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The effect of revascularization procedures on myocardial infarction incidence rates and time trends: The MONICA-Brianza and CAMUNI MI registries in Northern Italy

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ABSTRACT

Purpose: Clinical guidelines recommend early reperfusion treatment in myocardial infarction (MI) patients to reduce the cardiac damage. Epidemiologic definitions of MI are often based on the evolution of the cardiac lesion. We aim to study the effect of treatment on the estimates of rates and 20-year time trends of MI.
Methods: A Multinational Monitoring of trends and determinants in Cardiovascular disease (MONICA) register was active between 1985 and 2004 to survey 35- to 64-year-old residents in Brianza, Northern Italy. To the well-established MONICA definite MI, we added the MONICA possible nonfatal MI receiving either myocardial revascularization or thrombolysis within 24 hours from onset. The average annual relative changes in incidence rate and 28-day case fatality percentage were estimated from log-linear models.
Results: In our population, characterized by a monotonic decrease in coronary heart disease (CHD) mortality rates, the incident rate for the standard MONICA definite MI decreased yearly by 3% in both gender groups. The addition of selected revascularizations halved the downward trends in incidence rate in men and women; conversely, the decline in 28-day case fatality became steeper.
Conclusions: From an epidemiologic perspective, the increasing proportion of acute events efficaciously treated with revascularization therapy affects the estimate and the interpretation of time trends in MI incidence and CHD mortality.

Introduction

At the end of the 1990s the World Health Organization–Multinational Monitoring of trends and determinants in Cardiovascular disease (MONICA) project, a study including mainly European populations, demonstrated that two thirds of the observed decline in population-specific coronary heart disease (CHD) death rates could be attributed to a decrease in myocardial infarction (MI) attack rates related to favorable changes in major risk factors [1,2]. These overall trends were also observed in one of the two MONICA-investigated populations in Northern Italy, the Brianza area [3,4].

Thereafter, mixed results in time trends of MI incidence, attack rates and case fatality were observed in the United States [5–7] and in Europe [8–10]. In Italy, the decline in CHD mortality continued through the 1990s, although it was mainly attributed to a decrease in case fatality, particularly in less affluent social strata [11]. These findings [5–11] were obtained from population-based registries, which concurrently registered hospitalized events and out-of-hospital deaths, and assigned a diagnostic category on the basis of symptoms and signs, anamnestic information, cardiac enzymes, and evolution of the cardiac lesion.

Changes in diagnostic tools, disease severity, and treatment procedures may affect the estimate of the time trends of CHD rates. In the last decade, the replacement of traditional cardiac enzymes (creatinine kinase [CK] and CK-myocardial band) with troponin I and T as markers of myocardial tissue damage increased the sensitivity of the diagnosis of MI [12–14]. During the 2000s, percutaneous coronary interventions (PCIs) replaced the thrombolytic treatment as

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preferred revascularization procedure [15–17], especially for ST-elevated MIs [18,19], for which a primary PCI within 90 minutes from symptoms onset is currently recommended [20]. Coronary angiography also increased considerably from around 30% in 1987 and 1988 to more than 60% in 2001 [21]. As a consequence of the use of early reperfusion strategies in ST-elevation MIs, it has been suggested that an increasing proportion of acute events might be "interrupted" by treatment before they can evolve into clinically significant cardiac damage. One community-based study reported a decreasing trend in Q-wave and increasing trend in non–Q-wave MI incidence between 1975 and 1997 [22].

A number of studies have considered the effect of troponin on the estimation of CHD time trends [9,12,23–25]. Trends in treatment procedures have been so far monitored in clinical settings [15–19], and less attention has been paid to how the rising proportion of treated acute events can affect the MI trend estimates from an epidemiologic perspective. We aim to assess the potential impact of revascularization procedures in the estimation of 20-year trend in MI incidence and case fatality rates, in the 35- to 64-year-old MONICA-Brianza population.

Materials and methods

Population characteristics

The study population is 35- to 64-year-old residents of Brianza, which is located between Milan and the Swiss border. The area, characterized by a high level of industrialization and urbanization, has one of the highest average incomes in Italy. This population was originally identified within the MONICA project because it provided a satisfactory number of annual CHD deaths in men [26].

The MONICA and cardiovascular Monitoring Unit in Northern Italy MI registers in Brianza

The MONICA MI register was set up in 1985, after a 3-month pilot study in 1984, and continued through the entire 10-year observation period, up to the end of 1994. The cardiovascular Monitoring Unit in Northern Italy (CAMUNI) continued the surveillance on the same population and adopting the same procedures, for the biennia 1997–1998 and 2003–2004 (four time points available for analysis).

The MONICA and CAMUNI registers identified suspected fatal and nonfatal coronary events from death certificates and hospital discharge records. Investigated codes are summarized in Table 1. Based on the recognized low positive predictive value (about 3%, [11]) for in-hospital events with hospital discharge diagnosis codes of ICD-IX 412–414, in the last biennium those codes were reviewed only if they were reported as the main discharge diagnosis. The relevant clinical information available for the suspected hospitalized events was collected and reviewed to validate the event according to the MONICA diagnostic algorithm [26] on the basis of symptoms at onset, maximum levels of cardiac enzymes (CK, CK-myocardial band, and lactate dehydrogenase) at hospital arrival, and a sequence of up to four electrocardiograms (coded according to the Minnesota criteria) that describes the evolution of the cardiac lesion. A positive history of MI was defined on the basis of anamnestic information or documented evidence of a previous acute event in the clinical record. Out-of-hospital deaths were investigated through interview of a relative or of the decedent's general practitioner; necropsy findings and previous history of CHD contributed to the validation process. The validation algorithm did not change over time; specifically, although troponin was introduced in study-area hospitals in 2003 through 2005, it did not substitute for cardiac enzymes but was an addition. Traditional enzymes were routinely available to the patients independent of troponin assessment. The MI algorithm used in this paper does not include troponin.

Endpoint definition

Fatal cases (death within 28 days from onset) were classified according to the MONICA diagnostic categories as "definite MI" (F1), "possible MI" (F2), "non-MI" (F4), and "cardiovascular death with insufficient data" (F9), which includes coronary sudden deaths as a majority and some unwitnessed deaths with no alternative evident cause. Nonfatal events were classified as "definite MI" (NF1), "possible MI" (NF2), and "non-MI" (NF4). The MONICA NF2 category is a broad diagnostic group and includes minor forms of MIs, other acute coronary syndromes, angina pectoris, and typical chest pain in absence of other positive diagnostic criteria for definite MI. Successive hospitalizations on the same subject within 28 days from onset or hospitalization were considered as one event.

We considered three hierarchical endpoints of acute symptomatic CHD. The narrowest is "MONICA definite MI or fatal CHD" (F1 + NF1 + F2 + F9). An expanded category, "MONICA definite MI or fatal CHD, or MONICA possible nonfatal MI with at least one revascularization procedure (either thrombolysis or primary PCI) undertaken within the first 24 hours from symptoms onset" includes interrupted MIs and symptomatic events that would not have proceeded to MI, even without the intervention. We take the 24-hour period for the definition of this category because in the first decade only this choice is available. Finally, the MONICA "definite MI or fatal CHD or possible nonfatal MI" entity (F1 + NF1 + F2 + F9 + NF2) adds to the previous all the remaining MONICA possible MIs.

For any endpoint, 28-day case fatality is defined as the proportion of deaths within 28 days from the total number of events. For completeness we also present the CHD mortality rate (F1 + F2 + F9). The endpoints presented are for first event only (incidence rates).

Table 1
Definition and coverage of suspected in-hospital and out-of-hospital coronary events, during the entire surveillance period: The MONICA and CAMUNI MI registries, 1985–2004

Event type	Period	Source of notification	Coverage	Investigated codes
Out-of-hospital death	1985–2004	Death certificates	Italy	Underlying cause of death: ICD-IX 410–414, 798, 799; or 250, 420, 423–429, 440–449 in association with 410–414 in any other cause
Hospitalized events	1985–1988	HDD codes* (4 available)	Area hospitals (9) and major neighboring hospitals (6)	410–414 in any available field
	1989–1998	HDD codes† (4 available)		410–414 in any available field
	2003–2004	HDD codes† (6 available)		410–411 in any available field; 412–414 in the first field only

CAMUNI = Cardiovascular Monitoring Unit in Northern Italy; HDD = hospital discharge diagnosis (ICD-IX); MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease.

* Surveillance by trained nurses.

† Availability of Electronic records.

Table 2
Major characteristics of the MONICA and CAMUNI registries: The MONICA and CAMUNI MI registries, 1985–2004

	MONICA, 1985–1994		CAMUNI			
			1997–1998		2003–2004	
	Men	Women	Men	Women	Men	Women
Population in the age range 35–64 years old	165,158*	173,993*	186,441	189,440	202,009	203,340
Number of first MONICA Fatal MI or Coronary death	1297	344	195	42	160	39
Number of first nonfatal events	3148	652	846	236	719	165
MONICA definite MI	2373	349	532	77	323	60
MONICA possible MI with revascularization†	73	17	25	3	190	31
Residual MONICA Possible MI	702	286	289	156	106	74

Proportion of selected hospital discharge diagnosis that were MONICA MI	MONICA, 1985–1994			CAMUNI, 1997–1998			CAMUNI, 2003–2004		
	n	%‖	%¶	n	%‖	%¶	n	%‖	%¶
ICD-IX‡ 410	3136	83.6	85.4	672	88.1	89.7	788	46.1	70.0
ICD-IX‡ 411‡	130	10.0	11.5	346	0.9	4.9	228	4.4	11.8
ICD-IX‡ 412–414§	2710	2.5	4.1	589	2.4	2.9	144	6.3	17.4

CAMUNI = Cardiovascular Monitoring Unit in Northern Italy; MI = myocardial infarction; MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease.

* Population in 1990 (mid period).

† Acute nonfatal events with typical symptoms and revascularization therapy undertaken in the first 24 hours.

‡ Excluding records reporting 410 codes.

§ Excluding records reporting 410 or 411 codes.

‖ MONICA definite myocardial infarction (NF1).

¶ MONICA definite MI or possible NF MI with revascularization within 24 hours from symptoms onset.

Statistical analysis

From the number of observed events, 10-year age group annual coronary event rates (per 100,000 person-years) were estimated and age-standardized according to the direct method (European Standard [27] as reference population). Annual inter-censal estimates conveniently stratified by decade of age and gender were used as denominator for the rates. The 28-day case fatality was standardized using weights derived from the age distribution of cases. The average annual relative changes (AARC) in MI incidence and mortality rates were estimated by fitting log-linear Poisson models where the expected number of events (every MI event or MI death, respectively) was modeled from the corresponding gender, age group, and calendar period counts. A gender*period interaction term was also included, to allow gender-specific trends over time. The AARC in rates (in percent) were obtained as $100*[\exp(\beta)-1]$, where β is the coefficient of the calendar period estimated from the model and $\exp(\beta)$ represents the relative risk for unit changes of calendar year. Ninety-five percent confidence intervals were calculated assuming the Poisson distribution of errors and accounting for the extra-Poisson variability [28]. Piecewise log-linear models, using two intervals separated at the end of the MONICA registration period (1994) were also fitted, to test the hypothesis of no change in the AARC between the first and second decades (1985–1994 vs. 1995–2004). Similarly, the average annual changes in case fatality were calculated by fitting log-linear regression models. The average annual change in mortality is the sum of the average annual change in incidence rate and case fatality [1]. All analyses were conducted using SAS software version 9.2 [29].

Results

During the study period, the Brianza population in the 35- to 64-year-old range increased by about 20%, mainly owing to immigration (Table 2). Nonfatal MONICA definite MI was 72% of nonfatal MONICA definite or possible MI in 1985 through 1994, and definite MI or possible MI with revascularization was 74%. In 2003 through 2004, these percentages were 43% and 68%, respectively, indicating a decrease in the proportion of the broadest category of acute nonfatal events accounted for by the MONICA definite MI category.

In the 2003 through 2004 biennium, the proportion of ICD-IX 410 (acute MI) that were MONICA definite MI fell by almost a half to 46%, from above 80% in the 1985–1998 period; the proportion increased to 70% after the inclusion of acute events with revascularization in the endpoint definition. The discharge code ICD-IX 411 became more prevalent in the two CAMUNI registration biennia, possibly owing to a more widespread adoption of the clinical diagnosis of acute coronary syndrome. However, the proportion of definite MIs was quite low. Finally, in the last biennium the number of investigated events with discharge codes ICD-IX 412–414 decreased by 75%, but the number of MONICA definite MI or possible MI with revascularization increased (17 in 1997/1998, 25 in 2003/2004), thus improving the registry's efficiency.

Major clinical characteristics of hospitalized nonfatal events are presented in Table 3. In contrast with MONICA definite MIs, both acute events with revascularization and residual MONICA possible MIs were characterized by typical symptoms and nondefinite enzyme levels and nondefinite ECG findings; the difference among them was the prevalence of revascularization treatment. Data completeness for ECG findings and cardiac enzymes was very high across all the event definitions and stable over the entire time period.

Tables 4 (men) and 5 (women) show the age-standardized incidence rates and case fatality, as well as the average annual relative change for the three endpoints, along with the CHD mortality rates and its average annual relative change, over the entire 20-year period and for the two separate decades. The piecewise log-linear models to estimate the 20-year trend in incidence rates for the three endpoints are displayed in Figure 1. In men, an overall 5.3% average annual decrease was observed in validated CHD death rate, with no differences between the first and second decades. The decrease for the fatal incident CHD was slightly lower (AARC = 4.4%). In women, the corresponding AARC was −5.4%, but in the first decade the decrease was much higher (8.1%) than in the second (2.7%; *P*-value for testing the difference in trend = .05). The average CHD death rate during the second decade was particularly low in women (12.4 per 100,000 person-years), so

Table 3
Major clinical characteristics of hospitalized nonfatal events, men and women, aged 35–64: The MONICA and CAMUNI MI registries, 1985–2004

	MONICA, 1985–1994			CAMUNI, 1997–1998			CAMUNI, 2003–2004		
	Definite MI	Possible MI with Rev*	Residual possible MI	Definite MI	Possible MI with Rev*	Residual possible MI	Definite MI	Possible MI with Rev*	Residual possible MI
No. of first events	2722	90	988	609	28	445	383	221	280
Typical symptoms (%)	84.1	100.0	100.0	94.3	100.0	98.9	74.7	100.0	100.0
Enzymes† and ECG (%)									
Definite enzymes or ECG findings	98.7	11.1	6.0	99.3	10.7	3.2	96.3	0.5	2.1
Equivocal/normal enzymes and probable/normal/not evolving ECG	0.3	87.8	93.2	0.2	85.7	94.6	2.9	97.3	95.4
Unavailable ECG findings	0.9	1.1	0.2	0.5	3.6	0.9	0.3	1.4	0.4
Unavailable enzyme levels	0.2	0.0	0.6	0.0	0.0	1.4	0.5	0.9	2.1
Revascularization therapy‡ (%)	33.9	100.0	0.2	54.2	100.0	0.0	49.4	100.0	0.0

CAMUNI = Cardiovascular Monitoring Unit in Northern Italy; MI = myocardial infarction; MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease.

* Acute nonfatal events with typical symptoms and revascularization therapy undertaken in the first 24 hours.

† Creatinine kinase myocardial band; lactate dehydrogenase.

‡ Either thrombolysis or PCI or both within 24 hours from symptoms onset.

it is not surprising that the observed decrease was attenuated. Similar figures were observed for the fatal incident CHD rates.

The incidence rate for the standard MONICA definite MI plus fatal CHD declined both in men (3.3% per year) and women (3.0%) over the entire period. Among men, a steeper annual reduction was present in the second decade (5.6%) with respect to the first (0.8%; *P*-value for difference in trend = .08). When nonfatal MONICA possible MIs with revascularization within 24 hours were included, the AARC were reduced to −1.7% and −1.8%, for men and women, respectively, both still significantly different from zero. The incidence of the milder endpoint did not significantly change over time (AARC = −0.8% and −0.1% in men and women, respectively).

The average annual changes in 28-day case fatality are also shown in Tables 4 and 5 for the three endpoints. The reduction in CHD mortality rate was largely because of a decline in incidence rate for MONICA definite MI plus fatal CHD in both genders, in particular in the second decade. However, when all the MONICA possible MIs undergoing revascularization were added to the endpoint definition, case fatality was the major contributor to the change in mortality, except for men in the second period. A similar statement applies to the broadest acute CHD category.

Discussion

In this northern Italian population, we observed a significant 5% average annual decrease in MONICA validated CHD mortality between 1985 and 2004, both in men and in women. In the second decade in women, the reduction was lower, but the very low CHD death rate (12.7 per 100,000 per year as average) has to be considered. The incidence rate for MONICA definite MI declined in men (3.3% per year) and women (3.0% per year) during the same period. In men, but not in women, a steeper decline was observed in the second decade. The addition of MONICA possible MIs with revascularization within 24 hours to the MONICA definite MI attenuated the estimated downward trends to 1.7% and to 1.8% in men and women, respectively; both trends were significant. The attenuation was even more evident in the more recent decade. These favorable trends are of major interest from a public health perspective, because this is a low MI event rate population.

In the United States, the Minnesota Heart Study reported significant decreases of 20% in MI rates in men and women between 1985 and 1995 [5]. The Rochester Epidemiology Project reported a reduction in MI incidence rate in men between 1979 and 1994,

Table 4
Time trends of age-adjusted coronary heart disease (CHD) mortality and myocardial infarction (MI) incidence rates, and 28-day case fatality, according to different endpoint definitions (men, 35–64 years old): The MONICA and CAMUNI MI registries, 1985–2004

Men	Entire period: 1985–2004				First decade: 1985–1994				Second decade: 1995–2004			
	Average rate*	Average annual relative change†			Average rate*	Average annual relative change†,‡			Average rate*	Average annual relative change†,‡		
		Estimate	95% CI			Estimate	95% CI			Estimate	95% CI	
MONICA-validated CHD death												
First event or recurrences	99.0	−5.3	−6.6	−4.0	117.1	−3.6	−6.4	−0.9	60.3	−6.8	−9.4	−4.2
First event only	67.8	−4.4	−5.9	−2.9	77.9	−3.7	−6.8	−0.5	46.4	−5.1	−8.1	−2.1
MONICA definite MI or validated CHD DEATH												
Incidence rate	200.8	−3.3	−4.7	−1.8	220.4	−0.8	−3.9	2.3	159.1	−5.6	−8.5	−2.6
28-day case fatality	34.7	−1.1	−2.3	0.0	36.1	−2.8	−5.0	−0.6	30.1	0.4	−1.7	2.5
MONICA definite MI or validated CHD death or possible MI with revascularization												
Incidence rate	212.7	−1.7	−3.1	−0.4	224.8	−0.8	−3.8	2.2	187.3	−2.6	−5.4	0.3
28-day case fatality	32.7	−2.7	−3.7	−1.7	35.4	−2.8	−5.0	−0.7	25.5	−2.6	−4.6	−0.5
MONICA definite MI or validated CHD death or possible MI												
Incidence rate	262.0	−0.8	−2.2	0.5	267.0	0.4	−2.6	3.5	252.3	−2.0	−4.8	0.9
28-day case fatality	26.6	−3.6	−5.0	−2.2	29.9	−4.0	−6.8	−1.3	18.7	−3.2	−5.8	−0.5

CAMUNI = Cardiovascular Monitoring Unit in Northern Italy; CI = confidence interval; MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease.

P-values for testing the difference in the estimated annual change between the first and the second period: § $P < .05$; ** $P < .01$; *** $P < .001$.

* Age-standardized rate. MONICA-validated CHD death rates and all the incidence rates are expressed per 100,000 person-years; 28-days case fatality is percent.

† Estimated from age-specific rates, 2 age groups: <54 and 55–64 years old.

‡ Piecewise linear model with one spline at 1994.

Table 5
Time trends of age-adjusted coronary heart disease (CHD) mortality and myocardial infarction (MI) incidence rates, and 28-day case fatality, according to different endpoint definitions (women 35–64 years old): The MONICA and CAMUNI MI registries, 1985–2004

Women	Entire period: 1985–2004				First decade: 1985–1994				Second decade: 1995–2004			
	Average rate*	Average annual relative change†			Average rate*	Average annual relative change†,‡			Average rate*	Average annual relative change†,‡		
		Estimate	95% CI			Estimate	95% CI			Estimate	95% CI	
MONICA-validated CHD death												
First event or recurrences	20.2	−5.4	−6.8	−3.9	23.6	−8.1	−11.3	−5.0	12.7	−2.7	−5.7	0.3§
First event only	16.3	−5.9	−7.6	−4.2	19.2	−10.0	−13.6	−6.5	10.1	−1.9	−5.3	1.6§
MONICA definite MI or validated CHD death												
Incidence rate	35.0	−3.0	−4.5	−1.4	38.6	−3.2	−6.5	0.1	27.3	−2.8	−5.9	0.4
28-day case fatality	46.4	−2.9	−4.2	−1.6	49.8	−6.8	−9.4	−4.2	36.8	1.0	−1.6	3.5**
MONICA definite MI or validated CHD death or possible MI with revascularization												
Incidence rate	37.0	−1.8	−3.2	−0.3	39.5	−3.0	−6.2	0.2	31.4	−0.7	−3.7	2.3
28-day case fatality	44.0	−4.1	−5.3	−2.8	48.6	−7.1	−9.6	−4.5	31.9	−1.2	−3.7	1.4§
MONICA definite MI or validated CHD death or possible MI												
Incidence rate	56.9	−0.1	−1.5	1.3	55.5	0.2	−3.0	3.3	60.1	−0.3	−3.3	2.6
28-day case fatality	28.6	−5.8	−7.4	−4.2	34.7	−10.2	−13.4	−7.0	16.7	−1.5	−4.7	1.6**

CAMUNI = Cardiovascular Monitoring Unit in Northern Italy; CI = confidence interval; MONICA = Multinational Monitoring of trends and determinants in Cardiovascular disease.
P-values for testing the difference in the estimated annual change between the first and the second period: § $P < .05$; ** $P < .01$.
* Age-standardized rate. MONICA-validated CHD death rates and all the incidence rates are expressed per 100,000 person-years; 28-day case fatality is percent.
† Estimated from age-specific rates, 2 age groups: <54 and 55–64 years old.
‡ Piecewise linear model with 1 spline at 1994.

and an increase in women [6]. In the ARIC population there was no significant decrease in MI incidence between 1987 and 1994 in Caucasian men and women [7].

In Europe, three French MONICA registries reported a significant decline in CHD death in a 5-year period (1997–2000) in men only, and no significant trend in attack rate [8]. These findings may in part be because of their simplified MONICA registration procedures.

The rapid decline in CHD death registered in Finland in the period from 1983–1997 was attributed mainly to a reduction in recurrences. The limited availability of hospital PCI facilities was suggested by the authors as a possible explanation for the modest decrease of MI case fatality [10]. In the MONICA Northern Swedish population a substantial decrease in CHD incidence rate was found in men but not in women in the 20-year period from 1985–2004 [9]; the trend flattened in the last 5 years. The authors recognized the possible role of troponin, introduced into the algorithm for MI definition from 2000 on, in reducing the trend estimates. Population-based surveillance of trends in CHD faces the challenge, among

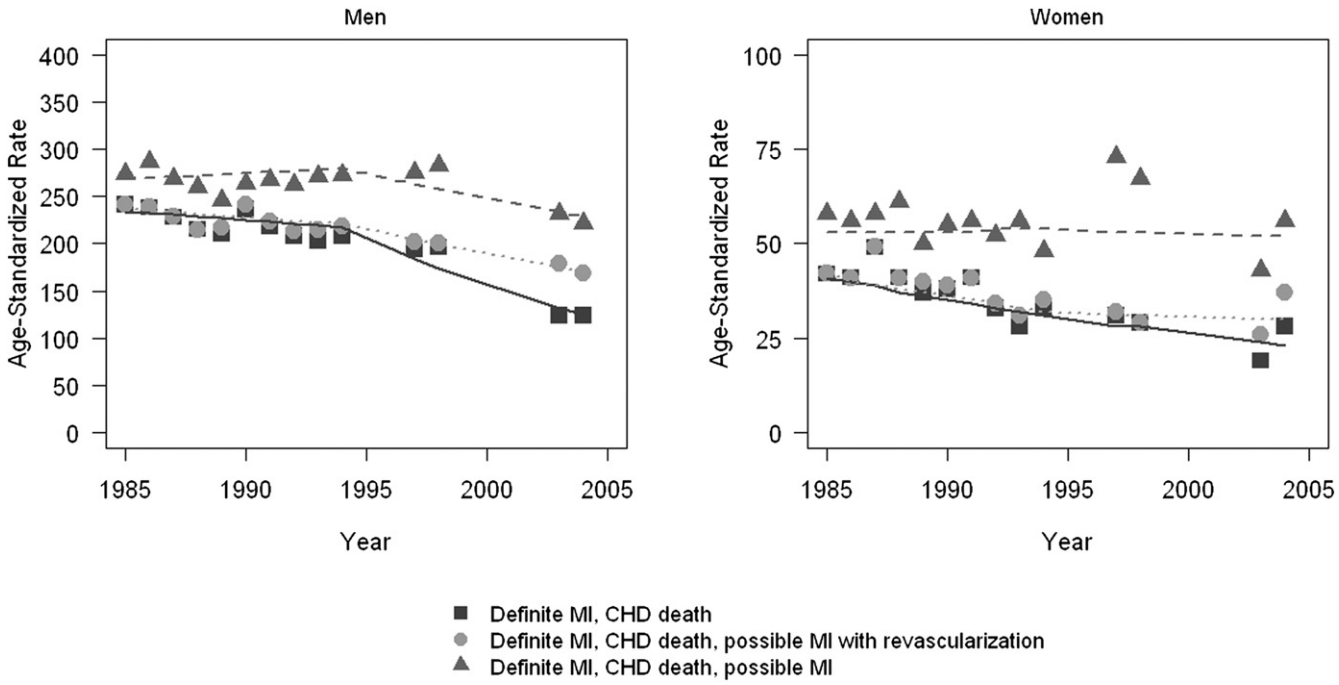

Fig. 1. Twenty-year time trend in MI incidence rate, for the 3 endpoints: Men (*left*) and women (*right*), 35–64 years old in the MONICA and CAMUNI MI Registries, 1985–2004. The points are the age-standardized event rates, by year, per 100,000 person-years. The lines are the time trend estimates, based on the piecewise log-linear model described in the method section. *Square*, MONICA definite MI or validated CHD death (NF1 + F1 + F2 + F9); *dot*, MONICA definite MI, possible MI with revascularization within 24 hours from symptom onset, or validated CHD death; *triangle*, MONICA definite or possible MI or validated CHD death (NF1 + F1 + F2 + F9 + NF2).

others, of a changing definition of MI [30]. In long-established registries, the inclusion of troponin into the MI definition led to spurious increasing trends or less pronounced downward trends in attack rate; at the same time, however, a validation algorithm that ignores troponin would underestimate the number of events, especially in recent years [12,23–25]. New definitions of MI have been recently suggested [31,32], whose effect on time trend estimate should be carefully evaluated.

From the early 2000s on, clinical cardiologists based their decision for undertaking thrombolytic treatment and coronary angiography with PCI on early ECG and enzyme findings, including troponin levels. The inclusion of MONICA possible MIs with a revascularization therapy brings into the MI endpoint definition the proportion of acute events without complete ECG evolution findings owing to the efficacy of the reperfusion treatment. Arciero et al [33] considered an "angiographically diagnosed coronary disease" according to the presence of a severe stenosis when the epidemiologic criteria for MI were not fulfilled, leading to changes in trend estimates similar to ours. It must be acknowledged that we considered a different standard from the current clinical setting for time to revascularization therapy [20]. From the epidemiologic perspective, the 24 hours limit allows exclusion of elective PCI and it can ensure consistency in our definition over the 20-year study period, because for the first period only a less than or greater than 24-hour classification is available. Nevertheless, it is of interest to monitor the category of "MONICA definite MI or possible MI undergoing revascularization" because the incidence rate of this entity is decreasing slower than definite MIs alone, while its case fatality is decreasing faster, suggesting that the intervention is having an effect. Other treatments and medications potentially affecting case fatality have been introduced during the 20-year study period, but they are generally given to MI patients undergoing PCI intervention or not. A greater bias may arise if cardiologists modify the criteria for primary PCI intervention, following the recent introduction of highly sensitive troponin measurements [34].

Our findings come from high-quality registry data. The ratio between the number of MONICA-validated CHD deaths and the number of CHD deaths from official mortality statistics, a measure of the coverage for fatal events [34], was consistently greater than 1 in all the years investigated. Coverage for nonfatal definite MIs, measured as the proportion of NF2 + NF4 on the total number of validated nonfatal events [35], was also greater than 50%. A crucial strength is a consistent validation algorithm over time [36]: troponin assessment was adopted by area hospitals only near the end of the period and not as a substitute for cardiac enzymes, but as an addition. Thus, we were able to omit troponins from MI to keep a standard definition over the entire period and be assured that there was no reduction in availability of enzyme data owing to troponin adoption.

Among the study limitations, we cannot exclude a possible bias in the time trend estimates of the endpoint including all MONICA possible MIs, because of the restrictions we adopted in the last biennium in the selection of less severe events (412–414 ICD-IX codes). Our findings are restricted to 35- to 64-year-old men and women, as imposed by the MONICA register age limits. We consider important to describe incidence rates in this age range, which is the preferred target for primary prevention. From 1997 on, the upper age limit was extended up to 74 years; preliminary analysis in the 35- to 74-year-old age group confirm the main findings presented here for 1997 through 2004 period.

Finally, the attempt to attribute the change in CHD death rate to incidence rate and case fatality is difficult, because it depends on the MI definition adopted. When the hard MONICA definition was used, incidence rate played the greatest role in CHD death reduction. However, when selected revascularizations were added to the endpoint definition, case fatality became the major contributor. This should be kept in mind when monitoring time trends to assess the efficacy of prevention population-based strategies or the effectiveness of hospital treatments.

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