Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population

Jan Mannsverk, MD; Tom Wilsgaard, MSc, PhD; Ellisiv B. Mathiesen, MD, PhD; Maja-Lisa Løchen, MD, PhD; Knut Rasmussen, MD, PhD; Dag S. Thelle, MD, PhD; Inger Njølstad, MD, PhD; Laila Arnesdatter Hopstock, MSc, PhD; Kaare Harald Bønaa, MD, PhD

Background—Few studies have used individual person data to study whether contemporary trends in the incidence of coronary heart disease are associated with changes in modifiable coronary risk factors.

Methods and Results—We identified 29 582 healthy men and women ≥25 years of age who participated in 3 population surveys conducted between 1994 and 2008 in Tromsø, Norway. Age- and sex-adjusted incidence rates were calculated for coronary heart disease overall, out-of-hospital sudden death, and hospitalized ST-segment–elevation and non–ST-segment–elevation myocardial infarction. We measured coronary risk factors at each survey and estimated the relationship between changes in risk factors and changes in incidence trends. A total of 1845 participants had an incident acute coronary heart disease event during 375 064 person-years of follow-up from 1994 to 2010. The age- and sex-adjusted incidence of total coronary heart disease decreased by 3% (95% confidence interval, 2.0–4.0; $P<0.001$) each year. This decline was driven by decreases in out-of-hospital sudden death and hospitalized ST-segment–elevation myocardial infarction. Changes in coronary risk factors accounted for 66% (95% confidence interval, 48–97; $P<0.001$) of the decline in total coronary heart disease. Favorable changes in cholesterol contributed 32% to the decline, whereas blood pressure, smoking, and physical activity each contributed 14%, 13%, and 9%, respectively.

Conclusions—We observed a substantial decline in the incidence of coronary heart disease that was driven by reductions in out-of-hospital sudden death and hospitalized ST-segment–elevation myocardial infarction. Changes in modifiable coronary risk factors accounted for 66% of the decline in coronary heart disease events. **(*Circulation*. 2016;133:74-81. DOI: 10.1161/CIRCULATIONAHA.115.016960.)**

Key Words: coronary disease ■ epidemiology ■ incidence ■ mortality ■ myocardial infarction ■ risk factors

Coronary heart disease (CHD) mortality rates have decreased in many countries during the last decades.[1,2] Both changes in the rates of out-of-hospital CHD deaths and hospitalization rates and the outcome of myocardial infarction (MI) with ST-segment elevation (STEMI) and non–ST-segment elevation (non-STEMI) will affect mortality.[3]

Editorial see p 8
Clinical Perspective on p 81

It has been suggested that 45% to 75% of the decrease in deaths from CHD can be attributed to decreases in smoking, blood pressure, and cholesterol.[4–8] These studies based their estimates on ecological data or mathematical modeling of aggregate data. Few studies used individual person data,[9,10] and the studies were limited to population subgroups and did not study out-of-hospital CHD or subtypes of MI.

We used individual person data from repeated surveys of a general population to study the rates of out-of-hospital CHD; the incidence, treatment, and outcome of hospitalized STEMI and non-STEMI; and the impact of changes in coronary risk factor levels during the years 1995 to 2010.

Methods

Study Population

The Tromsø Study is a population-based, prospective study of various health issues and chronic diseases. It consists of 6 surveys of both sexes conducted in the municipality of Tromsø, Norway, from

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From Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine (J.M., K.R.) and Department of Neurology, Division of Neurosciences and Orthopedics (E.B.M.), University Hospital of North Norway, Tromsø; Departments of Community Medicine (J.M., T.W., M.-L.L., I.N., L.A.H., K.H.B.) and Clinical Medicine (E.B.M., K.R.), UiT, Arctic University of Norway, Tromsø; Department of Biostatistics, Institute of Basic Medical Science, University of Oslo, Norway (D.S.T.); Clinic for Heart Disease, St. Olavs University Hospital, Trondheim, Norway (K.H.B.); and Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim (K.H.B.).

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Correspondence to Jan Mannsverk, MD, Department of Heart Disease, Division of Cardiothoracic and Respiratory Medicine University Hospital of North Norway, 9038 Tromsø, Norway. E-mail jan.mannsverk@unn.no

1974 to 2008.[11] The present study includes participants from the surveys undertaken in 1994 to 1995, 2001 to 2002, and 2007 to 2008, including a total of 29 582 individuals ≥25 years and older who participated in 1, 2, or all 3 surveys. The attendance rates of the 1994–1995, 2001–2002, and 2007–2008 surveys were 72%, 79% and 66%, respectively. Table I in the online-only Data Supplement shows a summary of the surveys. Participants who had previous MI (n=734) or had emigrated before the date of examination (n=45) were excluded from the analyses. Participants who were still free of MI and attended the later surveys in 2001 to 2002 or in 2007 to 2008 had their CHD risk factor values updated at the date of their examination. The study was approved by the Regional Committee for Medical and Health Research Ethics and the Data Inspectorate of Norway. Each subject gave written informed consent.

Coronary Risk Factors

Each survey used a standardized almost-identical protocol including physical examination, blood sampling, and questionnaires.[11,12] Blood pressure was measured with an automatic device.[12] Nonfasting blood samples were analyzed by standard methods at the University Hospital of Northern Norway.[12] Smoking status was self-reported in a questionnaire. Participants were defined as physically active if they performed strenuous physical activity (ie, became sweaty and breathless) at least 1 h/wk.

Identification and Validation of Incident CHD

Incident cases of CHD were recorded from each participant's study entry in 1994 to 1995, 2001 to 2002, or 2007 to 2008 until December 31, 2010. Adjudication of hospitalized and out-of hospital events was performed by an independent end-point committee using medical records and medical notes, autopsy records, and death certificates. The national unique 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of CHD were identified by linkage to the discharge diagnosis registry at the University Hospital of Northern Norway, the only hospital in the area, with search for *International Classification of Diseases, 10th Revision* codes I20 to I25, I46, R96, R98, and R99. Modified World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease (MONICA)/MONICA Risk, Genetics, Archiving and Monograph (MORGAM) criteria were used and included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable (http://www.thl.fi/publications/morgam/manual/contents.htm). Biomarkers considered were creatine kinase, its myocardial fraction (creatine kinase-MB), and troponin T beginning in 1999. Biomarker increases associated with revascularization procedures were not included as MI. The National Causes of Death Registry allowed identification of fatal cases of MI that occurred as out-of-hospital deaths and provided information on all-cause mortality. Death certificate information was used to collect relevant information from additional sources such as autopsy reports and records from nursing homes, ambulance services, and general practitioners. We classified hospitalized STEMI and non-STEMI by using standard criteria.[13] Out-of-hospital sudden death was defined as death caused by a probable MI (based on symptoms or autopsy) within 24 hours of symptom onset in nonhospitalized individuals or deaths in individuals brought to hospital with a cardiac arrest and unsuccessful resuscitation with no evidence of a noncoronary cause of death. Case fatality was defined as the proportion of incident CHDs that were fatal within 28 days. Dates of emigration were obtained from the Population Registry of Norway.

Statistical Analysis

Statistical analyses were performed with STATA 12 (StataCorp LP, College Station, TX) and SAS 9.3 (SAS Institute, Cary, NC). Age- and sex-adjusted means or prevalence of risk factors over time was estimated from generalized estimating equations to account for dependencies between repeated observations. The identity and logit link functions were used for continuous and binary variables, respectively, and the estimates were calculated with the use of the mean value for age and sex (57.9 years and 46% male) in the regression models. Follow-up extended from study entry to the date of incident event, date of emigration, death, or end of follow-up, whichever came first. Hazard ratios of CHD for coronary risk factors were estimated with Cox proportional hazards regression adjusted for age and sex. Hazard ratios of subtypes of CHD were estimated with the augmented data approach.[14] The proportional hazard assumption was verified by Schoenfeld residuals.

For incidence analysis, we used the split function to produce a new record for each follow-up year for each person, and age was updated every year that the participants were under follow-up. Crude event rates were estimated as the number of events per 100 000 person-years. Time trends in event and mortality rates and case fatality proportions were age and sex standardized with the Tromsø population in 2007 used as the standard population for the first 2 end points and the CHD event cohort for the last end point. We used a symmetrical moving average with a span of 5. This means that we calculated the average of the first 2 lagged values, the current value, and the first 2 forward terms of the series, with each term in the average receiving a weight of 1. The CHD mortality decline explained by out-of-hospital sudden deaths was estimated as the difference in out-of-hospital sudden death rate between 2010 and 1995 divided by the difference in total CHD mortality rate between 2010 and 1995. The proportion of the CHD mortality decline that was explained by the decline in incidence rates or case fatality was calculated as in the MONICA study: The average annual change in mortality rate is the sum of the average annual changes in event rate and case fatality proportion, expressed as percentages.[15] Poisson regression models were used to estimate linear time trends in events.

The proportion of the CHD incidence decline that was explained by change in each risk factor could be determined in those who participated in the 1994–1995 survey and was estimated by the expression $(\beta 0-\beta 1)/\beta 0$. We used the same long data set as for the incidence analyses described previously. The βs are time-trend coefficients from Poisson regression models, the former adjusted for age and sex and the latter with additional adjustment for risk factors added to the model as time-dependent covariates. End of follow-up was defined as 2001 for those who did not attend the 2001–2002 survey and as 2007 for those who did not attend the 2007–2008 survey. Individuals who had a CHD event were censored from the analyses at the time of their event. One thousand bootstrapped samples were simulated (with replacement) to estimate the 95% confidence interval (CI) for the explained decline. A 2-sided significance level was used.

Results

We identified 1845 patients (39% women) with an incident CHD event between 1995 and 2010, representing a period of 375 064 person-years (Table 1). Seventy-eight percent of the patients (n=1441) were hospitalized. Among those were 523 patients (36%) with STEMI, 869 (60%) with non-STEMI, and 49 with unclassifiable MI. A total of 236 hospitalized patients (16%) died within 28 days. Among the 404 nonhospitalized patients, there were 332 out-of-hospital sudden deaths and 341 deaths within 28 days after symptom onset. Thus, 58% of all fatal incident CHD events occurred as an out-of-hospital sudden death.

CHD Mortality

CHD mortality declined from 137 cases per 100 000 person-years in 1995 to 65 cases per 100 000 person-years in 2010 ($P<0.001$); out-of-hospital sudden death declined from 89 cases per 100 000 person-years in 1995 to 42 cases per 100 000 person-years in 2010 ($P<0.001$); and mortality rates among hospitalized MI patients declined from 50 cases per 100 000 person-years in 1995 to 28 cases per 100 000 person-years in 2010 ($P<0.001$; Figure, A). Thus, 65% of the decline in CHD mortality was attributable to a decrease in the rates of out-of-hospital sudden deaths.

Using Poisson regression models, we found that the age- and sex-standardized CHD mortality rate fell by 7.3% annually (95% CI, 5.6–8.9; $P<0.001$ for linear trend), the incidence of total CHD by 3.0% annually (95% CI, 2.0–4.0; $P<0.001$

Table 1. Baseline Distribution of Risk Factors According to Occurrence of CHD During Follow-Up: The Tromsø Study

Characteristic	No CHD (n=27 737), % (n)	Any CHD* (n=1845), % (n)	Out-of-Hospital Sudden Death†(n=332), % (n)	Hospitalized STEMI‡ (n=523), % (n)	Hospitalized Non-STEMI‡ (n=869), % (n)	*P* Value§
Male sex	46 (12 735)	61 (1130)	56 (186)	67 (351)	59 (515)	0.002
Age ≥60 y	17 (4750)	60 (1111)	73 (242)	49 (258)	61 (532)	<0.001
Hyperlipidemia‖	25 (6821)	51 (935)	47 (154)	55 (286)	50 (431)	0.05
Hypertension¶	31 (8725)	71 (1306)	76 (252)	65 (340)	72 (623)	0.002
Daily smoking	36 (9850)	41 (756)	39 (128)	49 (255)	37 (323)	<0.001
Overweight#	47 (12 942)	65 (1205)	60 (199)	67 (349)	67 (584)	0.04
Diabetes mellitus	2 (402)	7 (121)	7 (24)	5 (25)	8 (66)	0.11
Angina pectoris	2 (544)	14 (256)	15 (49)	10 (51)	16 (141)	0.003
High heart rate**	27 (7419)	33 (611)	40 (133)	32 (168)	32 (278)	0.02
Physical activity††	33 (9018)	20 (370)	15 (50)	23 (120)	21 (177)	0.02

CHD indicates coronary heart disease; and STEMI, ST-segment–elevation myocardial infarction.
*All baseline characteristics were significantly different among persons who did and did not develop CHD (all $P<0.001$).
†Nonhospitalized patients who survived 24 hours (n=72) were not included.
‡Patients hospitalized with unknown myocardial infarction subtype (n=49) were not included.
§*P* value for overall difference between out-of-hospital sudden death, hospitalized STEMI, and hospitalized non-STEMI.
‖Ratio of total cholesterol to HDL cholesterol >5.
¶Systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or using blood pressure lowering drugs.
#Body mass index >25 kg/m^2.
**Resting heart rate >80 bpm
††Strenuous physical activity ≥1 h/wk.

for linear trend), and case fatality by 4.0% annually (95% CI, 2.2–5.7; $P<0.001$ for linear trend; Figure, A–C). Thus, changes in incidence and case fatality contributed 43% and 57%, respectively, to the decline in CHD mortality.

Incidence of CHD

The age- and sex-adjusted incidence of hospitalized STEMI decreased from 132 cases per 100 000 person-years in 1995 to 80 cases per 100 000 person-years in 2010 (average annual decrease, 4.3%; 95% CI, 2.5–6.1; *P* value for linear trend <0.001; Figure, B). Similarly, there was a 7.6% (95% CI, 5.5–9.8; *P* value for linear trend <0.001) annual decline in out-of-hospital sudden death. In contrast, hospitalizations for non-STEMI increased from 120 cases per 100 000 person-years in 1995 to a peak of 203 cases per 100 000 person-years in 2003, followed by yearly decreases to 144 cases per 100 000 person-years in 2010. The increase in hospitalization for non-STEMI in the first half of the study period led to increased incidence rates for total CHD from 367 cases per 100 000 person-years in 1995

Table 2. Age-and Sex-Adjusted Hazard Ratios (95% CIs) for CHD by Baseline Risk Factors: The Tromsø Study

Characteristic	Any CHD (n=1845)	Out-of-Hospital Sudden Death* (n=332)	Hospitalized STEMI† (n=523)	Hospitalized Non-STEMI† (n=869)	*P* Value‡
Male sex	1.86 (1.70–2.05)	1.50 (1.21–1.86)	2.40 (2.00–2.88)	1.72 (1.50–1.97)	0.002
Age ≥60 y	7.60 (6.92–8.34)	12.95 (10.21–16.55)	4.75 (4.01–5.65)	8.11 (7.07–9.29)	<0.001
Hyperlipidemia§	2.01 (1.84–2.21)	1.66 (1.33–2.06)	2.41 (2.02–2.86)	1.94 (1.70–2.22)	0.02
Hypertension‖	1.82 (1.63–2.03)	1.75 (1.33–2.29)	1.70 (1.39–2.07)	1.92 (1.63–2.25)	0.63
Daily smoking	1.80 (1.64–2.00)	1.87 (1.49–2.35)	2.23 (1.87–2.65)	1.54 (1.34–1.77)	0.005
Overweight¶	1.43 (1.30–1.58)	1.10 (0.88–1.37)	1.58 (1.32–1.90)	1.55 (1.34–1.78)	0.02
Diabetes mellitus	2.44 (2.02–2.94)	2.18 (1.43–3.32)	1.88 (1.25–2.81)	2.86 (2.21–3.68)	0.19
Angina pectoris	2.19 (1.90–2.51)	1.78 (1.30–2.44)	1.73 (1.28–2.33)	2.74 (2.27–3.31)	0.01
High heart rate#	1.30 (1.18–1.43)	1.73 (1.39–2.16)	1.26 (1.05–1.52)	1.25 (1.08–1.44)	0.03
Physical activity**	0.84 (0.74–0.94)	0.73 (0.53–0.99)	0.88 (0.71–1.08)	0.85 (0.72–1.01)	0.60

CHD, coronary heart disease; CI, confidence interval; and STEMI, ST-segment–elevation myocardial infarction.
*Nonhospitalized patients who survived 24 hours (n=72) were not included.
†Patients hospitalized with unknown myocardial infarction subtype (n=49) were not included.
‡*P* value for overall difference between out-of-hospital sudden death, hospitalized STEMI, and hospitalized non-STEMI. All hazard ratios were adjusted for sex and age, except for male sex and age >60 years, which were not adjusted.
§Ratio of total cholesterol to high-density lipoprotein cholesterol >5.
‖Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of blood pressure–lowering drugs.
¶Body mass index >25 kg/m^2.
Resting heart rate >80 bpm.
**Strenuous physical activity ≥ 1 h/wk.

to a peak of 431 cases per 100 000 in 2000, then decreasing each year to 280 cases per 100 000 in 2010 (Figure, B).

Pre-Event Coronary Risk Factor Levels and Manifestations of CHD

Coronary risk factors were associated differently with out-of-hospital sudden death, hospitalized STEMI, and hospitalized non-STEMI (Table 2). Participants with sudden death were older, had higher resting heart rates, and were less likely to be physically active than those with STEMI or non-STEMI. Male sex, hyperlipidemia, and smoking were more strongly associated with STEMI than with non-STEMI and sudden death. Overweight was associated with increased risk of STEMI and non-STEMI but not with sudden death. Angina pectoris was a stronger risk factor for non-STEMI than for STEMI.

Changes in Coronary Risk Factors and the Decline in CHD

Major coronary risk factors changed favorably during the study period (Table 3). Mean levels of cholesterol, blood pressure, resting heart rate, and smoking were reduced, and physical activity was increased. In contrast, overweight and diabetes mellitus increased.

The proportion of the decline in the incidence of CHD that was attributable to changes in risk factors is presented in Table 4. The largest single contribution was declining cholesterol, which accounted for 32% of the observed 51% decline in incident CHD between 1995 and 2010. Changes in systolic blood pressure, smoking, resting heart rate, and physical activity each accounted for 9% to 14% of the decline in risk of CHD. Increases in body mass index and the prevalence of diabetes mellitus were associated with 7% and 2% increase in the risk of CHD, respectively. All risk factors together accounted for 66% of the decline in the incidence of CHD (Table 4): 64% in women and 61% in men (Tables II and III in the online-only Data Supplement).

Characteristics and Treatments of Hospitalized Patients

Peak creatine kinase levels was stable over time in patients with STEMI but decreased significantly in patients with non-STEMI, indicating that non-STEMIs became smaller in the latter part of the period (Table 5). The proportion of patients who developed Q waves on ECG decreased significantly over time among patients with both STEMI and non-STEMI. Revascularization and the proportion of patients receiving β-blockers, acetylsalicylic acid, and statins at discharge increased over time. Age- and sex-adjusted 28-day case fatality decreased by 26% (P=0.38) in STEMI patients and by 43% (P=0.01) in non-STEMI patients in 2005 to 2010 compared with 1995 to 1999.

Discussion

We found a substantial decline in CHD mortality between 1995 and 2010 that was driven by significant reductions in the incidence of out-of-hospital sudden death and STEMI. Changes in cardiovascular risk factors accounted for 66% of the change in hospitalized and nonhospitalized fatal and nonfatal CHD, with an upper CI close to 100%. This study thus extends results of previous studies that found modifiable risk factors to account for most cases of hospitalized, nonfatal MI.[16]

Table 3. Cardiovascular Risk Factor Levels in 1994 to 1995, 2001 to 2002, and 2007 to 2008: The Tromsø Study

Risk Factor	1994–1995 (n=15 718)	2001–2002 (n=6436)	2007–2008 (n=9569)	Relative Change From 1994–2008, %	*P* Value*
Age, mean (SD), y	54.8 (10.7)	62.9 (10.3)	59.7 (10.6)		<0.001
Male sex, % (n)	47 (7452)	42 (2686)	46 (4414)		0.81
Hyperlipidemia†	31 (30–32)	30 (29–31)	18 (17–19)	-42	<0.001
Total cholesterol, mmol/L	6.51 (6.49–6.53)	6.11 (6.09–6.14)	5.61 (5.59–5.63)	-14	<0.001
HDL cholesterol, mmol/L	1.55 (1.54–1.55)	1.45 (1.44–1.46)	1.52 (1.51–1.53)	-2	<0.001
Hypertension‡	52 (51–53)	47 (46–48)	48 (47–50)	-8	<0.001
Systolic blood pressure, mm Hg	141.9 (141.6–142.3)	136.6 (136.2–137.0)	135.5 (135.1–135.9)	-5	<0.001
Diastolic blood pressure, mm Hg	82.1 (81.9–82.3)	80.2 (79.9–80.4)	77.7 (77.5–78.0)	-5	<0.001
Drug-treated hypertension	8 (7–8)	14 (13–14)	19 (18–20)	138	<0.001
Daily smoking	34 (33–35)	31 (30–32)	22 (21–23)	-35	<0.001
Overweight§	55 (54–56)	63 (62–64)	63 (62–64)	15	<0.001
Diabetes mellitus	2.2 (1.9–2.4)	2.8 (2.5–3.1)	4.0 (3.7–4.4)	82	<0.001
Angina pectoris	3.1 (2.9–3.4)	2.9 (2.6–3.2)	2.2 (1.9–2.5)	-29	<0.001
High heart rate ‖	30 (29–31)	23 (22–24)	11 (10–11)	-63	<0.001
Physical activity¶	22 (21–23)	36 (34–37)	38 (37–39)	73	<0.001

Values (except for age and sex) are age- and sex-adjusted mean or prevalence (%) with 95% confidence interval for the age group of 40 to 79 years. HDL indicates high-density lipoprotein.

*Test for linear trend.

†Total cholesterol/HDL cholesterol ratio >5.

‡Systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or the use of blood pressure–lowering drugs.

§Body mass index ≥25 kg/m^2.

‖Resting heart rate >80 bpm.

¶Strenuous physical activity ≥1 h/wk.

Table 4. Decline in the Risk of a First CHD Event and Percentage of Risk Declines Accounted for by Risk Factors: The Tromsø Study

Models	Calendar Time β Coefficient per Year	Decline in Risk per Year, % (95% CI)	Decline in Risk per 15 Years, %*	Explained Decline by Risk Factors†, % (95% CI)‡
Model 1, age+sex adjusted	−0.0475	4.6 (3.3 to 5.9)	50.9	Referent
Model 1+total cholesterol	−0.0323	3.2 (1.8 to 4.5)	38.4	31.9 (22.7 to 48.9)
Model 1+HDL cholesterol	−0.0473	4.6 (3.3 to 5.9)	50.8	0.4 (−1.2 to 2.7)
Model 1+SBP	−0.0408	4.0 (2.7 to 5.3)	45.7	14.2 (9.5 to 20.4)
Model 1+daily smoking	−0.0411	4.0 (2.7 to 5.3)	46.1	13.4 (8.8 to 20.3)
Model 1+BMI	−0.0508	5.0 (3.6 to 6.3)	53.3	−7.0 (−11.4 to −3.6)
Model 1+diabetes mellitus	−0.0486	4.7 (3.4 to 6.0)	51.7	−2.3 (−4.7 to −0.5)
Model 1+resting HR	−0.0406	4.0 (2.6 to 5.3)	45.6	14.5 (6.9 to 24.0)
Model 1 + physical activity	−0.0431	4.2 (2.9 to 5.5)	47.6	9.2 (5.0 to 14.5)
Model 1 + all risk factors	−0.0162	1.6 (0.1 to 3.0)	21.6	66.1 (47.6 to 96.8)

Physical activity refers to strenuous physical activity ≥1 h/wk. BMI indicates body mass index; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, resting heart rate; and SBP, systolic blood pressure

*Decline in risk over 15 years=100%×[1−exp(β×15)].

†Percentage of the observed decline in risk explained by the risk factors=100%×(β0−β1)/β0, where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1) and β1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s).

‡The 95% CI are estimated with 1000 bootstrapped samples.

In line with others, we found that changes in the rates of out-of-hospital sudden death had a stronger impact on CHD mortality trends than changes in mortality of hospitalized patients.[17] The study demonstrates that primary prevention by modification of risk factors by means of a healthy lifestyle or medication will influence both incident CHD and case fatality

Table 5. Characteristics, Treatments, and Case Fatality for Patients Hospitalized With MI in 1995 to 1999, 2000 to 2004, and 2005 to 2010: The Tromsø Study

	1995–1999	2000–2004	2005–2010	*P* Value*
Patients hospitalized with STEMI				
Patients, n	190	162	171	
Age, mean (SD), y	67.5 (12.2)	66.1 (12.8)	66.5 (11.9)	0.46
Male sex, % (n)	68 (130)	62 (101)	70 (120)	0.93
Q-wave in ECG at discharge, % (n)	81 (103)	65 (104)	58 (95)	<0.001
Peak creatine kinase, median (IQR), U/L	1489 (661–3327)	1403 (601–2896)	1411 (551–2540)	0.09
Revascularization within 28 days, % (n)	14 (26)	64 (103)	87 (149)	<0.001
β-Blockers at discharge, % (n)	79 (90)	94 (129)	89 (116)	0.038
Acetylsalicylic acid at discharge, % (n)	79 (90)	97 (134)	97 (127)	<0.001
Statins at discharge, % (n)	57 (64)	83 (114)	95 (124)	<0.001
Case fatality within 28 d, % (n)	15 (29)	16 (26)	11 (18)	
Relative risk	1 (Referent)	1.11 (0.66–1.90)	0.74 (0.42–1.35)	0.38
Patients hospitalized with non-STEMI				
Patients, n	216	300	353	
Age, mean (SD), y	69.3 (12.5)	71.2 (13.0)	72.7 (13.1)	0.006
Male sex, % (n)	64 (139)	56 (169)	59 (207)	0.86
Q-wave in ECG at discharge, % (n)	37 (61)	14 (40)	13 (45)	<0.001
Peak creatine kinase, median (IQR), U/L	762 (432–1431)	404 (187–961)	326 (130–876)	<0.001
Revascularization within 28 days, % (n)	15 (32)	48 (145)	55 (195)	<0.001
β-Blockers at discharge, % (n)	80 (117)	78 (198)	84 (223)	0.02
Acetylsalicylic acid at discharge, % (n)	81 (120)	86 (217)	86 (227)	0.035
Statins at discharge, % (n)	48 (69)	58 (114)	73 (192)	<0.001
Case fatality within 28 d, % (n)	19 (42)	12 (37)	14 (50)	
Relative risk	1 (Referent)	0.55 (0.36–0.86)	0.57 (0.38–0.86)	0.01

IOR indicates interquartile range; MI, myocardial infarction; and STEMI, ST-segment elevation myocardial infarction.

*Age- and sex-adjusted *P* values for linear trend.

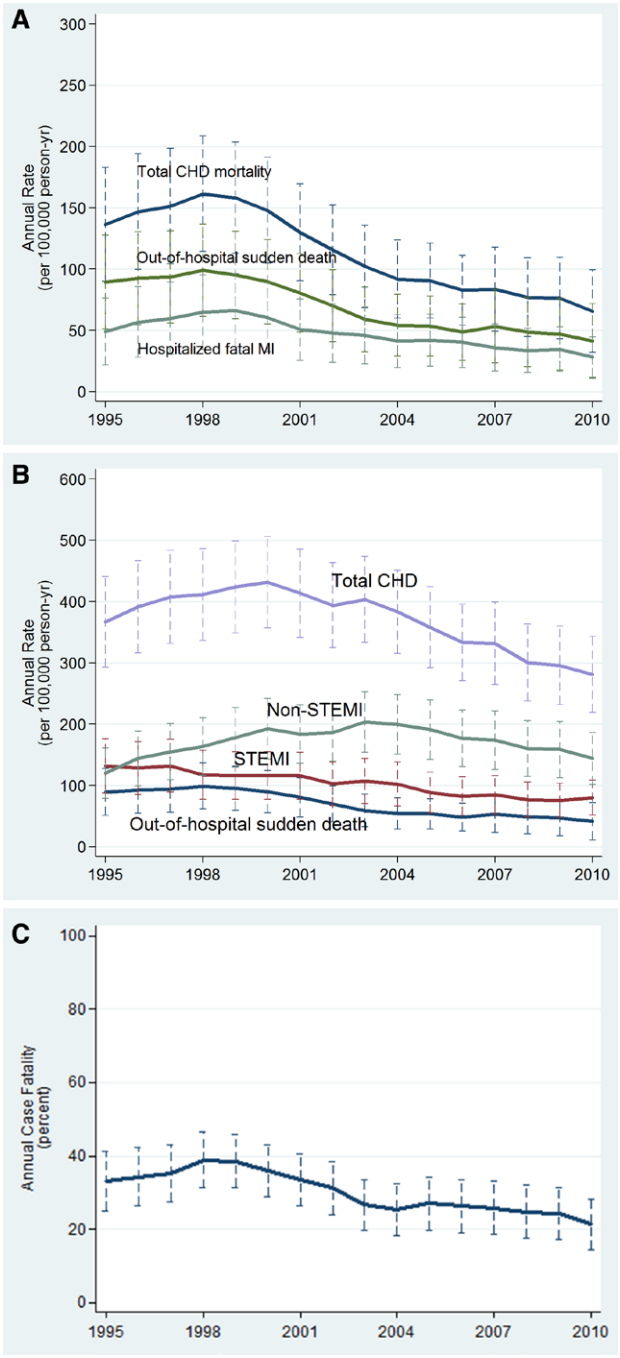

Figure 1. A, Trends in annual incidence rates of total coronary heart disease (CHD) mortality, out-of-hospital sudden death, and hospitalized fatal myocardial infarctions (MIs), 1995 to 2010, the Tromsø Study. The incidence rates are fitted as 5 years–moving mean. Each bar represents 95% confidence intervals. Rates are directly age- and sex-standardized to the Tromsø population. **B**, Trends in annual incidence rates of coronary heart disease, 1995 to 2010, the Tromsø Study. The incidence rates are fitted as 5 years–moving mean. Each bar represents 95% confidence intervals. Rates are directly age- and sex-standardized to the Tromsø population. STEMI indicates ST-segment–elevation myocardial infarction. **C**, Trends in annual case fatality proportion, 1995 to 2010, the Tromsø Study. The case fatality proportions are fitted as 5 years–moving mean and directly age- and sex-standardized with the event cohort as the standard population. Each bar represents 95% confidence intervals.

in populations, shown by the association between coronary risk factors and out-of-hospital sudden deaths. Thus, sudden death is a preventable condition.[18,19]

We found that cardiovascular risk factors had different impacts on subtypes of CHD, suggesting that the spectrum of CHD manifestations among populations and over time may differ, depending on the relative prevalence of the risk factors. Our findings suggest that reduced prevalences of hypercholesterolemia and smoking are major driving forces for the decline in the incidence of STEMI, indicating that primary prevention efforts result in fewer severe events.[20,21] In line with this, others have found that cholesterol is associated with rupture of vulnerable plaques and that smoking is associated with coronary thrombosis.[19]

Higher resting heart rate was more strongly associated with out-of-hospital sudden death than with STEMI or non-STEMI (Table 2). Higher heart rates are associated with myocardial ischemia, ventricular arrhythmias, and coronary atherosclerosis.[22–24] Correspondingly, we found that physical activity, which lowers resting heart rate, was associated with a lower risk of out-of-hospital sudden death and accounted for 9% of the decline in total CHD. The prevalence of self-reported angina pectoris fell by 29% (Table 3), suggesting that risk factor changes led to the less coronary atherosclerosis.

As observed earlier, we found an increasing incidence of non-STEMI in the first part of the study period,[21,25,26] likely reflecting the use of more sensitive biomarkers that detect smaller myocardial necrosis. This is supported by declining peak creatine kinase levels among non-STEMI patients, whereas the levels were stable in STEMI patients. We believe that the decline in STEMI is real and that the initial changes in non-STEMI reflect increased diagnostic sensitivity.

A strength of our study is that we used data on an individual level from a population-based study with a high attendance rate and standardized survey methods. In addition, case finding followed a standardized protocol for ascertainment of out-of-hospital and hospitalized events. The inclusion of incident cases only reduces the possibility that previous cardiovascular disease might have affected the risk factor levels. Finally, loss to follow-up is negligible because hospital treatment in Norway is free of charge and because of the use of the unique personal identity number to search official health registries.

Our study has limitations. We have included a largely homogeneous population from Norway that is distinct from the US population in which the rate of physical activity is lower, the rate of obesity is greater, and the smoking rate is lower. The autopsy rate for individuals with out-of-hospital deaths in our study was low (9%). This can lead to misclassifications even if the predominant cause of sudden death is CHD.[18,27,28] In addition, the true effect of changes in diagnostic sensitivity of biomarkers could not be fully quantified. The potential bias from this would be an overestimation of the incidence of MI in later years. The associations between trends in CHD and risk factors were necessarily based on attendees in subsequent surveys and not the entire source population, which could have introduced response and survival biases. The analysis was based on the assumption that the effects of changes in risk factors on CHD outcomes occurred within the time between consecutive surveys (≈6 years) or between the last survey and 2010 (≈3 years).

This might underestimate the effects of a risk factor change if a lag time of >3 to 5 years is present before the benefits of a risk factor change are realized. However, substantial benefits from smoking cessation, changes in blood lipids, and changes in blood pressure have been observed within 1 to 3 years.[29,30]

Conclusions

The substantial decline in CHD mortality was driven by significant reductions in the incidence of out-of-hospital sudden death and hospitalized STEMI and by a significant reduction in case fatality among hospitalized patients. The decline in event rates and the decline in case fatality each explained 50% of the decline in CHD mortality. Favorable changes in modifiable risk factors accounted for 66% of the decline in fatal and nonfatal CHD events in this population.

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Disclosures

None.

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CLINICAL PERSPECTIVE

We used individual person data from repeated surveys of a general population to study the incidence and outcome of myocardial infarction (MI). From 1995 to 2010, the age- and sex-adjusted incidence of MI decreased by 3%/y. The decline was driven by decreases in both out-of-hospital sudden death probably caused by MI and hospitalized ST-segment–elevation MI. In contrast, the incidence of hospitalized non–ST-segment–elevation MI increased in the first part of the study period, probably reflecting the use of more sensitive biomarkers for myocardial damage. We found a reduction in case fatality among hospitalized patients. The decline in event rates and case fatality each explained 50% of the decline in MI mortality. Sixty-six percent of the decline in MI incidence could be explained by favorable time trends in coronary risk factors. The population mean cholesterol level fell 14% between 1995 and 2008. This accounted for 32% of the decline in MI incidence. These results indicate that population-wide changes in risk factor levels have a large potential for reducing the MI incidence in a population. This study also found that risk factors had different impacts on subtypes of MI, suggesting that the spectrum of MI manifestations among populations and over time may differ, depending on the prevalence of risk factors. The association between risk factors and out-of-hospital sudden death indicates that primary prevention by modification of risk factors will influence both incident MI and case fatality in populations.

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Trends in Modifiable Risk Factors Are Associated With Declining Incidence of Hospitalized and Nonhospitalized Acute Coronary Heart Disease in a Population

Jan Mannsverk, Tom Wilsgaard, Ellisiv B. Mathiesen, Maja-Lisa Løchen, Knut Rasmussen, Dag S. Thelle, Inger Njølstad, Laila Arnesdatter Hopstock and Kaare Harald Bønaa

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SUPPLEMENTAL MATERIAL

Supplemental table 1. Study population. The Tromsø Study

Examination year	Age groups (years)	Invited	Attended (%)*
1994-95	25-97	37558	27158 (77)
2001-02	30-89	10353	8130 (79)
2007-08	30-87	19762	12984 (66)

*Adjusted for deaths, emigration from Tromsø during the survey period etc.

Supplemental table 2. Fall in the risk of a first coronary heart disease event and percentage of this fall explained by risk factors from Poisson regression analyses with time-dependent covariates in men. The Tromsø Study.

Models	Calendar time β–coefficient, per year	Fall in risk per year, % (95% CI)	Fall in risk per 15 years, %*	Explained decline by risk factors†, % (95% CI)‡
Model 1, age+ sex adjusted	-0.0500	4.9 (3.2, 6.5)	52.7	Ref
Model 1 + total cholesterol, mmol/l	-0.0330	3.2 (1.5, 4.9)	39.0	34.0 (22.1, 54.5)
Model 1 + HDL cholesterol, mmol/l	-0.0501	4.9 (3.2, 6.5)	52.8	-0.3 (-2.8, 2.1)
Model 1+ SBP, mmHg	-0.0450	4.4 (2.7, 6.0)	49.1	10.0 (5.7, 17.1)
Model 1 + daily smoking	-0.0435	4.3 (2.6, 5.9)	48.0	12.8 (7.3, 21.4)
Model 1 + BMI, kg/m^2	-0.0560	5.4 (3.8, 7.1)	56.9	-12.2 (-20.8, -6.7)
Model 1 + diabetes mellitus	-0.0510	5.0 (3.3, 6.6)	53.5	-2.1 (-5.1, -0.2)
Model 1 + resting HR beats/min	-0.0432	4.2 (2.5, 5.9)	47.7	13.6 (6.3, 24.1)
Model 1 + physical activity	-0.0455	4.4 (2.8, 6.1)	49.5	8.9 (4.5, 15.0)
Model 1 + all risk factors	-0.0194	1.9 (0.1, 3.7)	25.2	61.4 (41.4, 95.0)

* Fall in risk over 15 years=100% x [1-exp (β x 15)]. † Percentage of the observed decline in risk explained by the risk factors = 100% x (β0-β1)/β0 where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for

calendar time in the model with additional adjustment for the risk factor(s). ‡ 95% CI are estimated using 1000 bootstrapped samples. SBP denotes systolic blood pressure, BMI body mass index, HR resting heart rate, and physical activity strenuous physical activity ≥ 1 hour per week..

Supplemental table 3. Fall in the risk of a first coronary heart disease event and percentage of this fall explained by risk factors from Poisson regression analyses with time-dependent covariates in women. The Tromsø Study.

Models	Calendar time β–coefficient, per year	Fall in risk per year, % (95% CI)	Fall in risk per 15 years, %*	Explained decline by risk factors†, % (95% CI)‡
Model 1, age+ sex adjusted	-0.0382	3.7 (1.5, 5.9)	43.6	Ref
Model 1 + total cholesterol, mmol/l	-0.0295	2.9 (0.6, 5.2)	35.8	22.7 (6.5, 66.0)
Model 1 + HDL cholesterol, mmol/l	-0.0378	3.7 (1.5, 5.9)	43.3	1.0 (-1.8, 7.0)
Model 1+ SBP, mmHg	-0.0300	2.9 (0.7, 5.2)	36.3	21.4 (11.6, 48.3)
Model 1 + daily smoking	-0.0343	3.4 (1.1, 5.6)	40.2	10.1 (3.1, 27.1)
Model 1 + BMI, kg/m^2	-0.0391	3.8 (1.6, 6.0)	44.3	-2.2 (-6.8, 1.0)
Model 1 + diabetes mellitus	-0.0394	3.9 (1.6, 6.0)	44.6	-3.0 (-10.1, 1.0)
Model 1 + resting HR beats/min	-0.0315	3.1 (0.8, 5.4)	37.7	17.6 (1.5, 45.2)
Model 1 + physical activity	-0.0347	3.4 (1.1, 5.6)	40.5	9.3 (-2.4, 26.1)
Model 1 + all risk factors	-0.0136	1.4 (-1.1, 3.8)	18.5	64.3 (33.2, 152.0)

* Fall in risk over 15 years=100% x [1-exp (β x 15)]. † Percentage of the observed decline in risk explained by the risk factors = 100% x (β0-β1)/β0 where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for

calendar time in the model with additional adjustment for the risk factor(s). ‡ 95% CI are estimated using 1000 bootstrapped samples. SBP denotes systolic blood pressure, BMI body mass index, HR resting heart rate, and physical activity strenuous physical activity ≥ 1 hour per week..