Smoking and risk of myocardial infarction in women and men: longitudinal population study

Eva Prescott, Merete Hippe, Peter Schnohr, Hans Ole Hein, Jørgen Vestbo

Abstract

Objective: To compare risk of myocardial infarction associated with smoking in men and women, taking into consideration differences in smoking behaviour and a number of potential confounding variables.
Design: Prospective cohort study with follow up of myocardial infarction.
Setting: Pooled data from three population studies conducted in Copenhagen.
Subjects: 11 472 women and 13 191 men followed for a mean of 12.3 years.
Main outcome measures: First admission to hospital or death caused by myocardial infarction.
Results: 1251 men and 512 women had a myocardial infarction during follow up. Compared with non-smokers, female current smokers had a relative risk of myocardial infarction of 2.24 (range 1.85-2.71) and male smokers 1.43 (1.26-1.62); ratio 1.57 (1.25-1.97). Relative risk of myocardial infarction increased with tobacco consumption in both men and women and was higher in inhalers than in non-inhalers. The risks associated with smoking, measured by both current and accumulated tobacco exposure, were consistently higher in women than in men and did not depend on age. This sex difference was not affected by adjustment for arterial blood pressure, total and high density lipoprotein cholesterol concentrations, triglyceride concentrations, diabetes, body mass index, height, alcohol intake, physical activity, and level of education.
Conclusion: Women may be more sensitive than men to some of the harmful effects of smoking. Interactions between components of smoke and hormonal factors that may be involved in development of ischaemic heart disease should be examined further.

Introduction

Ischaemic heart disease is responsible for about 40% of deaths in Western countries, with smoking as a major modifiable risk factor.[1] The steep rise in the worldwide prevalence of smoking among women is expected to continue in the near future. At the start of the smoking epidemic, female smokers were few and differed extensively from male smokers in factors such as age of starting smoking, amount smoked, and inhalation habits, and the risk associated with smoking in women may have been underestimated.[2–4] Within the past two or three decades male and female smoking habits have become similar, and a more fair comparison of the risk associated with smoking in both sexes based on recent prospective population studies is now possible. From a public health point of view, as well as a clinical point of view, it is important to recognise sex differences in risk associated with smoking and elucidate possible mechanisms by which these differences could act.

We recently found that the relative mortality from vascular disease was higher in female smokers than in male smokers.[5] Consequently, we aimed to examine sex differences in smoking related risk of myocardial infarction while simultaneously including multiple cardiovascular risk factors in a prospective population study conducted in Copenhagen.

Methods

This study is based on data from three longitudinal population studies: the Copenhagen city heart study, with 15 789 subjects from central Copenhagen; the Glostrup population studies, with 6341 subjects from Copenhagen suburbs; and the Copenhagen male study, which sampled 3355 subjects from 14 large workplaces. All datasets with sufficient information on cardiovascular risk factors were included. The study population is outlined in table 1. Overall response rate at first examination was 77% (range 69-88%).

Cardiovascular risk factors were assessed by a self administered questionnaire and various laboratory tests. Tobacco consumption was studied in six categories: never smokers; ex-smokers; non-inhaling current smokers; and inhaling current smokers of 1-14, 15-24, and ⩾25 g tobacco per day. Type of tobacco (cigarette, cheroot, cigar, pipe, or mixed) was

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Table 1 Overview of study population

Cohort of origin*	No of women	No of men	Year of examination	Age at examination	No of myocardial infarctions
Copenhagen city heart study	8 395	7 033	1976/81	20-93	1368
Glostrup population studies	547	503	1976	40	30
	1 828	1 889	1982	30-60	119
	702	695	1987	30-60	25
Copenhagen male study	—	3 071	1985	45-64	221
Total	11 472	13 191	1976-87	20-93	1763

*Subjects with myocardial infarction before enrolment (n=627), double participants (n=191), and subjects lost to follow up (n=1) were excluded.

recorded for current smokers, as were years of smoking for both current and former smokers. Current tobacco consumption was calculated by equating a cigarette to 1 g tobacco, a cheroot to 3 g tobacco, and a cigar to 5 g tobacco. Pack years in current smokers was calculated as years of smoking multiplied by packs (of 20 cigarettes) currently consumed.

Arterial blood pressure was measured with the subject in a sedentary position after at least five minutes' rest. Blood lipids were non-fasting in the Copenhagen city heart study and fasting in the remaining cohorts. Body mass index was calculated as weight (kg) divided by height squared (m^2). Educational level was divided into three categories: <8 years of schooling (completed primary school), 8-11 years, and >11 years. Alcohol consumption was classified according to total weekly intake: <1 drink per week, 1-6 drinks, 7-13 drinks, 14-27 drinks, 28-41 drinks, and >41 drinks; one drink contained 9-13 g alcohol. Physical activity in leisure time was classified into three categories as sedentary; moderate activity <4 hours per week; and moderate activity >4 hours per week. Self reported diabetes was defined as an affirmative answer to the question "Do you have diabetes?"

Subjects were followed until 31 December 1993 for fatal and non-fatal myocardial infarction (ICD-8 diagnosis code 410); the information was obtained from the National Board of Health or the National Hospital Discharge Register. Subjects with myocardial infarction before enrollment were excluded; analyses therefore concern first myocardial infarction only.

Statistical analysis

Arterial blood pressure, total and high density lipoprotein cholesterol concentrations, triglyceride concentrations, height, weight, and body mass index were divided into fifths within cohorts, by sex and by 10 year age groups. In this way differences in methods of measurement between the three cohorts were taken into account. Association between risk factors and myocardial infarction was analysed by using Cox proportional hazards regression models with age as underlying timescale and delayed entry accordingly. Relative risks for covariates other than smoking did not differ between men and women, and the final analyses were performed on the pooled data stratified by sex; this assumed the same effect of covariates in men and women but allowed for different baseline hazard in men and women. All covariates were treated as categorical variables as described above, and tests for interaction were done by using the likelihood ratio test. There were no significant interactions between sex and cardiovascular risk factors other than smoking. Both incidence rate and distribution of risk factors differed in the three study groups, but risk estimates did not differ. We therefore report results from the pooled data adjusted for cohort of origin. Incidence rates were based on number of events and person years of observation in 5 year age bands. The Stata statistical package was used for estimation.[6]

Table 2 Background characteristics and risk factors by sex. Values are mean (SD) unless otherwise indicated

Characteristic	Women (n=11 472)	Men (n=13 191)	P value
Age (years)	49.7 (12.4)	52.5 (12.6)	<0.001
Body mass index (kg/m^2)	24.4 (4.4)	25.6 (3.6)	<0.001
Systolic blood pressure* (mm Hg)	130.4 (22.3)	135.6 (20.5)	<0.001
Diastolic blood pressure* (mm Hg)	79.2 (12.0)	83.3 (12.3)	<0.001
Plasma cholesterol* (mmol/l)	6.16 (1.28)	5.98 (1.19)	<0.001
Plasma triglyceride* (mmol/l)	1.37 (0.85)	1.89 (1.41)	<0.001
High density lipoprotein cholesterol* (mmol/l)	1.49 (0.46)	1.26 (0.37)	<0.001
No (%) current smokers	6461 (56.3)	8490 (64.5)	<0.001
Daily tobacco consumption†(g)	13.8 (7.9)	17.9 (9.8)	<0.001
No (%) with <8 years education	5071 (44.2)	6081 (46.1)	0.003
No (%) physically inactive in leisure time	2719 (23.7)	2454 (18.6)	<0.001
No (%) with intake >14 drinks/week	987 (8.6)	5514 (41.8)	<0.001
No (%) with self reported diabetes	149 (1.3)	303 (2.3)	<0.001

*In men, based on 10 120 subjects. Subjects from Copenhagen male study excluded because of difference in method of measurement.
†Among current smokers.

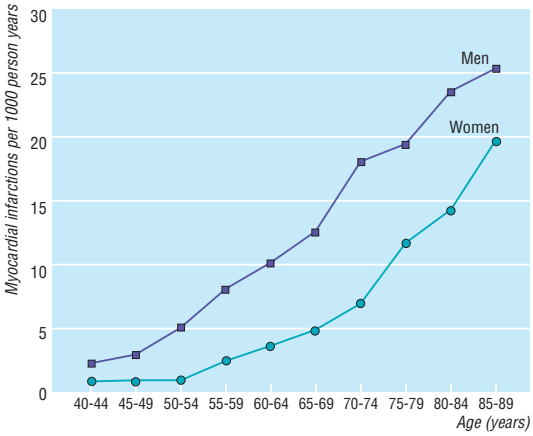

Fig 1 Age specific incidence rate of myocardial infarction in 11 472 women and 13 191 men from Copenhagen

Results

Analyses were based on 11 472 women and 13 191 men (table 1). During follow up, 512 women and 1251 men had myocardial infarctions, of which 104 and 274, respectively, were fatal.

With the exception of alcohol consumption and physical activity, men had a more disadvantageous cardiovascular risk profile (table 2).

Figure 1 shows age and sex specific incidence rates of myocardial infarction. Men had higher incidence rates than women at all ages but the male-female risk ratio decreased from about 3 in the younger groups to 1.5 in older groups.

Systolic blood pressure, diastolic blood pressure, total and high density lipoprotein cholesterol concentrations, triglyceride concentrations, body mass index, height, education, alcohol intake, leisure time physical activity, and diabetes were all strongly associated with risk of myocardial infarction, and relative risks were similar in men and women.

Female current smokers had a relative risk of 2.24 (range 1.85-2.71) and male smokers 1.43 (1.26-1.62) relative to non-smokers. This difference was significant (ratio 1.57 (1.25-1.97), P=<0.001) and was not changed after multiple adjustment for other risk factors. Risk in ex-smokers was not increased, but in current smokers there was a clear dose-response relation from a relative risk of 1.70 (1.31-2.21) and 1.26 (0.98-1.61) in female and male non-inhalers, respec-

Table 3 Relative risk (95% confidence interval) of myocardial infarction by current tobacco exposure in 11 472 women and 13 191 men. Results from Cox proportional hazards regression analysis

	Unadjusted*			Adjusted†		
Smoking status	**Women**	**Men**	**Ratio**	**Women**	**Men**	**Ratio**
Never smoker	1.0	1.0	1.0	1.0	1.0	1.0
Ex-smoker	0.99 (0.71 to 1.38)	1.14 (0.90 to 1.44)	0.87 (0.58 to 1.30)	1.05 (0.74 to 1.50)	1.11 (0.86 to 1.42)	0.95 (0.61 to 1.46)
Current smoker:						
Non-inhaling	1.70 (1.31 to 2.21)	1.26 (0.98 to 1.61)	1.35 (0.94 to 1.94)	1.82 (1.39 to 2.41)	1.37 (1.06 to 1.78)	1.33 (0.91 to 1.94)
Inhaling:						
1-14 g/day	2.59 (1.98 to 3.38)	1.52 (1.19 to 1.95)	1.70 (1.18 to 2.44)	2.76 (2.08 to 3.68)	1.60 (1.24 to 2.07)	1.72 (1.18 to 2.53)
15-24 g/day	2.99 (2.25 to 3.99)	1.72 (1.37 to 2.17)	1.74 (1.20 to 2.51)	3.27 (2.42 to 4.42)	1.75 (1.37 to 2.23)	1.87 (1.27 to 2.75)
>24 g/day	3.31 (1.91 to 5.73)	2.08 (1.60 to 2.69)	1.60 (0.87 to 2.93)	2.82 (1.45 to 5.46)	2.09 (1.58 to 2.77)	1.34 (0.66 to 2.75)
Test for interaction‡			P= 0.002			P= 0.005

*Adjusted for age and cohort.
†Cox regression model stratified by sex and adjusted for age, cohort of origin, smoking status, sex, systolic blood pressure, diastolic blood pressure, cholesterol, triglyceride, body mass index, education, alcohol, diabetes, physical activity, and height.
‡Likelihood ratio test for interaction between smoking and sex.

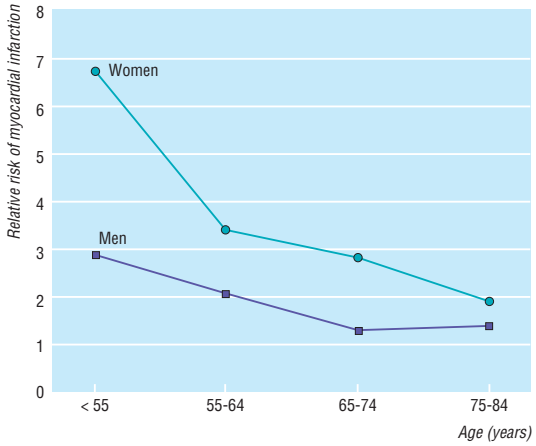

Fig 2 Relative risk of myocardial infarction for inhaling current smokers compared with never smokers

tively, to a maximum of 3.31 (1.91-5.73) and 2.08 (1.60-2.69) in heavy smokers (table 3). All risk estimates were higher in women than in men and were not affected by adjustment for other major risk factors, as indicated. Similar results were seen after categorisation by pack years: maximum risk was seen in inhaling smokers of more than 30 pack years (3.26 (2.36-4.50) in women, 1.76 (1.41-2.19) in men; ratio 2.13 (1.48-3.07)). There was no interaction between smoking and other risk factors.

Figure 2 shows relative risk for inhaling current smokers versus never smokers by age in men and women up to age 85. The risk of myocardial infarction decreased with age but was higher in women at all ages. The interaction term between smoking and sex did not differ in the four 10 year intervals (P = 0.73) and when the age dependence of the risk associated with smoking was adjusted for, the overall ratio between female and male relative risk was 2.01 (1.39 to 2.90).

Discussion

In this prospective study of almost 25 000 subjects the main result was that relative risk of myocardial infarction in female smokers exceeded that of male smokers by more than 50%. This difference was not affected by multiple adjustment for major cardiovascular risk factors.

Myocardial infarction

Our end point was defined as ICD-8 code 410, ascertained from the Hospital Discharge Register and from registration of cause of death with the National Board of Health, and included both fatal and non-fatal myocardial infarction. Some infarctions did not lead to hospital admission or may have been coded differently, for instance as codes 411 (other acute ischaemic heart disease), 427 (symptomatic heart disease), and 795 (sudden death). However, only differential misclassification (related to both sex and smoking status) will bias results, and there is no reason to suspect this.

Incidence rates of myocardial infarction in men were similar to those in other studies but the rates in women were higher. This is consistent with reports showing that mortality in middle aged Danish women is among the highest in western Europe and is at least partly caused by the high prevalence of smoking.[7] Consistent with the observation that ex-smokers reduce their excess risk of myocardial infarction by as much as 50% within the first year after quitting,[1] we found that myocardial infarction was more strongly associated with current exposure than with accumulated exposure to tobacco. This is in agreement with findings that the short term effects of components in tobacco smoke—on the haemodynamic system, for example—are more important than the chronic exposure in development of coronary thrombosis.

Comparison by sex

In a previous study we showed that female smokers have about a 50% higher relative risk of dying from vascular disease.[5] The present study confirmed this sex difference and found that the difference is not affected by adjustment for other cardiovascular risk factors.

Our analyses were based on baseline smoking status. If substantially more men than women gave up smoking during follow up, this could explain some of the observed difference. In 11 094 subjects in the Copenhagen city heart study who were re-examined after 5 years, 12.8% of men and 11.6% of women who smoked at baseline had given up smoking. As quitting rates were similar, this is not likely to have affected results.

A few studies have addressed the issue of sex difference in effect of smoking on ischaemic heart disease.[4 8–12] In a large prospective Norwegian study that included 11 843 subjects, relative risk of myocardial infarction was 3.3 in female current smokers

and 1.9 in male current smokers after adjustment for total and high density lipoprotein cholesterol concentrations, triglyceride concentrations, body mass index, and systolic blood pressure.[9] This study also showed that relative risks associated with other risk factors were similar in both sexes. In the West of Scotland study, in which 4696 women and 5714 men were followed for death from ischaemic heart disease, relative risk was 1.9 in women and 1.6 in men after adjustment for major risk factors.[10] In a Swedish study that included 10 945 twins, relative risk was 1.6 in female smokers and 1.4 in male smokers.[11] However, the Framingham study found no significant relation between smoking and ischaemic heart disease in women,[4] and in a study of death from ischaemic heart disease by LaCroix et al, which included 7178 subjects aged over 65, relative risks were 1.6 in female smokers and 2.0 in male smokers, with no adjustment for other risk factors.[12] In these and in other important studies of coronary mortality[2 3 13–15] an apparent lack of difference between the sexes in risk associated with smoking may be due to the extensive differences in smoking habits between male and female smokers from older birth cohorts.

Our results are based on a multiplicative model, which is the most widely used model in cardiovascular epidemiology. That cardiovascular risk factors should act multiplicatively is biologically plausible, given what we know of the pathogenesis of myocardial infarction. If effects of cardiovascular risk factors are additive, relative risks will vary between men and women simply because risks vary at baseline. In this and other studies, however, relative risks did not vary for the other cardiovascular risk factors examined,[9] and the sex difference in effect of tobacco thus cannot simply be put down to differing baseline rates. Although relative risks are higher in women, suggesting differences in mechanism of action of tobacco in men and women, smoking may well cause more cases of myocardial infarction among men. In our study population, the difference in risk was higher in men to age 65 and in women after age 65.

A possible cause of the sex difference is an interaction of some hormonal factors with components of the inhaled smoke. There is growing epidemiological evidence that women who smoke are relatively deficient in oestrogen: they have an earlier menopause, decreased risk of cancer of the endometrium, greater likelihood of osteoporosis and of osteoporotic fractures, and reduced incidence of a number of "minor" disorders such as uterine fibroids.[16] Possible biological mechanisms have been suggested.[16–18] Oestrogen deficiency, on the other hand, is associated with cardiovascular disease: rates of ischaemic heart disease increase sharply in women after menopause; young women with bilateral oophorectomy have an increased risk of ischaemic heart disease; and accumulating epidemiological data show that women who use hormone replacement therapy after menopause have lower rates of ischaemic heart disease.[19 20] This mechanism may be by lowering low density lipoprotein and fibrinogen, increasing high density lipoprotein cholesterol,[21 22] increasing blood flow, and reducing artherosclerosis.[19 23] Thus it is possible that tobacco smoke, in addition to the (partly unknown) mechanisms by which it increases risk of ischaemic heart disease in both men and women, interacts with sex hormones and thus increases risk of ischaemic heart disease relatively more in female smokers than in men. In support of this, Criqui et al found that hormone replacement therapy was protective only in smokers,[24] and in a study based on the Copenhagen city heart study Lindenstrøm et al found that hormone replacement therapy reduced the risk of stroke only in smokers,[25] results which have yet to be confirmed in other studies. Because of insufficient information on hormone replacement therapy we could not examine this.

Conclusion

Female smokers have a higher relative risk of myocardial infarction than male smokers, even after adjustment for major cardiovascular risk factors. This raises the question of whether tobacco smoke may be more harmful to women with regard to ischaemic heart disease, possibly because of constituents of tobacco smoke exerting anti-oestrogenic effects. Results from large ongoing clinical trials of hormonal replacement therapy may be able to elucidate this.

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Contributors: EP had the original idea for the present study, performed the data analyses, and is guarantor for the paper. MH and JV participated in data analyses and contributed to the paper. HOH and PS participated in data collection. The paper was written jointly by EP, MH, JV, HOH, and PS.

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Ecological study of reasons for sharp decline in mortality from ischaemic heart disease in Poland since 1991

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Abstract

Objective: To investigate the reasons for the decline in deaths attributed to ischaemic heart disease in Poland since 1991 after two decades of rising rates.
Design: Recent changes in mortality were measured as percentage deviations in 1994 from rates predicted by extrapolation of sex and age specific death rates for 1980-91 for diseases of the circulatory system and selected other categories. Available data on national and household food availability, alcohol consumption, cigarette smoking, socioeconomic indices, and medical services over time were reviewed.
Main outcome measures: Age specific and age standardised rates of death attributed to ischaemic heart disease and related causes.
Results: The change in trend in mortality attributed to diseases of the circulatory system was similar in men and women and most marked (>20%) in early middle age. For ages 45 to 64 the decrease was greatest for deaths attributed to ischaemic heart disease and atherosclerosis (around 25%) and less for stroke (<10%). For most of the potentially explanatory variables considered, there were no corresponding changes in trend. However, between 1986-90 and 1994 there was a marked switch from animal fats (estimated availability down 23%) to vegetable fats (up 48%) and increased imports of fruit.
Conclusion: Reporting biases are unlikely to have exaggerated the true fall in ischaemic heart disease; neither is it likely to be mainly due to changes in smoking, drinking, stress, or medical care. Changes in type of dietary fat and increased supplies of fresh fruit and vegetables seem to be the best candidates.

Introduction

From 1960 to 1991 mortality from diseases of the circulatory system in Poland was high and increasing. Death certification rates for this group of causes rose by about 70% in men and 15% in women, and in both sexes mortality from ischaemic heart disease roughly doubled.[1-4] Since 1991, however, the fall in death certification rates for ischaemic heart disease seems to have been larger than that previously observed in any country in peacetime. This sharp change in trend suggests a curtailment of the final, fatal steps of the disease in people with advanced coronary atherosclerosis.

The unplanned natural experiments taking place in Poland and neighbouring countries in association with the unusually rapid political and economic transformations that began in the late 1980s may elucidate why mortality from ischaemic heart disease varies more between populations and over time than has previously been accounted for by the classic risk factors.[5] Analyses in populations may yield such leads, notwithstanding the difficulties they face in taking adequate account of concurrent changes in confounders.[6] Such analyses may point to widely shared influences on disease incidence, especially those acting late in the disease process.[7]

We considered the possible roles of concomitant changes in the availability of foods and alcohol, smoking prevalence, socioeconomic indices, and medical care in explaining the recent decline in mortality from ischaemic heart disease in Poland.

Subjects and methods

Mortality data are from the Polish system of vital statistics and the mortality data bank of the World Health Organisation in Geneva. There were no significant inconsistencies between the two data sets.

National death certification rates were examined for five year age groups between 35 and ≥85 for 1970-94. Rates for ages 45-64 were standardised by five year age groups using weights of 6, 5, 4, and 4 respectively.[8] To minimise the effects of short term perturbations in rates around 1989-91, the subsequent changes in rates were measured as the percentage deviations in the reported rates for 1994 from rates predicted for 1994 by extrapolating the linear trends for 1980-91 (after

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Table 1 Death certification rates for circulatory disease, cancer, injury, and all causes in Poland 1970-94. Values are age standardised rates per 100 000 population for ages 45-64*

	ICD- 8, ICD-9	1970	1975	1980	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Men														
All diseases of circulatory system	390-459	486	539	658	704	722	729	712	732	742	777	738	690	650
Heart disease (excluding rheumatic disease) and hypertension	400-405, 410-429	327	368	454	478	496	498	481	499	501	529	498	463	438
Ischaemic heart disease	410-414	172	223	277	311	330	335	322	339	340	353	335	307	282
Hypertensive disease	400-405	29	27	29	38	35	35	34	33	33	39	36	34	32
Atherosclerosis and diseases of arteries	440-448	83	82	97	113	114	120	120	123	126	132	122	111	102
Stroke	430-438	51	65	85	87	90	91	90	91	94	98	100	99	94
Other circulatory diseases	390-398, 441-459	21	24	22	24	21	20	20	18	19	17	17	16	17
All cancer (except lung)	140-161, 163-208	238	242	255	277	280	286	290	290	287	287	287	285	284
Lung cancer	162	92	115	147	184	183	188	194	196	196	202	187	190	190
Injury	E800-E999	128	146	169	162	160	157	150	160	183	197	189	172	177
All causes	1-999	1326	1364	1580	1670	1677	1684	1659	1702	1735	1824	1748	1659	1618
Women														
All diseases of circulatory system	390-459	230	225	249	265	262	266	257	261	257	257	248	229	223
Heart disease (excluding rheumatic disease) and hypertension	400-405, 410-429	128	118	131	145	145	147	139	147	144	146	142	131	128
Ischaemic heart disease	410-414	39	47	57	68	69	71	70	77	76	76	77	70	64
Hypertensive disease	400-405	28	23	22	28	27	27	24	24	24	24	22	19	21
Atherosclerosis and diseases of arteries	440-448	35	35	38	42	41	44	45	44	44	43	39	35	32
Stroke	430-438	39	47	53	53	53	54	53	53	51	50	50	47	50
Other circulatory diseases	390-398, 441-459	28	25	26	24	23	21	20	17	18	17	16	15	14
All cancer (except lung)	140-161, 163-208	221	221	225	224	223	224	225	222	218	221	220	216	216
Lung cancer	162	11	14	19	20	22	22	24	24	25	27	26	27	27
Injury	E800-E999	32	32	32	32	33	33	29	32	34	36	33	33	31
All causes	1-999	668	644	674	685	678	678	664	669	662	672	655	621	615

* Directly age standardised, by 5 year age groups, to the world standard population (weights 6, 5, 4, and 4).

confirming the goodness of a linear fit). Categories of primary interest were all diseases of the circulatory system (codes 390-459 of the ninth revision of the international classification of diseases (ICD-9)), all non-rheumatic heart disease plus hypertension (400-405, 410-429), ischaemic heart disease (410-414), hypertensive disease (400-405), atherosclerosis and diseases of the arteries (440-448), cerebrovascular disease (430-438), and other circulatory diseases (390-398, 441-459). Deaths from influenza and pneumonia (480-487) were checked to see whether they contributed to short term fluctuations.

Available data from national food balance sheets and national household budget surveys were reviewed for salient changes since 1989. Polish food balance sheets have been prepared according to the protocols of the Food and Agriculture Organisation for each of the years under consideration and provide estimates of quantities of foods potentially available for human consumption.[9] Published estimates of the availability of fats, by animal or vegetable source and by saturation class, were used. These estimates were derived using national food composition tables to estimate the average composition of the aggregate categories of foods in the food balance sheets—and then using constant conversion factors throughout the whole period under consideration.[7] Changes inferred from food balance sheets were cross checked with data from the ongoing, standardised, household budget survey.

Data on smoking prevalence were obtained from national smoking surveys, based on probability samples and conducted using unchanging methods by the Department of Epidemiology and Cancer Prevention of the National Cancer Institute, Warsaw.[10] Estimates of alcohol consumption, from the Polish national statistical office, have tried to include the contributions of smuggling and home distilling.

Results

Mortality trends by sex and age group for the categories of circulatory system disease considered were mostly roughly linear during 1980-91. For all diseases of the circulatory system the percentage falls to 1994 relative to the rates predicted by extrapolating the linear trends from 1980 to 1991 were similar in men and women, greatest at ages 35-60 (when they exceeded 20% in several age-sex categories), and more modest above age 70 (mostly below 10%). (For the five year age groups between 40 and 69 all but one of the sex specific slopes were significantly different from zero.) The change in trend occurred consistently after 1991.

Table 1 shows age standardised death rates for selected causes for people aged 45-64. In this age group the percentage falls in 1994 were 19% for men and 17% for women for all diseases of the circulatory system, 26% for men and 25% for women for ischaemic heart disease, and 8% for men and 4% for women for stroke. (The slope coefficients were significant ($P < 0.05$), except for mortality from stroke in women.)

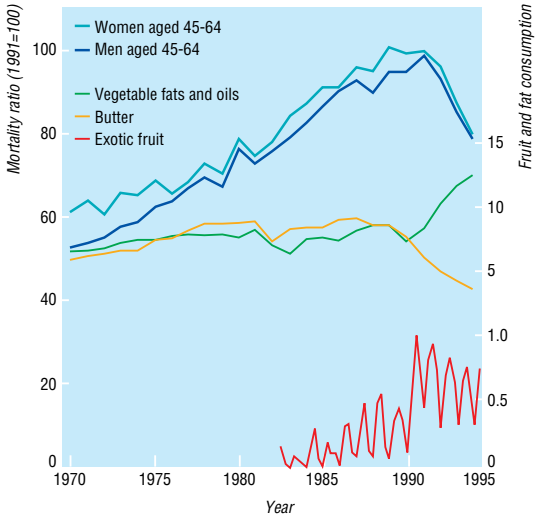
Deaths coded as influenza and pneumonia were relatively constant during the study period (data not shown). Death certification rates for lung cancer plateaued for middle aged men in the late 1980s and for women in the early 1990s (table 2).

Table 2 and the figure show data on diet, smoking, and alcohol consumption. The most striking change was the switch from animal to vegetable fats. The estimated ratio of polyunsaturated to saturated fat, below 0.35 during the 1980s, was 0.49 by 1994. Estimated

Table 2 Estimates of availability of selected foods, amount of fat from animal and vegetable sources, ratio of polyunsaturated to saturated fat, availability of alcohol, and prevalence of smoking in Poland, 1970-94

Amount per person year	1970	1975	1980	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Meat (kg)[7]	53.0	70.3	74.0	60.2	66.0	66.7	68.3	68.6	68.6	73.2	70.3	67.5	62.5
Fruits (kg)[7]	32.8	34.4	37.7	28.9	35.7	18.9	32.2	31.2	28.9	37.2	40.7	45.2	34.6
Vegetables (excluding potatoes) (kg)[7]	111	109	101	105	114	116	115	116	119	126	116	122	116
Milk (litres)[7]	262	264	262	273	280	270	271	260	241	231	217	209	200
Eggs (No)[7]	186	209	223	220	209	199	203	194	190	175	173	157	146
Alcohol (litres of ethanol)[10 11]	5.2	6.9	8.4	6.8	6.9	7.0	6.8	7.5*	ND	9.6*	10.2*	ND	9.0*†
Fats from animal sources (kg)[7]	87.5	99.6	104.9	96.0	102.0	101.4	101.2	101.4	97.1	95.8	91.4	86.1	77.2
Fats from vegetable sources (kg)[7]	23.8	25.3	26.4	26.0	25.7	27.1	28.4	28.2	25.1	27.2	32.1	35.7	39.8
Ratio of polyunsaturated to saturated fat [7]	0.34	0.33	0.32	0.33	0.32	0.33	0.34	0.34	0.33	0.36	0.41	0.46	0.49
Prevalence of smoking (% of people aged ≥16)‡													
Men	ND	59.3	62.2§	54.8	54	53.1	51.6	ND	51.5	47.8	52.5	47.9	50.4
Women	ND	17.8	30.3§	27.9	27.1	22	25.2	ND	24.6	24.7	22.6	25.4	23.3

ND=no data. *Estimates are more uncertain (smuggling is included). †1995. ‡Surveys of Department of Epidemiology and Cancer Prevention, National Cancer Institute, Warsaw. §1982.



Mortality ratios for ischaemic heart disease plus atherosclerosis and arterial diseases, with estimates of butter and vegetable fats and oils (kg/person/year)[7] and of exotic fruits (kg/person/quarter)[12] available for consumption by quarter from 1970 to 1994. Data for years are plotted to mid-year and for quarters to mid-quarter. Mortality ratios are age standardised

household availability of exotic fruit—for example, imported citrus fruits and bananas—doubled from 1991. Trends evident in the household budget surveys accorded with those shown by the food balance sheets.

Alcohol consumption rose sharply (perhaps by 30-40%) immediately after the political changes and subsequently declined.[7]

Discussion

Polish mortality statistics cover all Polish nationals irrespective of where they die.[13] The recording of deaths occurring within Poland has remained almost complete during the transition period.[11] Any bias from underreporting of deaths of people temporarily abroad would have been maximal during 1989-91 and could not account for progressive falls after 1991. There is no evidence that the denominator was progressively inflated after 1991.[14]

Changes in certifying and coding practices could not explain the fall in mortality from diseases of the circulatory system because there is no other major category to which so many deaths could have been transferred (and neither is there suggestive evidence). Polish certification and coding practices have differed from those in the West.[15] A larger proportion of deaths has been attributed to hypertensive disease in Poland than elsewhere—in many cases because it is recorded as the underlying cause when elsewhere this would be recorded as stroke. Similarly, a larger proportion of deaths has been attributed to atherosclerosis and arterial diseases—in many cases where the death would elsewhere be attributed to ischaemic heart disease. (This pattern of attribution has also been shown for the former German Democratic Republic.[16]) Death certification rates for both hypertensive disease and stroke have shown modest changes in parallel since 1991, while rates for atherosclerosis and arterial disease have fallen in parallel with those for ischaemic heart disease. The relative changes in attributed cause cannot be due to a convergence towards Western practice because such a convergence would have increased the proportion of circulatory deaths assigned to ischaemic heart disease. The decline in mortality from ischaemic heart disease is therefore unlikely to have been exaggerated by information error.

Magnitude of change

For men aged 45-64 the proportional reduction in 1994 was 26% when calculated as a departure from the trend during 1980-91, 20% when compared with the peak year of 1991, and 16% when 1994 was compared (more conservatively) with the three years before that peak year. For women the corresponding figures were 25%, 16%, and 16%.

This decline is apparently without precedent in peacetime. During the second world war mortality from circulatory diseases in German occupied Norway fell by around 20% within 2-3 years.[17] This accompanied dramatic enforced dietary changes—notably, a radical decrease in the consumption of meat, whole milk, cream, cheese, eggs, and margarine and a considerable increase in the consumption of fish and fresh vegetables.[18] During the late 1960s and 1970s the trend in male mortality from ischaemic heart disease changed sharply in several Western countries, including Australia, New Zealand, the United States, Finland,

and Belgium. In Australia—where the change in trend was perhaps the sharpest—male mortality at ages 45 to 64 fell about 12% below its previous trend in the third year after it peaked,[19] which is well below the corresponding figure in Poland.

Possible causes

Neither access to medical services nor their effectiveness has obviously improved since 1989. The health service budget did not increase after 1989,[20] and annual state expenditure per person is currently about $130 (£81).[21] Access to modern medical technology is limited: fewer than 60 percutaneous transluminal coronary angioplasties are performed per million population annually compared with 900 in Western Europe and 1300 in the United States.[21]

Sudden reductions in deaths from ischaemic heart disease that cannot be explained by changes in medical care suggest sudden beneficial effects on later stages of the underlying disease processes. What else could have caused such an effect?

Smoking is an important determinant of circulatory disease. Lung cancer peaked earlier in Poland than in former socialist countries further south, where death certification rates for circulatory disease in men either declined a little (Hungary) or continued to rise (Romania and Bulgaria) (World Health Organisation, unpublished data). However, the sharpness of the change in mortality from ischaemic heart disease and its consistency by age and sex all count against a dominant role for reduced exposure to tobacco.

We found no evidence of a progressive increase in the proportion of people gaining protection against ischaemic heart disease by consuming an average of two or more alcoholic drinks per day.[22]

The recent transition period has probably not led to reduced stress. Despite the rapid recovery of economic output,[23] unemployment remained at around 15% of the workforce,[24] in contrast to the preceding era of state assured job security. Between 1989 and 1994 suicide rates increased by about 25% in men and 10% in women and homicide increased by over 50%.[25,26]

Among documented dietary trends the only plausible candidates we found to explain the fall in deaths from ischaemic heart disease were changes in types of fat consumed and increased supplies of fresh foods.

Consumption of fresh fruit and vegetables has been associated with reduced risk of circulatory disease,[27] but the association is generally stronger for stroke than for ischaemic heart disease (contrary to the observed change in Poland). Although low consumption of vitamin C in winter and excess mortality from circulatory causes in winter has a close temporal association,[28] changes in excess winter mortality were not a distinctive component of the decline in mortality in Poland. Furthermore, since total fruit and vegetable consumption doubled between 1989 and 1992 in the former German Democratic Republic,[29] any quick acting benefit should have caused a greater decline in mortality from circulatory diseases than was observed (unpublished data).[14] However, given that the supply of fresh fruit and vegetables in winter and spring constituted perhaps the strongest dietary contrast between eastern and western Europe before 1989, a reduction in that difference should remain a candidate to explain any observed convergence in mortality from circulatory causes.[30]

Key messages

- Among former socialist countries Poland has undergone unusually rapid social and economic changes since 1988-9, including aspects of diet
- Mortality from heart disease declined sharply during 1991-4 after long term increases; mortality from stroke declined less strongly
- This study investigated what has changed in Poland to reduce the risks of fatal events in people with established ischaemic heart disease
- Candidate dietary explanations were the substitution of unsaturated for saturated fats and increased consumption of fresh fruit and vegetables

The change in fat consumption has been a consequence of market conditions. General purchasing power fell after 1989, and the withdrawal of large consumer subsidies, especially for foods of animal origin, reduced purchasing power for those foods sharply.[31] The consequent shifts in demand towards vegetable fats were exploited vigorously—for example, by margarine manufacturers. These margarines were produced with new technology and had low contents of *trans* fatty acid (K Krygier, personal communication).

Although dietary estimates from food balance sheets are poor measures of absolute consumption, any changes in trend cannot be attributed either to random error or to constant bias. Such changes must reflect either a true change or a new and constantly increasing bias. The latter is an unlikely consequence of administrative disruption, and data collection and processing have not changed in a way that increases bias. Data from the independent household budget survey showed a pattern of change for the major dietary sources of fat consistent with that inferred from the food balance sheets.[32] This was also shown in the Krakow cohort of the MONICA (monitoring trends and determinants in cardiovascular disease) study (A Gilis-Januszewsk et al, European regional meeting of the International Epidemiological Association, Munster, September 1997). The procedures used for both the food balance sheets and the household budget surveys have remained consistent through the transition period (W Sekula, personal communication).

If a switch from animal to vegetable fats has contributed to the fall in deaths from ischaemic heart disease it does not seem to have acted through reducing cholesterol concentrations.[33] Such concentrations have not been high in Poland, and neither of the cohorts in the international MONICA programme (Warsaw and Krakow) showed much change in the 10 years to 1993 (A Pajak, personal communication).[34]

Could changes in type of dietary fat produce benefits by other pathways? Two trials in subjects at high risk because of previous heart attacks have shown

this to be so.[35 36] Influences on late stage coronary artery disease—for example, by stabilising plaque—on blood coagulability, and on myocardial susceptibility to arrhythmia induced by hypoxia[37 38] could all contribute to these benefits. Death is more likely to be averted quickly through effects on blood coagulability and on myocardial susceptibility, each of which is quickly affected by dietary change.

There is much still to be explained about why death rates from circulatory diseases vary between populations and over time. After two decades in which mortality rates from circulatory diseases were comparatively stable in women and stable or rising in men in all countries of central and eastern Europe, trends in mortality from these diseases are contrasting in the 1990s. The most recent data show that death rates from ischaemic heart disease in Poland have declined further, albeit less sharply than during 1991-4, and that a decline of almost equal magnitude (though contrasting less with the previous trend) has occurred in the Czech Republic.[39] Meanwhile, in Hungary, Romania, and Bulgaria there has been little apparent decline.[40] The scientific opportunities that this heterogeneity of experience presents, particularly to explore effects of dietary changes, should not be missed.

Data were obtained from the Mortality Data Bank of the World Health Organisation, Geneva. We alone accept responsibility for their interpretation. Urszula Wojciechowska helped prepare the data.

Contributors: WAZ initially observed trends in mortality from ischaemic heart disease in Poland. He and AJM assessed various factors that could have contributed to the pattern. WAZ supplied data on mortality and putative causes. JWP prepared the mortality series and the initial draft of the paper. All authors contributed to interpreting the data and to finalising the text. WAZ is guarantor for the study.

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Conflict of interest: None.

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Endpiece

Alternative definitions

Circumlocution: A literary trick, whereby the writer who has nothing to say breaks it gently to the reader.

Ambrose Bierce, *The Cynic's Word Book* (1906), subsequently titled *The Devil's Dictionary*

Point of care testing: randomised controlled trial of clinical outcome

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Abstract

Objectives: To describe the proportion of patients attending an accident and emergency department for whom blood analysis at the point of care brought about a change in management; to measure the extent to which point of care testing resulted in differences in clinical outcome for these patients when compared with patients whose samples were tested by the hospital laboratory.

Design: Open, single centre, randomised controlled trial. Blood samples were randomly allocated to point of care testing or testing by the hospital's central laboratory.

Setting: The accident and emergency department of the Bristol Royal Infirmary, a large teaching hospital which cares for an inner city population.

Subjects: Representative sample of patients who attended the department between April 1996 and April 1997 and who required blood tests. Data collection was structured in 8 hour blocks so that all hours of the day and all days of the week were equally represented.

Main outcome measures: The proportion of patients for whom point of care testing brought about a change in treatment in which timing was considered to be critical to clinical outcome. Mortality, the length of stay in hospital, admission rate, the amount of time spent waiting for results of blood tests, the amount of time taken to decide on management plans, and the amount of time patients spent in the department were compared between patients whose samples were tested at the point of care and those whose samples were sent to the laboratory.

Results: Samples were obtained from 1728 patients. Changes in management in which timing was considered to be critical occurred in 59 out of 859 (6.9%, 95% confidence interval 5.3% to 8.8%) patients in the point of care arm of the trial. Decisions were made 74 minutes earlier (68 min to 80 min, $P < 0.0001$) when point of care testing was used for haematological tests as compared to central laboratory testing, 86 minutes earlier (80 min to 92 min, $P < 0.0001$) for biochemical tests, and 21 minutes earlier (-3 min to 44 min, $P = 0.09$) for analyses of arterial blood gases. There were no differences between the groups in the amount of time spent in the department, length of stay in hospital, admission rates, or mortality.

Conclusion: Point of care testing reduced the time taken to make decisions on patient management that were dependent on the results of blood tests. It also brought about faster changes in treatment for which timing was considered to be critical in about 7% of patients. These changes did not affect clinical outcome or the amount of time patients spent in the department.

Introduction

Point of care testing is becoming increasingly popular; it has been defined as any laboratory test performed outside a hospital's central laboratory.[1] Several factors are associated with the growing interest in point of care testing [2]; however, it is not clear whether the technology has been developed in response to clinical need or whether marketing strategies have led to the perception that there is a need for the technology.[3] The availability of faster test results should expedite diagnosis and the initiation of treatment, both of which should have a positive impact on patient care. These benefits might also be expected to reduce the amount of time a patient spent waiting in an accident and emergency department. The Executive Health Technology Assessment Group of the NHS has concluded that an evaluation of the cost effectiveness of point of care testing is necessary.[4] Such an evaluation would need to determine whether point of care testing benefits the patient and whether it is cost effective.

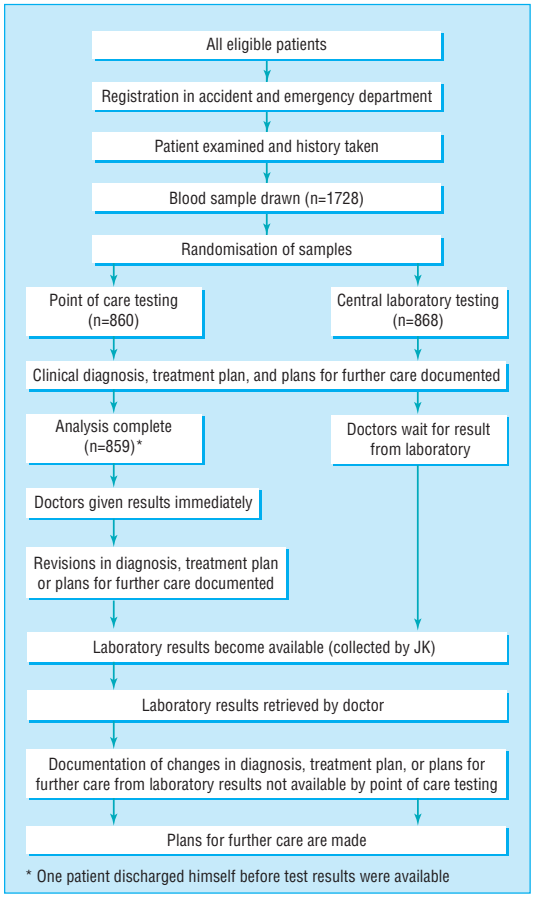
Previous evaluations of point of care testing have failed to address the issues of benefit to patients and cost effectiveness.[5–10] We designed a randomised controlled trial to compare point of care testing with testing by the hospital laboratory in our accident and emergency department as part of a wider study which included an analysis of costs[11] and an assessment of the accuracy and reproducibility of the results of the tests.[12] This paper addresses issues of clinical outcome, and focuses on results obtained with a portable whole blood analyser designed for bedside use. We sought to describe the proportion of patients for whom point of care testing brought about a change in management in which timing was considered to be critical to clinical outcome. We also wanted to measure the extent to which such changes resulted in a difference in clinical outcome for patients when compared with patients whose samples were tested by the hospital laboratory.

Subjects and methods

Study design

Descriptive measures were used to evaluate changes in management that resulted from point of care testing. A randomised controlled trial was used to compare clinical outcomes. A sample of patients who presented to the accident and emergency department was selected between April 1996 and April 1997. Data were collected over 8 hour periods structured so that all hours of the day and all days of the week were represented equally. The 210 sampling periods (1680 hours) represented about 20% of the total number of hours in a year. All procedures were piloted before the start of the study, and data collection was performed by a single investigator (JK).

Patient information, the source of referral, the presenting complaint, and the date were recorded at the time of registration in the department (figure). The



Design of randomised controlled trial comparing blood analysis at the point of care with testing by the central hospital laboratory

attending doctor assessed the patient and drew blood for urgent analysis if appropriate. In addition to samples for the central laboratory, the doctor also drew a 5 ml heparinised sample for randomisation as part of the same venepuncture. The heparinised sample was immediately randomised to either point of care testing or testing by the central laboratory. All samples were randomised and no samples were withdrawn from the study. The results were recorded when the analysis was completed.

Blood samples were chosen as the units of randomisation. Randomisation of blocks was done with computer generated codes using MINITAB version 10 (State College, PA). Allocations were concealed in consecutively numbered, sealed opaque envelopes. All codes were generated by BR before the study; BR was not involved in data collection or patient care. For some patients more than one sample was analysed, for example when a venous blood profile and arterial blood gas analysis were required. However, only one sample, selected randomly, from each patient was included in the analyses reported here.

The attending doctor was interviewed by JK to determine the diagnosis, treatment plan, and plans for further care based on the doctor's clinical impression. The interview was brief and the same questions were asked of all doctors—what is the clinical differential diagnosis? what is your treatment plan? what is your plan for further care? Results from the point of care tests were given to the doctor immediately and their consequences for the patient's management were elicited by asking whether the results influenced the diagnosis, treatment plan, or plans for further care. Changes in any of these areas were recorded. When point of care results were not provided, because of randomisation, the patient was managed according to the initial plans.

Results from the hospital laboratory were automatically printed in the department[13]; they were retrieved by JK, but were not necessarily given to the attending doctor. If a doctor had asked to be made aware of a result as soon as possible, the doctor was informed by JK when the results arrived. Otherwise, doctors had to approach JK for the results, mimicking the way in which they would have normally retrieved results. The time that the patient left the department, plans for future care, and the grade of the attending doctor were also documented.

The same procedure was followed for tests measuring arterial blood gas, except that samples were taken to the intensive therapy unit rather than being sent to the central laboratory; samples for point of care testing were obtained by taking a small amount of blood from the arterial blood gas syringe.

The study was approved by the local research ethics committee. Written consent was not required since no additional procedure was done, patients were not exposed to additional harm, and it would not have been practicable in many circumstances (for example, in the case of comatose patients). None the less, an information sheet was available if requested by patients.

Patients

The study population was a representative sample of patients seen at our accident and emergency department; the Bristol Royal Infirmary cares for an inner city population. Children are not seen in the department. About 50 000 new patients are seen in accident and emergency each year; this includes patients referred to emergency by general practitioners for inpatient care. Blood samples from any patient seen in the department for whom an urgent blood test was requested were eligible for inclusion in the study. There were no exclusion criteria, and samples from all patients who attended during periods of data collection were included.

Outcome measures

Several outcomes were assessed (box). Mortality, the length of stay in hospital, admission rates from accident and emergency, the amount of time the doctor spent waiting for results from blood tests, the amount of time taken to decide on a management plan, and the amount of time the patient spent in accident and emergency were compared between those patients whose samples were analysed by point of care testing and those whose samples were analysed by the hospital laboratory. Differences between the two groups were anticipated to occur only in the time spent waiting for results from blood tests, the time taken to decide on a management plan, and the time spent in the department.

Outcome measures

- Mortality
- Length of stay in hospital
- Admission rates from the accident and emergency department
- Amount of time spent waiting for results of blood tests
- Amount of time taken to decide on patient's management
- Amount of time patient spent in accident and emergency
- Proportion of patients for whom point of care testing changed diagnosis, treatment plan, or plans for further care
- Proportion of patients for whom point of care testing brought about time critical changes in treatment

Point of care testing

This study evaluated the i-STAT system (Princeton, NJ) for blood analysis, which is designed to be used at the patient's bedside. It is battery powered, hand held, and uses disposable cartridges that can perform several analyses simultaneously.[14–17] Results are available in 2 minutes. We evaluated two cartridges. One cartridge measures concentrations of sodium, potassium, chloride, urea, and glucose; measures packed cell volume; and calculates haemoglobin concentration from packed cell volume. The other cartridge measures pH, partial pressure of carbon dioxide, and partial pressure of oxygen; and calculates bicarbonate concentration, total carbon dioxide, base excess, and oxygen saturation.

Changes in treatment

Seventeen consultants and senior registrars experienced in emergency care used a visual analogue scale (range 0 to 10) to evaluate how important timing was to the clinical outcome for treatment changes instituted as a result of point of care testing (time critical changes). A score of zero indicated that the timing of the change was not critical; a score of 10 indicated that the change in treatment should be made as soon as the need for it was discovered. Interventions with median scores of 7 or greater were classed as time critical changes.

Table 1 Characteristics of patients whose blood samples were allocated to point of care testing or to testing by the hospital's central laboratory. Values are numbers of patients (percentages) unless indicated otherwise

	Point of care testing (n=860)	Laboratory testing (n=868)
Mean (interquartile range) age (years)	55 (34-73)	57 (36-74)
Men	465 (54)	463 (53)
Patients referred to emergency by general practitioners	451 (52)	428 (49)
Grade of attending doctor:		
House officer	98 (11)	89 (10)
Senior house officer	661 (77)	683 (79)
Other	101 (12)	96 (11)
Presenting complaint:		
Shortness of breath	118 (14)	99 (11)
Abdominal pain	139 (16)	139 (16)
Chest pain	137 (16)	142 (16)
Collapse	89 (10)	103 (12)
Feeling unwell	71 (8)	72 (8)
Overdose	53 (6)	57 (7)
Trauma	44 (5)	52 (6)
Gastrointestinal bleeding	42 (5)	29 (3)
Other	167 (19)	175 (20)

Statistical analysis

The sample size was chosen to estimate with a precision of ±2% the proportion of patients for whom time critical changes in treatment occurred; this was considered to be sufficiently precise to judge the value of point of care testing. The results of the pilot study of 150 patients in July 1995 indicated that this proportion was about 9%. A sample size of 1000 patients in the point of care arm of the study gives a 95% confidence interval of ±1.8%, which gave us a targeted sample size of 2000.

This sample size allowed the study to detect small differences in continuous outcomes between groups (for example, time spent in the department). However, the study had low power to detect a clinically important difference in mortality (20% power for a 1% difference, assuming an average mortality of 8%). A difference in this outcome was not anticipated, and a prohibitively large sample (about 20 000 patients) would have been required to have 80% power to detect a 1% difference. Comparisons between the two arms of the study were made using unpaired Student's *t* tests for continuous outcomes and z tests for differences in proportions.

Results

Samples from 1728 patients were entered into the trial (figure). All patients entered into the study were accounted for. The characteristics of patients in the two arms of the study were similar (table 1).

The mean times between presentation and the attending doctor's awareness of test results are shown in table 2. Decisions on management were made 74 minutes earlier (95% confidence interval 68 min to 80 min, $P<0.0001$) when point of care testing was used for haematological tests as compared to central laboratory testing, 86 minutes earlier (80 min to 92 min, $P<0.0001$) for biochemical tests, and 21 minutes earlier (−3 min to 44 min, $P=0.09$) for analyses of arterial blood gases. The mean time spent between presentation and drawing of blood was similar between the two groups (difference between groups 1 min, −4 min to 6 min, $P=0.78$); this shows that the differences in the amount of time taken to make a decision on management were the result of the faster availability of results with point of care testing.

The difference between groups in the time between a patient's presentation in the department and the time until the doctor's awareness of test results disguises a smaller difference between groups in the time until the doctor became aware of the results of arterial blood gas measurements (5.5 minutes, $P<0.0001$). Patients allocated to laboratory testing waited 14 minutes longer ($P=0.18$) for blood to be drawn than patients allocated to point of care testing.

Results from point of care testing influenced treatment in 120 out of 859 patients (13.9%, 11.7% to 16.5%) and influenced plans for further care in 25 out of 859 (2.9%, 1.9% to 4.3%). One patient discharged himself before test results were available. The influence of point of care testing on diagnosis, treatment plan, and plans for further care is shown in table 3.

Table 2 Mean time (minutes) between patient's presentation in the accident and emergency department, time until blood sample taken, and time until attending doctor's awareness of result of blood test for patients whose samples were allocated to point of care testing or to testing by the hospital's central laboratory

	Point of care testing		Laboratory testing		Point of care *v* laboratory testing	
	No of patients	Mean time (95% CI)	No of patients	Mean time (95% CI)	Difference between means (95% CI)	P value
Time until blood sampling	860*	65 (62 to 69)	868†	66 (63 to 69)	1 (–4 to 6)	0.78
Time until doctor aware of result of arterial blood gas measurement‡	43	62 (48 to 91)	43	82 (65 to 100)	21 (–3 to 44)	0.09
Time until doctor aware of result of haematological test	815	80 (76 to 83)	748	154 (150 to 159)	74 (68 to 80)	<0.0001
Time until doctor aware of result of biochemical test	815	80 (76 to 83)	765	165 (160 to 170)	86 (80 to 92)	<0.0001

*Information is missing for one point of care patient who discharged himself before blood test results were available.
†Haematology and biochemistry results were not retrieved for all patients allocated to laboratory testing.
‡ One point of care outlier, with a time to awareness of test result more than five times greater than the mean, was excluded from this comparison.

We suspected that point of care testing might influence treatment more frequently in some subgroups of patients than others, although we had no hypotheses about which subgroups would be most affected by point of care testing. There was pronounced variation in the proportion of patients for whom point of care results caused changes in treatment depending on the presenting complaint (table 4).

Frequencies of observed changes in treatment are categorised in table 5. This table also shows the median score of the importance of the timing of the change in treatment as rated by the panel of clinicians. Altogether 59 out of 859 patients (6.9%, 5.3% to 8.8%) whose samples were analysed at the point of care had changes in management in which timing was considered to be critical (score ≥ 7). This summary statistic disguises disagreement between some members of the panel which evaluated the score for each treatment group.

There were no differences between the groups in the amount of time spent in accident and emergency, either for the sample as a whole or individually for patients admitted or discharged; there were also no differences in the length of inpatient stay, mortality, or admission rates (table 6).

Discussion

Point of care testing resulted in significantly faster decision making; experienced clinicians perceived that this produced a time critical clinical benefit for 6.9% of patients. Point of care tests influenced treatment in 14% of cases overall, although a proportion of these interventions were considered less clinically important by the panel. Unnecessary treatment was prevented in 3.6% of the patients whose blood samples were tested at the point of care; this may not have been a benefit for which timing was critical, but it represents a cost saving (quantification of which is outside the scope of this paper). Point of care testing also influenced plans for further care in 2.9% of patients.

There were no differences in the amount of time spent in the department, in admission rate, in the length of stay in hospital, or mortality between those patients whose samples were tested at the point of care and those whose samples were tested by the hospital laboratory. The lack of a difference in the amount of time spent in the department, despite a reduction in the time taken to make management decisions, implies that the availability of blood test results is not a rate limiting step. In our department, about 85% of patients are not discharged, and their further care is almost always limited by the availability of inpatient beds. There was no difference in the amount of time spent in the department for those patients who were discharged; this implies that the availability of blood test results is not the rate limiting step for these patients either.

It is important to consider the validity of our findings and their applicability in different settings. The structured sampling method used ensures that the findings are representative of patients attending the accident and emergency department at our hospital. Although there were no differences in admission rates or mortality between the two groups, this does not exclude the possibility that an important difference

Table 3 Number (percentage) of 859 patients whose samples were allocated to point of care testing for whom diagnosis, treatment plan, or plans for further care were changed because of the earlier availability of test results. Information is missing for one patient who discharged himself before test results were available

Variable influenced by earlier results*	No of patients	Percentage (95% CI)
Diagnosis or treatment or plans for further care	202	23.5 (20.7 to 26.5)
Diagnosis	133	15.5 (13.1 to 18.1)
Diagnosis alone	65	7.6 (5.9 to 9.5)
Treatment	120	13.9 (11.7 to 16.5)
Treatment alone	50	5.8 (4.4 to 7.6)
Diagnosis and treatment	61	7.1 (5.5 to 9.0)
Plans for further care	25	2.9 (1.9 to 4.3)
Plans for further care alone	16	1.9 (1.1 to 3.0)
Diagnosis and plans for further care	1	0.1 (0 to 0.6)
Treatment and plans for further care	3	0.4 (0.1 to 1.0)
Diagnosis and treatment and plans for further care	5	0.6 (0.2 to 1.4)

*Changes in diagnosis, treatment, or plans for further care could occur alone or in combination with other changes. For example, the diagnosis was changed in 133 patients, but diagnosis alone changed in 65 of the 133; for the other 68 patients treatment or plans for further care, or both, were changed in addition to the diagnosis.

Table 4 Presenting complaints of patients allocated to point of care testing by number of patients with complaint and number (percentage) of patients for whom point of care testing influenced treatment

Presenting complaint	No influenced	Percentage (95% CI)
Shortness of breath (n=118)	27	22.9 (15.7 to 31.5)
Abdominal pain (n=139)	10	7.2 (3.5 to 12.8)
Chest pain (n=137)	5	3.6 (1.2 to 8.3)
Collapse (n=89)	12	13.5 (7.2 to 22.4)
Feeling unwell (n=71)	10	14.1 (7.0 to 24.4)
Overdose (n=53)	0	0 (0 to 6.7)*
Trauma (n=44)	4	9.1 (2.5 to 21.7)
Gastrointestinal bleeding (n=42)	26	61.9 (45.6 to 76.4)
Other (n=167)	26	15.6 (10.4 to 22.0)

*One sided 97.5% confidence interval.

Table 5 Number (percentage; 95% CI) of times treatment was changed because of earlier availability of test results with point of care testing by type of treatment change and median (range) score on scale of the importance of the timing of the change. Scores ⩾7 (range 0 to 10) indicate that timing of the treatment change was considered to be critical

Change in treatment	Median (range) score of importance of timing	No (%; 95% CI) of times treatment changed (n=120)*
Start intravenous glucose	10 (9 to 10)	3 (2.5; 0.5 to 7.1)
Start intravenous potassium	7 (1 to 10)	14 (11.7; 6.5 to 18.8)
Start intravenous insulin	8 (4 to 10)	7 (5.8; 2.4 to 11.6)
Start intravenous hydrocortisone	5 (0 to 10)	1 (0.8; 0 to 4.6)
Start intravenous aminophylline	6 (2 to 10)	1 (0.8; 0 to 4.6)
Start intravenous antibiotics	3 (0 to 10)	1 (0.8; 0 to 4.6)
Stop intravenous potassium	7 (2 to 10)	1 (0.8; 0 to 4.6)
Stop intravenous insulin	8 (3 to 10)	2 (1.7; 0.2 to 5.9)
Start intravenous infusion for dehydration	5 (1 to 7)	18 (15.0; 9.1 to 22.7)
Start intravenous infusion in diabetic ketoacidosis	9 (4 to 10)	3 (2.5; 0.5 to 7.1)
Stop intravenous infusion	3 (0 to 6)	2 (1.7; 0.2 to 5.9)
Change rate of intravenous infusion	3 (0 to 7)	7 (5.8; 2.4 to 11.6)
Start urgent blood transfusion	8 (1 to 10)	11 (9.2; 4.7 to 15.8)
Stop inappropriate blood transfusion	5 (1 to 10)	26 (21.7; 13.7 to 30.1)
Start oxygen therapy	10 (7 to 10)	2 (1.7; 0.2 to 5.9)
Change oxygen therapy	9 (4 to 10)	11 (9.2; 4.7 to 15.8)
Intubate or ventilate	10 (4 to 10)	5 (4.2; 1.4 to 9.5)
Start intravenous bicarbonate	6 (0 to 10)	1 (0.8; 0 to 4.6)
Start oral potassium	1 (0 to 6)	3 (2.5; 0.5 to 7.1)
Start fluid restriction	3 (0 to 7)	1 (0.8; 0 to 4.6)

*Treatment was changed more than once for some patients because of point of care results. Only the treatment change that was most dependent on time is shown for each patient

may exist; however, the estimates of differences in outcome are close to zero.

Confounding was minimised by the design of the study and the large sample size. Bias was minimised by appropriate design features: randomisation was carefully concealed from the investigator; only one investigator was involved in data collection; and all patients entered into the trial were accounted for. However, the open design of the trial is a potential source of bias since documenting changes in management required JK to interview the attending doctors. It is possible that JK may have influenced doctors' responses by altering his questioning as a result of knowing a patient's allocation. This possibility was minimised by using a standard set of neutral questions.

The applicability and relevance of the findings needs to be considered carefully, given the diversity of care provided by accident and emergency departments. The precise research question was debated because it was easy to speculate when point of care testing might be more useful or less useful. However, we decided it would be most valuable to study a completely representative sample that could act as a baseline for future study. Our findings suggest that point of care testing may be clinically beneficial for some presenting complaints. Further studies are required to investigate this.

We cannot be certain that samples from all eligible patients were included. The representativeness of the sample could have been undermined if treatment changes would have been initiated earlier as a result of point of care testing in a disproportionate number of patients who were eligible for the study but were not included. Patients may have been missed if a blood sample was taken by a paramedic or by a doctor who forgot to take an appropriate sample, or if the investigator was involved in the emergency resuscitation of a patient where duty of care took precedence over the study. Patients who were missed because their blood sample was taken by a paramedic or by a doctor who neglected to take an appropriate sample are unlikely to have had a probability of a change in treatment that was different from the study population. Although patients whom the investigator helped to resuscitate may have had a higher probability of benefit, there were fewer than 5 such patients during the study.

We are confident that our findings are a representative, valid, and precise estimate of the proportion of patients seen in accident and emergency for whom point of care testing would result in a clinically important reduction in the time taken to make differential diagnoses and treatment decisions. This proportion is unlikely to vary more than the estimate of precision of the study unless a department has restrictions on the types of patients that it accepts. Our findings can also be used to interpret the consequences of implementing point of care testing when the availability or performance of local central laboratory testing differs from our institution. Where central laboratory times might vary in a clinically important way, they can be estimated locally on relatively small samples. Local estimates, in conjunction with our findings, can be used to evaluate the benefit of point of care testing in the local setting. This study was unable to quantify potential benefit in settings where the rate limiting step in time to making arrangements for further care is not the availability of beds.

Maddi Barley, of the Clinical Audit Department, United Bristol Hospitals Trust, helped develop the database. We would also like to acknowledge the support of all of our clinical colleagues who worked in the accident and emergency department during the period of data collection.

Table 6 Comparison of the mean total time patients spent in the emergency department, length of stay in hospital, number of admissions, and mortality for patients whose samples were allocated to point of care testing or to laboratory testing

	Point of care testing		Laboratory testing		Point of care *v* laboratory testing	
	No of patients*	Mean (95% CI) or No (%)	No of patients	Mean (95% CI) or No (%)	Difference (95% CI)	P value
Mean (95% CI) time spent in emergency department (min)	859	188 (181 to 194)	868	193 (186 to 200)	5 (–5 to 15)	0.30
Mean (95% CI) length of stay in hospital (days)†	730	7.8 (6.9 to 8.6)	720	8.3 (7.5 to 9.1)	0.5 (–1 to 2)	0.37
No (%) admissions	860	733 (85.2)	868	725 (83.5)	1.7 (–1.7 to 5.1)	0.33
No (%) deaths‡	859	55 (6.4)	867	48 (5.5)	0.9 (–1.4 to 3.1)	0.45

*One patient discharged himself before test results became available.
†Information on length of stay in hospital was not available for three point of care patients and three patients allocated to laboratory testing who were transferred to other hospitals. Information was missing from the hospital information system for two additional patients allocated to laboratory testing.
‡Information was not available for one point of care patient and one patient allocated to laboratory testing because they were transferred to other hospitals.

Contributors: JK, BR, and MC were all involved in designing and executing the study as well as in writing the paper. JK collected the data and is guarantor for the paper.

Funding: During data collection, JK's salary was provided by a grant from Hewlett Packard UK.

Conflict of interest: The i-STAT system is manufactured by Hewlett Packard. Hewlett Packard was not involved in any stage of the study design, execution, analysis of data, writing up of the findings, or decisions about publication, although comments on the manuscript were sought as a matter of courtesy to the sponsor.

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Key messages

- Point of care testing reduced the amount of time doctors spent waiting for results of blood tests when compared to the time spent waiting for results from the hospital laboratory in an accident and emergency department
- The time taken to decide on a management plan was also reduced as a result of the shorter time spent waiting for results of point of care tests
- About 7% of patients who needed urgent blood testing had changes in treatment in which timing was considered to be critical when point of care testing was used
- Patients did not spend less time in the accident and emergency department even when test results were available more quickly and patient management decisions were made more quickly. This suggests that the availability of test results is not the factor which slows down the arrangement of further care
- Improvements in process, such as a reduction in the time doctors wait for test results and the ability to make clinical decisions more quickly, do not seem to improve clinical outcome in this sample of patients

Aspirin for prophylaxis against headache at high altitudes: randomised, double blind, placebo controlled trial

Martin Burtscher, Rudolf Likar, Werner Nachbauer, Michael Philadelphy

At altitudes of 3000-5000 m about 20-50% of skiers and mountaineers experience headache, the main symptom of acute mountain sickness.[1] Although most mountaineers know that they should avoid climbing great heights too early on and too fast, they may not always act accordingly. The use of drugs to prevent and treat headaches at high altitudes is therefore widespread, aspirin being one of the most commonly taken. We tested the efficacy of aspirin as prophylaxis against headache at high altitudes.

Subjects, methods, and results

Twenty nine volunteers with a history of headache at high altitude were randomly assigned in a double blind fashion to receive placebo (eight men, six women, mean age 38 (SD 12) years) or 320 mg aspirin (nine men, six women, mean age 38 (14) years). After examination at low altitude (600 m), subjects were transported to high altitude (3480 m) for 24 hours. We gave them three tablets, one every 4 hours, starting 1 hour before arrival at high altitude. We scored headache on a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) and measured heart rate, blood pressure, and arterial oxygen saturation 1 hour before and 3, 7, 10, and 19 hours after arrival. In addition, subjects exercised for 2 minutes by stepping 60 times up and down a 24 cm step, at low altitude and within 2-5 hours after arrival at high altitude during which we continuously monitored gas exchange, heart rate, and oxygen saturation.

Seven subjects given placebo and only one given aspirin developed mild to severe headache ($P = 0.01$ for differences in proportions). Although mean oxygen saturation was not different between the two groups 3 hours after arrival at high altitude, the individual values were accurate predictors of the subsequent development of headache. Those who had taken aspirin developed headache at lower oxygen saturation than those who had taken placebo ($< 83\%$ v $< 88\%$; figure). The difference between mean heart rates at the end of the exercise test at high and low altitudes was smaller in those who had taken aspirin (134 (7) v 118 (10) beats/min) than in those who had taken placebo (142 (13) v 116 (15)) ($P = 0.01$, analysis of variance for repeated measures), in whom ventilation responses to exercise

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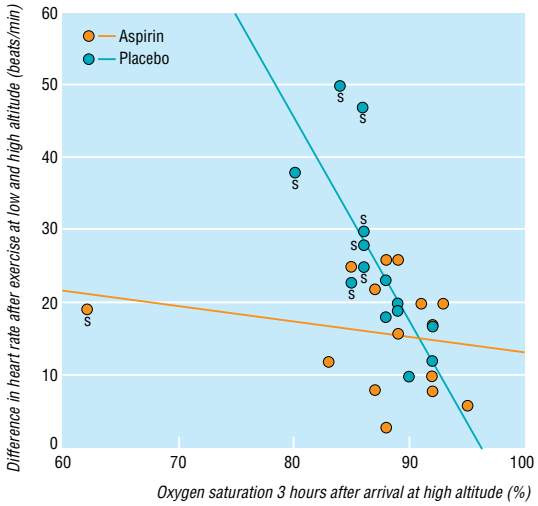

Relation between arterial oxygen saturation values 3 hours after arrival at high altitude, and difference in heart rate after exercise at high and low altitudes in subjects taking placebo or aspirin. s shows subjects who developed headache at high altitude

tended to be higher ($P=0.07$). In the placebo group, the difference in heart rate at high altitude was positively correlated with maximum headache scores ($r=0.8$, $P<0.01$) and inversely related to saturation values 3 hours after arrival at high altitude ($r=-0.8$, $P<0.01$; figure).

Comment

The incidence of headache at high altitude increases when arterial oxygen saturation and associated oxygen partial pressure decline with increasing altitude.[2] In this study, however, aspirin prevented headache without improving oxygenation. Pretreatment with aspirin raised the headache threshold, which was indicated by toleration of lower saturation values. Moreover, intake of aspirin was associated with less pronounced cardiorespiratory responses to short term exercise at high altitude. Since acute hypoxia augments prostaglandin concentrations,[3] and prostaglandins increase ergoreceptor activation and accompanying sympathetic stimulation,[4] aspirin probably prevents headache by diminishing these responses. Prostaglandins also enhance nociception, and reduced hyperalgesia may therefore have contributed additionally to the prophylactic efficacy of aspirin. Nevertheless, within the first few days of exposure to high altitude, symptoms of acute mountain sickness usually disappear even without drugs. Simultaneously, sympathetic responsiveness decreases due to desensitisation of adrenoceptors,[5] again indicating some relation between sympathetic activity and development of headaches at high altitude. If this relation is true, aspirin may support adaptation to high altitude by reducing sympathetic activity mediated by prostaglandins.

Contributors: MB designed the study, examined the subjects, did exercise testing, performed the statistical analysis and took various measurements. RL did the headache scoring and supervised the health of the subjects. WN undertook the randomisation, distribution of tablets, control of data and statistics. MP took various measurements (blood sampling)and did exercise testing.

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Prevalence of inflammatory bowel disease in British 26 year olds: national longitudinal birth cohort

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Inflammatory bowel disease has become more common in developed countries this century. Mayberry et al reported incidences of Crohn's disease in Wales of 0.18 cases/10^5/year in the 1930s and 5.95 cases/10^5/year in the 1970s.[1] We investigated the prevalence of inflammatory bowel disease at age 26 years in a nationally representative birth cohort. Associations of sex and social class with risk of the disease have previously been shown,[1–3] and these were also investigated.

Subjects, methods, and results

A postal survey of the 1970 British cohort study was conducted in 1995-6 among individuals aged 25 or 26 years, asking if respondents had a diagnosis of Crohn's disease or ulcerative colitis. The cohort study is a longitudinal study of those living in England, Scotland, and Wales born 5 to 11 April 1970.[4] The target population was estimated as 16 000, and we sent questionnaires to the 13 099 cohort members whom we traced. In all, 9803 completed questionnaires were returned; 309 addresses were identified as no longer current; and 12 people refused to participate. Excluding invalid and untraced addresses, the response rate was 77%. The social statistics research unit at City University, London, provided most (7430) of the addresses. To minimise bias, we traced the remaining 2373 cohort members through a letter forwarding service provided by the Driver and Vehicle Licensing Agency. The cohort remained largely representative, with some loss from the most disadvantaged groups: the proportion in social class V at birth dropped from 6.4% to 4.7% in the respondents.

Inflammatory bowel disease among 26 year olds in 1970 British cohort study. Values are numbers (%) unless stated otherwise

Characteristics	No inflammatory bowel disease	Crohn's disease		Ulcerative colitis	
		All cases	Confirmed	All cases	Confirmed
Social class:					
I	504 (5.2)	1 (3)		2 (9)	1 (8)
II	1204 (12.3)	4 (13)	3 (14)	3 (14)	3 (25)
III Non-manual	1318 (13.5)	5 (17)	5 (24)		
III Manual	3990 (40.9)	11 (37)	9 (43)	10 (46)	4 (33)
IV	1331 (13.6)	4 (13)	2 (10)	3 (14)	2 (17)
V	456 (4.7)	1 (3)	1 (5)	1 (5)	
Other	118 (1.2)				
Unsupported*	36 (0.4)				
Missing	794 (8.1)	4 (13)	1 (5)	3 (14)	2 (17)
Sex:					
Male	4834 (50)	14 (47)	9 (43)	13 (59)	7 (58)
Female	4917 (50)	16 (53)	12 (57)	9 (41)	5 (42)
Total	9751 (100)	30 (100)	21 (100)	22 (100)	12 (100)
Prevalence per 10 000 (95% CI)		29.8 (19.0 to 40.6)†	21.4 (12.3 to 30.6)	19.4 (10.5 to 28.1)†	12.2 (5.3 to 19.2)

*Single mothers who were not working—social class could not be assigned on the basis of current or previous occupation.
†Assuming that the unconfirmed cases have the same disease specific, false positive rates as the entire sample.

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Cohort members who reported inflammatory bowel disease were contacted again for details of their diagnosis and permission to contact their physicians. If permission was not granted, diagnosis was not confirmed. The registrar general's social class was based on father's occupation, collected prospectively in 1970.

The table shows the prevalence of Crohn's disease and ulcerative colitis in the cohort, by social class and age. Thirty two and 27 cohort members reported Crohn's disease and ulcerative colitis respectively. For two reports of Crohn's disease and five of ulcerative colitis, the diagnosis was subsequently refuted by cohort members themselves or their physicians. The diagnosis was confirmed for 21 cohort members with Crohn's disease and 12 with ulcerative colitis. On the basis of physician confirmed cases only, the prevalence per 10 000 was 21.4 (95% confidence interval 12.3 to 30.6) for Crohn's disease, 12.24 (5.3 to 19.2) for ulcerative colitis, and 33.7 (22.2 to 45.1) for inflammatory bowel disease. If it is assumed that the unconfirmed cases had the same disease specific, false positive rates as the entire sample, the estimated prevalences per 10 000 were 29.8 (19.0 to 40.6), 19.4 (10.5 to 28.1), and 49.2 (35.3 to 63.0) respectively.

Social class was modelled by using logistic regression, both as a six category ordinal variable and as a binary (manual *v* non-manual) dummy. Neither social class nor sex was significantly associated with Crohn's disease, ulcerative colitis, or both diseases combined ($P > 0.1$).

Comment

We found a higher prevalence for Crohn's disease and for ulcerative colitis than other studies in Britain have found for comparable age groups (Keighley et al found a prevalence of 6.49/10 000 for Crohn's disease among 25-29 year olds in 1973[2] and Evans et al 7.59/10 000 for ulcerative colitis among 25-34 year olds in 1960[3]). In part, this may be because a general population based sample was used, but it is also likely to reflect a genuine rise in the prevalence of inflammatory bowel disease, particularly for Crohn's disease. The lack of significant association of both social class and sex with inflammatory bowel disease may be a function of the small number of cases. Alternatively, there may be a homogenisation of the pattern of exposure to risk factors for inflammatory bowel disease that reflects improved material conditions in infancy in comparison with those born earlier this century: improved conditions in early life have been identified as a risk for later inflammatory bowel disease.[5] This is a relatively young cohort, and we expect the prevalence of inflammatory bowel disease to continue rising both in the 1970 British cohort study and in the general population.

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Contributors: SMM wrote the original draft of the paper, planned the data collection, was responsible for the data analysis, participated in all components of the study, and will act as guarantor for the paper. All authors contributed to the design, data interpretation, and writing of the paper. DLM was responsible for ensuring confirmation of the diagnosis of Crohn's disease or ulcerative colitis in cohort members who reported having inflammatory bowel disease. NPT and JS assisted in data collection and data preparation. REP and AJW were responsible for originating and overseeing the study.

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Correction

Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs

An editorial error occurred in this paper by Moore et al (31 January, 333-8). The *x* axis of figure 3, the percentage with successful outcome, should have been divided as 0, 20, 40, 60, 80, and 100 [not 0.1, 1, 10, 100, 10, 100, as published].