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# Age and gender differences in incidence and case fatality trends for myocardial infarction: a 30-year follow-up. The Tromsø Study

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Jan Mannsverk<sup>1,2</sup>, Tom Wilsgaard<sup>2</sup>, Inger Njølstad<sup>2</sup>,  
Laila Arnesdatter Hopstock<sup>2</sup>, Maja-Lisa Løchen<sup>1,2</sup>,  
Ellisiv B Mathiesen<sup>3,4</sup>, Dag S Thelle<sup>5</sup>, Knut Rasmussen<sup>4</sup>  
and Kaare Harald Børnaa<sup>2,6,7</sup>

## Abstract

**Background:** Although the mortality of coronary heart disease (CHD) has declined in Western countries during the last decades, studies have suggested that the prevention and treatment of CHD may not have been as effective in women as in men. We examined gender- and age-specific trends in incidence, case fatality and the severity of first myocardial infarction (MI) in a large Norwegian population-based study.

**Design:** Prospective population-based cohort study.

**Methods:** A total of 31,323 participants enrolled between 1974 and 2001 were followed throughout 2004 for a total of 400,572 person-years. Suspected coronary events were adjudicated by a review of hospital records and death certificates. A total of 1669 events fulfilled standardized criteria of first-ever fatal or non-fatal MI.

**Results:** In the age group 35–79 years, the age-adjusted incidence of MI declined significantly in men, whereas an increase was observed in women. For men and women  $\geq 80$  years the incidence rates remained unchanged. The severity of MI and the 28-day and 1-year case fatality rates declined significantly and similarly in men and women.

**Conclusion:** Trends in MI incidence differed by sex and age; in the age group 35–79 years a marked decrease was observed among men but an increase was observed among women, while no change was observed among older patients. MI severity and case fatality were clearly reduced for both sexes. These data suggest that the burden of CHD is shifting from middle-aged men toward middle-aged women and elderly patients.

## Keywords

Myocardial infarction, incidence, case fatality, epidemiology, gender

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## Introduction

Age-standardized coronary heart disease (CHD) mortality has declined substantially in most industrialized countries during the last several decades.<sup>1,2</sup> The decline is thought to represent effects of changes in

<sup>1</sup>Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine, University Hospital of North Norway, Tromsø, Norway.

<sup>2</sup>Department of Community Medicine, University of Tromsø, Tromsø, Norway.

<sup>3</sup>Department of Neurology, Division of Neurosciences and Orthopedics, University Hospital of North Norway, Tromsø, Norway.

<sup>4</sup>Department of Clinical Medicine, University of Tromsø, Tromsø, Norway.

<sup>5</sup>Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway.

<sup>6</sup>Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.

<sup>7</sup>Clinic for Heart Disease, St Olav's University Hospital, Trondheim, Norway.

### Corresponding author:

Jan Mannsverk, Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine, University Hospital of North Norway, N-9038, Tromsø, Norway  
Email: jan.mannsverk@unn.no

lifestyle factors and treatment approaches, which in turn affect incidence of coronary events and survival of those affected.<sup>3,4</sup> However, evaluating temporal trends in the incidence and outcome of myocardial infarction (MI) is challenging since there have been changes over time in the criteria utilized for the diagnostic confirmation of MI.<sup>5</sup> Increased use of the highly sensitive biomarker troponin, enabling the detection of smaller amounts of necrosis, might increase the incidence of MI and decrease the severity of diagnosed cases.<sup>6</sup>

Concern has been raised that the favourable trends in CHD mortality and MI incidence may be less impressive in women than in men.<sup>7–11</sup> Emerging trends in coronary risk factors support these observations.<sup>7,12</sup> The increasing prevalence of obesity in Western populations is associated with diabetes mellitus, hypertriglyceridaemia, and the metabolic syndrome, which are stronger CHD risk factors in women than in men.<sup>13–15</sup> Furthermore, in some populations there has been only a modest or no decrease in smoking in women.<sup>16</sup> In addition, cardiovascular risk in women may traditionally have been underestimated, which may have led to deficient prevention and treatment efforts.<sup>12</sup>

The changes in diagnostics and inconsistent findings regarding the MI incidence in the two genders indicate a need for population-based long-term data on sex- and age-specific incidence and case fatality of first coronary event, taking into account more sensitive diagnostics. The main purpose of this study was to describe sex- and age-specific trends in incidence and case fatality rates of MI and the severity of the disorder in a Norwegian population from 1974 to 2004. We used a cardiovascular research registry set up as part of the population-based Tromsø Study, where each MI event

has been validated according to standardized diagnostic criteria.

## Methods

### Study population and follow-up

The Tromsø Study is an ongoing, open, population-based cohort study in the municipality of Tromsø, Norway. Tromsø is the largest town in Northern Norway with a current population of 68,000 inhabitants. The Tromsø Study started in 1974 as a cardiovascular survey among 20–49-year-old men, with additional surveys being conducted in 1979–80, 1986–87, 1994–95, 2001 and 2007–8. A detailed description of the study population and study design has been published.<sup>17</sup> The surveys differed by size as well as age- and birth-cohort composition (Table 1). Women were included in the 1979 survey and onwards. Information on cardiovascular diseases and risk factors was obtained through standardized questionnaires, physical examinations and laboratory tests.<sup>18</sup> The surveys were performed by the University of Tromsø in cooperation with the National Health Screening Service. Approvals were obtained from the Regional Board of Research Ethics, the Data Inspectorate and the Directorate of Health and Social Affairs. The 38,164 who participated in at least one of the surveys up to 2001 form the basis of this longitudinal analysis. We excluded 5469 participants who were younger than 35 years, 390 participants with a history of prior MI, 160 participants not officially registered as inhabitants of Tromsø at the date of enrolment and 222 participants who did not give written consent to research. Follow-up time was assigned from the date of first attendance until date of first-ever fatal or non-fatal

**Table 1.** Year of screening, birth year and number of participants and percentage of eligible population examined (The Tromsø Study)

Year of screening	Gender	Birth year	Participants <sup>a</sup> N%
1974–75 (Tromsø 1)	Men	1925–1954	6595 83
1979–80 (Tromsø 2)	Men	1925–1959	8477 82
	Women	1929–1959	8143 88
1986–87 (Tromsø 3)	Men	1922–1974	10,963 78
	Women	1920–1974	10,863 85
1994–95 (Tromsø 4)	Men	1897–1969	12,865 74
	Women	1897–1969	14,293 79
2001 (Tromsø 5)	Men	1912–1971	3511 76
	Women	1912–1971	4619 81

<sup>a</sup>N denotes the total number of persons attending the screening, and % denotes N as a percentage of the eligible population.

MI, emigration from Tromsø, death from other causes or 31 December 2004, whichever came first. All analyses were stratified by sex and age (35–49 years, 50–64 years, 65–79 years and 80 years and older). To ensure valid trends with stable average age within each age group, we had to take into account that the oldest birth cohorts were recruited later than the younger ones (Table 1).<sup>17</sup> Therefore, for men, age-specific trend analyses for the age groups 35–49 years, 50–64 years and 65 years and older could be performed for the time periods 1974–2004, 1988–2004 and 1995–2004, respectively. For women, age-specific trend analyses for the age groups 35–49 years, 50–64 years and 65 years and older could be carried out for the time periods 1979–2004, 1993–2004 and 1995–2004, respectively. Due to these age-limitations set for the trend analyses, we excluded an additional 600 subjects. Thus, a total of 31,323 participants were included in the present analysis, 15,566 men and 15,757 women.

### Identification and validation of first MI

Hospitalized cases of incident MI were identified by linking the Tromsø Study participant list to the discharge diagnosis register at the University Hospital of North Norway, the only local hospital serving the Tromsø population. To identify all possible first-ever MI cases, we used a wide search strategy that included the following diagnostic codes of cardiovascular diseases (CVD): from 1974–79 International Classification of Diseases (ICD) 8 codes 410–414, 430–438; from 1980–98 ICD 9 codes 410–414, 430–438; and thereafter ICD 10 codes I20–I25, I60–I69 were used. The hospital medical record was then retrieved for case validation. Discharge letters from hospitalizations in other hospitals were also collected when appropriate. Further, the Tromsø Study participant list was linked with the National Causes of Death Registry at Statistics Norway and the death certificates were retrieved for those with an underlying or contributing diagnosis of CVD or sudden unexpected death. Relevant information was collected from additional sources such as autopsy reports and records from nursing homes, ambulance services and general practitioners. This procedure identified fatal incident cases of MI that occurred as out-of-hospital deaths, including deaths that occurred outside Tromsø. Dates of emigration were obtained from the Population Registry of Norway.

Medical records and death certificates were reviewed by trained physicians of the Tromsø Study Endpoint Committee. Cases meeting diagnostic criteria for definite or probable fatal or non-fatal first-ever MI were classified as MI. WHO MONICA/MORGAM criteria were used in the algorithms and included clinical

symptoms and signs, findings in electrocardiograms (ECG), values of cardiac biomarkers and (when applicable) autopsy reports.<sup>19</sup> Autopsy was performed in 25% of those who died on the day of attack. At the University Hospital, biomarkers used included creatine kinase (CK) (throughout the study period), its MB fraction (CK-MB) (from 1990) and troponin (from 2000). Biomarker levels were generally recorded three times during the first 3 days following admission or MI onset. When circumstances that might invalidate biomarker values were present, the biomarker results were downgraded from abnormal to equivocal in our algorithm. Silent MIs as defined by ECG only were not included as cases because of difficulties in determining the exact date of the event. Case fatality was defined as the proportion of all incident MIs that were fatal within 28 days and 1 year. Trends in MI severity (1995–2004) were evaluated by calculating the proportion of events with new Q-waves and ST-segment elevation in ECG, and the peak CK values. All blood measurements were done at the Department of Clinical Chemistry, the University Hospital of North Norway. The methods of measurements, the upper limits of normal, and the number of assays performed during hospitalization for MI, did not change over time.

### Statistical analysis

Statistical analyses were performed using STATA version 10 (Stata Corp LP Texas, USA). The split function in STATA was used to produce a new record for each follow-up year for each person. Years were adjusted to a 365.25-day length and age was updated on the first of July in every year the participants were being followed up. The MI incidence rates were calculated by dividing the number of all events over a period of time by the corresponding person-years at risk. Calendar year-specific MI incidence rates were estimated per 1000 person-years of observation. To account for non-linear time trends, calendar year was fitted using fractional polynomials and regressed on MI incidence and case fatality in Poisson and logistic regression models, respectively. All analyses of incidence rates and case fatality were age adjusted by including age as a continuous variable in the regression models, and stratified on sex and age (35–49 years, 50–64 years, 65–79 years and 80 years and older). Differences in hospitalized MI severity across time (2000–4 compared to 1995–99) were assessed by logistic regression for binary severity indicators (new Q-wave or ST-segment elevation in ECG) and linear regression for the natural log of peak CK, adjusted for age and sex. Trends across age and between sexes were compared by including two-way interaction terms between year and age and year and sex. All significance

tests were two-sided with the significance level set at 5%.

## Results

From 1974 to 2004, 1669 incident MIs occurred among the 31,323 participants during a total follow-up time of 400,572 person-years. Seventy-one percent of incident MIs occurred in men (supplementary Table 1 and supplementary Table 2). At the time of the index event, the mean age was 62 years (SD 13) for men and 73 years (SD 12) for women. Seventy-nine percent of all events were treated in hospital, whereas 15% of all events were out-of-hospital deaths. Sixty-three percent of all fatal cases on the day of the event were out-of-hospital deaths. The overall 28-day case fatality was 32%. Of all incident events, troponins were measured in 458 cases. Among these, 23 (5%) did not meet MI criteria for CK/CK-MB and/or ECG and met only troponin-based criteria.

### Incidence of MI

Trends in the incidence of MI differed significantly by sex and age over the time periods under study (Figures 1 and 2). MI incidence fell significantly among men below the age of 80 years: in men aged 35–49 years, incidence fell by 52% ( $p=0.001$ ) between 1974 and 2004; in men aged 50–64 years, incidence fell by 49% ( $p<0.001$ ) between 1988 and 2004; and in men aged 65–79 years, incidence fell by 34% ( $p=0.027$ ) between 1995 and 2004. Conversely, in women non-significant increases in MI incidence were found in the age groups 35–49, 50–64 and 65–79 years. In both genders, MI incidence among patients over 80 years did not change.

From 1995 to 2004 (the time period when we have follow-up data for all age groups) the age-adjusted incidence of MI in participants of 35–79 years declined by 26% (95%CI 6–42%) in men, but increased by 61% (95%CI 3–151%) in women (Figure 2) ( $p=0.012$  for the time  $\times$  sex interaction term). Temporal trends in the incidence of MI did not change notably when troponin-only cases were excluded.

### Case fatality of first MI

From 1995 to 2004 the age-adjusted odds of death within 28 days fell by 52% (95%CI 14–73%) among men and by 59% (95%CI 2–83%) among women aged 35–79 years (Table 2). Trends in 28-day case fatality were similar when cases meeting only troponin-based criteria were excluded. For patients older than 80 years, case fatality decreased significantly in men, but not in women. Among patients younger than 50 years of age,

case fatality did not change in men whereas in women there were too few cases for analysis. Among all incident MIs, the age- and sex-adjusted odds ratio of death within 1 year for an MI occurring in 2004 as compared with 1994 was 0.48 (95%CI, 0.32–0.71;  $p<0.001$ ), indicating a 52% decline in the odds of 1-year case fatality over the last decade. The temporal trends did not differ by age or sex (year  $\times$  age interaction,  $P=0.07$ ; year  $\times$  sex interaction,  $P=0.22$ ) and were similar regardless of troponin.

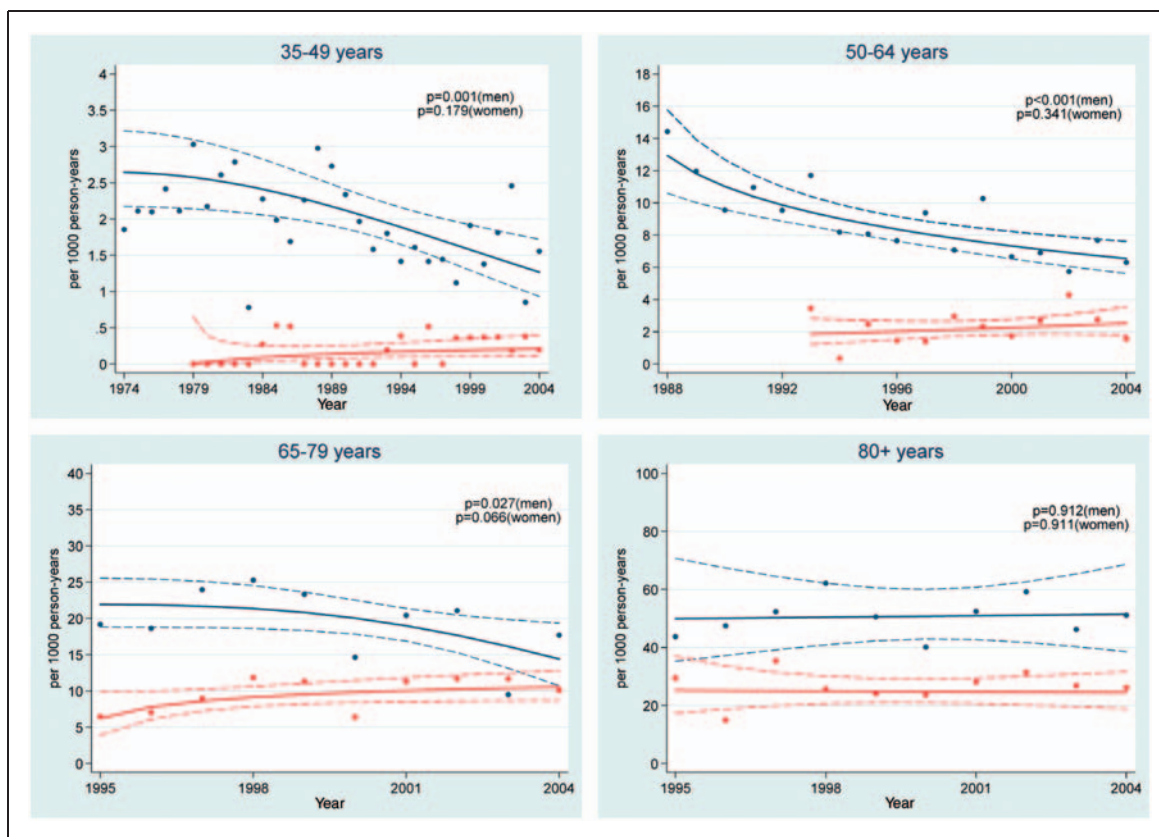
### Severity and treatment of hospitalized cases with first MI

When all hospitalized patients with MIs between 1995 and 2004 were analysed, the proportion with Q-wave pattern on ECG decreased significantly ( $p<0.001$ ), as did the peak CK level ( $p<0.001$ ), and a similar trend was observed for the frequency of ST-segment elevation in ECG ( $p=0.078$ ) (Table 3). Furthermore, the 28-day case fatality declined significantly ( $p=0.004$ ). The trends in case fatality, ECG findings and CK were similar in men and women and across all age groups, and also when cases meeting only troponin criteria were excluded. Among all hospitalized MIs between 1995 and 2004, the use of revascularization (percutaneous coronary intervention and/or coronary artery bypass grafting) within 28 days and the use of aspirin,  $\beta$ -blockers and statins at dismissal increased markedly over time (Table 3).

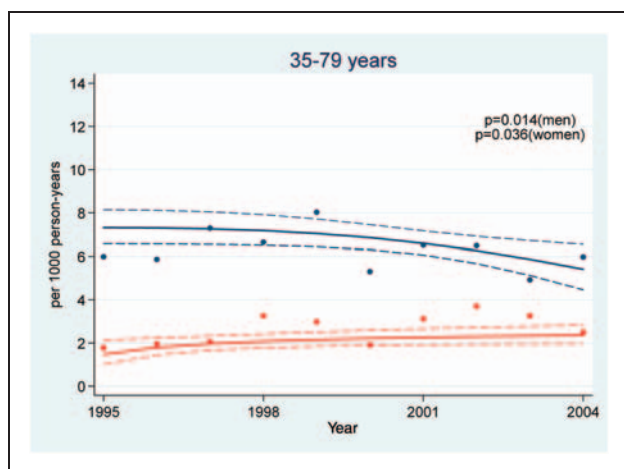
## Discussion

Temporal trends in MI incidence differed markedly by sex and age. Among persons below 80 years of age, MI incidence decreased in men and increased in women, whereas in persons aged  $\geq 80$  years the trends remained stable in both genders. In contrast to these opposing incidence trends, we found similar reductions among men and women in case fatality and in the severity of first MI. Notably, these changes were not related to the introduction of troponin measurements.

Our results are in line with findings in other populations. In the Olmsted County Study the incidence of hospitalized MI in men decreased from 1979 to 1994, whereas an increase was observed in women and the elderly.<sup>8</sup> In Northern Sweden, MI incidence was reduced in middle-aged men, but not in middle-aged women during 1985–2004.<sup>9</sup> Similarly, two large Finnish population-based MI registers suggested smaller declines in incidence of MI events in women than in men.<sup>10</sup> A recent survey of the US population found that MI prevalence had increased among middle-aged women during the past two



**Figure 1.** Age-adjusted time trends in incidence rates of myocardial infarction among men and women stratified by age. Note that start of follow-up differ according to sex and age-group. Blue dots and lines represent men, red dots and lines represent women. Each dot represent annual rate per 1000 person-years with best fitted regression lines (solid lines) and 95% confidence interval (dashed lines). *P* values are for time trends using fractional polynomials. (The Tromsø Study).



**Figure 2.** Age-adjusted time trends in incidence rates of myocardial infarction 1995–2004 among men and women aged 35–79 years. Blue dots and lines represent men, red dots and lines represent women. Each dot represent annual rate per 1000 person-years with best fitted regression lines (solid lines) and 95% confidence interval (dashed lines). *P* values are for time trends using fractional polynomials. (The Tromsø Study).

decades, while declining in men.<sup>7</sup> Similarly, cardiovascular risk factor levels showed decreasing trends in men, but increasing trends in women.<sup>7</sup> These findings are supported by autopsy studies of non-natural deaths showing greater temporal declines in high-grade coronary artery disease during 1981–2004 for males than for females, and greater for younger than for older individuals.<sup>20</sup>

The observed increase in MI incidence in middle-aged women is noteworthy. Does it reflect a true increase, or an increased detection of events that formerly went unrecognized? Recent surveys of the general public in the US indicate that the awareness of heart disease in women has increased in recent years.<sup>21</sup> It may be that women with chest discomfort during the follow-up period in our study have been more inclined to seek health advice, and that some of the increasing incidence is due to detection bias. In 2000, the European Society of Cardiology and the American College of Cardiology recommended that any elevation of troponin in the context of symptoms and signs of an acute coronary syndrome (ACS) should be considered diagnostic of MI.<sup>5</sup> Compared with CK and its myocardial band

**Table 2.** Secular trends in 28-day case fatality of incident myocardial infarction according to gender, age, and time period (The Tromsø Study)

Gender	Age (years)	Time period	Fatal MI/all MI <sup>b</sup>	Case fatality <sup>a</sup>		OR(95%CI) <sup>c</sup>	P-value for trend
				First year of time period	Last year of time period		
Men	35–49	1974–2004	56/258	20.1	20.9	1.05 (0.35–3.14)	0.926
	50–64	1988–2004	118/490	30.6	15.3	0.41 (0.21–0.82)	0.011
	65–79	1995–2004	106/295	44.8	26.3	0.44 (0.20–0.98)	0.044
	80+	1995–2004	72/138	73.5	34.4	0.19 (0.06–0.62)	0.006
	35–79	1995–2004	188/664	28.5	16.2	0.48 (0.27–0.86)	0.014
Women	35–49	1979–2004	4/23	NA	NA	NA	NA
	50–64	1993–2004	17/103	27.2	8.1	0.24 (0.04–1.33)	0.102
	65–79	1995–2004	61/195	37.4	24.5	0.54 (0.20–1.49)	0.236
	80+	1995–2004	95/167	62.2	48.5	0.57 (0.20–1.63)	0.297
	35–79	1995–2004	78/303	24.1	11.5	0.41 (0.17–0.98)	0.044

MI, myocardial infarction; OR, odds-ratio; CI, confidence interval; NA, not applicable. <sup>a</sup>Percentage of all MIs that were fatal within 28 days. The figures are age-adjusted estimates from logistic regression analyses using fractional polynomials. <sup>b</sup>The figures are number of MIs (N). <sup>c</sup>Age-adjusted OR for case fatalities between the last year (2004) and first year of each time period.

**Table 3.** Clinical characteristics in 962 patients hospitalized with first myocardial infarction in 1995–1999 and 2000–2004 (The Tromsø Study)

Characteristics	1995–1999 estimate <sup>a</sup> (n = 459)	2000–2004 estimate <sup>a</sup> (n = 503)	OR <sup>b</sup> or ratio <sup>c</sup> (95%CI)	P-value for trend
<b>MI severity indicators</b>				
Q-waves (%)	52	24	0.30 (0.23, 0.40)	<0.001
ST-segment elevation (%) <sup>d</sup>	43	37	0.77 (0.57, 1.03)	0.078
Peak creatine kinase (U/l) <sup>e</sup>	935	615	0.66 (0.56, 0.77)	<0.001
28-day case fatality (%)	22	15	0.61 (0.44, 0.85)	0.004
<b>Treatment</b>				
Revascularization within 28 days (%) <sup>f</sup>	11	52	8.92 (6.29, 12.64)	<0.001
B-blockers at discharge (%) <sup>g</sup>	76	83	1.57 (1.02, 2.41)	0.039
Aspirin at discharge (%) <sup>g</sup>	80	89	2.12 (1.32, 3.40)	0.002
Statins at discharge (%) <sup>g</sup>	42	65	2.60 (1.77, 3.80)	<0.001

Percentage missing values for Q-waves, ST-segment elevation, creatine kinase, 28-day case fatality, revascularization within 28 days, and use of β-blockers, aspirin and statins were 6.9, 12.4, 11.7, 0.0, 0.0 and 12.1 respectively. <sup>a</sup>The values are age- and sex-adjusted estimates from logistic regression models, or, for peak creatine kinase, a linear regression model, with year modelled as a two-level categorical variable. <sup>b</sup>Age- and sex-adjusted odds ratio (95%CI) for 2000–04 compared to 1995–99 as estimated from a logistic model. <sup>c</sup>For peak creatine kinase, the ratio estimates are age- and sex-adjusted ratio (95%CI) of the level in 2000–04 to the level in 1995–99 as estimated from a linear model. Analyses were done on log transformed data. <sup>d</sup>ST-segment elevation in hospitalized incident myocardial infarctions from 1996 to 2004. <sup>e</sup>Geometric mean. <sup>f</sup>Revascularization means percutaneous coronary intervention and/or coronary artery bypass grafting. <sup>g</sup>Based on 763 patients discharged from hospital alive.

fraction (CK-MB), troponins are more sensitive, enabling the detection of smaller amounts of necrosis. This may increase the number of MIs, shift the clinical spectrum of the disease toward smaller MIs and change case fatality estimates.<sup>6,22</sup> Women with ACS have a higher prevalence of unstable angina rather than MI, and a higher likelihood of having clinically insignificant

disease on coronary angiography.<sup>23</sup> In the FINAMI study, correction for the effect of troponins reduced the incidence of MI especially in women and elderly subjects.<sup>24</sup> However, the use of troponins is not likely to explain temporal trends in the Tromsø population, because the trends did not differ whether or not cases meeting only troponin-based MI criteria were included

in the analyses. Furthermore, the trends were emerging before the introduction of troponin in 2000 (Figures 1 and 2). In our study, 5% of the cases with troponin measurements met only troponin-based criteria. This figure is smaller than in comparable studies,<sup>25</sup> probably due to incomplete implementation of the new criteria in clinical practice.<sup>26</sup>

Previous studies have shown favourable trends in CHD risk factor levels in both genders, but less pronounced in women.<sup>12</sup> The proportion of daily smokers among Norwegian men fell from 51% in 1974 to 27% in 2004, but fell less in women (from 32 to 25%) and even increased slightly in some age groups (from 22 to 25% in the age group 55–64 years and from 10 to 15% in age group 65–74 years).<sup>27,28</sup> Data from the Tromsø Study surveys show similar trends.<sup>29</sup> Body mass index and prevalence of diabetes mellitus also increased in both genders.<sup>29,30</sup> Smoking and diabetes mellitus appear to be stronger MI risk factors in women than in men<sup>13,28,31</sup> and could thus partly account for the opposing incidence trends among men and women. In one study, first MI occurred significantly earlier in female smokers compared to male smokers, implying that twice as many years were lost by female as by male smokers.<sup>28</sup>

In line with results from other studies,<sup>25,32</sup> we found a substantial decline in the severity of first MI as evaluated by biomarkers and ECG. The consistency across MI severity indicators supports the robustness of the trends, and the hypothesis of declining MI severity over time. Possible explanations may be improved risk factors levels and advances in evidence-based treatments (increased use of aspirin, statins,  $\beta$ -blockers and revascularization). We did not assess time trends in the delay between the onset of symptoms and hospitalization, which may confound any association between calendar year and MI severity. However, time to admission did not change over time in two comparable studies.<sup>25,32</sup> It is likely that the decline in MI severity is a major determinant of the decline in case fatality in the Tromsø population. Case fatality has been reported to be higher among women compared with men, possibly due to differences in the level of acute coronary care.<sup>33</sup> However, we found no significant gender differences in MI severity or case fatality and no gender differences in the use of invasive revascularization or medications.

The strengths of the present study are its population-based design, the standardized diagnostic criteria, simultaneous measurement of both sets of biomarkers (since 2000 or later), the inclusion of both hospitalized and out-of-hospital cases of first-ever MIs, and the high participation proportion. Whereas these features support the internal validity of the study, our findings may not necessarily be generalizable to other populations

because of regional differences in risk factor levels, treatments and CHD rates.<sup>4</sup>

The present study indicates that the burden of CHD is shifting towards women and elderly patients, suggesting that preventive gains have not penetrated equally throughout the population. The severity of the disease, however, is declining in all groups. A substantial fraction of this fall may be due to therapeutic efforts. However, the disease is not disappearing and a maintained therapeutic alertness is therefore warranted.

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### Conflicts of interest

None declared.

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