

Original Scientific Paper

Sex-based differences in premature first myocardial infarction caused by smoking: twice as many years lost by women as by men

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Received 14 May 2008 Accepted 10 December 2008

Background It has been debated whether smoking increases the risk of heart disease relatively more in women than in men. It is not known whether there are sex differences with regard to how many years prematurely smoking causes acute myocardial infarction (AMI) to occur. We aimed to determine how smoking affects the age of onset of first myocardial infarction in both the sexes.

Design Clinical data were consecutively entered into a database and were analysed with a multivariate regression technique.

Methods In the years 1998–2005, data on 1784 consecutive patients (38.3% women) who were discharged from or died in a district general hospital with a diagnosis of first myocardial infarction were included in the study. Age at first AMI was analysed.

Results Unadjusted mean ages were 76.2 years for women and 69.8 years for men, a difference of 6.4 years ($P < 0.001$). Mean age within the various groups was: women nonsmokers 80.7 years, women smokers 66.2 years, difference 14.4 years ($P < 0.001$); men nonsmokers 72.2 years, men smokers 63.9 years, difference 8.3 years ($P < 0.001$). After adjustment for risk factors (hypertension, cholesterol levels, diabetes) and patient characteristics (history of angina, history of stroke) 13.7 years of the age difference in women were attributed to smoking; the corresponding figure in men was 6.2 years ($P < 0.001$).

Conclusion First AMI occurred significantly more prematurely in women than in men smokers, implying that twice as many years were lost by women as by men smokers. *Eur J Cardiovasc Prev Rehabil* 16:174–179 © 2009 The European Society of Cardiology

European Journal of Cardiovascular Prevention and Rehabilitation 2009, 16:174–179

Keywords: epidemiology, myocardial infarction, risk factors, sex, smoking

Introduction

Many population-based studies have revealed that smoking is a major risk factor for ischaemic heart disease, including acute myocardial infarction (AMI) [1–5]. It has been debated whether there are sex differences in the effects of smoking, implying that smoking increases the risk of ischaemic heart disease relatively more in women than in men. Some population-based studies have not reported

sex-based differences [2,6,7], whereas others have found a sex-based effect, with smoking entailing an increased relative risk in women [4,5,8,9].

Research studies must be viewed in light of the fact that, in general, it is only during the past two decades that women have experienced the same long-term exposure to tobacco as men, because women have adopted the smoking habit historically later than men. Therefore, new population studies with recently collected data should contribute to an improved understanding of possible sex differences in this area.

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Likewise, the previous decade has been an appropriate period to collect other types of data, which could supplement the standard risk analysis of the smoking and sex relationship. Against this background, we decided to explore information on patients hospitalized with AMI entered consecutively into a database in the years from 1998 to 2005. In particular, we aimed to quantify the extent to which smoking causes premature first AMI in women and men.

Methods

Patients

The study consisted of patients with a permanent address in Norway who were discharged alive or dead from the district general hospital in the city of Lillehammer with a diagnosis of first AMI in the 8-year period from January 1998 to December 2005. The hospital had a catchment population of approximately 90 000 individuals. Owing to the hospital's geographical location and to the organization of the hospital services nearly all admitted AMI patients within the catchment area came to this hospital. Therefore, it was estimated that more than 98% of the AMI patients admitted to the hospital in the catchment area were included in the study.

As the patient administration system lacked essential clinical information, we established a database that might be helpful for the hospital's quality control of the management of AMI. By the use of standard data collection forms, information on history, presenting features and treatment received was acquired. The data were consecutively registered by doctors working in the hospital's medical department and were entered into the database by a research nurse. The patient administrative system was checked retrospectively every month to ensure that patients and patient data were not omitted. The records of patients diagnosed with unstable angina were reexamined by a senior cardiologist to ensure that valid diagnostic criteria that distinguished unstable angina and AMI were applied. The discharge of all patients with myocardial infarction between 1 January 1998 and 31 December 2000, were classified according to the WHO criteria, and from 1 January 2001 to 31 December 2005, according to the joint definition of the European Society of Cardiology/American Heart Association/American College of Cardiology [10].

The following recorded variables were used for the present analyses: age, sex, history of smoking, history of treatment for hypertension, cholesterol values, presence of noninsulin-dependent or insulin-dependent diabetes mellitus, presence of angina pectoris and history of stroke. In an alternative specification (not reported in tables), the variables describing the history of stroke and angina were excluded from the analysis. If a smoking history was missing, the patient or his family was

contacted by telephone to obtain the data. As a consequence, smoking history was known for all patients.

The variable defining smoking had three categories: 'current smoker', if the patient smoked or had done so up until 3 months previously; 'exsmoker', if the patient was a former smoker and had stopped more than 3 months previously; and 'nonsmoker', if the patient had never smoked.

The reported cholesterol values were those measured at admission, because representative 'true' cholesterol levels are not obtained if sampled on subsequent days. Neither the later cholesterol values nor the cholesterol values of patients with a history of chest pain for more than 24 h were included. Thus, the information on serum cholesterol values usable for analyses was obtained from 1372 out of 1784 patients. As the group with missing values for this variable was of a substantial size, we analysed two different samples to test the stability of our basic results, the total sample and a reduced sample. In the latter, patients without usable cholesterol values were excluded. Data on population smoking habits were downloaded from Statistics Norway and prepared for presentation [11].

Statistical methods

Risk factors other than the variable describing cholesterol levels were coded as categorical variables (Table 1), with reference units (no events) given the value of zero. Comparisons for categorical variables were made by χ^2 tests. Continuous variables were described by means and standard deviations and were compared by *t*-tests within a General Linear Model (GLM) procedure.

The association between risk factors and age at first AMI was analysed by multivariate regression. The variable describing cholesterol levels was normalized to its mean value (5.62) in the regression analyses. We report the analyses of associations between these risk factors and age at first AMI for the entire sample, for the sample that included data on cholesterol levels, and separate analyses of the sexes including the variable describing cholesterol levels. Explicit tests of the sex differences in the effects of smoking on age at first AMI after control for relevant confounders were performed within a model including interaction terms between sex and smoking status. Only the result of the significance tests from this model is reported. All *P* values are from two-sided tests. Statistical analyses were performed with SAS, version 9.1 (Cary, North Carolina, USA).

Results

Descriptive statistics

In the complete sample, 1784 patients [1100 men, 684 (38.3%) women] were discharged or died with a diagnosis of first AMI. Patient characteristics and risk factors are

Table 1 Baseline characteristics for patients hospitalized with first acute myocardial infarction

Variables	Total	Men	Women	Differences (<i>P</i> value)
Demographic variables				
Sex	1784	1100 (61.7%)	684 (38.3%)	23.4% (<0.001)
Age (years)				
All patients	72.3 (13.3)	69.8 (13.4)	76.2 (12.1)	-6.4 (<0.001)
Nonsmokers	77.1 (12.3)	72.2 (13.7)	80.7 (9.6)	-8.5 (<0.001)
Exsmokers	74.6 (10.5)	74.7 (10.5)	74.4 (10.5)	0.3 (0.805)
Current smokers	64.5 (13.1)	63.9 (13.1)	66.2 (12.8)	-2.3 (0.037)
Classical risk factors				
Smoking				
Exsmoker (%)	505 (28.3)	374 (34.0)	131 (19.2)	14.8 (<0.001)
Current smoker (%)	580 (32.6)	426 (38.7)	155 (22.5)	16.2 (<0.001)
Hypertension (%)	671 (37.7)	357 (32.6)	314 (46.0)	-13.4 (<0.001)
Diabetes mellitus				
Without insulin (%)	159 (8.9)	85 (7.7)	74 (10.8)	-3.1 (0.026)
With insulin (%)	113 (6.3)	59 (5.4)	54 (7.9)	-2.5 (0.033)
Cholesterol (mmol/l)	5.6 (1.3)	5.5 (1.2)	5.8 (1.4)	-0.3 (<0.001)
Other characteristics				
History of angina pectoris (%)	466 (26.1)	255 (23.2)	211 (30.9)	-7.7 (<0.001)
History of stroke (%)	226 (12.8)	132 (12.1)	94 (14.0)	-1.9 (0.250)

Categorical variables described by frequencies and percentages of the total. Continuous variables described by means (standard deviations). Differences are calculated as values for men minus values for women.

given in Table 1. Smoking was more frequent among men, whereas a markedly higher proportion of women had hypertension and slightly higher proportions of women had angina pectoris or had suffered a stroke.

The unadjusted mean age at the time of hospitalization for first AMI was 72.3 years for the entire sample, 69.8 years (range 28–99, median 71.7) for men and 76.2 years (range 27–103, median 79.1) for women, a difference of 6.4 years ($P < 0.001$). The unadjusted age at first hospitalization was 12.6 years lower in the current smokers than in the nonsmokers ($P < 0.001$), but with considerable variation between the sexes (Table 1). In men, the unadjusted mean age at hospitalization for first AMI was 72.2 years for nonsmokers and 63.9 years for current smokers, a difference of 8.3 years ($P < 0.001$). In women, the unadjusted age was 80.7 years in nonsmokers and 66.2 years in current smokers, a difference of 14.4 years ($P < 0.001$). The age distribution analysed by sex and smoking status (exsmokers not included) is shown in Fig. 1.

Effects of smoking

There were only marginal differences between the estimates of the regression analyses based on the total sample and those of the analyses based on the reduced sample from which patients without usable cholesterol levels were excluded (Table 2). As the inclusion of cholesterol levels better explained the variance in the data, the following presentation and discussion are based on that sample.

With no hypertension, no former diabetes, no smoking history, no angina, no former stroke and cholesterol at the average level, the mean age at first AMI is given by the intercept and equals 67.1 years in men and 77.3 years in women. In women, smoking caused a lowering of age at first AMI of 13.7 years, whereas the corresponding

figure in men was 6.2 years (test of differences in effects on the two sexes from the interaction model: $P < 0.001$). Former smoking affected age at first AMI somewhat differently in the two sexes, as it was associated with 6 years lowering of age of first AMI in women and an increase of 3.5 years in men.

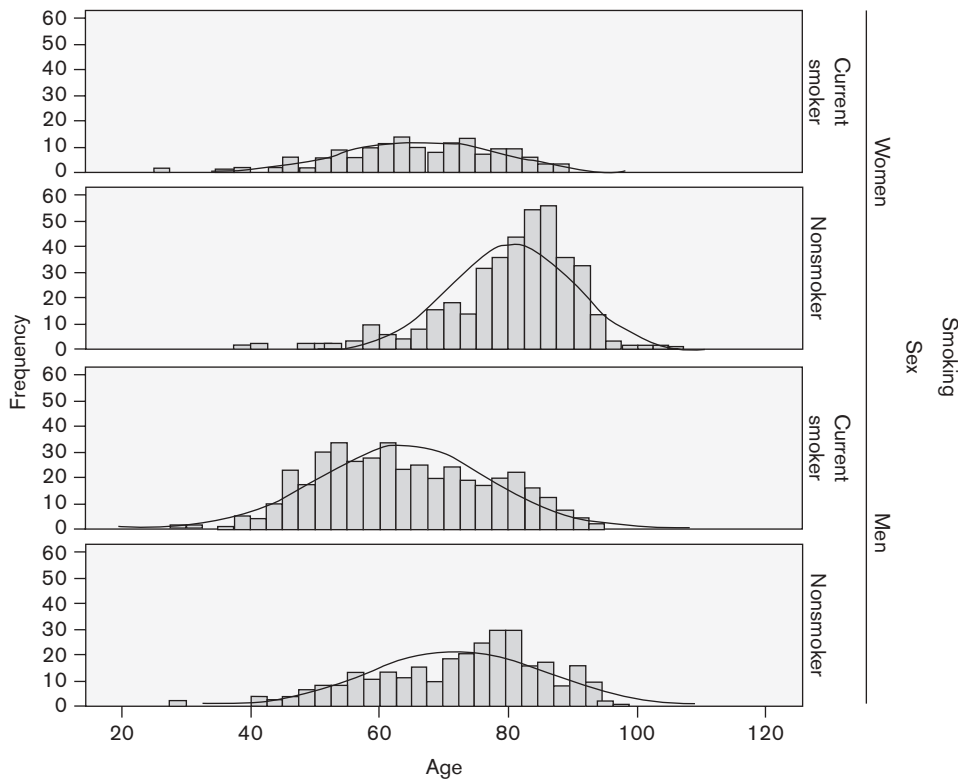
Both former angina and former stroke increased the age at first AMI, *Ceteris paribus*. In men, age at first AMI was increased by 6.8 years by former angina and by 6.9 years by former stroke, whereas the corresponding figures in women were 4.3 and 4.1 years, respectively. The mean age at first AMI decreased with increasing levels of cholesterol in both sexes, but significant only in men. The alternative specification, where the variables describing history of stroke and history of angina were excluded from the analysis, did not significantly change the effects attributed to the smoking variables, and the effects were of the same magnitude as those found in the main analysis (data not shown).

Smoking in the Norwegian population

Smoking in the Norwegian adult population has been gradually reduced from approximately 40% smokers in 1970 to about 25% in 2005, which brings Norway close to the average of the Organisation for Economic Co-operation and Development (OECD) countries [12]. The sex differences in smoking in Norway are shown in Fig. 2. Negative numbers in Fig. 2 appear when more women than men smoke.

In the early 1970s a huge difference in smoking habits between the two sexes existed. The gap diminished in the following years but it was not until the years 1990–1995, that the smoking pattern became comparable in women and men.

Fig. 1



Age at first acute myocardial infarction. Unadjusted frequencies according to sex and smoking status (exsmokers not included).

Table 2 Association between risk factors/patient characteristics and age at first acute myocardial infarction

Variables	Total sample	Reduced sample	Reduced sample – men	Reduced sample – women
Intercept ^a	72.1 (0.6)**	69.9 (0.7)**	67.1 (0.9)**	77.3 (0.9)**
Demographic variables				
Women	4.1 (0.6)**	4.2 (0.7)**	–	–
Classical risk factors				
Smoking				
Exsmoker	–0.8 (0.7)	–0.0 (0.8)	3.5 (1.0)**	–6.0 (1.3)**
Current smoker	–10.1 (0.7)**	–9.3 (0.8)**	–6.2 (1.0)**	–13.7 (1.2)**
Hypertension	–0.2 (0.6)	0.4 (0.7)	0.4 (0.9)	–0.3 (1.0)
Diabetes mellitus				
Without insulin	1.3 (1.0)	1.8 (1.1)	1.8 (1.4)	1.9 (1.6)
With insulin	–1.8 (1.1)	–2.8 (1.4)*	–1.4 (1.9)	–5.1 (2.0)*
Cholesterol (centred)	–	–1.1 (0.2)**	–1.55 (0.3)**	–0.3 (0.4)
Other characteristics				
History of angina pectoris	6.0 (0.6)**	6.3 (0.7)**	6.8 (1.0)**	4.3 (1.1)**
History of stroke	4.9 (0.8)**	6.1 (1.0)**	6.9 (1.3)**	4.1 (1.5)**
N	1765	1357	878	479
Adjusted R ²	0.25	0.26	0.24	0.29

Estimates from ordinary least-squares regression (standard error in parentheses). ^aEstimated mean age at time of hospitalization for patients with no smoking history, no hypertension, no diabetes, mean cholesterol value (cholesterol value extrapolated to zero in the analysis of the total sample), no angina pectoris and no stroke. *P<0.05; **P<0.01.

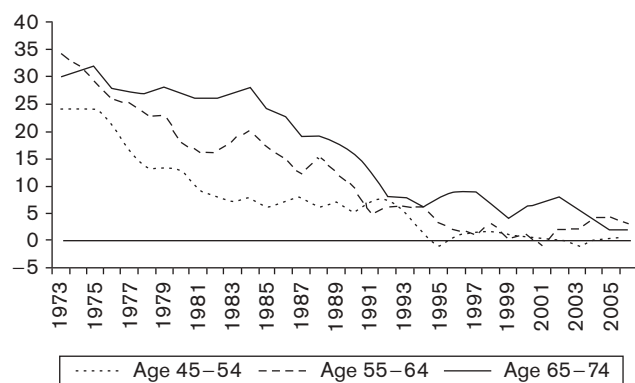
Discussion

Our findings indicate a striking effect of smoking in women. Even after adjustment was made for other risk factors, the number of years lost (i.e. years expected to be free of myocardial infarction) was on an average 13.7 years, as compared with 6.2 years in men. This strongly

indicates that a sex difference exists in the effect of smoking on coronary arteries, and shows in clinical terms that an additional significant risk is incurred by women.

Our findings, which are based on data acquired in hospitalized AMI patients, are consistent with those of

Fig. 2



Sex differences in smoking in Norway, 1973–2006. The y-axis shows the proportion (%) of male smokers minus the proportion (%) of female smokers by age group. Source: Graph prepared by authors based on data from Statistics Norway.

population-based studies, which have shown a higher risk in women than in men. In a Danish study, current female smokers had a relative risk of AMI of 2.2 compared with that of nonsmokers, whereas the relative risk for male smokers was 1.4 [4]. The corresponding figures in a Norwegian study were 3.3 and 1.9 for women and men, respectively [5]. With regard to the risk of death from ischaemic heart disease, some studies have indicated that smoking increases the risk more in women than in men [8,9], whereas others have not reported a sex-based difference [2,6].

When assessing the population-based studies, it is important to take into consideration that among current smokers, total exposure, including the number of years of tobacco smoking, may vary between the sexes. Women took up the smoking habit later than men, and, for example, in Norway, it was not until the early 1990s that smoking patterns were similar in both the sexes. Only then were the proportions of smokers in the different age groups similar for both women and men. This means that the latest studies might better compare the effect of smoking between the sexes than those undertaken some decades ago. Tobacco exposure in women is less likely to have been underestimated in recent studies. Interestingly, when assessing the population-based studies retrospectively, it seems that it is the latest studies, and not the earlier studies, that have shown an increased risk in women [4,5,8,9].

In addition, in support of our findings are two recent studies based on heart-disease registry data. In a Japanese case–control study of the risk of first AMI, sex differences were observed for the risk factor, smoking, with a markedly higher risk in women, but no sex differences were identified for the other risk factors [13]. A recent

presentation of data from a percutaneous coronary interventions registry emphasized that the risk factors for ST-segment elevation myocardial infarction were of similar magnitudes in women and men, except for smoking, which was associated with a definitely higher risk in women [14].

We observed that, among women exsmokers, the age at presentation with first AMI was reduced by 6 years, whereas no negative effect was found in men. In fact, men who were exsmokers had their first AMI at a slightly higher average age than nonsmokers. The reason for these observations is not obvious and several explanations are possible. The discrepancy might be related to differences in total tobacco exposure, not least the possibility that men quit smoking at an earlier age, which is consistent with the fact that the trend to smoking cessation among men took place earlier than in women. A more recent abandonment of smoking might have had less effect [15]. Moreover, a particularly healthy lifestyle among exsmoking men might have counteracted the negative effects of a much earlier period of smoking. It is also possible that more deleterious effects of smoking in women might have placed them at enhanced risk after shorter smoking periods. Also of note in this study is the fact that a high proportion of patients, three-fourths of men and two-fifths of women, were or had been smokers during their life course.

Our findings could also be considered the other way around. As smoking is a particularly powerful predictor of negative outcome in women, the prospects of nonsmoking women are quite good. They will have high chances to become very old without having any cardiac event. In addition to classical risk factors, our database contained information regarding the presence of angina pectoris and previous stroke. Both these variables increase the age at first AMI, which at first sight must be regarded as counterintuitive. The fact that these conditions were, however, experienced in the few years preceding the AMI and that these patients received more cardiovascular drugs (data obtained but not shown) is a possible explanation for these findings.

Although smoking history – with classification into pre-defined categories – was known for all patients, it is a limitation of our study that we were not in possession of further details about smoking habits. Smoking pattern, duration of smoking and amount of smoking were not available in this clinical data set, but have recently been examined in analyses of risk of nonfatal AMI [16].

Is it biologically plausible that there is a sex difference in the effects of smoking? Hormonal, genetic and metabolic differences between the sexes have been proposed to explain why women are more susceptible to the ill effects

of tobacco [17,18]. However, a comprehensive biological model providing a detailed understanding of the sex differences is lacking, and should be sought for. It should be noted that smoking among women has been linked not only to a disproportionately high risk of myocardial infarction, but also to a correspondingly high risk of other smoking-related diseases, such as chronic obstructive pulmonary disease and lung cancer [17,19].

Acknowledgements

This study was funded by Internal hospital and university funding only. The authors have no conflict of interest to declare.

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