Natural history of coronary heart disease and heart disease of uncertain etiology: Findings from a 50-year population study

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ABSTRACT

Objectives: To describe the natural history of common heart disease incidence on a population study.
Material and methods: A sample of 1712 men aged 40–59 was enrolled in 1960 and followed-up for 50 years. Coronary heart disease (CHD) was categorized if manifested as sudden death, fatal and non-fatal myocardial infarction and other acute coronary syndromes, and as Heart Disease of Uncertain Etiology (HDUE) if manifested as heart failure, chronic arrhythmia, blocks, diagnoses of chronic CHD or hypertensive heart disease. Their characteristics and prognosis in terms of age at event, mortality and expectancy of life up to 50 years were analyzed.
Results: Incidence of first CHD and HDUE event or diagnosis was of 26.9 and 20.6%, respectively. First events were equally manifested as fatal or non-fatal occurrences among CHD, while non-fatal occurrences were almost always observed among HDUE. Cases of HDUE presented at a more advanced age and also average age at death was significantly more advanced than in CHD, respectively around 79 and 76 years. Expectancy of life was significantly longer for HDUE (30.7 years) than for CHD (27.6 years). Strokes were more frequently ascertained among HDUE (14%) while 14% of death causes were due to cancer in both CHD and HDUE. Cancers were much higher (40%) among those never diagnosed CHD or HDUE who also had more stroke-due deaths (17%).
Conclusion: This is the first investigation to report heart disease incidence and its natural history in a *quasi*-extinction cohort data from Italy in a pre-cardiac surgery era.

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1. Introduction

Extremely long-term duration follow-up of population studies leading to extinction of the initially enrolled cohorts is quite rare in the literature [1–8] and the natural history of lifetime incident heart diseases has been mostly related to analysis of mortality and age at death as a function of various parameters measured at base-line [1–14]. Indeed, incident non-fatal events are quite difficult to measure and evaluate and very long-term longitudinal investigations require several generations of researchers involved and continuous commitment.

The Italian Rural Areas (IRA), as part of the Seven Countries Study (SCS), a large classic of international cardiovascular epidemiology [8, 10], have been analyzed in reference to 40- and 50-year follow-up [9, 12,13]. The IRA study obtained a full long-term measure of incident events including fatalities. The purpose is to describe the natural history of coronary and non-coronary heart disease incidence, including first presentation, immediate or later mortality, among middle-aged men followed to almost extinction of the initially enrolled cohort 50 years earlier.

Within previous analyses performed in the context of the SCS it was observed that fatal cases where the presentation was congestive heart failure, chronic arrhythmia, blocks or with the generic mention of "chronic coronary heart disease" or hypertensive heart disease were not predicted by serum cholesterol, whereas fatal coronary heart disease cases manifested with sudden death, acute myocardial infarction and acute ischemic attack had a strong positive association with serum cholesterol [15–17]. In this context the latter cases were referred as typical (TYP), whereas the formers were considered atypical (ATYP). Moreover, a stronger association with age was observed for ATYP than for TYP [15–17]. That initially raised the hypothesis on a possible different etiology of the two groups. The same differences between TYP and ATYP cases were more recently confirmed among men and women followed-up 20 years who participated to the Gubbio cohort study, carried out in central Italy [18].

In the present study the authors wanted to analyze the heart disease's natural history and to provide, for the first time, the full incidence and mortality data also presenting evidence in support to the proper partition of TYP versus ATYP events among IRA initially CHD-free middle aged men followed-up for half a century.

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For the sake of clarity, on this occasion, we prefer to adopt another arbitrary and operational terminology, i.e. CHD to identify typical coronary heart disease and Heart Disease of Uncertain Etiology (HDUE) for the group previously named ATYP. Data on prevalent cases are also presented. In an accompanying investigation, specifically constructed predictive models are presented on CHD versus HDUE manifestations [19] whose final re-classification was based on part of the evidence presented here.

2. Material and methods

This analysis was based on IRA epidemiological material of the SCS dealing with population samples, enrolled in 1960 in northern and central Italy. The cohorts were made of 1712 men aged 40–59 years, representing 98.5% of defined population samples [9,12,13]. After entry examinations, repeated surveys were made every 5 years until year 40 of follow-up, except for year 15 when the field examination was substituted by a systematic search for new fatal and non-fatal cardiovascular events in local hospitals, clinics and family doctors' offices. This procedure was repeated again on other occasions.

At periodical examinations a number of personal characteristics were measured together with data useful for the diagnosis of cardiovascular disease, based on history, physical examination and ECG recording. All these allowed to create diagnosis of different types of cardiovascular diseases at different times and to estimate entry prevalence and then the incidence of defined events. In parallel, systematic collection of mortality data including date and causes of death was performed for 50 years and was based (beyond the death certificates) for at least half of cases on a procedure [9–11] that anticipated the structure and the concepts of the so called verbal autopsy [20]. Cases of death were coded following the 8th Revision of the WHO-ICD [21] and were allocated by a single reviewer (AM). In the presence of multiple causes and in case of serious doubts a hierarchical rank was adopted with violence, cancer, CHD, stroke and other causes in sequence.

Major heart disease events or first diagnoses were classified into two large groups, arbitrarily named respectively CHD and HDUE, using information from periodical examinations, special search and mortality data including secondary causes [8–11]. There were cases of: a) CHD including: sudden coronary death (when other causes could reasonably be excluded), definite fatal and non-fatal myocardial infarction, and other 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 myocardial infarction used in successively historic time periods also depending on the state of the art knowledge, opinion leaders' preferences or simply different disciplines [22–27]; b) HDUE including: heart failure, diagnoses of hypertensive heart disease, or "chronic" CHD, severe arrhythmia (such as stable atrial fibrillation), severe heart blocks (possibly leading to the implant of a pace-maker), all these in the absence of manifestations described as CHD. The assumption was made that clinical manifestations described as in the HDUE group and found in subjects suffering a CHD were due to CHD, and therefore the classification of CHD was not changed. As a consequence the two large groups were defined in a mutually exclusive way.

The occurrence of Angina Pectoris (AP), diagnosed with the Rose LSH questionnaire [28], was also recorded but initially not used for the choice of either types of event. The starting date of AP could not be easily located and therefore we dealt with AP accompanying the cases at any time. The role of AP was analyzed separately.

Other types of rare heart disease (corresponding to less than 7% of all fatal heart disease in 50 years) were not considered for the analysis.

Each individual could suffer none, one or more than one event (of the same or different types) but only the first occurred with its date was used for the analysis. For indirect comparison, a group defined as OTHERs included subjects who never met a CHD or a HDUE manifestation.

In about 5% of the exposure, expressed by the amount of person/years, the diagnosis of the first major event could rely only on causes of death (multiple in 50% of cases) while the diagnosis of AP could not be ascertained in about 15% of the explored men, again expressed by person/years.

The entry examination of this study was carried out before the era of the Helsinki Declaration. Subsequently, oral consent was obtained for the collection of follow-up data.

2.1. Data analysis

The analysis was focused on simple comparisons of CHD versus HDUE characteristics. A first section dealt with entry prevalent cases of CHD and HDUE manifestations, that were subsequently excluded from analysis. The remaining heart disease-free subjects became 1677 and on these the subsequent analysis was performed.

A second section dealt with the following characteristics of CHD and HDUE incident events during 50 years: incidence (proportion), age at entry (mean), age at first event (mean), details on the first clinical manifestations (proportions). Then the following characteristics were estimated in relation with the fate of the two large groups: total mortality in 50 years (proportions), age at death (years), life expectancy in 50 years (mean), survival after first event (mean), and different causes of death (proportions).

The analysis of the group defined OTHERs gave the numbers at entry (proportion), age at entry (mean), age at death (mean), life expectancy in 50 years (mean), total mortality in 50 years (proportions) and causes of death in 50 years (proportions).

All differences between CHD and HDUE cases were tested by the *t* test of means, or the test of proportions depending on the nature of the variable. Separately, the role of AP was explored which was a possible tool to validate the CHD diagnoses.

3. Results

There were 35 subjects with prevalent heart disease at entry among 1712 enrolled initially (2%). No significant differences were found between CHD and HDUE cases in ages at entry or death (and the derived life expectancy) nor in the distribution of major causes of death, although the small numbers involved might in part explain these findings (Table 1). Notably, none of the prevalent subject survived the 50-year observation period and life expectancy was relatively short, especially considering their middle age at entry.

Age at first event among incident cases was significantly more advanced in HDUE than in CHD ones with a difference of almost 6 years (Table 2). About half of first clinical CHD manifestations were fatal

Table 1
Prevalent cases of heart disease at entry with their characteristics and outcome.

	CHD	HDUE	P
Proportions (n, %)	19/1712 (1.1)	16/1712 (0.9)	0.6772
Age at entry (years; mean ± SD)	51.5 ± 4.5	53.0 ± 4.6	0.3399
Age at death (years; mean ± SD)	65.9 ± 9.0	68.3 ± 10.9	0.4782
Life expectancy (years; mean ± SD)	14.4 ± 10.0	15.3 ± 8.9	0.7822
Total mortality	100%	100%	–
Major causes of death (%)			
CHD	57.8	25.0	0.1060
HDUE	5.3	12.5	0.8793
Rare heart disease	10.5	6.3	0.8699
Stroke	5.3	12.5	0.8793
Peripheral artery disease	5.3	–	0.9358
Cancer	10.5	25.0	0.4940
Other causes	5.3	18.7	0.0982

CHD: Coronary Heart Disease; HDUE: Heart Disease of Uncertain Etiology.