Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study

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BMJ 1997;315:722–9

Abstract

Objective: To compare prediction by 27 different factors in men and women of coronary heart disease events, coronary deaths, and deaths from all causes.
Design: Cohort study.
Setting: Scottish population study.
Subjects: In 1984-7 random sampling of residents aged 40-59 produced 11 629 men and women who generated survey clinic questionnaires, examination findings, and blood and urine specimens.
Main outcome measures: Subsequent death, coronary artery surgery, and myocardial infarction. Risks were calculated for each category of factor or fifth of continuous variables. 27 factors were ranked by descending age adjusted hazard ratio of the top to bottom class in each factor, by sex and end point.
Results: Follow up averaged 7.6 years, during which the 5754 men had 404 coronary events, 159 coronary deaths, and 383 deaths and the 5875 women 177, 47, and 208 respectively. The rankings for factors for the three end points were mainly similar in men and women, although hazard ratios were often higher in women. Classical risk factors ranked better for predicting coronary risk than newer ones. Yet strong prediction of coronary risk was no guarantee of significant prediction of all cause mortality. Findings included an anomalous coronary protective role for type A behaviour in women; raised plasma fibrinogen as a strong predictor of all end points; and an unexpectedly powerful protective relation of dietary potassium to all cause mortality.
Conclusions: These initial unifactorial rankings and comparisons must be interpreted with caution until potential interaction, confounding, and problems of measurement and causation are further explored.

Introduction

With few exceptions,[1-3] studies identifying risk factors for coronary heart disease have focused on men,[4-9] with their higher incidence rates,[10] yet women live longer and lifetime risk is almost equal.[11] All cause mortality is now a standard end point in intervention studies but relatively neglected in studies of risk factors. There is a need for studies which include standardised measurement of lifestyle and coronary risk factors in men and women and where all cause mortality is reported alongside coronary end points.

The Scottish heart health study[12] began in 1984, when Scotland was in the premier league for death from coronary heart disease in both men and women. It reported lifestyle and risk factor status for representative samples of men and women across Scotland[13 14] and showed how regional variations in risk factors correlated with mortality from coronary heart disease.[15]

We always intended to see how well older and new factors compared in predicting coronary risk,[12] and after eight years' follow up we now compare 27 factors in the two sexes for three end points— major coronary events (non-fatal myocardial infarction, death from coronary heart disease, or coronary artery surgery), deaths from coronary heart disease, and all deaths.

Methods

Recruitment—Twenty five districts of Scotland were visited in two contrasting seasons in November 1984 to October 1987. General practitioners were recruited randomly and their patients enumerated in the eight five year age-sex bands 40-59. A constant percentage in each district band was selected by random sampling.[12 16] In 23 districts the target total was 450 people from 10 general practitioners but the Edinburgh and north Glasgow MONICA (monitoring trends and determinants in cardiovascular disease) population surveys[17] each included 30 general practitioners and 800 participants aged 40-59. Joint letters were sent out from survey and practice enclosing appointments for local clinics, plus a 20 page personal health record for self completion. This included several classical cardiovascular questionnaires,[18] a food frequency questionnaire adapted from Caerphilly,[19] and the Bortner questionnaire for type A personality.[20]

Survey clinic procedures—Clinics were run by survey nurses. Participants reported without fasting and progressed through three stations. Firstly, after removing shoes and outer clothing, they were weighed, had their height measured, and gave informed consent, including to follow up of medical records. The questionnaire was checked. Blood pressure was measured twice by random zero sphygmomanometer

seated after five minutes' rest. Station two recorded a 12 lead electrocardiogram and measured expired air carbon monoxide. At station three venepuncture and a subcutaneous fat biopsy were performed and a 2.5 litre container for 24 hour urine collection was supplied.[12]

Processing and quality control—Serum was separated within two hours and chilled at 4°C while plasma was separated immediately and stored at −20°C before both were transferred within five days to Dundee. Urine collections were weighed and analysed for electrolytes and for creatinine. The latter and most serum analyses were analysed in duplicate shortly after reaching Dundee. Serum cotinine and adipose tissue fatty acids were analysed subsequently by gas chromatography. After storage at −40°C plasma specimens were assayed in Glasgow by coagulometer for fibrinogen.[21] Survey and laboratory procedures including lipid analyses were standardised on the World Health Organisation's MONICA protocol and its lipid laboratory.[22] Electrocardiograms were coded by two

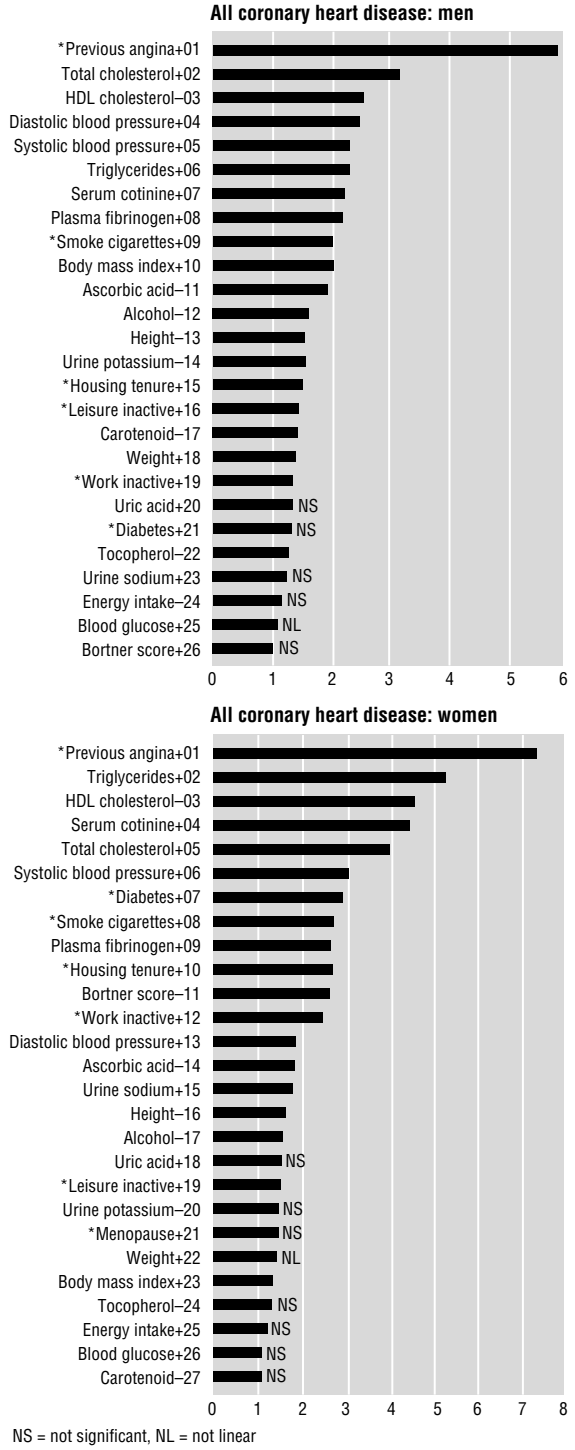

Fig 1 Ranking of risk factors for all coronary events in men and women by age adjusted hazard ratios between highest and lowest category (fifths unless indicated). *Factors with fewer than five classes

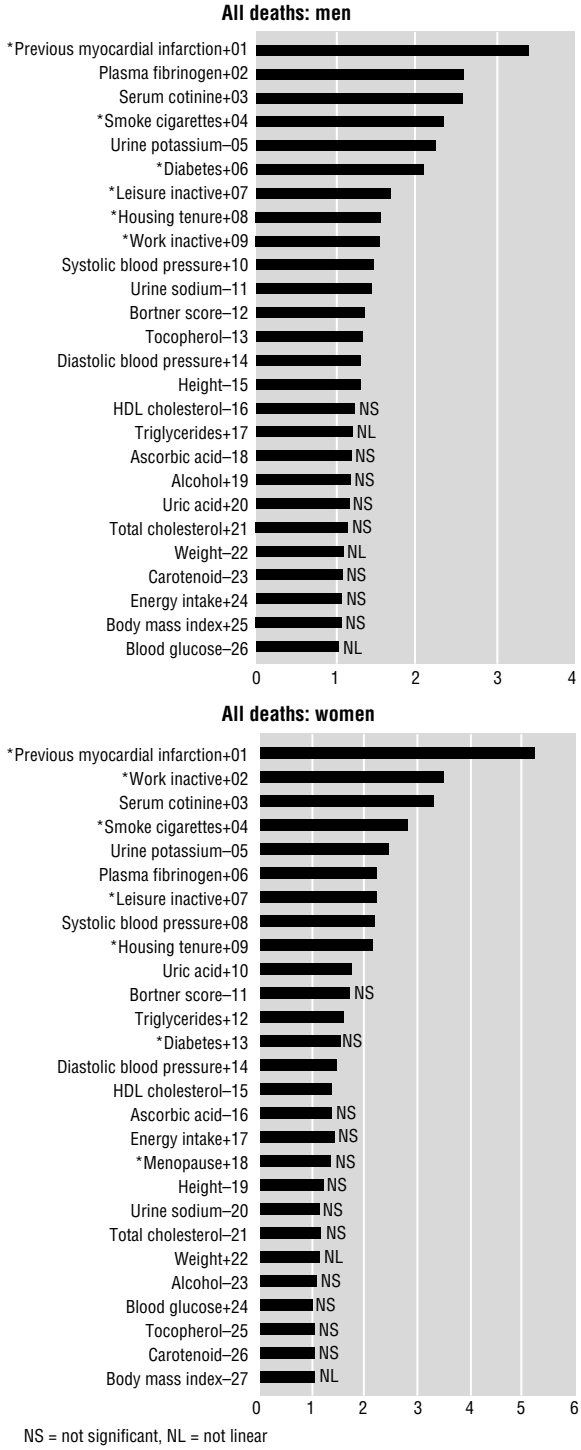

Fig 2 Ranking of risk factors for all cause mortality in men and women by age adjusted hazard ratios between highest and lowest category (fifths unless indicated). *Factors with fewer than five classes

Table 1 Numbers of people at risk and numbers experiencing a qualifying end point event during follow up

	Age group				
	40-44	45-49	50-54	55-59	All ages
Men:					
All people at baseline	1398	1370	1521	1465	5754
All coronary heart disease*	66	68	106	164	404
Fatal coronary heart disease	21	15	45	78	159
Deaths from all causes	42	54	110	177	383
Women:					
All persons at baseline	1503	1438	1521	1413	5875
All coronary heart disease*	17	32	43	85	177
Fatal coronary heart disease	0	5	13	29	47
Deaths from all causes	21	32	54	101	208

*Endpoint of all coronary heart disease includes coronary death, or coronary artery surgery, or non-fatal definite or possible myocardial infarction but the latter only qualifies in the absence of a previous history of myocardial infarction.

observers with a third adjudicating discrepancies.[23] Questionnaires were part coded by nurses before transfer to Dundee, where they were checked, double coded, keyed, and verified on microcomputer. Data underwent range and logic checks and were assembled by individual anonymous code on the mainframe. Personal identifiers were stored elsewhere.

Follow up—Participants were flagged on the Scottish NHS Register, which forwarded copies of death certificates. The Scottish heart health study register of participants, updated with information from health boards, was run against a central file of hospital discharge data by the information and statistics division of the Scottish Common Services Agency, generating a list of all hospital admissions from before the study began to the end of 1993,[24] which was also used as the cut point for mortality follow up.

End points—Case notes were requested for all hospital episodes of myocardial infarction and other emergency admissions for coronary heart disease. These were extracted and coded according to MONICA project criteria as definite, possible, or no myocardial infarction, the first two categories being included as end points.[10 22 25] Hospital diagnoses of coronary artery surgery (coronary artery bypass grafts or percutaneous transluminal coronary angioplasty) were accepted without verification, as were out of hospital coronary deaths, as further inquiry in the Scottish MONICA project rarely changes the diagnosis.[25] We report three overlapping end points. Participants progressing to myocardial infarction, coronary artery surgery, or death from coronary disease qualified for all coronary heart disease, barring those few who had non-fatal recurrence of a prerecruitment myocardial infarction. Two fatal end points were deaths from coronary heart disease and deaths from all causes.

Table 2 Age adjusted hazard ratios for two and three class categorical data

	Men					Women				
				Missing					Missing	
Class	1	2	3	Multiplicative constant (95% CI)	P value	1	2	3	Multiplicative constant (95% CI)	P value
Housing tenure (owned/rented)										
Tenure	*Own*	*Rent*				*Own*	*Rent*			
%	53.5	46.5		19		51.4	48.6		25	
All CHD	1	1.48		1.48 (1.21 to 1.80)	***	1	2.64		2.64 (1.89 to 3.68)	***
CHD deaths	1	1.56		1.56 (1.13 to 2.14)	**	1	2.42		2.42 (1.28 to 4.59)	**
All deaths	1	1.55		1.55 (1.26 to 1.90)	***	1	2.12		2.12 (1.58 to 2.84)	***
Diabetes mellitus (no/yes)										
Diabetes	*No*	*Yes*				*No*	*Yes*			
%	98.4	1.6		65		98.5	1.5		87	
All CHD	1	1.31		1.31 (0.67 to 2.53)	NS	1	2.91		2.91 (1.43 to 5.92)	**
CHD deaths	1	2.14		2.14 (0.95 to 4.85)	BS	1	4.03		4.03 (1.25 to 12.99)	*
All deaths	1	2.08		2.08 (1.22 to 3.55)	**	1	1.50		1.50 (0.62 to 3.66)	NS
Menopausal status (no/yes)										
Menopause						*No*	*Yes*			
%						42.3	57.7		36	
All CHD	—	—				1	1.48		1.48 (0.92 to 2.40)	NS
CHD deaths	—	—				1	1.07		1.07 (0.36 to 3.19)	NS
All deaths	—	—				1	1.35		1.35 (0.86 to 2.11)	NS
Cigarette smoking (never/ex/current smoker)										
Status	*Never*	*Ex*	*Current*			*Never*	*Ex*	*Current*		
%	25.7	34.8	39.5	41		41.6	20.2	38.2	39	
All CHD	1	1.38	2.02	1.43 (1.25 to 1.63)	***	1	1.16	2.70	1.69 (1.42 to 2.02)	***
CHD deaths	1	1.54	2.50	1.60 (1.28 to 1.98)	***	1	1.73	3.24	1.81 (1.27 to 2.57)	***
All deaths	1	1.54	2.34	1.53 (1.33 to 1.75)	***	1	1.56	2.80	1.68 (1.43 to 1.99)	***
Physical inactivity in work (active/average/inactive)										
Status	*Active*	*Average*	*Inactive*			*Active*	*Average*	*Inactive*		
%	42.4	44.4	13.2	62		47.4	48.1	4.5	25	
All CHD	1	1.18	1.35	1.17 (1.01 to 1.34)	*	1	1.13	2.45	1.35 (1.05 to 1.74)	*
CHD deaths	1	1.57	1.84	1.39 (1.11 to 1.34)	**	1	0.82	3.79	1.44 (0.88 to 2.35)	NS††
All deaths	1	1.32	1.55	1.26 (1.09 to 1.45)	**	1	1.10	3.50	1.54 (1.22 to 1.94)	***††
Leisure physical inactivity (active/average/inactive)										
Status	*Active*	*Average*	*Inactive*			*Active*	*Average*	*Inactive*		
%	22.8	59.0	18.2	27		19.2	62.1	18.7	23	
All CHD	1	1.11	1.45	1.21 (1.03 to 1.41)	*	1	1.26	1.51	1.23 (0.96 to 1.56)	BS
CHD deaths	1	1.28	2.07	1.46 (1.14 to 1.87)	**	1	0.78	2.22	1.68 (1.04 to 2.70)	*†
All deaths	1	1.08	1.66	1.31 (1.11 to 1.54)	**	1	0.99	2.20	1.61 (1.29 to 2.02)	***††

CHD=coronary heart disease.
Log linear significance testing: NS=not significant ($P \geq 0.10$), BS=borderline ($0.05 \leq P < 0.1$), *=significant ($0.01 \leq P < 0.05$), **=highly significant ($0.001 \leq P < 0.01$), ***=very highly significant ($P < 0.001$). Residual non-linear significance testing uses † instead of *.

Statistical procedures

Cox's proportional hazards model[26] allows for the different follow up times from attendance at the initial clinic until the end of 1993. Survival was counted to the first qualifying event. Loss to follow up for coronary end points occurred through death from a non-coronary cause and for all end points through emigration.

For continuously distributed factors the population was partitioned into fifths, up to and including the 20th, 40th, 60th, and 80th centiles. The tables specify the quintile values, but also those of the 1st and 99th centiles, rather than extreme readings. Values of zero identified the lowest class for alcohol consumption and for serum cotinine concentration; partitioning at and below the 25th, 50th, and 75th centiles classified others with positive values into the four remaining classes. For categorical factors class sizes were uneven and their number, 2-5, implicit.

For each factor, end point, and sex, after age adjustment, the risk in the lowest class was set at unity and the

Table 3 Age adjusted hazard ratios for five class discontinuous factors

	Men							Women						
						Missing							Missing	
Class	**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**	**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**
Previous coronary heart disease														
	None	*Rose+*	*ECG+*	*Angina*	*MI*			*None*	*Rose+*	*ECG+*	*Angina*	*MI*		
%	78.5	6.4	6.9	3.4	4.8	134		79.1	7.7	8.2F	3.4	1.6	135	
All CHD	1	1.57	2.69	5.83	NA	1.75 (1.60 to 1.92)	***	1	1.75	2.67	7.31	NA	1.86 (1.63 to 2.12)	***
CHD deaths	1	1.90	3.783	5.41	8.04	1.70 (1.54 to 1.87)	***	1	1.88	5.44	3.77	25.32	2.10 (1.74 to 2.54)	***
All deaths	1	1.53	2.15	2.36	3.39	1.36 (1.27 to 1.46)	***	1	1.60	2.19	2.21	5.23	1.44 (1.29 to 1.60)	***
Bortner score (type A personality)														
	⩽134	*135-*	*160-*	*179-*	*⩾203*			*⩽138*	*139-*	*162-*	*178-*	*⩾199*		
%	19.9	20.1	19.8	20.0	20.0	481		19.9	20.5	19.6	20.3	19.8	670	
All CHD	1	1.08	0.87	0.78	1.04	0.98 (0.91 to 1.05)	NS	1	0.52	0.64	0.57	0.38	0.82 (0.73 to 0.93)	**
CHD deaths	1	1.16	0.90	0.76	1.08	0.98 (0.87 to 1.10)	NS	1	0.39	0.62	0.34	0.35	0.77 (0.60 to 0.99)	*
All deaths	1	0.86	0.69	0.73	0.74	0.92 (0.85 to 0.99)	*	1	0.66	0.75	0.84	0.59	0.92 (0.82 to 1.02)	NS
Serum cotinine (ng/ml)														
	0	*0.01-*	*2.17-*	*59.31-*	*⩾ 285.0*			*0*	*0.01-*	*1.40-*	*14.21-*	*⩾248.1*		
%	13.9	21.5	21.5	21.5	21.6	1409		22.5	19.4	19.3	19.5	19.3	1656	
All CHD	1	1.19	1.13	1.72	2.18	1.23 (1.13 to 1.35)	***	1	0.91	0.96	2.61	4.48	1.59 (1.38 to 1.83)	***
CHD deaths	1	1.39	0.89	2.01	2.91	1.32 (1.14 to 1.54)	***	1	1.20	1.65	2.90	10.73	2.05 (1.46 to 2.87)	***
All deaths	1	1.18	1.43	2.09	2.56	1.29 (1.18 to 1.42)	***	1	0.52	1.17	1.92	3.30	1.48 (1.30 to 1.68)	***†
Alcohol (units/week)														
Units	*0*	*1-7*	*8-15*	*16-29*	*⩾30*			*0*	*1-2*	*3-5*	*6-9*	*⩾10*		
%	20.0	20.4	19.7	20.1	19.7	15		38.0	414.6	17.8	14.5	15.0	22	
All CHD	1	1.00	0.59	0.82	0.62	0.89 (0.83 to 0.95)	**†	1	0.70	0.64	0.56	0.64	0.86 (0.77 to 0.96)	***
CHD deaths	1	0.87	0.63	0.94	0.62	0.92 (0.82 to 1.03)	NS	1	0.49	0.58	0.36	0.52	0.79 (0.62 to 1.00)	*
All deaths	1	0.90	0.84	0.83	1.17	1.02 (0.95 to 1.10)	NS	1	0.64	0.85	0.79	0.93	0.97 (0.88 to 1.07)	NS

CHD=coronary heart disease. ECG=electrocardiogram. MI=myocardial infarction. See footnote to table 1 for P values.

Table 4 Age adjusted hazard ratios by fifths of physical attributes

	Men								Women							
Centile	**1**	**20**	**40**	**60**	**80**	**99**	**Missing**		**1**	**20**	**40**	**60**	**80**	**99**	**Missing**	
Fifth		**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**		**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**
Height (m)																
	1.57F	1.67	1.71	1.74	1.78	1.88	27		1.46	1.55	1.58	1.61	1.65	1.75	9	
All CHD		1	0.94	0.76	0.78	0.66	0.90 (0.84 to 0.97)	**		1	0.65	0.62	0.61	0.63	0.89 (0.80 to 0.98)	*
CHD deaths		1	0.92	0.75	0.69	0.80	0.93 (0.83 to 1.03)	NS		1	0.82	0.82	0.88	0.91	0.98 (0.80 to 1.20)	NS
All deaths		1	1.06	0.76	0.78	0.78	0.92 (0.86 to 0.99)	*		1	0.86	1.11	1.10	0.84	1.00 (0.91 to 1.10)	NS
Weight (kg)																
	53	68	74	80	87	111	6		44	56	61	66	74	103	3	
All CHD		1	1.01	1.23	1.12	1.40	1.08 (1.01 to 1.16)	*		1	0.79	0.69	0.75	1.40	1.08 (0.97 to 1.20)	NS†
CHD deaths		1	0.88	0.90	0.77	1.31	1.05 (0.94 to 1.18)	NS		1	0.42	0.85	0.63	1.40	1.11 (0.91 to 1.37)	NS
All deaths		1	0.83	0.66	0.64	0.92	0.96 (0.89 to 1.03)	†		1	0.75	0.78	0.67	1.13	1.02 (0.92 to 1.12)	†
Body mass index (kg/m^2)																
	18.8	23.3	25.1	26.7	28.7	36.2	27		18.0	22.1	24.0	26.0	28.9	41.1	10	
All CHD		1	1.71	1.47	1.52	1.97	1.12 (1.05 to 1.20)	**		1	0.69	0.71	0.98	1.37	1.13 (1.01 to 1.25)	*
CHD deaths		1	1.77	1.11	1.25	1.68	1.06 (0.95 to 1.19)	NS		1	0.40	0.29	0.68	1.20	1.13 (0.92 to 1.40)	NS†
All deaths		1	0.98	0.86	0.78	1.05	0.99 (0.92 to 1.06)	NS		1	0.57	0.69	0.77	0.97	1.03 (0.93 to 1.13)	†
Systolic blood pressure (mm Hg)																
	98	118	127	136	148	190	6		95	113	123	133	148	192	6	
All CHD		1	1.07	1.54	1.65	2.25	1.23 (1.15 to 1.33)	***		1	1.22	1.38	1.84	3.10	1.35 (1.20 to 1.52)	***
CHD deaths		1	0.54	1.26	0.98	1.62	1.18 (1.05 to 1.32)	**†		1	1.65	6.48	5.08	13.1	1.76 (1.33 to 2.33)	***
All deaths		1	0.77	1.20	1.13	1.43	1.12 (1.04 to 1.20)	**		1	1.02	0.84	1.07	2.18	1.25 (1.12 to 1.39)	***††
Diastolic blood pressure (mm Hg)																
	59	74	80	86	93	115	7		58	71	78	83	90	113	7	
All CHD		1	1.52	1.47	1.51	2.47	1.21 (1.12 to 1.30)	***		1	0.98	1.13	1.08	1.85	1.17 (1.05 to 1.30)	**
CHD deaths		1	1.40	1.54	1.06	2.43	1.19 (1.06 to 1.34)	**†		1	0.94	3.25	0.60	3.63	1.31 (1.05 to 1.63)	*††
All deaths		1	0.82	1.06	0.96	1.29	1.08 (1.00 to 1.16)	*		1	0.73	1.23	0.85	1.45	1.11 (1.00 to 1.22)	*

CHD=coronary heart disease. See footnote to table 1 for P values.

Table 5 Age adjusted hazard ratios by fifths of metabolic and haemostatic factors

	Men								Women							
Centile	**1**	**20**	**40**	**60**	**80**	**99**	**Missing**		**1**	**20**	**40**	**60**	**80**	**99**	**Missing**	
Fifth		**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**		**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**
Total serum cholesterol (mmol/l)																
	3.96	5.41	6.01	6.56	7.31	9.44	424		3.98	5.47	6.16	6.80	7.65	10.25	733	
All CHD		1	1.13	2.05	2.15	3.15	1.34 (1.34 to 1.44)	***		1	2.43	2.97	3.51	3.94	1.28 (1.12 to 1.45)	***
CHD deaths		1	1.14	1.50	1.74	2.21	1.23 (1.09 to 1.38)	***		1	1.10	3.23	1.87	2.27	1.14 (0.88 to 1.48)	NS
All deaths		1	0.88	1.04	0.93	1.13	1.03 (0.96 to 1.11)	NS		1	0.83	1.00	0.73	0.86	0.96 (0.86 to 1.07)	NS
HDL cholesterol (mmol/l)																
	0.68	1.06	1.23	1.40	1.64	2.43	676		0.86	1.32	1.54	1.74	2.00	2.90	926	
All CHD		1	0.65	0.54	0.42	0.40	0.79 (0.73 to 0.85)	***		1	0.59	0.44	0.35	0.22	0.69 (0.61 to 0.78)	***
CHD deaths		1	0.71	0.65	0.43	0.44	0.80 (0.71 to 0.91)	***		1	0.87	0.53	0.53	0.32	0.76 (0.60 to 0.97)	*
All deaths		1	0.81	0.91	0.81	0.82	0.95 (0.88 to 1.02)	NS		1	0.74	0.59	0.35	0.71	0.87 (0.78 to 0.97)	*†
Serum triglycerides (mmol/l)																
	0.57	1.23	1.68	2.30	3.25	7.27	430		0.50	0.91	1.22	1.59	2.23	5.55	735	
All CHD		1	1.48	1.65	2.11	2.25	1.21 (1.12 to 1.30)	***		1	2.21	1.86	3.90	5.23	1.46 (1.28 to 1.67)	***
CHD deaths		1	1.69	1.36	2.18	1.70	1.13 (1.00 to 1.27)	*		1	3.50	4.11	5.25	6.21	1.33 (1.01 to 1.74)	*
All deaths		1	1.29	0.79	1.27	1.20	1.03 (0.96 to 1.12)	†		1	1.01	1.24	1.50	1.61	1.15 (1.02 to 1.29)	*
Blood glucose (mmol/l)																
	3.28	4.35	4.69	5.02	5.54	11.24	421		3.29	2.44	4.62	4.80	5.21	9.55	731	
All CHD		1	1.11	0.68	0.73	1.12	0.99 (0.92 to 1.06)	NS††		1	1.01	0.87	0.79	1.14	1.01 (0.90 to 1.13)	NS
CHD deaths		1	1.12	0.63	0.66	1.07	0.97 (0.86 to 1.09)	NS		1	1.14	0.90	0.71	1.60	1.09 (0.86 to 1.37)	NS
All deaths		1	0.89	0.72	0.64	0.96	0.97 (0.90 to 1.04)	†		1	0.88	0.78	0.69	1.06	1.00 (0.89 to 1.11)	NS
Uric acid (μmol/l)																
	185.6	264.2	295.7	327.4	367.3	488.2	421		127.6	193.9	221.5	248.3	285.9	426.8	730	
All CHD		1	1.02	1.10	0.97	1.32	1.06 (0.98 to 1.14)	NS		1	1.17	1.20	1.10	1.54	1.09 (0.97 to 1.23)	NS
CHD deaths		1	0.57	1.05	0.81	1.26	1.08 (0.96 to 1.22)	NS		1	1.71	0.58	1.48	1.84	1.14 (0.89 to 1.46)	NS
All deaths		1	0.96	1.01	0.95	1.16	1.03 (0.96 to 1.11)	NS		1	0.95	1.11	1.05	1.72	1.15 (1.03 to 1.29)	*
Plasma fibrinogen (g/l)																
	1.06	1.83	2.10	2.36	2.75	4.61	659		1.07	1.90	2.17	2.44	2.82	4.51	1015	
All CHD		1	1.21	1.30	1.30	2.16	1.19 (1.10 to 1.29)	***		1	1.59	1.66	1.91	2.70	1.24 (1.09 to 1.40)	***
CHD deaths		1	1.38	1.36	1.49	3.01	1.30 (1.14 to 1.48)	***		1	0.88	1.39	2.15	3.42	1.45 (1.11 to 1.91)	**
All deaths		1	1.40	1.34	1.56	2.59	1.25 (1.15 to 1.35)	***		1	0.87	1.09	1.20	2.20	1.26 (1.12 to 1.41)	***

CHD=coronary heart disease. See footnote to table 1 for P values.

hazard ratios relative to that calculated for the remaining one to four classes. Significance tests were applied both for a linear trend in the logarithm of hazard ratios and for a residual non-linear effect where appropriate. Rather than calculating confidence intervals for each class, we calculated an estimate and 95% confidence limits for the multiplicative constant of risk across consecutive classes. After converting hazard ratios of < 1.0 to their reciprocals for protective factors we ranked those for the top class of each factor in bar charts for all coronary heart disease and all deaths, although this meant mixing results for continuous and categorical factors. Complex issues of interaction, confounding, measurement, and causation are deferred to later analyses.

Results

After allowing for wrong addresses, the 11 629 men and women in the Scottish heart health study follow up study were 72% of those originally invited. Numbers at risk and numbers of end points by age and sex are given in table 1. Annual event rates in men were 9.6 per 1000 for all coronary heart disease, 3.7 for coronary heart disease deaths, and 8.9 for all deaths. In women the equivalent rates were 4.0, 1.1, and 4.7.

Tables 2-6 shows the relation of different types of factors to the risk of the three end points. Fuller details of the categories are referenced where necessary.

Housing tenure[27]—Renters had highly significant excess hazard ratios than owner occupiers for all end points, higher for women than men.

Diabetes mellitus had the same low prevalence of 1.5% in both sexes. A highly significant excess of all deaths existed in men and of all coronary heart disease in women; other hazard ratios were less significant.

Women who underwent the *menopause* [28] before recruitment, after age adjustment, had insignificantly raised hazard ratios.

Current *cigarette smokers*[29-32] had very highly significant increases in hazard ratios over never smokers for all end points, greater in women.

Physical inactivity at work[33] was associated with increased risk for all end points, but the proportion admitting to it was small, particularly in women.

Self reported *leisure physical inactivity*[33] was also associated with significantly increased risks for all end points.

Previous coronary heart disease[34] was analysed for four categories compared with those with no evidence of it from their medical history, Rose questionnaire, or electrocardiogram.[18] These were: a positive score on the Rose questionnaire alone; an electrocardiogram positive for ischaemia without a diagnosis; diagnosed angina without myocardial infarction; diagnosed myocardial infarction. Those with past myocardial infarction could not score for non-fatal recurrence, hence the missing cells. Hazard ratios were greatly increased for all categories of coronary heart disease and for all cause mortality.

A high *Bortner score*[20 35] for type A personality in men showed no significant effect in predicting coronary end points but was significantly protective against all deaths. In women it showed a protective effect for coronary end points too.

Serum cotinine values,[29-32] measuring exposure to tobacco smoke, showed a two to threefold increase in hazard ratio in men for all end points; hazard ratios in women were even higher.

Alcohol consumption[36] differed in dosage between the sexes. In women the large group of abstainers did worst for all end points: alcohol had a very highly significant protective effect against all coronary heart disease. Men showed similar protection against all coronary heart disease. The male risk curve for all deaths was a shallow non-significant "U" shape, with the higher limb in the high consumption group (≥30 units/week), whereas in women the curve was tilted marginally the other way.

Height was significantly protective against all coronary heart disease in both sexes and all deaths in men.

Weight showed a "U" shaped relation to death from all causes in both sexes. For other end points the curve was not significant or was "J" shaped.

Body mass index produced a significant excess risk of all coronary heart disease with obesity but a "U" shaped curve for all deaths, which was shallow in women and non-significant in men.

The mean of the two *systolic blood pressure*[37] readings showed highly significant gradients for all end points in both sexes. Gradients were steeper in women.

For *diastolic blood pressure*[37] gradients in men were similar to those for systolic pressure, but in women they were somewhat reduced.

The gradient with *total serum cholesterol* concentration[38] was very highly significantly positive for all coronary heart disease, weaker for coronary heart disease deaths, and undetectable for all deaths.

By contrast, *high density lipoprotein cholesterol* concentration showed a protective negative gradient for coronary end points, more marked in women, in whom it also related significantly to all deaths; men also showed a negative tendency, albeit insignificant.

Serum triglyceride concentrations (measured without fasting) showed significant positive gradients for five of the six end points, steeper in women. All deaths in men was the exception.

Blood glucose (measured without fasting) showed shallow insignificant "U" shaped risk curves for all end points in women and significantly non-linear effects for two end points in men.

There seemed to be no general pattern of risk for *uric acid* concentration beyond a slightly raised risk in the highest class for all end points in both sexes.

Plasma fibrinogen[21 28 39] showed highly significant positive trends in both sexes for all end points.

Sodium excretion[40] did not predict coronary heart disease in men and showed a borderline negative gradient for all deaths, whereas in women it was just positive for all coronary heart disease.

In contrast, *potassium excretion*[40] showed a highly significant protective gradient for all deaths in both sexes and significantly protected against all coronary heart disease in men.

Estimated *energy intake*[41] from the food frequency questionnaire showed no significant effects.

Carotenoids[42] (part of vitamin A) were significantly protective for all coronary heart disease in men.

That finding was even stronger for *ascorbic acid*[42] (vitamin C).

Tocopherol[42] (vitamin E) intake was just significantly protective for male end points.

Risk factor ranking—Figs 1 and 2 display the ranking in men and women for the different factors for all

Table 6 Age adjusted hazard ratios by fifths of dietary factors

	Men								Women							
Centile	**1**	**20**	**40**	**60**	**80**	**99**	**Missing**		**1**	**20**	**40**	**60**	**80**	**99**	**Missing**	
Fifth		**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**		**1**	**2**	**3**	**4**	**5**	**Multiplicative constant (95% CI)**	**P value**
Urinary sodium ion excretion (mmol/day)																
	46.8	129.6	168.4	204.1	251.3	416.7	1634		37.8	98.0	123.4	149.0	187.3	319.3	1906	
All CHD		1	1.18	1.11	1.26	1.23	1.05 (0.96 to 1.14)	NS		1	0.93	01.97	1.09	1.76	1.16 (1.00 to 1.33)	*
CHD deaths		1	0.96	0.62	0.97	10.92	0.98 (0.86 to 1.13)	NS		1	1.36	0.41	0.85	2.05	1.14 (0.87 to 1.49)	NS
All deaths		1	0.99	0.65	0.86	0.71	0.92 (0.84 to 1.00)	BS		1	0.61	0.82	0.67	0.85	0.97 (0.86 to 1.10)	NS
Urinary potassium ion excretion (mmol/day)																
	17.6	47.2	59.5	71.3	86.3	138.1	1633		15.3	39.7	49.4	58.5	70.2	116.4	1906	
All CHD		1	0.62	0.87	0.58	0.66	0.91 (0.83 to 0.99)	*		1	0.91	0.57	0.79	0.67	0.90 (0.79 to 1.04)	NS
CHD deaths		1	0.57	0.76	0.59	0.60	0.89 (0.77 to 1.03)	NS		1	0.73	0.51	0.62	0.45	0.83 (0.63 to 1.10)	NS
All deaths		1	0.57	0.58	0.58	0.45	0.84 (0.77 to 0.92)	***		1	0.74	0.86	0.48	0.41	0.81 (0.81 to 0.92)	**
Dietary energy intake (kcal/day)																
	1174	1845	2148	2433	2802	4135	12		812	1380	1611	1834	2107	3142	18	
All CHD		1	1.04	1.01	0.89	0.85	0.95 (0.89 to 1.02)	NS		1	1.05	0.80	0.84	1.23	1.03 (0.91 to 1.14)	NS
CHD deaths		1	0.90	0.69	1.01	0.77	0.96 (0.86 to 1.07)	NS		1	0.69	0.53	0.94	0.75	0.97 (0.79 to 1.19)	NS
All deaths		1	0.82	0.86	1.10	1.07	1.04 (0.97 to 1.12)	NS		1	1.01	0.97	0.95	1.38	1.07 (0.97 to 1.18)	NS
Carotenoid intake (mg/day)																
	0.12	1.51	2.04	3.27	4.64	10.06	319		0.16	1.59	2.94	3.35	4.74	10.12	224	
All CHD		1	1.11	1.03	0.73	01.70	0.90 (0.84 to 0.96)	**		1	0.75	1.07	0.73	0.89	0.97 (0.87 to 1.08)	NS
CHD deaths		1	1.09	1.26	0.87	0.87	0.95 (0.85 to 1.07)	NS		1	0.54	1.32	0.87	0.93	1.01 (0.82 to 1.24)	NS
All deaths		1	1.11	0.99	0.95	0.93	0.97 (0.90 to 1.04)	NS		1	0.83	0.87	0.81	0.96	0.99 (0.90 to 1.09)	NS
Ascorbic acid intake (mg/day)																
	14.9	34.7	44.2	54.5	70.2	116.1	50		10.9	30.5	42.1	55.2	72.3	118.5	30	
All CHD		1	0.87	0.83	0.63	0.52	0.85 (0.80 to 0.91)	***		1	0.59	0.85	0.81	0.56	0.92 (0.82 to 1.02)	BS
CHD deaths		1	0.98	1.03	0.86	0.72	0.93 (0.83 to 1.04)	NS		1	1.17	2.12	1.61	0.76	0.99 (0.81 to 1.21)	NS
All deaths		1	1.09	1.00	0.87	0.85	0.95 (0.88 to 1.02)	NS		1	0.98	0.79	1.03	0.72	0.95 (0.86 to 1.04)	NS
Tocopherol intake (mg/day)																
	2.2	4.0	5.1	6.3	9.0	27.4	51		1.9	3.5	4.4	5.4	7.8	23.7	32	
All CHD		1	0.88	0.72	0.76	0.79	0.94 (0.87 to 1.00)	BS		1	0.79	0.71	0.75	0.75	0.94 (0.84 to 1.04)	NS
CHD deaths		1	0.76	0.75	0.58	0.67	0.89 (0.80 to 1.00)	*		1	0.87	1.10	0.37	1.06	0.96 (0.78 to 1.18)	NS
All deaths		1	0.81	0.86	0.64	0.76	0.92 (0.86 to 0.99)	*		1	1.30	1.18	1.12	0.94	0.97 (0.88 to 1.07)	NS

CHD=coronary heart disease. See footnote to table 1 for P values.

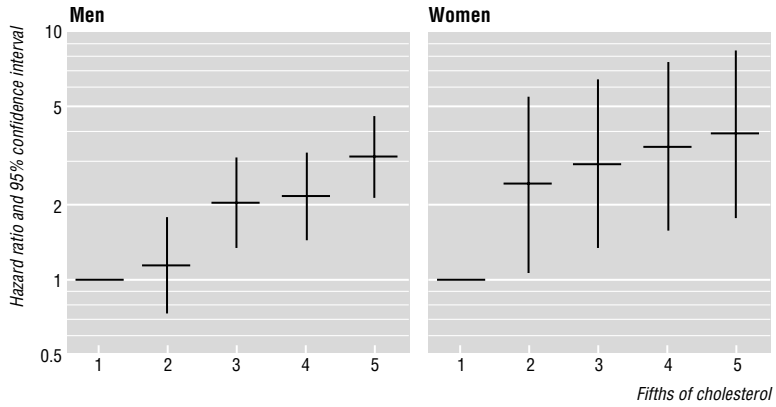

Fig 3 Age adjusted hazard ratios (and 95% confidence limits) for all coronary heart disease events by fifths of total cholesterol in men and women (lowest fifth=1)

coronary heart disease and for all deaths, in descending order of hazard ratios for the top class. Harmful factors have a plus sign. For protective factors (minus sign) the reciprocal was used.

Discussion

Our 27 factors cover the full range of classical and candidate factors included when the Scottish Heart Health Study was planned, but to prevent overload we chose single exemplars for social status[27 43] and tobacco smoke inhalation,[29 32] restricted diet to six factors, and left fat biopsy analyses for later. The three end points are also a subset. Early cohort studies emphasised first development of coronary heart disease,[1 4] but table 3 shows that over 20% of the participants had evidence of coronary heart disease when seen, and 8.2% of men and 5.0% of women had been already diagnosed. We found similar risk factor rankings to those in fig 1 in people with no evidence or history of previous coronary heart disease but the number of end points was halved. The total study population is relevant to reality, where middle aged people are at all stages of coronary heart disease but the same risk factors operate across them. Our results emphasise that existing coronary heart disease is the most powerful of its own predictors—and therefore the importance of secondary prevention. Death from coronary heart disease provides a specific, severe end point linking all coronary heart disease with all deaths, the ultimate arbiter.

Failure of some coronary risk factors to predict all cause mortality has been explained previously by separating early from late deaths.[44] Our results for four and eight years were similar. Alternatives to the Cox model[26] produced similar findings, showing that our results are robust.

We have not preselected risk factors by results. Twenty seven of our own and others' favourite factors were entered as starters, without bias, handicap, or disqualification, into three competitions for rankings run in parallel in each sex.

Men and women, coronary end points and all cause mortality

Results of comparing men and women are illustrated in fig 3, which shows confidence limits for hazard ratios in the different fifths of total cholesterol concentration. Limits were wider in women, as the numbers of end points were smaller, but the extremes of risk, as in many factors, appeared greater. Risk overall is lower in women so a larger hazard ratio may conceal a smaller excess risk between top and bottom fifth, a situation analogous to the effect of age in factors such as smoking, where relative risk is very high in young people, in whom risk is low.[45] Rankings used in the figures, based on the extreme classes, and the multiplicative constant between adjoining classes, both summarise the results. The tables sometimes suggest other complex distributions and thresholds not simply summarised. Comprehensive ranking of factors in figs 1 and 2 was feasible only by mixing together the categorical factors with continuous ones.

Men and women show different rankings for the factors but considerable agreement. For all coronary heart disease the same eight factors appear in the top 12 for both sexes, for coronary heart disease death the same nine, and for all deaths the same 10—which is surprising in view of the heterogeneity in cause of death between men and women. Random variation could account for much of the differences in ranking between the sexes. It would be reduced with larger numbers. The multiplicative constants in tables 2-6 are often very close, and their confidence limits overlap. When we tested the hazard ratios for evidence of differences between the two sexes a few were of borderline statistical significance, but the most extreme was the Bortner score, which is ranked 11th in women and 26th in men for all coronary heart disease, a finding consistent with reported sex differences in responses.[46]

Association, causation, interaction, confounding, and regression dilution

Observational epidemiological studies are better placed to show association than causation. Early disease may change factors so that associations are concealed or causation reversed. Factors may be associated sufficiently closely to cause confounding[47] and lack of independence. Difficulties of measurement and within person variability may conceal or minimise true effects—so called regression dilution.[48] There may be a threshold. High ranking of a factor does not guarantee causation, nor low rank lack of it.

Nevertheless, the strength of associations, or hazard ratios, is important evidence for causation. The associations help show relevance in a British population targeted for change whose pattern of risk factors overlaps that in many industrialised countries.[49] Our results emphasise the importance of coronary heart disease itself as a marker for risk warranting intervention, and also that of the classical coronary risk factors in coronary heart disease risk. Reasons why other factors have done unexpectedly well or badly warrant investigation both within the dataset of the Scottish Heart Health Study and elsewhere, as do the discrepancies between risk factors for coronary heart disease and all cause mortality.

We thank the 300 general practitioners and the survey nurses, technicians, data clerks, and research assistants; the agencies for providing death certificates and data on hospital admissions; other past contributors (referenced coauthors); and, above all, 11 629 men and women across Scotland who willingly participated.

Key messages

- Among Scottish men and women studied for 27 risk factors for coronary heart disease and followed up for eight years classical risk factors scored strongly in predicting coronary risk but the performance of new ones was more variable
- Risk factors for coronary disease, and also for death, showed few, albeit interesting, differences between men and women
- Relative risk was often higher for risk factors in women but they had low levels of absolute risk when risk factor levels were low
- Smoking, blood pressure, and fibrinogen predicted coronary disease and also death, but other factors are less consistent
- Unifactorial results should not be overinterpreted, but the protective effect of potassium consumption is of particular interest

Funding: Scottish Office, British Heart Foundation, and BUPA (an earlier version of this paper, confined to coronary end points won the 1996 BUPA epidemiology prize).

Conflict of interest: None.

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(Accepted 17 June 1997)