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Lifetime prediction of coronary heart disease and heart disease of uncertain etiology in a 50-year follow-up population study

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ABSTRACT

Objectives: The relationships of four basic risk factors with 50-year incidence of coronary heart disease (CHD) and Heart Disease of Uncertain Etiology (HDUE) were investigated in a population study.
Material and methods: There were 1712 men aged 40–59 years in 1960 and 1677, heart disease free, were followed-up for 50 years. Incidence of first event for CHD (sudden death, fatal and non-fatal myocardial infarction, other fatal and non-fatal coronary syndromes) and HDUE (heart failure, chronic arrhythmia, blocks, "chronic CHD", hypertensive heart disease) was estimated and the relationships of four basic risk factors analyzed.
Results: In 50 years incidences of CHD and HDUE were respectively 26.9 and 20.6%. Cox proportional hazards models showed serum cholesterol as a strong CHD predictor (hazard ratio, HR, for 1 mmol/l difference 1.22 and confidence intervals, CI, 1.11 to 1.33), irrelevant for HDUE (HR 1.02 and CI 0.87 to 1.18). Age at entry was a stronger predictor for HDUE (HR for 5 year difference 1.65 and CI 1.46 to 1.86) than for CHD (HR 1.26 and CI 1.14 to 1.39). Systolic blood pressure and cigarette smoking had similar predictive power. The diagnosis of angina pectoris (AP) recorded at any time during the study was strongly associated with CHD but not with HDUE. A HDUE subgroup with AP had similar life-expectancy to CHD, suggesting the need to re-classify them as CHD.
Conclusions: Due to important differences in predictors (risk factors) and expectancy of life CHD and HDUE are probably manifestations of different etiologies.

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1. Introduction

In previous papers published between 1998 and 2013 [1–4], we showed that cases of coronary heart disease (CHD) defined as typical (sudden death, acute myocardial infarction and other acute coronary syndromes) had different relationships with preceding risk factors compared with cases defined as atypical CHD (heart failure, chronic arrhythmia, blocks, chronic CHD or hypertensive heart disease). In particular, the basic finding was that typical CHD were strongly predicted by serum cholesterol, which was not the case for atypical CHD where the association was null. On the other hand, age at entry was a stronger predictor for atypical CHD compared to typical CHD. The hypothesis was made that the two groups represent two different diseases.

The above findings concentrated on mortality data where a uniform coding system was adopted and, for most cases, one or more secondary causes were available. Similar results were found for different duration of follow-up, ranging from 20 to 40 years, and in different population settings of different Countries. Despite the uniformity of findings, residual doubts remained about the correct classification of causes of death in those two nosologic groups.

In the present analysis it was possible to tackle again the problem using a combination of fatal and non-fatal events in a single population during a very long follow-up of 50 years using incidence, instead of mortality, as end-point. To avoid confusion in terminology, here we adopt the terms of coronary heart disease (CHD) and Heart Disease of Uncertain Etiology (HDUE), instead of typical and atypical CHD as in previous papers [1–4]. These two groups are rather common and combined together and simply in terms of mortality they cover about 93% of all fatal heart disease in the 50-year follow-up of the study population.

The null hypothesis was that findings of previous analysis could not be replicated, that is no difference could be found between the two groups of incident heart diseases in the predicting power of basic risk factors.

2. Material and methods

2.1. Study population and data collection

The analysis was made on data of the Italian Rural Areas of the Seven Countries Study of Cardiovascular Diseases, enrolled in 1960 and made

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of 1712 men aged 40–59 years, representing 98.5% of defined samples [5–7].

Risk factors used of the analysis were measured at entry examination as follows: age in years, approximated to the nearest birthday; number of cigarettes smoked on average per day, recorded from a standard questionnaire (0 cigarettes for ex and never smokers); systolic blood pressure in mm Hg measured in supine position, at the end of a physical examination, using mercury sphygmomanometers and following the technique described in the WHO Cardiovascular Survey Methods manual [8]; serum cholesterol in mmol/L measured in casual blood samples following the technique from Anderson and Keys [9].

Disease occurrence was estimated from data obtained at baseline, at quinquennial re-examinations (until year 40 of follow-up, except for year 15), at periodic systematic search of possible new events from local hospitals, clinics and physicians (the first of these operations having substituted the 15-year survey), and causes of death, including secondary causes, up to year 50 of follow-up when the cohort was almost extinct (all-cause mortality: 97.5%). Causes of death were systematically collected and codes were based (beyond the information of the death certificate) for at least half of cases on a procedure that anticipated the structure and the concepts of the so-called WHO Verbal Autopsy [10]. Final cause of death was allocated by a single reviewer (AM) on the basis of defined criteria using the WHO-ICD-8 [11]. In the presence of multiple causes of death (available in about 50% of all cases) and of serious doubts about the final cause, a hierarchical rank was adopted with violence, cancer, coronary heart disease, stroke and other causes in sequence.

Exploiting history, physical examination, ECG tracings, causes of death and occasionally documented diagnoses, prevalence and incidence of heart disease were estimated and two heart disease groups were identified: A) CHD, including cases manifested as sudden coronary death (when other cases could be reasonably excluded), definite fatal and non-fatal myocardial infarction, fatal and non-fatal acute coronary syndromes; the latter arbitrary term includes cases when typical history was not accompanied by the occurrence of a Q wave and it corresponds to other common terms such as possible myocardial infarction, minor infarction, intermediate syndrome, acute ischemic attack and non-Q wave myocardial infarction used in successively historic time periods also depending on the state of the art knowledge, opinion leaders' preferences or simply different disciplines [8,12–14]. B) Heart disease of uncertain etiology (HDUE), including cases manifested as fatal and non-fatal heart failure, fatal and non-fatal severe arrhythmia (such as atrial fibrillation), severe heart blocks (possibly leading to the implant of a pace-maker), and documented or reported diagnoses of "chronic CHD" and hypertensive heart disease, all these in the absence of manifestations described in the CHD group. Subjects presenting both manifestations described for CHD and HDUE were arbitrarily classified as CHD. Thus the two groups were mutually exclusive.

In parallel, cases of angina pectoris (AP), diagnosed following the criteria of the Rose questionnaire [8], were independently recorded but initially its presence was not used for the classification of the two groups. Due to uncertainties in assigning the date of start of AP, the condition was considered as accompanying the either heart disease at any time (before, during or after the first recorded event).

There were incompleteness in collection of disease data. In particular: for about 5% of the exposure expressed by the amount of person/years observation the diagnosis of the first major event could rely only on causes of death while the diagnosis of AP could not be ascertained in about 15% of the time exposure, again expressed by person/years. Other rare cases of heart disease of defined etiology were not considered for analysis.

Baseline data were collected in the 1960s before the era of the Helsinki Declaration. Subsequently, oral informed consent was obtained in view of collecting follow-up data.

2.2. Data analysis

Cases of CHD and HDUE found at baseline (35 overall) were excluded from further analysis that focused on incidence. As a consequence the denominator changed from 1712 to 1677 units. Each individual could suffer none, one or more events but only the first event with its date of occurrence was used for analysis. Mean values of risk factors at entry examination were computed and compared between the two heart disease groups. Cox proportional hazards models were solved with 25- and 50-year CHD and HDUE incidences as end-points and the risk factors measured at entry as predictors. Similar models were solved for CHD and HDUE mortality in 50 years.

Due to reasons documented elsewhere [15] and quoted in the result section, the presence of AP was used for validating CHD cases and re-classifying part of HDUE cases. Therefore, other models were computed including also the presence of accompanying AP and then after having re-classified part of the HDUE cases. The association of AP with CHD and HDUE was investigated also computing logistic models. Comparisons of multivariate coefficients (for both Cox's and logistic regressions) of CHD versus HDUE models were made using a t test and standard level of significance.

3. Results

3.1. Initial findings

Among 1677 heart disease-free subjects, 451 (26.9%) developed a first CHD event and 346 (20.6%) a first HDUE event. The difference in incidence was largely significant ($p < 0.0001$).

Risk factor levels at entry examination for CHD and HDUE (Table 1) were not different between the two groups, except for serum cholesterol that was slightly but significantly higher among CHD future cases. Mean age at first event was largely and significantly greater for HDUE (74.3 ± 9.9 years) than for CHD (68.9 ± 11.2 years) ($p < 0.0001$) [15].

Cox proportional hazards models for incidence in 25 and 50 years of follow-up with four risk factors as possible predictors are reported in Table 2. The predictive power of age was significantly greater for HDUE events than for CHD events, although for both it was independently significant. The reverse was true for serum cholesterol that strongly predicted CHD events, while it was irrelevant for HDUE events. No differences were found between the two groups for the predictive power of systolic blood pressure and smoking habits.

A comparison of 25- versus 50-year incidence coefficients, within the single end-points, did not show any significant difference, suggesting that along the follow-up the predictive power of risk factors remained substantially stable.

In the same Table 2, models that are reported for CHD and HDUE deaths in 50 years, show the same picture as for incidence, except that the magnitude of the HRs was slightly greater.

The relationship of the four risk factors with CHD and HDUE events in 50 years is graphically displayed in Figs. 1 to 4 where the only great differences between the two end-points are those for age and especially for serum cholesterol.

Table 1
Mean levels of risk factors at entry examination in cases later becoming CHD and HDUE events.

Risk factors	CHD N = 451	HDUE N = 346	P
	Mean ± SD	Mean ± SD	
Age, years	48.8 (5.0)	49.1 (5.3)	0.4137
Cigarettes, N/day	9.1 (9.5)	8.3 (9.5)	0.2964
Systolic blood pressure, mm Hg	143.6 (20.0)	142.6 (21.4)	0.4976
Serum cholesterol, mmol/L	5.37 (1.1)	5.16 (1.0)	0.0058

Mean ± SD.

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