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Primary care

Sex inequalities in ischaemic heart disease in general practice: cross sectional survey

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Abstract

Objective To study differences in treatment for men and women with ischaemic heart disease by using standards defined in England's national service framework for coronary artery disease.

Design Cross sectional survey using routinely collected data.

Setting 18 practices in 18 primary care groups in Trent Region.

Subjects 5891 men and women aged over 35 years with a diagnosis of ischaemic heart disease or prescription for nitrates recorded on computer.

Main outcome measure Difference in the proportion of men and women with ischaemic heart disease and taking lipid lowering treatment.

Results Women were less likely than men to have a recording of body mass index (79% (2197/2783) v 82% (2552/3102), P = 0.002), smoking (86% (2386) v 89% (2779), P < 0.0001), and blood pressure (95% (2643) v 96% (2986), P = 0.04). Women were also less likely to have a recording of fasting cholesterol concentration (35% (968) v 50% (1550), P < 0.0001) but were more likely to be obese (25% (558/2197) v 20% (514/2552), P < 0.0001) and have their most recently recorded blood pressure value over the recommended 140/85 mm Hg (60% (1598/2643) v 52% (1553/2986), P < 0.0001). Although a higher proportion of women had a raised serum cholesterol concentration (77% (749/968) v 67% (1043/1550), P < 0.0001), men were more likely to take aspirin (76% (2358) v 71% (1979), P < 0.0001), have a recorded diagnosis of hyperlipidaemia (13% (418) v 10% (274), P < 0.0001), and be prescribed lipid lowering drugs (31% (973) v 21% (596), P < 0.0001). These differences remained despite adjustments for the practice where the patient is registered, age, smoking status, obesity, diabetes, and hypertension.

Conclusion The results suggest a systematic bias towards men compared with women in terms of secondary prevention of ischaemic heart disease.

Introduction

The UK Department of Health's publication *Our Healthier Nation* outlines its aims to improve the health of the poorest people and narrow the health gap in England.[1] The national service framework for coronary artery disease sets out the blueprint for tackling heart disease, one of the leading causes of death in Britain.[2] It requires general practitioners to identify all patients with ischaemic heart disease and offer appropriate treatment to reduce their coronary risk. In secondary care, inequalities exist in access to treatment for coronary heart disease. There is a strong social gradient, for example, for access to coronary artery bypass grafts and angiography, with poorer patients having less access than more affluent patients.[3] Similarly, women with angina are less likely to be referred to a specialist[4] or to have revascularisation[5] than men. In secondary care, further inequalities exist between the sexes—in investigation and use of drug treatment.[6 7]

Inequalities may exist in primary care for patients with ischaemic heart disease, although the evidence so far is limited to the prescription of aspirin—women with angina are less likely to be prescribed antiplatelet treatment than men.[8]

We aimed to determine the extent of sex inequalities in the management of ischaemic disease in primary care using standards defined in the national service framework for coronary artery disease.[2] Our principal objective was to determine differences in the proportion of men and women with ischaemic heart disease who are tested and treated for hyperlipidaemia.

Methods

Recruitment and ethical approval

We invited all 51 primary care groups in the Trent health region to enter the study, of whom 19 volunteered. We asked primary care groups to produce a list of general practices that used computer systems compatible with MIQUEST software (EMIS/Meditel systems). We numbered each practice and randomly selected three practices per primary care group using the random number function on SPSS. We invited these practices to join the study, and the first one from each group of three to reply was recruited; if all three refused, we selected another three practices (or as many as possible if there were fewer than three) from that primary care group. In total, 65 practices were contacted, 24 volunteered, and 19 were recruited. One accepting practice had inadequate diagnostic data recorded on computer, and it was excluded from the study. Thus we recruited 18 practices. Ethical approval was obtained for the study.

Our main target population included all registered patients aged over 35 years with a Read code for

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ischaemic heart disease or with at least one prescription for a nitrate.[9] (Morbidity records are 80% sensitive for myocardial infarction,[10] and nitrate prescriptions are 73% sensitive for angina.[11]) Given the hierarchical nature of Read codes, we used the highest level Read code (G3 for the five byte version of Read and G4 for four byte version of Read) to ensure that we would identify all relevant codes for ischaemic heart disease.

Variables

We used MIQUEST[12] to extract the following data for the target population:
- Details of ischaemic heart disease: first recorded onset of ischaemic heart disease and myocardial infarction
- Comorbidity: diabetes, hypertension, and stroke
- Drug treatment: name and date of last prescription of aspirin, β blockers, calcium channel blockers, lipid lowering drugs, diuretics, and other antihypertensive drugs
- Recorded contraindications for aspirin: upper gastrointestinal disease, clotting or bleeding disorder, and history of intracranial bleeding
- Other risk factors for heart disease: age, sex, family history of cardiovascular disease, most recent smoking status, weight, height, body mass index, systolic and diastolic blood pressure, recorded HbA_{1c}, and all fasting serum cholesterol values.

These data were used to compare levels of computer recording for morbidity and lifestyle data as well as disease management, such as the proportion of patients taking aspirin or lipid lowering drugs and whose blood pressure was controlled ($<140/85$ mm Hg).

Analysis

The main outcome variable was the difference in the proportion of men and women with ischaemic heart disease taking lipid lowering drugs. We used unconditional logistic regression to determine differences in the recording and management of ischaemic heart disease between men and women, simultaneously adjusting for known cardiovascular risk factors (age, smoking status, obesity, diabetes, hypertension). We also included a factor for the patients' general practice in the multivariate logistic regression analysis. We performed a subgroup analysis for patients with either a recorded myocardial infarction or prescriptions for two or more different anti-anginal drugs.

We based our analysis on the "first step" interventions for patients with ischaemic heart disease as laid out in the national service framework for coronary artery disease (box). We examined:
- Computer recording for men compared with women for *(a)* comorbidity (ischaemic heart disease, myocardial infarction, diabetes, hypertension, or stroke); *(b)* lifestyle data (height, weight, body mass index, smoking status, and blood pressure); *(c)* cardiovascular risk factors (for example, age, family history of cardiovascular disease, obesity (body mass index (kg/m^2) >30)); and *(d)* fasting serum cholesterol values and recorded diagnoses of hyperlipidaemia.
- Disease management for men compared with women: *(a)* proportion of men and women with established cardiovascular disease recorded as taking aspirin; *(b)* proportion taking lipid lowering drugs; *(c)* proportion taking β blockers after a myocardial infarc-

> ### "First step" interventions for people with established coronary artery disease*
>
> *Patients with established coronary artery disease should have*
> - Advice on how to stop smoking, including advice on the use of nicotine replacement therapy
> - Advice and information recorded about modifiable risk factors, such as smoking, diet, weight, and alcohol
> - Advice and treatment to maintain blood pressure below 140/85 mm Hg
> - Low dose aspirin (75 mg daily)
> - Statins and dietary advice to lower serum cholesterol concentrations to below 5 mmol/l
> - β Blockers (if they have also had a myocardial infarction)
> - Meticulous control of blood pressure and glucose concentrations (if they also have diabetes)
>
> *As described in the national service framework for coronary artery disease[2]

tion; *(d)* proportion of patients whose last recorded blood pressure was under 140/85 mm Hg; *(e)* proportion of men and women with diabetes who had satisfactory glucose control.

Sample size

Before the study we established that a sample of 4224 patients with ischaemic heart disease (2112 men and 2112 women) would have a 95% power at the 0.01 significance level to detect a relative risk of 1.5 for the use of lipid lowering drugs in men. This was based on an exposure to lipid lowering drugs in women of 10% (pilot data). Nineteen practices would need to be recruited to generate such a sample.

Results

Study practices

The 18 practices were representative in terms of morbidity, number of hospital admissions, and socio-demographic characteristics. Six practices had electronic links to the pathology laboratories (blood test results are posted into the patients' records automatically).

Study population

Of the 98 137 patients registered with the study practices, 5891 (6%) had a recorded diagnosis of ischaemic heart disease or at least one prescription for nitrate ever, or both of these. Of the 5891 patients (2783 women) in the target group, 4326 (73%) had a Read code for ischaemic heart disease and 1565 had at least one nitrate prescription but no Read code for ischaemic heart disease. Of 1571 patients with a recorded diagnosis of myocardial infarction, 1083 (69%) were men.

Of the 1565 patients without a Read code for ischaemic heart disease, 856 patients (55%) had previous prescriptions for at least one other anti-anginal drug, such as β blockers or calcium channel antagonists.

Comorbidity and lifestyle data

Men were more likely than women to have a recorded diagnosis of myocardial infarction (table 1). Women were more likely to have a recorded diagnosis of

Table 1 Characteristics of 2783 women and 3108 men with recorded ischaemic heart disease in 18 general practices in Trent region

	No (%) of women	No (%) of men	P value (χ^2 test)
Age group (years):			<0.0001
35 to 44	73 (3)	112 (4)	
45 to 54	217 (8)	417 (13)	
55 to 64	495 (18)	757 (24)	
65 to 74	831 (30)	998 (32)	
≥75 years	1167 (42)	824 (27)	
Myocardial infarction	488 (18)	1083 (35)	<0.0001
Hypertension	1209 (43)	1022 (33)	<0.0001
Diabetes	288 (10)	367 (12)	0.08
Stroke	274 (10)	306 (10)	0.99

Table 3 Secondary prevention measures in 2783 women and 3108 men with ischaemic heart disease

Variable	No (%) of women	No (%) of men	P value (χ^2 test)
Fasting serum cholesterol recorded:	968 (35)	1550 (50)	<0.0001
Maximum level >5 mmol/1	749 (77)	1043 (67)	<0.0001
Most recent level >5 mmol/l	809 (84)	928 (60)	<0.0001
Recorded diagnosis of hyperlipidaemia	274 (10)	418 (13)	<0.0001
Lipid lowering treatment	596 (21)	973 (31)	<0.0001
Aspirin	1979 (71)	2358 (76)	<0.0001
Recorded contraindication to aspirin	602 (22)	642 (21)	0.36
β blocker	1369 (49)	1589 (51)	0.14

hypertension, which was largely explained by the greater proportion of women aged >75 years. No significant differences were found between men and women for the recording of diabetes or stroke.

Women were on average older (mean age 72 years, compared with 67 years for men, P<0.0001). Men were more likely to have their height, weight, and body mass index recorded (table 2); of patients with a recorded body mass index, women were more likely to be obese. Men were more likely to have smoking status recorded (table 2); men were more likely to be former or current smokers.

Use of aspirin and β blockers
Men were more likely to be recorded as taking aspirin (table 3). No difference was found in the proportion of men and women with a computer recorded contraindication to aspirin. No sex differences were found in the proportion of patients taking β blockers in the whole population with ischaemic heart disease (table 3) or in the subgroup of patients with a recorded myocardial infarction (data not shown).

Men were more likely to have a blood pressure value recorded (table 2), although the difference was not clinically important. Women were more likely, however, to have their last blood pressure reading above the new target value of 140/85 mm Hg (table 2).

Recording of fasting serum cholesterol concentration
Men were more likely to have a fasting serum cholesterol concentration recorded (table 3); in the

subgroup of practices with electronic links for pathology results, men were still more likely than women to have a recorded fasting serum cholesterol concentration (odds ratio 1.8 (95% confidence interval 1.5 to 2.1); P<0.0001). This suggests that the differences are not just a recording phenomenon but that men are more likely to have their cholesterol concentration measured.

Diagnosis and treatment of hyperlipidaemia
Although men were more likely to have a test result recorded, women were more likely to have an abnormal reading (fasting serum cholesterol concentration >5 mmol/l). Despite this, men were more likely to have a recorded diagnosis of hyperlipidaemia and to have received lipid lowering treatment (table 3). When we restricted the analysis to patients with a fasting serum cholesterol concentration >5 mmol/l, men were still more likely to receive lipid lowering treatment (odds ratio 1.30 (1.08 to 1.58); P=0.0007).

Multivariate analysis
Table 4 shows the results of the multivariate analysis to determine factors associated with having a fasting serum cholesterol concentration recorded on computer. Men were almost twice as likely to have this measurement recorded despite adjustments for their general practice, age, diabetes, hypertension, obesity, and smoking status (adjusted odds ratio 1.97 (1.67 to 2.32); P<0.0001). Similarly, men were also more likely

Table 2 Lifestyle data for 2783 women and 3108 men with ischaemic heart disease

Variable	No (%) of women	No (%) of men	P value (χ^2 test)
Height recorded	2218 (80)	2589 (83)	<0.0001
Weight recorded	2305 (83)	2645 (85)	0.02
Body mass index recorded:	2197 (79)	2552 (82)	0.002
Index >30 (kg/m²)	558 (25)	514 (20)	<0.0001
Blood pressure recorded:	2643 (95)	2986 (96)	0.04
Last recording >160/90 mm Hg	675 (26)	544 (18)	<0.0001
Last recording >140/85 mm Hg	1598 (60)	1553 (52)	<0.0001
Smoking status recorded:	2386 (86)	2779 (89)	<0.0001
Non-smoker	1648 (69)	1477 (53)	<0.0001
Former smoker	330 (14)	686 (25)	
Current smoker	408 (17)	616 (22)	
Any family history recorded	1526 (55)	1805 (58)	0.01
Family history of cardiovascular disease	881 (32)	995 (32)	0.77

Table 4 Multivariate analysis to determine factors associated with having recorded fasting serum cholesterol concentration

Variable	Adjusted odds ratio (95% confidence interval)*	P value
Men v women	1.97 (1.67 to 2.32)	<0.0001
Age (years):		
35 to 44	1.00	
45 to 54	2.37 (1.48 to 3.81)	0.0004
55 to 64	3.17 (2.01 to 4.99)	<0.0001
65 to 74	2.06 (1.32 to 3.21)	0.002
≥75	0.40 (0.24 to 0.59)	<0.0001
Diabetic v non-diabetic	3.70 (2.78 to 4.94)	<0.0001
Hypertensive v non-hypertensive	1.59 (1.34 to 1.90)	<0.0001
Obese v non-obese	1.22 (1.00 to 1.48)	0.05
Smoking status:		
Non-smoker	1.00	
Former smoker	1.08 (0.87 to 1.34)	0.50
Current smoker	0.78 (0.63 to 0.96)	0.02

*Adjusted for sex, age, diabetes, hypertension, obesity, smoking status, and patient's general practice.

Table 5 Multivariate analysis to determine factors associated with treatment with lipid lowering drugs

Variable	Adjusted odds ratio for lipid lowering drugs (95% confidence interval)*	P value
Men *v* women	1.42 (1.22 to 1.65)	<0.0001
Age (years):		
35 to 44	1.00	
45 to 54	1.66 (1.04 to 2.65)	0.03
55 to 64	2.45 (1.56 to 3.82)	0.0001
65 to 74	1.66 (1.06 to 2.58)	0.03
≥75	0.37 (0.23 to 0.59)	<0.0001
Diabetic *v* non-diabetic	1.50 (1.20 to 1.86)	0.0003
Hypertensive *v* non-hypertensive	1.26 (1.07 to 1.47)	0.004
Obese *v* non-obese	0.95 (0.80 to 1.13)	0.56
Smoking status:		
Non-smoker	1.00	
Former smoker	1.11 (0.91 to 1.35)	0.31
Current smoker	0.85 (0.70 to 1.03)	0.10

*Adjusted for sex, age, diabetes, hypertension, obesity, smoking status, and patient's general practice.

to receive lipid lowering drugs (1.42 (1.22 to 1.65); $P < 0.0001$) (table 5).

To examine the association between age and sex and the use of lipid lowering drugs, we analysed the data by 10 year age group, adjusting for their general practice, age, sex, diabetes, hypertension, obesity, and smoking status. We found that *(a)* men of 45 to 54 years were more than twice as likely as women of the same age to have lipid lowering treatment (2.61 (1.64 to 4.18); $P < 0.0001$); *(b)* men of 55 to 64 were 50% more likely to have lipid lowering treatment than women of the same age, although this only just reached significance (1.46 (1.01 to 1.96); $P = 0.05$); and *(c)* no significant differences existed in the use of lipid lowering treatment between men and women aged ≥65 years.

We repeated the above analysis taking into account treatment with β blockers and aspirin in the multivariate model. Sex differences persisted despite the inclusion of these variables.

Diabetes mellitus

Patients with both ischaemic heart disease and diabetes were more likely to be tested and treated for hyperlipidaemia than patients without diabetes. Despite adjusting for age, men with both diabetes and ischaemic heart disease were more likely to have their most recently recorded blood pressure below 160/90 mm Hg (1.9 (1.3 to 2.8); $P = 0.001$) and below 140/85 mm Hg (1.40 (1.04 to 1.97); $P = 0.030$).

We found no difference in the proportion of men and women with a recorded value for glycated haemoglobin concentration in the 655 patients who had diabetes in addition to ischaemic heart disease (odds ratio 1.2 (0.8 to 1.8); $P = 0.34$). In addition, we found no difference in the proportion of diabetic men and women with ideal control, according to the value of the most recently recorded glycated haemoglobin concentration ($< 7.5\%$).

Smoking status

We found that patients aged ≥75 years and those recorded as current smokers were less likely to be tested for hyperlipidaemia (table 4). Patients aged ≥75 years were less likely to receive lipid lowering drugs than younger patients (table 5). Both age and smoking

status were included as potential confounding variables, and, although the differences were statistically significant, we need to be cautious in how these findings are interpreted.

Patients with more severe ischaemic heart disease

The analyses were repeated for the subgroup of patients with a diagnosis of myocardial infarction or two or more anti-anginal drugs. These patients represent those with more severe ischaemic heart disease. We found similar patterns both in the degree of differences between men and women and in the significance of the analysis.

Discussion

We found that among patients with ischaemic heart disease, women were less likely than men to have their risk factors (body mass index, smoking, blood pressure) recorded. Men are also more likely to have a fasting cholesterol concentration recorded. This is despite the higher consultation rates for women in general practice.[13]

Men were more likely to be smokers or former smokers, but women had higher rates of obesity and blood pressure readings over 140/85 mm Hg. A higher proportion of women had raised serum cholesterol concentrations. Clearly women with ischaemic heart disease in our study do not have lower risk profiles than men.

Despite this, more men take aspirin, have a diagnosis of hyperlipidaemia, and take lipid lowering drugs. These differences persist when age and other risk factors are adjusted for, and they suggest a systematic bias towards men in terms of secondary prevention of ischaemic heart disease. Our findings are consistent with the sex bias reported in studies of the management of ischaemic heart disease in secondary care.[6 7]

What is already known on this topic

England's national service framework for coronary artery disease requires general practitioners to identify and treat patients at high risk of ischaemic heart disease

Substantial evidence of sex inequality for this disease exists for access to secondary care less but less is known about equity for its management in general practice

What this study adds

Among patients with ischaemic heart disease, men were more likely than women to have cardiovascular risk factors and serum cholesterol concentration recorded on computer

A higher proportion of women, however, had raised cholesterol concentrations recorded on computer, but more men were treated with lipid lowering drugs

The results suggest a systematic bias towards men compared with women in terms of secondary prevention of ischaemic heart disease.

The results of the Scandinavian simvastatin survival study and the cholesterol and recurrent events study have shown that lipid lowering treatment is clinically effective in both men and women.[14] [15] The national service framework for coronary artery disease does not suggest sex differences in the management of secondary prevention of ischaemic heart disease.[2] We have searched the websites of *Clinical Evidence*, *Bandolier*, and the NHS Centre for Reviews and Dissemination and have found no authoritative guideline or statement recommending sex differences in management.

Strengths and weaknesses

We identified our target population from the practices' computer system. We used powerful NHS software (MIQUEST) to collect standardised datasets from practices and aggregate them for analysis. We could not adjust for deprivation as the ethical considerations meant that we were not allowed to extract strong patient identifiers, such as postcodes. We have not been able to validate the diagnoses of ischaemic heart disease by reference to manual records and previous investigations (for example, exercise electrocardiography, angiography), although validations done in previous studies show that important discrepancies are unlikely.[9] We do not think this factor has confounded our results as the practices' diagnostic criteria and recording accuracy would apply equally to men and women. In addition, we performed a subgroup analysis on patients with more severe ischaemic heart disease (defined as those with a myocardial infarction or taking more than one anti-anginal drug), and our findings remained unchanged. Any misclassification would have tended to underestimate the odds ratios rather than the converse.

We used a large sample recruited from 18 practices spread throughout the Trent region of the NHS, giving us good statistical power and generalisability. The differences we detected are likely to be not only significant but clinically important.

We thank the 18 general practices that participated in the study.

1 Department of Health. *Our healthier nation.* London: Stationery Office, 1998.
2 Department of Health. *National service framework for coronary artery disease: modern standards and service models.* London: Stationery Office, 2000.
3 Hippisley-Cox J, Pringle M. Inequalities in access to coronary angiography and revascularisation: the effect of deprivation and location of primary care services. *Br J Gen Pract* 2000;50:449-54.
4 Vogels E, Lagro-Janssen A, van Weel C. Sex differences in cardiovascular disease: are women with low socio-economic status at high risk? *Br J Gen Pract* 1999;49:963-6.
5 Kee F, Gaffney B, Currie S, O'Reilly D. Access to coronary catheterisation: fair shares for all? *BMJ* 1993;307:1305-7.
6 Spencer I, Unwin N, Pledger G. Hospital investigation of men and women treated for angina. *BMJ* 1995;310:1576.
7 McLaughlin T, Soumerai S, Willison D, Gurwitz J, Borbas C, Guadagnoli E. Adherence to national guidelines for drug treatment of suspected acute myocardial infarction. Evidence of under treatment in women and the elderly. *Arch Int Med* 1996;156.
8 Bouvy M, Heerdink E, Klungel O, de Boer A, Stuurman-Bieze A, Leufkens H. Do women with angina receive less antiplatelet treatment than men? *Br J Gen Pract* 1999;49:299-300.
9 Campbell N, Thain J, Deans H, Ritchie L, Rawles J. Secondary prevention in coronary heart disease: baseline survey of provision in general practice. *BMJ* 1998;316:1430-4.
10 Whitelaw FG, Nevin SL, Milne RM, Taylor RJ, Taylor MW, Watt AH. Completeness and accuracy of morbidity and repeat prescribing records held on general practice computers in Scotland. *Br J Gen Pract* 1996;46:181-6.
11 Cannon P, Connell P, Stockley I, Garner S, Hampton J. Prevalence of angina as assessed by a survey of prescriptions for nitrates. *Lancet* 1988;i:979-81.
12 Hammersley V, Meal A, Wright L, Pringle M. Using Miquest in general practice. *J Inf Primary Care* 1998;1:3-7.
13 Royal College of General Practitioners. *Morbidity statistics from general practice: fourth national morbidity survey 1991-2.* London: HMSO, 1995.
14 Scandinavian Simvastatin Survival Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;344:1383-9.
15 Sacks FM, Pfeffer MA, Moye LA. The effects of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.