovascular Diseases were used 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 [14]. Prevalent cases of CHD were kept in.

2.1. Risk factors

A few, basically cardiovascular, risk factors were considered for the analysis: 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 [20] (WHO Manual); d) arm circumference (mm) measured at right arm following the technique described in the WHO Manual [20] and mathematically cleaned from the contribution of bicipital skinfold thickness; e) systolic blood pressure (mm Hg) measured at right arm, in supine position following the technique described in the WHO Manual [20] 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 [20] and using the best of 3 attempts; h) serum cholesterol (mmol/l) measured on casual blood sample following the technique of Anderson and Keys [21]; i) corneal arcus (present-absent) as judged by a physician; j) diabetes (present-absent) derived from history, possible specific treatment and urine glucose measurement.

2.2. End-points

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 [22], 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 [15,16]. Causes of death, accompanied by the respective date, were coded by the WHO ICD-8 [23] and based on defined criteria.

Primary cause of death was arbitrarily subdivided into 12 groups that reflected some etiological aspects and convenience: CHD = coronary heart disease; HDUE = heart disease of uncertain etiology; STR = stroke; PAD = peripheral artery disease; OCV = other cardiovascular diseases; LUCA = lung cancer; OCA = other cancers; CB = chronic bronchitis; INF = infectious diseases; VIOL = violence; UNK = cause unknown; OTH = all other causes.

CHD were cases manifested as sudden death (when other causes could be reasonably excluded), fatal myocardial infarction, and other fatal acute ischemic syndromes. Fatal 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 [15,16] and they received the label of Heart Disease of Uncertain Etiology (HDUE). However, if these cases were accompanied by documented angina pectoris they were classified as CHD deaths [15,16]. Mortality from CHD in 50 years of follow-up was considered as primary end-point for the standard comparisons.

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 1712 units. Mean values of risk factors at entry examination were computed and the same risk factors were fed into the various predictive models. We used the Cox proportional hazards model, as reference, CHD deaths as primary events and the sum of All other causes of death as competing risks. The computations were performed, alternatively, as either considering All other causes of death with CHD deaths (coding them 1) or with Survivors (coding them 0). Then, Fine-Gray model were computed [7] whereby either CHD were the primary event (and All other causes of deaths were the competing risks) or All other causes of deaths were the primary event (and CHD deaths were the competing risks). In these latter Fine-Gray models Survivors were censored.

Then, eleven Fine-Gray models for competing risks identification were solved [7] with CHD deaths as primary end-point and, one by one, each of the 11 other groups of causes of death as competing risks. Although this procedure someway distorts the population structure, it is the only possible one if coupled comparisons are aimed at. In all instances, the same risk factors were used, and groups of causes of death not considered in each case were excluded. Again, for comparative purposes the reverse condition was considered, whereby, using the Fine-Gray model, the primary event was represented by each of the other 11 causes of death and CHD deaths were the competing risk condition. Coefficients and hazard ratios (with 95% confidence intervals) were calculated and statistical significance was ascertained at $p < 0.05$.

3. Results

In 50 years out to the initial total of 1721 middle-aged men, 1669 died and 43 survived with an overall mortality of 98.5%, very close to

Table 1
Mean entry levels of covariates for the categories described in the text (*panel A*), and p of t test (*panel B*) comparing the various categories (test of proportions for corneal arcus and diabetes).

Panel A	Survivors ($N = 43$)		CHD deaths ($N = 318$)		All other causes of death ($N = 1351$)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	42.72	2.37	49.08	4.97	49.31	5.05
Cigarettes (*n*/day)	5.26	8.30	8.75	9.30	8.85	9.57
Body mass index (units)	24.98	2.53	25.74	3.79	25.08	3.70
Arm circumference (mm)	274.57	19.12	270.30	22.71	267.95	23.91
Systolic blood pressure (mm Hg)	130.35	11.56	146.21	21.85	143.46	20.81
Heart rate (beats/min)	67.49	11.04	70.87	12.62	71.53	12.98
Vital capacity (l/m^2)	1.80	0.17	1.64	0.26	1.64	0.24
Cholesterol (mmol/l)	4.95	0.98	5.38	1.09	5.18	1.04
Corneal arcus (%)	0.02	0.15	0.14	0.35	0.14	0.35
Diabetes (%)	0	0	0.05	0.23	0.05	0.21

Panel B	Survivors versus CHD deaths	Survivors versus All other causes of death	CHD deaths versus All other causes of death
	p	*p*	*p*
Age (years)	**0.00**	**0.00**	0.45
Cigarettes (*n*/day)	**0.02**	**0.01**	0.86
Body mass index (units)	0.21	0.86	**0.00**
Arm circumference (mm)	0.24	**0.07**	0.11
Systolic blood pressure (mm Hg)	**0.00**	**0.00**	**0.04**
Heart rate (beats/min)	0.10	**0.04**	0.41
Vital capacity (l/m^2)	**0.00**	**0.00**	0.60
Cholesterol (mmol/l)	**0.01**	0.16	**0.00**
Corneal arcus (%)	**0.03**	**0.03**	0.88
Diabetes (%)	0.12	0.14	0.65

SD: standard deviation. Significant results are in bold.