JAMA Internal Medicine | Original Investigation

Lifelong Gender Gap in Risk of Incident Myocardial Infarction
The Tromsø Study

Grethe Albrektsen, PhD; Ivar Heuch, PhD; Maja-Lisa Løchen, MD, PhD; Dag Steinar Thelle, MD, PhD; Tom Wilsgaard, PhD; Inger Njølstad, MD, PhD; Kaare Harald Bønaa, MD, PhD

IMPORTANCE It is not clear to what extent the higher incidence of coronary heart disease (CHD) in men vs women is explained by differences in risk factor levels because few studies have presented adjusted risk estimates for sex. Moreover, the increase in risk of CHD in postmenopausal women, possibly hormone related, may eventually eliminate the sex contrast in risk, but age-specific risk estimates are scarce.

OBJECTIVE To quantify the difference in risk of incident myocardial infarction (MI) between men and women.

DESIGN, SETTING AND PARTICIPANTS Population-based prospective study from Tromsø, Norway, comprising 33 997 individuals (51% women). Median follow-up time during ages 35 to 102 years was 17.6 years. Incidence rates (IRs) and incidence rate ratios (IRRs, relative risk) of MI were calculated in Poisson regression analysis of person-years at risk. The data analysis was performed in November 2015.

EXPOSURES Sex, age, birth cohort, serum lipid levels, blood pressure, lifestyle factors, diabetes.

MAIN OUTCOMES AND MEASURES Incident MI.

RESULTS A total of 2793 individuals (886 women) received a diagnosis of MI during follow-up in the period 1979 through 2012. The IR increased with age in both sexes, with lower rates for women until age 95 years. Adjusted for age and birth cohort, the overall IRR for men vs women was 2.72 (95% CI, 2.50-2.96). Adjustment for high-density lipoprotein cholesterol and total cholesterol levels had the strongest impact on the risk estimate for sex, followed by diastolic blood pressure and smoking. However, the sex difference remained substantial even after adjustment for these factors (IRR, 2.07; 95% CI, 1.89-2.26). Men had higher risk throughout life, but the IRRs decreased with age (3.64 [95% CI, 2.85-4.65], 2.00 [95% CI, 1.76-2.28], and 1.66 [95% CI, 1.42-1.95] for age groups 35-54, 55-74, and 75-94 years, respectively). Adjustment for systolic blood pressure, diabetes, body mass index, and physical activity had no notable impact.

CONCLUSIONS AND RELEVANCE The observed sex contrast in risk of MI cannot be explained by differences in established CHD risk factors. The gender gap persisted throughout life but declined with age as a result of a more pronounced flattening of risk level changes in middle-aged men. The minor changes in IRs when moving from premenopausal to postmenopausal age in women make it unlikely that changes in female hormone levels influence the risk of MI.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Grethe Albrektsen, PhD, Norwegian University of Science and Technology, Unit for Applied Clinical Research, Faculty of Medicine, Olav Kyrres Gate 14, PB 8905, 7491 Trondheim, Norway (grethe.albrektsen@ntnu.no).

JAMA Intern Med. doi:10.1001/jamainternmed.2016.5451
Published online September 12, 2016.

Cardiovascular disease was long thought of as a disease primarily affecting men but is now recognized as the number 1 killer in women, despite the lower incidence, in particular among young and middle-aged women.[1-4] Early reports based on comparison of crude age-standardized mortality rates from ischemic heart disease found 3- to 4-fold higher rates in men than women.[5] It was not clear whether this sex contrast wholly or in part was due to different exposure to established risk factors. A review from 1997[6] concluded that the gender gap could not be explained by differences in the levels of known risk factors, though based on results from few studies. One additional study found a 2-fold higher risk in men than women after adjustment for coronary heart disease (CHD) risk factors.[7] The scarcity of adjusted risk estimates for sex partly relates to the fact that previous studies mainly examined men.[4] Those including a sufficient number of women have focused on sex-specific effects of CHD risk factors, rather than comparing risk between men and women.[1,4,6,8-13] Thus, it is still not clear how large the sex contrast in risk of CHD is after adjustment for differences in the level of established risk factors.

Despite limited empirical evidence, several hypotheses on biological mechanisms have been proposed for explaining a potential sex difference in the risk of CHD.[3,4,6,12,14] The low risk of CHD in premenopausal women is suggested to be related to a protective effect of endogenous female hormones,[3,4] but this theory has been questioned.[6,14] Sex heterogeneity in insulin resistance mechanisms, favorable low-density lipoprotein cholesterol characteristics in women, and differences in aging processes influencing arterial stiffness have also been hypothesized to be of importance.[3,6,12] The increase in risk of CHD in postmenopausal women, possibly hormone related[3,4] or due to age-related changes in risk factor levels,[3,15] may lead to a diminishing sex contrast in risk of CHD with increasing age. However, few studies have presented age-specific adjusted risk estimates for sex or age-incidence curves of CHD during a complete life span.

The aim of the present study was therefore to quantify the difference in risk of incident myocardial infarction (MI) between men and women and to examine to what extent any potential sex contrast can be explained by differences in the levels of CHD risk factors. Both overall and age-specific risk estimates are presented, together with unadjusted and adjusted age-incidence curves. Our results are based on data from a large, population-based, prospective study in Tromsø, Norway.

Key Points

Question Is the gender contrast in risk of myocardial infarction explained by differences in risk factors, and does the postmenopausal risk increase eliminate the sex difference?

Findings In this cohort study, men had roughly twice the risk of women after adjustment for serum lipid levels, blood pressure, smoking, diabetes, body mass index, and physical activity. The gender gap persisted throughout life but declined with age due to a flattening of the incidence curve in men. In women, risk increased steadily with age.

Meaning The higher risk of myocardial infarction in men compared with women cannot be explained by differences in established risk factors.

Methods

Study Population

The present study comprised individuals who participated in the Tromsø Study[16] at least once at age 20 years or older during the period 1979 through 2008 (2nd to 6th survey). The participation rate was high for all surveys, but the number and age range of persons invited (new and previous participants) varied between surveys (range, 8130 to 27 158 persons; mainly ages ≥20 or ≥30 years).[16] At each survey, participants completed a questionnaire regarding demographic and clinical information, as well as lifestyle factors. Anthropometric measures, blood pressure (BP) measurements, and blood samples were assessed through physical examinations.[16] The Tromsø Study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics. Written informed consent for using information in future research projects was introduced in 1994 (4th and later surveys).

Each individual was considered to be at risk of MI (first occurring) from age 35 years (no women received a diagnosis of MI before that age), or from first survey participation at a higher age, until date of diagnosis, emigration, death, or closing date of study (December 31, 2012). Dates of diagnoses were assessed retrospectively by linking to information from the local hospital discharge register and the national Cause of Death Registry by means of unique 11-digit personal identification numbers. Dates of emigration or death (censoring dates) were obtained from the Central Population Register of Norway. A total of 33 997 individuals (51% women) were included, contributing 600 452 person-years at risk (292 160 and 308 292 for men and women, respectively) at ages 35 to 102 years. Median follow-up time was 17.6 years (range, 1 month to 33 years). A total of 35.7%, 22.9%, 19.2%, 12.8%, and 9.4% had participated in 1, 2, 3, 4, and 5 surveys at age 20 years or older, respectively.

Diagnosis of Myocardial Infarction

Modified World Health Organization–MORGAM (MONICA Risk, Genetics, Archiving and Monograph) criteria for the diagnosis of MI were applied, based on clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable. Information on diagnoses was initially assessed by linking data from the Tromsø Study with the discharge diagnosis register at the University Hospital of North Norway, the only hospital in the area, searching for *International Classification of Diseases, Eighth Revision,* codes 410 to 414, 427, 795, and 796 (for diagnoses before 1980), *International Classification of Diseases, Ninth Revision,* codes 410 to 414, 427.5, 798, and 799 (1980-1998), and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* codes I20-I25, I46, R96, R98,

Table 1. Characteristics of Study Population at Start of Follow-Up, the Tromsø Study, Continuous Variables[a]

Coronary Heart Disease Risk Factor	Mean (SD) Men (n = 16 625)	Mean (SD) Women (n = 17 372)	Categories, No.[b]	Interval Size	First Category	Last Category
Total cholesterol, mmol/L	5.9 (1.2)	5.7 (1.3)	10	0.5	<5.0	≥9.0
HDL-C, mmol/L	1.4 (0.4)	1.7 (0.4)	12	0.15	<1.00	≥2.50
HDL-C/total cholesterol, %	24.3 (7.9)	30.5 (8.8)	6	5	<15	≥35
Systolic BP, mm Hg	133 (15)	126 (20)	8	10	<120	≥180
Diastolic BP, mm Hg	80 (12)	76 (12)	8	5	<70	≥100
BMI[c]	24.9 (3.2)	23.8 (4.0)	5	5-7.5	<18.5	≥35.0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL-C, high-density lipoprotein cholesterol.

SI conversion factor: To convert cholesterol components to milligrams per deciliter, divide by 0.0259.

[a] Median age at measurement, 35 years (interquartile range, 31-44 years).

[b] Number of exposure categories defined.

[c] Categorized into underweight (<18.5), normalweight (18.5-24.9), overweight (25.0-29.9), obese 1 (30.0-34.9), and obese 2-3 (≥35).

Table 2. Characteristics of Study Population at Start of Follow-Up, the Tromsø Study, Categorical Variables

Coronary Heart Disease Risk Factor	% Men (n = 16 625)	% Women (n = 17 372)
Smoking, daily		
No	30.0	38.0
Former	24.8	21.7
Yes	45.0	40.0
Missing	0.2	0.2
Physical activity[a]		
Low, sedentary only	22.2	22.8
Moderate, <4 h/wk	47.1	62.4
High,[b] ≥4 h/wk	30.4	14.4
Missing	0.3	0.4
Diabetes		
No	98.8	98.4
Yes	1.0	1.3
Missing	0.2	0.3

[a] Leisure time physical activity.

[b] Two last original response categories combined.

and R99 (1999 and after). Linkage to the national Cause of Death Registry allowed identification of out-of-hospital fatal incident cases of MI. An independent end point committee validated all diagnoses based on records from hospital and out-of-hospital settings, autopsy records, and death certificates.

Statistical Analysis

Age-specific crude incidence rates (IRs), crude incidence rate ratios (IRRs), and incidence rate difference (IRDs) between men and women within 5-year categories were calculated on the basis of observed number of incident MIs and person-years at risk. Unadjusted and adjusted age IRs (per year) and overall and age-specific IRRs (relative risk) with 95% confidence intervals for men vs women were then calculated on the basis of log-linear Poisson regression analyses of person-years at risk.[17(pp120-150)] The full-parametric Poisson regression model is similar to the semiparametric Cox proportional hazards model, but because the timescale (age) is included as a parameter in the model, age-incidence curves and age-specific risk estimates can be assessed directly. Interaction terms between sex and age (modeled as a fourth-order polynomial) were included in the statistical model to test for differences in the shape of the age-incidence curves between men and women, and thereby also evaluate whether the sex contrast in risk of MI differed by age. A significance level of .05 was applied.

The extent of confounding by CHD risk factors was evaluated through percentage change in the regression coefficient for sex when adding 1 factor at a time into a regression model adjusted for age and birth cohort and into a model adjusted for other CHD risk factors. A risk factor that leads to a change in parameter estimate of at least 20% is considered a confounder by Hosmer and Lemeshow.[18] In our study, the final adjusted model included CHD risk factors that changed the regression coefficient for sex by at least 5% when added into the model with mutual adjustment for all factors. Potential confounders were systolic and diastolic BP (mean of 2 last measurements), serum total cholesterol and high-density lipoprotein cholesterol (HDL-C), smoking, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), leisure time physical activity, and diabetes. The Akaike information criterion (lowest value) was applied for choosing the most appropriate model when adjusting for serum lipid levels. All factors were treated as categorical in the Poisson regression model, allowing for nonlinear associations. Categorization is a prerequisite for the generation of the person-years at risk table (information on a group level), but intervals can be as narrow as needed. The mean values of risk factors measured on a continuous scale at the start of follow-up, and categorization used in the analyses, are shown in **Table 1**. Original response categories were used for risk factors measured on a nominal scale (**Table 2**). Missing categories were excluded from the analyses.

In the generation of the person-years at risk table (group level), attained age (1-year intervals) was defined as the timescale. Sex and birth cohort (10 5-year categories) were considered as time-independent categorical covariates, whereas all other risk factors were treated as time-dependent covariates, allowing for a shift in exposure category during follow-up. Thus, the most recent measure defined the

Table 3. Crude Age-Specific Risk Estimates of Incident Myocardial Infarction (MI) by Sex, the Tromsø Study, 1979-2012

	Men			Women			Men vs Women	
Age, y	Incident MI, No.	Person-years	IR[a]	Incident MI, No.	Person-years	IR[a]	IRD[b]	IRR[c]
35-39	29	44 519.6	6.5	2	48 241.0	0.4	6.1	15.7
40-44	79	50 865.3	15.5	9	53 670.2	1.7	13.9	9.3
45-49	173	49 456.5	35.0	23	51 248.4	4.5	30.4	7.8
50-54	261	44 296.2	58.9	47	43 576.0	10.8	48.1	5.5
55-59	310	36 624.4	84.6	74	33 653.1	22.0	62.7	3.8
60-64	281	26 305.8	106.8	84	23 994.7	35.0	71.8	3.1
65-69	190	16 506.4	115.1	78	16 515.9	47.2	67.9	2.4
70-74	182	10 362.6	175.6	119	12 976.4	91.7	83.9	1.9
75-79	165	7060.1	233.7	137	10 570.3	129.6	104.1	1.8
80-84	141	4035.7	349.4	140	7778.0	180.0	169.4	1.9
85-89	74	1679.2	440.7	104	4263.8	243.9	196.8	1.8
90-94	20	391.0	511.5	54	1512.6	357.0	154.5	1.4
≥95	2	57.1	350.0	15	291.3	515.0	−165.0	0.7

Abbreviations: IR, incidence rate; IRD, incidence rate difference; IRR, incidence rate ratio.

[a] Incidence rate per 10 000 person-years, calculated as observed number of MIs divided by person-years at risk within each 5-year age group, multiplied by 10 000.

[b] Calculated as difference between IR for men and IR for women.

[c] Calculated as ratio between IR for men and IR for women.

exposure category. The initial exposure category for time-dependent variables was defined according to levels closest in time before the age of 35 years, or to levels recorded at first survey participation at an older age. The generation of the person-years table based on individual data and the Poisson regression analyses, with calculation of maximum likelihood estimates and likelihood ratio tests, was performed by means of the EPICURE software package.[19]

Results

Crude Incidence Rates of MI by Age and Sex

A total of 2793 persons, 886 women and 1907 men, received a diagnosis of incident MI during follow-up at ages 35 to 102 years in the period 1979 through 2012. The crude IR increased with increasing age (5-year categories) for both sexes, rather slowly until the age of 65 to 69 years (**Table 3** and **Figure**, A), then more rapidly up to age 95 years, although with an almost linear increase on a logarithmic scale, in particular among women (Figure, B). Except among the very old (≥95 years), the IR for women was lower than for men, similar to the IR among men 10 to 15 years younger (Table 3 and Figure, A). The IRD between men and women increased with age (Table 3) (IRD in the range 6.1-196.8 per 10 000 person-years at ages 35-89 years), whereas the IRR decreased (Table 3) (IRR in the range 15.7-1.4 at ages 35-94 years). Data were scarce for the oldest (≥95 years), in particular in men (2 MIs, 57.1 person-years), and further analyses were therefore restricted to the age interval 35 to 94 years.

The sex-specific predicted age-incidence curves (1-year intervals), calculated on the basis of a fourth-order polynomial in Poisson regression analysis (unadjusted for other factors), fitted the crude (observed) age incidence curves well (Figure, B). The overall test for interaction between sex and age (4 terms) was statistically significant ($P < .001$). For age groups 35 to 54, 55 to 74, and 75 to 94 years, the IRRs for men vs women, adjusted for age (1-year intervals, categorical) within each broad age group, were 6.78 (95% CI, 5.37-8.56), 2.73 (95% CI, 2.42-3.09), and 1.83 (95% CI, 1.59-2.11), respectively (Figure, B).

Evaluation of Extent of Confounding

Adjusted for age and birth cohort, the overall relative risk of MI for men vs women was 2.72 (95% CI, 2.50-2.96), close to the overall age-adjusted IRR (**Table 4**). When other risk factors were adjusted for 1 at a time (Table 4), HDL-C and total cholesterol level, and the ratio between these lipid components, were the factors with strongest impact on the association with sex (change in regression coefficient of −19.0%, 14.2%, and −17.1%, respectively), followed by diastolic BP (−5.9%) and daily smoking (−5.6%). No notable change in the regression coefficient for sex was seen when adjusting for systolic BP (−1.7%), diabetes (0%), BMI (−0.2%), or physical activity (3.3%). Although HDL-C level was the factor with strongest impact, close to the predefined level for being a confounder (±20%), adjustment for both total cholesterol level and HDL-C, or HDL-C in percent of total cholesterol, gave a slightly better fit to the data (Akaike information criterion).

Adjusted for factors that changed the regression coefficient for sex by at least 5% in a model adjusted for all risk factors (Table 4) (total cholesterol, HDL-C, diastolic BP, and smoking), with lipid profile represented by the ratio between HDL-C and total cholesterol, the contrast in risk between sexes remained substantial (IRR, 2.07; 95% CI, 1.89-2.26; regression coefficient reduced by 27.3%).

Adjusted Incidence Rates of MI by Age and Sex

The age-incidence curves for men and women were somewhat closer when calculated on the basis of a regression model

adjusted for birth cohort, HDL-C in percent of total cholesterol, diastolic BP, and smoking (Figure, C). The adjusted risk curves were close to parallel (on log-scale) before age 45 to 50 years and after age 70 years, but the distance between the curves was considerably smaller among the oldest (Figure, C). A less steep increase in the oldest compared with the youngest was seen for both sexes, but the flattening of the incidence curve was considerably more pronounced and started roughly a decade earlier for men than women (Figure, C) (45-50 years vs 55-60 years). In women, no sudden changes in risk were seen when moving from premenopausal to postmenopausal ages (Figure, C).

The interaction between sex and age remained significant in the adjusted analysis ($P < .001$, overall test for interaction). The sex difference in risk of MI diminished with age but persisted throughout life. For age groups 35 to 54, 55 to 74, and 75 to 94 years, adjusted IRRs for men vs women were 3.64 (95% CI, 2.85-4.65), 2.00 (95% CI, 1.76-2.28), and 1.66 (95% CI, 1.42-1.95), respectively. In view of the adjusted age incidence curves (Figure, C), the decreasing sex contrast with increasing age was related to the more pronounced flattening of risk level in middle-aged men, approaching the risk level for women.

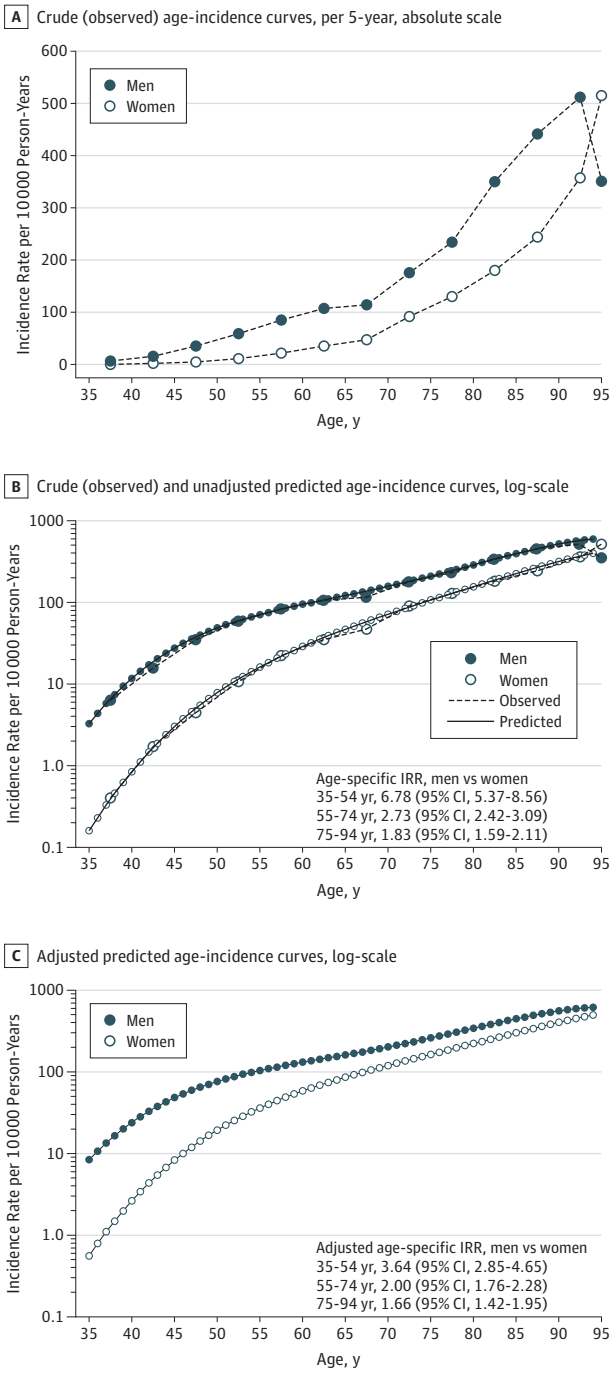
Discussion

The present large, population-based prospective study shows that the risk of MI increases with age in both sexes, with lowest risk for women. The gender gap persists throughout life, but whereas relative risk estimates diminish with age, absolute differences in risk increase. Overall, men have roughly twice the risk of MI compared with women, a contrast that cannot be explained by differences in the levels of other CHD risk factors.

The sex-specific age-incidence curve in our study, showing low risk of MI in young and middle-aged women, with risk level in women corresponding to that in men 10 to 15 years younger, is consistent with the few previous reports presenting crude age-incidence or age-mortality rates.[6,20-22] It has been suggested that the low risk in women at premenopausal ages is related to a positive effect of female hormones on lipid profile, vascular activity, endothelial function, or other cardioprotective substances.[3,23] A recent randomized clinical trial[24] found that postmenopausal estradiol therapy was associated with less progression of subclinical atherosclerosis, in contrast to another study[25] that reported a lack of correlation between time since menopause and atherosclerosis measures. A few previous studies have found no, or even an adverse effect of hormone therapy on risk of MI, despite a beneficial effect on CHD risk factors.[3]

It is difficult to distinguish between effects of menopause and age,[26] but the age-incidence curve for hormone-related diseases would be expected to be influenced by changes in hormone levels, possibly with a delay in effect.[27] In our study, only minor changes in the IR of MI were seen when moving from premenopausal to postmenopausal age in women. In

Figure. Age-Incidence Curves for Incident Myocardial Infarction (MI) in Men and Women



A, Crude incidence rates increase with age for both sexes rather slowly until the age of 65 to 69 years, then more rapidly up to age 95 years. B, Predicted age-incidence rates, modeled as a fourth-order polynomial in Poisson regression analysis of person-years at risk, fit crude (observed) age-incidence curves well. The incidence rate ratio (IRR) of MI for men vs women decreased with age but persisted throughout life. C, Sex heterogeneity in risk of MI (IRR) remains substantial in young and old persons after adjustment for birth cohort, HDL-C in percent of total cholesterol, diastolic blood pressure, and daily smoking (incidence rates shown for reference categories of adjustment factors).

Table 4. Relative Risk of Myocardial Infarction in Men vs Women; Extent of Confounding by Coronary Heart Disease (CHD) Risk Factors

Risk Factors Included in the Regression Model	IRR[a] (95% CI), Men vs Women	Change (Δ) in Regression Coefficient for Sex When Adjusting for CHD Risk Factors		
		Δ, %[b]	Δ, %[c]	Δ, %[d]
Initial models				
Sex, adjusted for age, 1-y intervals	2.78 (2.56-3.02)	...	...	...
Sex, adjusted for age and birth cohort	2.72 (2.50-2.96)	...	...	...
Additional adjustment, 1 CHD risk factor				
Total cholesterol	3.08 (2.83-3.35)	14.2	...	...
HDL-C	2.22 (2.04-2.42)	−19.0	...	...
HDL-C in percent of total cholesterol	2.29 (2.11-2.50)	−17.1	−15.8	...
Systolic BP	2.67 (2.46-2.91)	−1.7	−1.7	...
			2.4[e]	...
Diastolic BP	2.56 (2.36-2.79)	−5.9	−7.8	...
			−3.9[e]	...
Smoking, daily	2.57 (2.36-2.80)	−5.6	−7.5	...
Body mass index category	2.72 (2.50-2.96)	−0.2	0.6	...
Physical activity	2.81 (2.59-3.06)	3.3	1.9	...
Diabetes	2.72 (2.50-2.96)	0	−0.7	...
Additional adjustment, all CHD risk factors	2.16 (1.97-2.37)	−23.0	...	...
Final model[f]	2.07 (1.89-2.26)	−27.3		
HDL-C in percent of total cholesterol		...	...	−16.6
Diastolic BP		...	...	−6.9
Daily smoking		...	...	−7.6

Abbreviations: BP, blood pressure; ellipses, not applicable; HDL-C, high-density lipoprotein cholesterol; IRR, incidence rate ratio.

[a] Calculated as the exponential of the regression coefficient for sex in the log-linear Poisson regression model.

[b] Percent change when a single CHD risk factor (or all factors, or the subset of 3 factors in the final model) is added into a model adjusted for age and birth cohort.

[c] Percent change when a single CHD risk factor is added into a model adjusted for age, birth cohort, and all other CHD risk factors, except SBP.

[d] Percent change when a single CHD risk factor (1 of 3) is added as last factor into the final model.

[e] Additional adjustment for diastolic or systolic BP, respectively.

[f] Model including sex, age, birth cohort, and CHD risk factors that change the regression coefficient for sex by at least 5% when added into a model adjusted for all other CHD risk factors, that is, HDL-C in percent of total cholesterol, diastolic BP, and daily smoking.

fact, the log-linear increase in risk of MI was slightly less pronounced after the age of 55 to 60 years, though almost linear on a logarithmic scale in the age span of 35 to 94 years, consistent with previous reports.[6,20-22] A curvilinear shape was more evident in men, with a flattening of risk level change from age 45 to 50 years, in line with previous reports.[6,20-22] On an absolute scale, a sharp increase in risk was seen for both sexes after the age of 69 years, even slightly more pronounced for men than women. The decrease in IR after the age 95 years in men in our study may relate to a selection of very healthy, though extremely few individuals. The results for this subgroup were unreliable because of scarce data.

The present finding that men have an overall adjusted risk roughly twice that of women is consistent with results from 2 previous studies.[7,28] One of these studies[28] was based on comparisons of cumulative probabilities in subgroups defined by several risk factors. In our study, the sex difference was strengthened when comparing men and women with similar total cholesterol level, whereas adjustment for HDL-C weakened the association. These lipid components had a stronger confounding effect than BP and smoking, consistent with results from another study.[7] A recent study identified BP as the strongest mediator for the association between sex and cardiovascular risk, followed by cholesterol levels.[29] Similarly to our findings, these risk factors explained only part of the sex contrast in risk of MI.

Consistent with others,[8,29,30] we observed that the association with sex, in terms of relative risk, diminished with increasing age. In contrast, the absolute difference in risk increased, as reported previously.[7] The apparent contrast between absolute and relative effect measures when evaluating interaction effects is well known.[20] In our study, the decreasing IRR values for sex with increasing age seem to relate to the more pronounced flattening of risk level in middle-aged men, rather than a postmenopausal risk increase in women.[4] In fact, the age-incidence curves for men and women were almost parallel (on a logarithmic scale) during ages 70 to 94 years.

A strength of the present study is that risk factors were assessed repeatedly during follow-up, making it possible to take into account changes in exposure levels, thus minimizing misclassification bias in the risk estimates. The application of a parametric survival model is essential for estimating time-related effects. Most established risk factors for MI were considered as potential confounders. Information on alcohol was incomplete in our study, but adjustment for being a teetotaler (8.1% with missing data) did not notably influence risk estimates for sex (−0.3%). We are not aware of any other factors that are strongly related to the risk of MI and also differ sufficiently between the sexes to introduce bias in risk estimates. The extent of confounding, quantified by change in regression coefficient for sex, will depend on both the risk profiles in men and women in the empirical data and the strength of association between confounders and main outcome, as well as the model applied. Sex heterogeneity in the association with CHD risk factors was not considered in the present study. Different manifestation and symptoms of disease[1,31,32] may have led to underdiagnosis of MI in women, possibly leading to overestimation of relative risk for men vs women. However, it is unlikely that the observed sex heterogeneity can be completely explained by differences in diagnostic sensitivity.

Conclusions

Men have roughly twice the risk of MI compared with women, a contrast that cannot be explained by established CHD risk factors. The sex difference persists throughout life but declines with age. The minor changes in IRs when moving from premenopausal to postmenopausal age in women make it unlikely that changes in female hormone levels influence the risk of MI. A better understanding of the mechanisms behind the observed gender gap in risk of MI is important both for prevention and treatment of disease in women, as well as in men.

ARTICLE INFORMATION

Accepted for Publication: July 25, 2016.

Published Online: September 12, 2016. doi:10.1001/jamainternmed.2016.5451

Author Affiliations: Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway (Albrektsen, Bønaa); Department of Mathematics, University of Bergen, Norway (Heuch); Department of Community Medicine, Faculty of Health Sciences, UiT-The Arctic University of Norway, Tromsø, Norway (Løchen, Wilsgaard, Njølstad, Bønaa); Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Norway (Thelle); Section for Epidemiology and Social Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden (Thelle); Clinic for Heart Disease, St Olavs University Hospital, Trondheim, Norway (Bønaa).

Author Contributions: Drs Albrektsen and Bønaa had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Albrektsen, Bønaa.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Albrektsen, Bønaa.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Albrektsen, Heuch, Bønaa.
Obtained funding: Løchen.
Administrative, technical, or material support: Wilsgaard.
Study supervision: Bønaa.

Conflict of Interest Disclosures: None reported.

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