

# Favourable trends in the incidence and outcome of myocardial infarction in nondiabetic, but not in diabetic, subjects: findings from the MONICA myocardial infarction registry in northern Sweden in 1989–2000

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**Abstract.** Rautio A, Lundberg V, Messner T, Nasic S, Stegmayr B, Eliasson M (Sunderby Hospital, Luleå; Umeå University, Umeå; Kiruna Hospital, Kiruna; and Kalix Hospital, Kalix, Sweden). Favourable trends in the incidence and outcome of myocardial infarction in nondiabetic, but not in diabetic, subjects: findings from the MONICA myocardial infarction registry in northern Sweden in 1989–2000. *J Intern Med* 2005; **258**: 369–377.

**Background:** The aim of this study was to compare time trends in incidence, case fatality and mortality due to myocardial infarction (MI) in patients with or without diabetes.

**Methods:** This study was based on the Northern Sweden MONICA Project MI registry with a target population of about 200 000 inhabitants in the age group 35–64 years in the two northernmost counties of Sweden. During 1989–2000, 6254 patients who had had an MI according to MONICA

criteria were included in this study: 4569 patients had a first MI and 1685 had a recurrent MI. Sixteen per cent of the men and 20% of the women had had diabetes mellitus diagnosed prior the MI.

**Results:** Over the 12-year period, there was a declining trend in incidence and case fatality in first MI. Also, the event rates (first ever and recurrent MI) declined in men without diabetes. In women without diabetes favourable time trends were seen in first ever MI, recurrent MI and in case fatality. There were no favourable time trends for any of these outcomes in patients with diabetes.

**Conclusion:** In nondiabetic subjects below the age of 65, the incidence of, and case-fatality in, MI declined. This led to a decreased mortality over the 12-year period. These favourable trends over time were not observed in diabetic subjects.

**Keywords:** acute myocardial infarction, diabetes mellitus, incidence, mortality, time trends

## Background

The Framingham Study from 1988 showed a heavy impact of diabetes mellitus (DM) on the risk of, and for the prognosis in, cardiovascular disease (CVD) [1]. Several other studies have confirmed that DM is an independent risk factor for coronary heart disease (CHD) and that patients with DM have a poorer prognosis [2–12]. However, the strength of DM as a risk factor is debated. Some studies indicate that DM, as a risk factor for a coronary event, is comparable to

already known or established CHD [13–15]. However, these results were recently called into question by a combined cross-sectional and cohort study which found that patients with type-2 DM are at lower risk of death from CHD and hospital admission for MI than patients with established CHD [16]. A study from 2004 showed that diabetic patients without previous MI had a lower risk of CHD events and mortality from CVD than with nondiabetic patients with previous MI. However, the risk of stroke was similar in the two groups [17].

Several studies from western Europe and the USA indicate a declining incidence, case fatality and mortality in CHD. The decline in CHD mortality is also associated with a decline in the number of out-of-hospital coronary deaths [18–22]. Very little is known if this beneficial trend also applies to patients with DM. There are few studies describing time trends in incidence, case fatality and mortality in subjects with DM. A follow-up study of the NHANES survey cohorts showed that the decline in heart disease and CHD mortality in diabetic subjects was clearly smaller than in the US general population, particularly in women [23]. A population-based study in Rochester, Minnesota, found that the mortality burden associated with DM increased significantly between 1970 and 1994, probably due to increases in DM incidence and smaller declines in mortality for persons with DM than without DM [24]. A report from 1991 from The Minnesota Heart Survey suggests that the risk for CHD and cardiovascular mortality attributable to DM may be increasing over time [25].

Some questions are raised from these findings. Are the results from early studies, showing unfavourable time trends for the diabetic population, still valid? Do they apply to European population? What are the possible explanations for such differences in time trends? Several studies have shown that interventions against common risk factors such as hyperlipidaemia [26], hypertension [27] and high blood sugar [28] are beneficial for diabetic subjects. Several studies indicate worse outcome in CHD for diabetic subjects. This may be due to the underutilization of evidence-based primary and secondary prevention in diabetic subjects or that the DM is such a strong risk factor for CHD that a substantial residual risk remains despite optimal risk factor intervention.

The aim of this study was to compare time trends on the incidence of myocardial infarction (MI), case fatality and mortality after an MI in patients with and without DM in a region with a population with high occurrence of CVD using a population-based registry [19].

## Methods

The WHO MONICA Project (multinational monitoring of trends and determinants in CVD) is a major international collaboration developed with the objective of measuring the trends and determinants in CVD. The project focused on trends in event rates

for validated fatal and nonfatal coronary heart attacks and strokes, and on trends in cardiovascular risk factors in men and women aged 25–64 in a defined population [29, 30].

The Northern Sweden MONICA Project is ongoing in Västerbotten and Norrbotten counties since 1985 and covers the two northernmost counties of Sweden, with a total population of around half a million inhabitants. The population and age structure in the area have been stable during these 12 years [31–33]. There has been no significant change in the prevalence of DM (clinically diagnosed or oral glucose tolerance test, OGTT) in 25–64-year olds according to four population surveys from this area from 1986 to 1999 [34, 35] supported by unpublished data from the 2004 MONICA survey.

In this study, all coronary events, including deaths outside hospitals, in subjects 35–64 years old were registered from 1 January 1989 to 31 December 2000 in The MONICA coronary event registry [33].

A total of 6616 cases fulfilled the MONICA criteria for an MI. All events were validated and registered in a standardized way according to the WHO MONICA manual [36]. Due to insufficient data regarding previous MI or the presence of diabetes, 362 patients were excluded (Fig. 1). The diagnosis of DM was based on medical records. A total of 1051 of the cases (795 men and 256 women) had DM.

To estimate the incidence of MI in a diabetic population the exact prevalence of DM in that population needs to be known. For this purpose data from the four MONICA population surveys in the same area during the same time period were used [34, 35]. The prevalence of DM during 1986–1999 was 3.6% in men and 2.4% in women aged 35–64 years [34]. The number of male subjects with diabetes in the background population ranged between 3194 and 3466 during the study period. The number of diabetic women ranged from 2103 to 2226. As no significant time trend in prevalence was evident, the pooled and age-stratified estimate for the time period was used. The corresponding number of subjects with diabetes was calculated from the total population in 10 year age strata for each of the four periods.

## Definitions

The following definitions were used. Incidence is the rate at which new events occur in a population. The

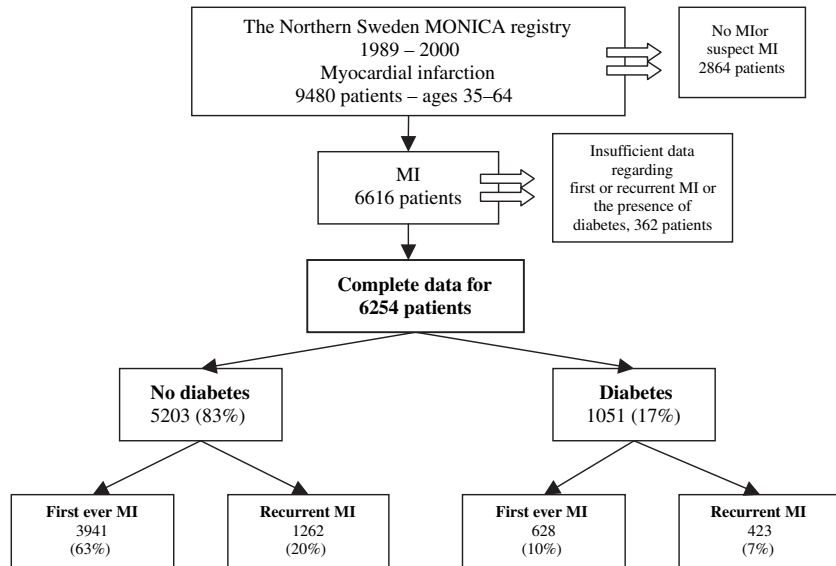


Fig. 1 Study population.

numerator is the number of new cases in a defined period and the denominator is the population at risk of experiencing the event during this period. Mortality is the annual number of fatal events (within 28 days from onset). Case fatality is defined in the MONICA project as the proportion of all cases which are fatal within 28 days. MI, according to The WHO MONICA Project, is defined as follows:

- Definite ECG (the development in serial records of a diagnostic Q-wave and/or the evolution of an injury current which lasts more than 1 day as described in the MONICA manual [36].
- Symptoms typical or atypical or inadequately described, together with probable ECG and abnormal enzymes.
- Symptoms typical and abnormal enzymes with an ischaemic or noncodable ECG or ECG not available.
- Fatal cases, whether sudden or not, with naked-eye appearance of fresh MI and/or recent coronary occlusion found at necropsy.

**Statistical procedures**

The incidence of MI was based upon each year’s individual population data in the age range 35–64. During the study period the population was stable and ranged between 257 000 and 264 000 inhabitants in this age group. Poisson regression was used to test for time trends in annual number of events and logistic regression was used to test for time

trends in annual incidence rates.  $P < 0.05$  was considered as significant. The models were built separately for men and women. As a first step we built separate models for groups with and without DM to test for time trends within each group. To test if the difference between trends was statistically significant an interaction term,  $\text{year} \times \text{DM}$  was included in the models, where DM was a dummy variable for diabetes. A similar model was used to test for interaction between time and gender amongst subjects with DM. A variable for age group (35–44, 45–54 and 55–64 years) was included in all regression models to control for possible different age distributions between the groups. When using Poisson regression we calculated trends in annual rates ( $r_t$ ) with the log-linear model, where  $\log$  denotes the natural logarithm,  $t$  the year and  $e_t$ , the error term of the regression model:

$$\log r_t = a + b1 \times t + b2 \times (\text{age group}) + e_t$$

The estimate  $100 \times [\exp(b1) - 1]$  was average annual percentage change. For small changes,  $100 \times b1$  can be used as approximated annual percentage change, which is presented in this paper. Confidence intervals for  $b1$  from the regression models were used to estimate confidence intervals for percentage annual change. Similar approximations were made when logistic regression was used. The SAS v.8 software package was used for statistical analysis.

The Northern Sweden MONICA study was approved by the Research Ethics Committee of Umeå University and data handling procedures by the National Computer Data Inspection Board.

## Results

Between 1989 and 2000, 7323 men and 2157 women with acute coronary events were registered, 6254 of these fulfilled inclusion criteria for the study. DM was present in 15.9% of the men and in 20.1% of the women. The mean age for patients without DM was 55.7 years in men and 56.4 in women. Patients with DM were slightly older, but the prevalence of smoking was less in patients with DM (Table 1).

### Trends in incidence of myocardial infarctions

Men without DM had a declining incidence in first MI. The change was  $-3.0\%$  per year (Fig. 2a). The incidence for men with DM was approximately eight times higher than for nondiabetic men, and there was no significant decline in the time trends (Fig. 2b). The time trend for incidence of MI differed significantly between the two groups (Table 2a).

A similar significantly declining time trend was also seen in men with recurrent MI, but not for men with DM. However, time trends did not differ significantly between the two groups (Table 2a).

In women with or without DM there was no significant decline in the incidence of first MI (Table 2a, Fig. 2a). A declining trend of almost  $8\%$  per year in recurrent MI was seen in women without DM. No favourable changes were noted for diabetic patients, and the difference between groups was significant (Table 2a). The difference in the incidence rate in MI between diabetics and nondiabetics was even more marked in women than in men, and the incidence of first MI for diabetic women was 15 times higher than in nondiabetic women.

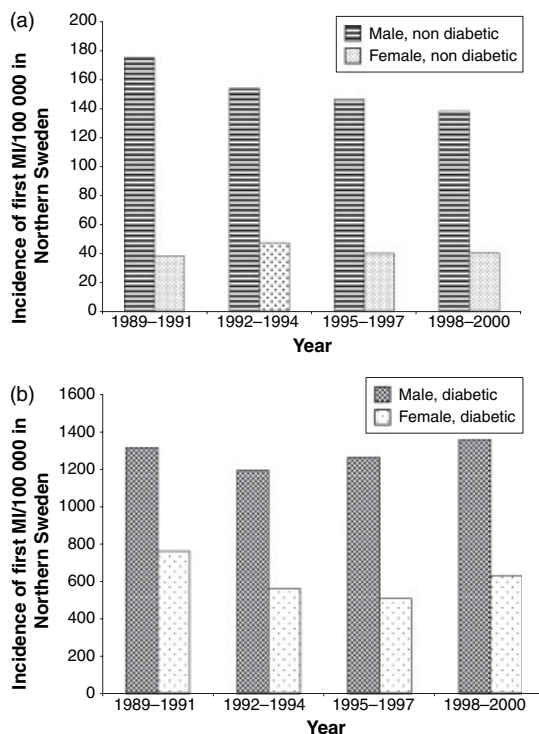


Fig. 2 Incidence of first myocardial infarction (MI) in northern Sweden in patients without (a) and with (b) diabetes, according to gender.

### Trends in number of myocardial infarctions

A significant decrease by  $3\%$  per year in the annual number of first MI was found in men without DM (Table 2b). In men with DM, there was no significant change over time. The difference in time trends between the two groups was significant.

In men without DM, a declining time trend was also seen in the number of recurrent MI (Table 2b). No significant trends were found in men with DM and the difference between groups was not significant.

	Men (4977)		Women (1277)	
	Nondiabetic (4182)	Diabetic (795)	Nondiabetic (1021)	Diabetic (256)
Mean age (SD)	55.7 (6.9)	56.9 (6.5)	56.4 (6.8)	58.2 (6.2)
First MI (%)	3107 (62.5)	470 (9.4)	834 (65.3)	158 (12.4)
Recurrent MI (%)	1075 (21.6)	325 (6.5)	187 (14.6)	98 (7.7)
Smoker (%)	33.8	21.1	45.5	25.7

MI, myocardial infarction.

Table 1 Description of the study population

**Table 2a** Trends in age-adjusted incidence of first/recurrent MI according to gender and presence of diabetes, 1989–2000

Sex	First MI		Recurrent MI	
	95% CI <sup>a</sup>	P-value <sup>b</sup>	95% CI <sup>a</sup>	P-value <sup>b</sup>
<b>Men</b>				
No diabetes	-4.1*** (-5.1 to -3.0)	0.002**	-3.7*** (-5.4 to -1.9)	0.198
Diabetes	0.5 (-2.1 to 3.1)		-1.3 (-4.5 to 1.8)	
<b>Women</b>				
No diabetes	-0.35 (-2.3 to 1.6)	0.258	-7.9* (-12.2 to -3.8)	0.021*
Diabetes	-3.1 (-7.7 to 1.3)		0.4 (-5.3 to 6.1)	

MI, myocardial infarction. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ . <sup>a</sup>Indicates yearly change (%) within the group. <sup>b</sup>Indicates difference in trend between the groups.

In women without DM, there was a significant decrease in the number of recurrent MI by 7.2% per year, but not in the number of first MI (Table 2b). No other significant time trends were seen in women with or without DM (Table 2b). The proportion of diabetic patients amongst women with recurrent MI was 26.3% during 1989–1991 when compared with 45.5% for the last 3 years of the study period (Fig. 3).

#### Trends in case fatality

In men without DM and with a first MI, the 28-day case fatality decreased by 2.7% per year (Table 2c). Otherwise, there were no significant trends over time in nondiabetic men and diabetic men or significant differences in trends between the two groups.

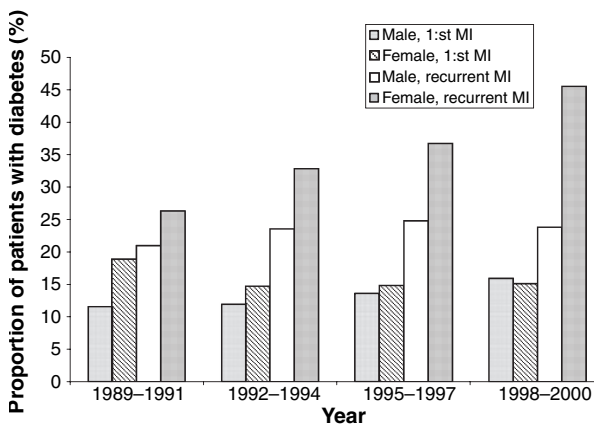
Also in women without DM and with a first MI, the 28-day case fatality decreased significantly by 6.8% per year. No significant time trends were seen in women with DM (Table 2c). Although the time

trends were not significant for nondiabetic women, they indicate a declining case fatality of almost the same magnitude as for nondiabetic women (-5.0%, 95% CI -15.3 to 5.1%).

#### Trends in mortality rates

In men without DM with a first MI, there was a significant decrease by 5.1% per year in mortality rates (Table 2d, Fig. 4a). The difference in trends in mortality rates between men with or without DM was significant for the first ever MI. Mortality rates in recurrent MI did not decrease significantly. The decreasing trend in mortality rates for all MI (first and recurrent) was significant. In men with DM, no change in mortality rates was seen over time (Table 2d, Fig. 4a).

In women without DM, mortality rates decreased significantly both for first and for recurrent MI by 5.1% and 11.9% per year respectively (Table 2d, Fig. 4b). There was a nonsignificant decrease in diabetic women with first MI by 6.6% per year (95% CI -15.8 to 1.8). No significant changes were seen in diabetic women regarding recurrent MI and the difference in trends between patients with or without DM was significant for recurrent MI.



**Fig. 3** Proportion of subjects with diabetes amongst incident cases of myocardial infarction (MI) according to gender.

## Discussion

This study confirms previous studies which report a decline in the incidence and mortality in MI in the western world. We found these favourable time trends only for patients without DM; no significant improvement in any outcome was found for subjects with DM. The declining trend in mortality in MI patients without DM probably depends mainly on fewer first-ever infarctions and, to a lesser extent, on fewer recurrent MI.

Sex	First MI		Recurrent MI	
	95% CI <sup>a</sup>	P-value <sup>b</sup>	95% CI <sup>a</sup>	P-value <sup>b</sup>
<b>Men</b>				
No diabetes	-3.0*** (-4.0 to -1.9)	0.001**	-2.6* (-4.3 to -0.8)	0.199
Diabetes	1.6 (-1.0 to 4.2)		-0.2 (-3.4 to 2.9)	
<b>Women</b>				
No diabetes	0.5 (-1.5 to 2.4)	0.256	-7.2* (-11.5 to -3.0)	0.021*
Diabetes	-2.4 (-6.9 to 2.1)		1.2 (-4.5 to 7.0)	

MI, myocardial infarction. \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001. <sup>a</sup>Indicates yearly change (%) within the group. <sup>b</sup>Indicates difference in trend between the groups.

**Table 2b** Trends in age-adjusted annual number of first/recurrent MI according to gender and presence of diabetes, 1989–2000

Sex	First MI		Recurrent MI	
	95% CI <sup>a</sup>	P-value <sup>b</sup>	95% CI <sup>a</sup>	P-value <sup>b</sup>
<b>Men</b>				
No diabetes	-2.7** (-5.2 to -0.2)	0.519	0.5 (-3.0 to 4.0)	0.559
Diabetes	-0.9 (-6.4 to 4.7)		2.3 (-4.2 to 8.8)	
<b>Women</b>				
No diabetes	-6.8** (-11.7 to -2.0)	0.777	-5.9 (-14.7 to 2.7)	0.529
Diabetes	-5.0 (-15.3 to 5.1)		-2.7 (-14.2 to 8.3)	

MI, myocardial infarction. \*\**P* < 0.01. <sup>a</sup>Indicates yearly change (%) within the group. <sup>b</sup>Indicates difference in trend between the groups.

**Table 2c** Trends in age-adjusted annual case-fatality in first/recurrent MI according to gender and presence of diabetes, 1989–2000

Sex	First MI		Recurrent MI	
	95% CI <sup>a</sup>	P-value <sup>b</sup>	95% CI <sup>a</sup>	P-value <sup>b</sup>
<b>Men</b>				
No diabetes	-5.1*** (-7.4 to -2.9)	0.024*	-2.3 (-4.9 to 0.2)	0.209
Diabetes	0.8 (-3.8 to 5.4)		0.9 (-3.4 to 5.2)	
<b>Women</b>				
No diabetes	-5.1* (-9.4 to -0.9)	0.751	-11.9* (-18.8 to -5.2)	0.018**
Diabetes	-6.6 (-15.3 to 1.8)		0.14 (-7.2 to 7.5)	

MI, myocardial infarction. \**P* < 0.05; \*\**P* < 0.01; \*\*\**P* < 0.001. <sup>a</sup>Indicates yearly change (%) within the group. <sup>b</sup>Indicates difference in trend between the groups.

**Table 2d** Trends in age-adjusted annual number of fatal events in first/recurrent MI according to gender and presence of diabetes, 1989–2000

Our study indicates, although not significantly, a declining case fatality in women with diabetes. In fact, a similar trend was described in a Swedish Public Health Report from 2005 with improved survival for diabetic women, but not for diabetic men [37].

This study is the first population-based survey, which has been based on a well-defined population during 12 consecutive years, and which has analysed time trends in both incidence and case fatality in MI in more than 1000 patients with DM.

One of the few previous studies of this issue suggested that in Minnesota, between 1970 and 1985, CHD morbidity and mortality attributable to

DM have increased over time [25]. A limitation in that study was that it only included patients from hospital records and thus excluded all out-of-hospital deaths. A follow-up of the NHANES study showed a similar pattern with a smaller decline in heart disease and CHD mortality in diabetic subjects for the 1982–1984 cohort than for the 1971–1975 cohort [23]. By contrast, a recent study showed a beneficial time trend between 1975 and 1999 even for the diabetic patients with decreased hospital death rate after MI [38].

There are several potential limitations to our study. It is well known that a considerable proportion of patients with MI have undiagnosed diabetes

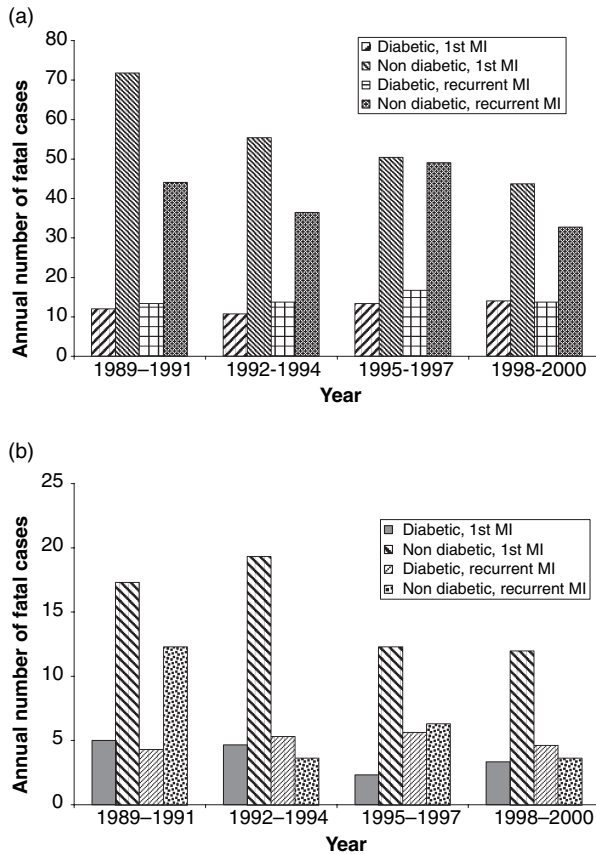


Fig. 4 (a) Annual number of fatal cases in first and recurrent myocardial infarction (MI) in men (a) and women (b) according to the presence of diabetes.

or impaired glucose tolerance [39–41]. Our aim was to mirror the impact of CHD in subjects with previously diagnosed diabetes. In these retrospective data it is not possible to know how many nondiabetic patients would have been diagnosed as diabetic if other definitions had been used. How this would have influenced the results is not possible to know. For this reason, the main criterion for the diagnosis of diabetes in this study was that this diagnosis had been made previously. In our study 41 patients were diagnosed as diabetics during the event and excluded from the study. Nevertheless, the main conclusion in our study remains unquestionable: that time trends for subjects with known diabetes are not as beneficial as time trends for nondiabetic subjects.

The results of our study are dependent on the estimates of the number of diabetic men and women in the background population, and are based on the assumption that the number of diabetic people remained stable over time. The background popula-

tion has been very stable and the prevalence of diabetes has been relatively unchanged according to a previous study. The proportion of DM diagnosed with OGTT was unchanged over time in the background population [34].

The age range in our study was somewhat narrow with an upper age limit of 65 years, and thus we have no information about the time trends for older patients. When the WHO MONICA Project started, the age of patients who were included was below 65 years but since 2000 the Northern Sweden Monica Project also registers patients up to 75 years of age.

The quality and internal validity in the WHO Monica Project is well recognized [32]. We believe that our results also have good external validity and accurately describe the time trends for the actual population as these data are truly population based and includes all events, and not only those subjects who were admitted to hospital. The 12-year study period should have been sufficient to detect differences in time trends. Still, we could not rule out that the study had insufficient power to detect modest changes over time in subjects with DM, such as are implicated in women with first MI.

Patients with DM were only slightly older than patients without DM. The age difference between groups remained unchanged during the study period. For this reason the difference in outcome for patients without and with DM was not likely to be due to age difference. It is not possible to reliably assess if there were differences in the presence of hypertension or lipid abnormalities from the registry. Other studies report that subjects with type 2 DM have higher blood pressure and a more atherogenic lipid profile.

There are several theories which try to explain why DM is such a severe risk factor for CHD and why it indicates a poorer prognosis with established CHD. Studies have shown differences in symptoms, management and prevention. Atypical symptoms or asymptomatic MI is more common in patients with DM [42]. Individuals with DM are admitted later and are less likely to receive thrombolytic therapy [7, 43, 44]. A large recent Swedish study has shown that patients with DM received significantly less treatment with heparins, intravenous beta blockade, thrombolysis and acute revascularization than nondiabetic patients. Patients with diabetes were significantly less likely to be treated with reperfusion

therapy, heparins, statins or to be revascularized within 14 days from hospital discharge [45].

Risk factor intervention, management of MI and secondary prevention have all been intensified and improved considerably during the study years [18]. Why do not patients with DM benefit from these improvements in management of CHD? Although the negative role of DM for the development of CHD is increasingly recognized, many differences in the prevention and treatment of MI still remain. It is also possible that DM is so strong as independent risk factor for CHD that a residual risk remains in spite of optimal risk factor intervention. This may be partly due to the fact that even the most optimal treatment against hyperglycaemia usually does not lead to normalized glucose metabolism [26, 28].

The Northern Sweden MONICA Project MI registry also registers pre- and post-event medication as well as treatment during the event. As discussed above, the adverse prognosis of patients with DM may partly be due to differences in the management of diabetics with MI. An important follow-up to the present study is to investigate differences in time trends in primary and secondary prevention and in management of MI for patients with or without DM. This is particularly interesting as the cardiovascular prevention for diabetic patients has clearly been more promoted after The United Kingdom Prospective Diabetes Study UKPDS [27, 28].

If the differences in time trends shown in our study persist in future, the proportion of patient with DM will increase even further in the MI population. That increase has already become obvious amongst women with recurrent MI.

Our findings are consistent and show that diabetic patients have not benefited from intensified cardiovascular prevention and treatment to the same degree as patients without DM. These findings should be explored in further studies and populations.

### Acknowledgements

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### Conflict of interest statement

No conflict of interest was declared.

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