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Abstract

Objective

Most historical studies of cardiorespiratory risk factors as predictors of mortality have been based on men. This study examines whether they predict mortality over long periods in women and men.

Design

Prospective cohort study.

Setting

Participants were employees of the General Post Office.

Methods

Risk factor data were collected via clinical examination and questionnaire, 1966–67. Associations between cardiorespiratory risk factors and 40-year mortality were determined for 644 women and 1272 men aged 35–70 at examination.

Main outcome measures

All-cause, cardiovascular (CVD), cancer, and respiratory mortality.

Results

Associations between systolic blood pressure and all-cause and stroke mortality were equally strong for women and men, hazard ratio (95% confidence interval): 1.25 (1.1–1.4) and 1.18 (1.1–1.3); and 2.17 (1.7–2.8) and 1.69 (1.4–2.1) respectively. Cholesterol was higher in women and was associated with all-cause 1.22 (1.1–1.4) and CVD 1.39 (1.2–1.7) mortality, while associations between 2-hour glucose and all-cause 1.15 (1.1–1.2), coronary heart disease (CHD) 1.25 (1.1–1.4) and respiratory mortality 1.21 (1.0–1.5) were observed in men. Obesity was associated with stroke in women 2.42 (1.12–5.24) and CHD in men 1.59 (1.02–2.49), while ECG ischaemia was associated with CVD in both sexes. The strongest, most consistent predictor of mortality was smoking in women and poor lung function in men. However, evidence of sex differences in associations between the cardiorespiratory risk factors measured and mortality was sparse.

Conclusions

Data from a 40-year follow-up period show remarkably persistent associations between risk factors and cardiorespiratory and all-cause mortality in women and men.

MESH Keywords Adult ; Aged ; Blood Pressure ; physiology ; Body Mass Index ; Cause of Death ; Cohort Studies ; Female ; Heart Diseases ; mortality ; physiopathology ; Humans ; Male ; Middle Aged ; Respiratory Function Tests ; Respiratory Tract Diseases ; mortality ; physiopathology ; Risk Factors ; Smoking ; mortality ; physiopathology

Author Keywords cardiorespiratory mortality ; risk factors ; 40-year mortality ; 1960s

Almost all of the early studies identifying risk factors for all-cause and cardiorespiratory mortality included only middle-aged men.1–6 The few early studies that included women tend to be limited to US cohorts, such as Framingham and the Chicago Heart Association Detection Project in Industry.7–9 One notable exception based in the UK is the Renfrew and Paisley study in which over 15,000 women and men from the general population of a deprived area of west-central Scotland were screened between 1972 and 1976.10 Recent papers from the Renfrew and Paisley study have reported persistent associations between risk factors and all-cause and cardiorespiratory deaths

up to 25 years.11–16 However, there appear to be no UK cohorts currently with data to examine longer-term mortality follow-up in both sexes.

The purpose of the present analysis is to describe long-term all-cause and cause-specific mortality in an historical UK cohort, the General Post Office (GPO) study, and to determine associations between cardiorespiratory risk factors measured at baseline and mortality outcomes over a period of 40-years in women and men.

METHODS

Study population

The GPO study was designed as a pilot for the first Whitehall study (1968–70) of 19,000 men, all white-collar civil servants.1;17 However, observations from the GPO study were not published until 2006.18 During the 1960s the GPO was a Civil Service department. It had a monopoly of all mail, telegraph and telecommunications services in the UK and was one of the largest employers in the country.19 The target population for the GPO study was women and men aged 15–73 employed by the telecommunications arm of the GPO in central London in late 1966. Of the 4,230 invited, 3,345 women and men completed a short questionnaire and participated in a clinical examination, a response rate of 79%. Clinical examinations took place during working hours between October 1966 and April 1967 and covered both day and night shifts. Participants aged 15–34 and those over 70 (n=1429) were excluded from the current analyses, which were restricted to the 644 women and 1272 men aged 35 to 70. One reason for this restriction is that cholesterol, lung function and ECGs were measured only in those aged 35 and over, the other was to increase the homogeneity of the sample and thereby render safer the assumption that risk factors were stable and acted uniformly over the age range analyzed.

Measurements

Age was determined from the participant's date of birth and date of examination. Questions on smoking covered current tobacco use and smoking history. Measures taken during the clinical examination used standard protocols for the study period.1 A single reading of blood pressure was measured on the left arm with the participant seated. Systolic blood pressure was recorded at the first appearance of the Korotkoff sounds and diastolic at both muffling (phase 4) and disappearance of the Korotkoff sounds (phase 5). Phase 4 readings were used in the analyses. To reduce observer bias and variation, observers were specially trained20 and used the London School of Hygiene sphygmomanometer.21

After an overnight fast, two samples of capillary blood were taken from the participant's ear lobe, two hours after a glucose preparation equivalent to 50g anhydrous dextrose. Blood glucose (2-hour glucose) was estimated by the ferricyanide reduction micromethod on an autoanalyser (Technicon method N-9a). Total plasma cholesterol concentration was estimated using the standard Technicon method N24a.1

Height was measured to the nearest ¼ inch (6.3mm) below and weight was recorded to the nearest ½ pound (227g) below.22 Weight in kilograms and height in meters were used to calculate body mass index (BMI) as weight/height2. BMI was categorised to include the World Health Organisation cut-points for overweight (BMI=25–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) as well as categories for underweight ≤ 18.5 kg/m^2 and normal weight 18.5–24.9 kg/m^2. Lung function was assessed as forced expiratory volume in 1 second (FEV_1). The mean of three satisfactory measurements was used for analysis. FEV_1 is presented in liters. Electrocardiograms (ECG) were restricted to participants over 35 years and taken using limb leads only with a Mingograph 31B. Five technically adequate complexes were recorded for each of the six limb leads.1 Each ECG was interpreted independently by two trained coders, and an arbitrated ruling was given in cases of disagreement.22 The Minnesota code system was used throughout.23 ECGs with Q/QS items (codes 1.1–3), ST/T items (codes 4.1–4 or 5.1–3) or left bundle branch block (code 7.1) present were combined to form the category ECG ischaemia. Further details of the study population, definitions and measurement techniques used for screening have been described previously.18

Mortality

Participants were traced for mortality through the National Health Services (NHS) Central Registry using the NHS identification number assigned to each British citizen. Mortality follow-up was available on 1819 participants (95%) for a minimum of 40 years to the 31 st December 2007. As the deaths occurred over a long period, certificates were originally coded using the International Classification of Disease (ICD) 8^{th}, 9^{th} and 10^{th} revisions. For comparability, all certificates were manually recoded to ICD-9. Deaths were categorized as; cardiovascular disease (CVD) ICD-9 codes 390–459, coronary heart disease (CHD) ICD-9 codes 410–414, stroke ICD-9 codes 430–438, respiratory disease ICD-9 codes 460–519, and trachea, bronchus or lung cancer ICD-9 code 162; referred to as 'lung cancer'.

Statistical analysis

Participants who had missing values for the risk factors of interest - systolic blood pressure (0.2% both sexes), diastolic blood pressure (0.3% women; 0.4% men), cholesterol (14.1% women; 26.9% men), glucose (3.4% women; 3.1% men), BMI (0% women; 0.1% men) FEV_1 (1.6% women; 3.7% men) and ECG (9.3% women; 9.7% men) were excluded from the analyses for that risk factor.

Cox proportional hazard models with follow-up period as the time scale were used to examine associations between the cardiorespiratory risk factors and subsequent mortality. Initial analyses used risk factor categories based on sex-specific tertiles of systolic and diastolic blood pressure, cholesterol and $FEV_{1,}$ and four categories of BMI; ≤ 18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2 and ≥ 30 kg/m^2. In addition, restricted cubic splines with various degrees of smoothing were used to examine the form of the relationship between total mortality and cholesterol in women and men separately.24 Known diabetics (n=16) and participants with glucose values ≥ 11.1 mmol/L (n=4) were excluded from the glucose-mortality analyses. Although 2-hour glucose measures were within a few minutes of 2 hours, they were adjusted, by regression, to their exact 2-hour value. Since these initial analyses showed no evidence of any departure from linearity except for BMI, the effects of the risk factors on mortality have been analyzed using a linear term and summarized as the standardized hazard ratios (HR) and 95% confidence intervals (95% CI) associated with a one standard deviation (SD) increase in each risk factor in women and men separately. Tests for sex differences in the effect of each risk factor on mortality were obtained by fitting an interaction term. Smokers were divided into never smokers, ex-smokers, pipe/cigar smokers (men only), and current cigarette smokers. As the proportions of participants with ischaemia indentified by ECG were very low only associations with all-cause, CVD and CHD mortality were examined.

To examine associations with premature mortality the analyses were re-run using only deaths before the age of 65. Although the study is rather underpowered in this respect all-cause mortality and cancer for both sexes and CVD and CHD in men could be included. Forty two of the 348 (12%) deaths in women occurred before the age of 65 and 149 (17%) of the 871 deaths in men. Of these, 22 deaths were due to cancer in women and 79, 26 and 38 deaths due to CVD, CHD and cancer respectively in men.

In analyses comparing the distribution of risk factors by sex, smoking prevalence was age-standardized using the total analytic sample as the standard. For continuous variables, least squares means were used to present age-adjusted means with sex differences tested using analysis of covariance. Baseline risk factor levels (1966–67) were compared with those for a nationally representative survey, the Health Survey for England (HSE) 2006. Data for women and men aged 35–70 who were in employment were analyzed. Details of the survey methods for the HSE are reported elsewhere.25 All analyses were performed using SAS version 6.12 for Windows (SAS Institute Inc., 1990).

RESULTS

Population characteristics

Table 1 describes the distribution of cardiorespiratory factors for women and men. Women had lower blood pressure and 2-hour glucose levels than men, but higher cholesterol. Although FEV_1 was lower in women they were more likely to be never smokers. By the 31st December 2007, 348 (58%) women and 871 (72%) men aged 35–70 at study entry had died. These 1219 deaths represented 87.5% of deaths in the whole cohort over the 40-year follow-up period. CVD, CHD and respiratory disease accounted for 44%, 22% and 13% of the deaths in women and 50%, 32% and 9% in men.

Blood pressure and blood metabolites

In general, absolute death rates at every level of cardiorespiratory risk were lower in women than in men. For example, women in the upper third of the blood pressure distribution had a lower death rate than men in the lower third (data not shown). Nonetheless, there was little evidence that associations between the major cardiorespiratory risk factors and mortality were different between the sexes. Interactions with sex were observed only for the associations between cholesterol and all-cause mortality ($p<0.01$), cholesterol and CVD mortality ($p=0.05$), and smoking and CVD mortality ($p=0.05$) – Tables 2 and 4.

Although systolic blood pressure was lower in women than men associations with all-cause, CVD and stroke mortality were equally strong. However, the association between systolic blood pressure and CHD mortality observed in men was not evident in women - Table 2 . Findings for diastolic blood pressure (web-based Table 2a) were similar to those for systolic pressure. Use of hypertensive medication was reported by 0.9% of women and 1.3% of men. Removal of these participants produced findings almost identical to those reported. The association between total mortality and cholesterol showed little evidence of non-linearity in either women ($p>0.39$) or men ($p>0.10$). There was good evidence that cholesterol, which was higher in women, was associated with all-cause, CVD, CHD, and stroke mortality, but little evidence of associations in men. Conversely, there was no strong evidence of associations between 2-hr glucose and mortality in women, but evidence of associations with all-cause, CVD, CHD and respiratory mortality in men.

BMI and lung function

There was good evidence of an association between obesity and all-cause mortality in women. Higher risk of mortality in the underweight as well as the obese in both sexes provided evidence indicative of a U-shaped association between BMI and mortality. In women, obesity was associated with CVD mortality, stroke in particular, while in men it was associated with CHD. Hazard ratios for cancer and respiratory mortality were high among the underweight of both sexes with strong evidence of an association in men – Table 3.

In contrast to most other risk factors, higher rather than lower values of FEV_1 are protective of health – Table 4. Thus a one SD increase in FEV_1 was associated with a lower risk of all-cause and respiratory mortality in both sexes, and CVD, CHD and lung-cancer mortality in men. A comparison with never smokers provided strong evidence for an association between current smoking and all-cause and respiratory mortality in both sexes; CVD and CHD mortality in women, and lung cancer in men.

Smoking

In general, associations between smoking and mortality were stronger in women than men, but there were insufficient lung cancer deaths in women to provide firm evidence of an association – Table 4. As there were no lung cancer deaths among never smokers, analyses of lung cancer mortality compared ex-smokers and current smokers. Additional analyses that compared ex-smokers with never smokers provided strong evidence of associations with CVD and stroke mortality in women HR (95% CI); CVD 1.83 (1.14–2.84), stroke 1.72 (0.81–3.65). However, the risk of respiratory mortality among women ex-smokers was closer to that for never smokers HR (95% CI); 0.74 (0.27–2.16). In general, the mortality risk in men ex-smokers was close to that for never smokers for all causes of death.

ECG ischaemia

There was an association between ECG ischaemia and all-cause mortality in men, but the study was underpowered to detect an association in women although findings were indicative. Strong associations were observed between ECG ischaemia and CVD and CHD mortality in both sexes.

Time dependence of the associations

The effects of blood pressure decreased over time for all-cause mortality in women (systolic p=0.05, diastolic p=0.03) and CVD (systolic p=0.02) and CHD mortality (systolic p=0.06) in men. Similarly, decreases over time were observed for the effect of underweight on all-cause (p=0.007) and cancer (p=0.04) mortality in women. The strong negative association between FEV and respiratory mortality (p =0.001) in men also decreased over time.

Premature mortality

The associations between blood pressure, cholesterol, BMI and FEV_1 and all-cause and cause-specific mortality before the age of 65 were similar to those observed for all mortality at any age. The associations between cholesterol and all-cause mortality in women, cholesterol and cancer mortality, and FEV1 and CHD mortality in men were weaker for premature mortality. Associations between smoking and premature death from any cause were stronger, although, as for the other risk factors, small numbers widened the confidence intervals and reduced the p-values (data available on request).

DISCUSSION

As in most industrialized countries, the main cause of death among participants in the GPO study over the past 40 years has been cardiovascular disease, which accounted for 44% of deaths in women and 50% in men. Overall, associations between the cardiorespiratory risk factors examined and mortality were similar in women and men and evidence of differences by sex was sparse. Smoking was the strongest and most consistent predictor of mortality in women, while lung function was the most consistent predictor in men. These findings from the GPO study add to the existing literature by showing that the major cardiorespiratory risk factors remain strong predictors of mortality over 40 years and that associations are similar in both sexes.

Comparison with findings from contemporary cohorts

Part of the interest in historical cohorts is that they document changes in risk factors levels over time. We compared the distribution of cardiorespiratory risk factors in the GPO cohort with those for the general working population of England aged 35 – 70 in 2006, 40 years later – Box 1.25 Blood pressure was higher among women and men in the GPO cohort compared with workers of the same age 40 years later, but cholesterol levels were lower and BMI markedly lower. Changes in methods of measuring blood pressure and cholesterol over 40 years will mean the two groups are not strictly comparable with regard to these measures, a problem inherent in all comparisons over time. However, the differences observed in blood pressure are substantial and reflect earlier work indicating declining secular trends in blood pressure.26 Differences observed in BMI will be relatively unaffected by change in methods of measurement over the period. Smoking prevalence was much higher in the GPO study than in 2006 and figures for the two periods illustrate the observation that smoking rates have declined rapidly in men since 1970.

Box 1

Comparison of cardiorespiratory risk factors among employed women and men aged 35–70 among GPO participants at baseline and in the general population in England in 2006[*]

Cardiorespiratory risk factor	Women		Men	
	GPO 1966	HSE 2006	GPO 1966	HSE 2006
	Mean	Mean	Mean	Mean
Systolic blood pressure (mmHg)	125.7	122.5	134.6	130.6
Diastolic blood pressure (mmHg)	81.6	74.5	84.3	77.0
Total cholesterol (mmol/L)	5.19	5.57	5.06	5.65
Body Mass Index (kg/m^2)	24.9	27.1	25.0	28.0
	Percent	Percent	Percent	Percent
Cigarette smoking status:				
Never cigarette smoker	35.6	49.8	14.0	45.9
Ex-cigarette smoker (includes both occasional and regular past use)	13.4	29.2	18.7	32.7
Current cigarette smoker	51.1	21.0	58.0	21.4

[*] data from Health Survey for England (HSE) 2006

Age-specific death rates for 1968–2005 show mortality rates for CHD in women and men aged 35 and over have plummeted since 1968.27 In the GPO study the two most important risk factors for CHD mortality were cholesterol and smoking in women, and blood pressure and glucose in men. Forty years later the most important risk factors for CHD are abdominal obesity, high blood pressure, and abnormal lipids,28 and INTERHEART has shown abnormal lipids and smoking to be the most important risk factors for initial acute myocardial infarction.29

Comparison with findings from historical cohorts

Our findings are in line with those from other historical cohorts.1;8;10;30–37 Most historical studies have demonstrated major roles for blood pressure, cholesterol, BMI, lung function and smoking as predictors of cardiorespiratory mortality. However, weak associations between cholesterol and cardiovascular mortality in the GPO men replicate findings from the Renfrew and Paisley study,35 while the inverse association observed between cholesterol and cancer mortality, in common with the associations between underweight and death from cancer or respiratory disease, is likely to be due to reverse causality.38 As seen among men in the GPO study, 2-hour post-load blood glucose has been shown to be an important predictor of cardiovascular events.39 Stroke deaths were more common in GPO women while CHD deaths were more common in men. Blood pressure was the strongest predictor of stroke in both sexes, however, contrary to findings from Renfrew and Paisley cholesterol and obesity were associated with stroke mortality in women but no associations were observed between glucose, FEV_1 or smoking and stroke in either sex.12;13

Associations between lung function and all-cause, CHD, respiratory disease and lung cancer mortality observed previously in both sexes were replicated among GPO men.40 However, in a study that examined lung function and CVD mortality in four cohorts of men, the strong association seen in the GPO men was only observed in one of the cohorts, although there was the indication of an association in the remaining studies.41 Among women in the GPO study poor lung function was associated only with all-cause and respiratory mortality. This finding is in strong contrast to that for smoking which was the strongest and most consistent predictor of mortality in women. The slower decline in smoking rates among women may partially explain the higher mortality hazards observed for women smokers compared to men in the GPO study. However, the absence of any association between smoking and stroke mortality probably reflects observations that the risk of stroke diminishes to that of non-smokers within 5 years of smoking cessation.42;43 Data on lung function and smoking habits collected 40 years ago cannot take account of subsequent smoking history which is likely to have a significant effect on lung function over time.

ECGs have been widely used in epidemiological research as a valid and reproducible diagnostic tool for assessing ‘silent' heart disease. Although ECGs in the GPO study were not of the highest quality, recorded using limb leads only, the observation of strong associations with CVD and CHD mortality are in line with both historical and contemporary studies.44,45 In common with the present study associations between ECG ischaemia and CVD and CHD, as well as ischaemic heart disease, have been shown to be similar in both sexes.44–46 As for ECG ischaemia, there was little evidence of sex differences in associations between the cardiorespiratory risk factors and mortality in the GPO study. This finding reflects those from previous studies that associations between the established coronary risk factors and CHD mortality are similar in both sexes, despite lower absolute death rates in women.11;33;35 Work by Prescott et al indicated that women may be more susceptible to the adverse effects of smoking than men, at least in relation to cardiorespiratory disease.47 This observation seems to be endorsed in the present study and in the Nurses Health Study where smoking was the strongest predictor of all-cause, cardiovascular and cancer mortality over 24 years.37 However, attempts to replicate the findings of Prescott et al have been unsuccessful.48 The greater risk of CVD and stroke mortality among women ex-smokers in the GPO study suggests that these women may have quit subsequent to disease diagnosis. However, the absence of any association between smoking and respiratory mortality in women ex-smokers and between smoking and all-cause mortality in men ex-smokers emphasizes the benefits of quitting.

Study limitations

Although the GPO study benefits from a high response rate no information is available for non-responders. Non-responders are more likely to have been less healthy than participants. The exclusion of non-responders may thus result in biased estimates of risk factor levels in the target population. An inevitable problem with historical data is the lack of detail and, with the benefit of hindsight, lack of key data such as cholesterol sub-fractions, echocardiography, and waist circumference. A further limitation is that standard protocols for the measurement of several of the common cardiovascular risk factors in the late 1960s were rudimentary. In the present study there is a clear issue with relying upon a single blood pressure reading as regression dilution bias, arising from risk assessments based on a single measurement, may result in underestimation of associations.49 For example, it has been shown that the mean of two measures of blood pressure, as well as the maximum and the baseline measure corrected for regression dilution bias, have a stronger relationship with stroke than a single measure.50 Reliance in the present study on self-reported data rather than carboxyhaemoglobin concentration for the assessment of smoking is also likely to have resulted in an underestimation of the associations between smoking and mortality.16

One drawback of the GPO study is that no data are available between the baseline questionnaire and death. This means that the study is limited to a single measure of each of the cardiorespiratory risk factors and so unable to take account of changes in risk factor status over

time. For example, some GPO participants are likely to have enjoyed therapeutic gains from medications, such as statins and ACE inhibitors, introduced during the 1980s when the youngest were in their fifties. However, although the study has no data on these, adjustment for such treatment would have strengthened rather than attenuated the associations observed between blood pressure and mortality. As a precaution, we examined mortality to the end of 1997, a 30-year follow-up period, that included deaths occurring before the widespread use of statins.51 Associations between a one standard deviation increase in systolic blood pressure or total cholesterol and mortality were very close to those observed over the 40-year follow-up (data available on request).

A disadvantage that attends a study population recruited from one public sector employer is that the occupational range is more limited than in the general population. However, conversely, this homogeneity has the advantage for mortality analyses of reducing potential confounding due to occupational variation. In addition, cohorts of employees are open to healthy worker bias.52 This is also likely to result in an underestimation of both risk factor prevalence and mortality rates compared with the general population of the same age, as the latter will also include people who are unemployed and those economically inactive because of ill-health.

Public Health Implications

The original purpose of the GPO study was not only to assess the prevalence of heart disease, diabetes and bronchitis but to initiate research into their prevention. Participants judged to be at high risk of cardiorespiratory disease were given advice on giving up smoking and those with "borderline" diabetes or who were obese were given advice on dietary restriction via their doctor. We have no idea how many of the GPO participants acted on the advice they were given, but findings from the EUROASPIRE study show that, even in patients who have survived a myocardial infarction, risk factor modification is not easy.53 Our findings from the GPO study show that 40-years on the public health impact of these risk factors remains considerable. Furthermore, the graded associations between level of exposure and mortality observed for many of the risk factors in both sexes strengthen the call for population approaches to the problems of hypertension, high cholesterol and smoking.54

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Footnotes:

The authors have no relevant financial interest in this article.

CONFLICT OF INTEREST: None.

Abbreviations

BMI: body mass index
CHD: coronary heart disease
CVD: cardiovascular disease, forced expiratory volume in 1 second (FEV_1)
GPO: General Post Office
ICD: International Classification of Disease
HR: hazard ratio
HSE: Health Survey for England
NHS: National Health Services
SD: standard deviation

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Table 1

Distribution of cardiorespiratory risk factors among women and men

	Women		Men		
Cardiorespiratory risk factor	**N**	**Mean (SD)** *	**N**	**Mean (SD)**	**p-value for difference**
Age (years)	644	46.6 (7.0)	1272	48.0 (8.2)	<0.001
Systolic blood pressure (mmHg)	643	126.5 (20.4)	1269	134.2 (21.4)	<0.001
Diastolic blood pressure (mmHg)	642	81.7 (14.9)	1267	84.2 (14.4)	0.01
Total cholesterol (mmol/L)	553	5.20 (1.14)	930	5.05 (1.16)	<0.001
2-hr glucose† (mmol/L)	622	4.08 (0.68)	1233	4.32 (0.87)	<0.001
Body Mass Index (kg/m^2)	644	24.93 (4.03)	1271	24.97 (3.22)	0.79
FEV_1 (L)	634	2.14 (0.50)	1225	3.07 (0.76)	<0.001
		Percent		Percent	
Smoking status:					
Never smoker	229	35.4	178	14.2	<0.001
Ex-smoker	86	13.9	238	18.5	0.008
Pipe and cigar (men only)	n/a	n/a	118	9.3	-
Current cigarette smoker	329	50.8	738	57.9	0.005
ECG ischaemia	584	2.4	1149	3.8	0.11
Mortality Outcomes	Deaths	(% of all cause mortality)	Deaths	(% of all cause mortality)	
All cause mortality	348	(100.0)	871	(100.0)	-
CVD mortality	152	(43.7)	434	(49.8)	0.06
CHD mortality	75	(21.6)	281	(32.3)	<0.001
Stroke mortality	46	(13.2)	74	(8.5)	0.02
Cancer mortality	100	(28.7)	224	(25.7)	0.31
Lung cancer	13	(3.7)	62	(7.1)	0.04
Respiratory mortality	45	(12.9)	114	(13.1)	0.98
Other deaths	51	(14.7)	99	(11.4)	0.14

* All proportions and means (apart from age) are adjusted for age. Standard deviations shown are of the unadjusted distributions

† 2-hr glucose adjusted for time since glucose load (see statistical methods)

Table 2

Standardized hazard ratios for mortality associated with a one standard deviation increase in systolic blood pressure, total cholesterol and 2-hour glucose

	Systolic blood pressure		
	HR* (95% CI), p-value	**HR* (95% CI), p-value**	
	WOMEN	**MEN**	**p-value for sex interaction**
All cause mortality	1.25 (1.13–1.39), <0.001	1.18 (1.10–1.27), <0.001	0.57
CVD mortality	1.45 (1.25–1.68), <0.001	1.38 (1.26–1.51), <0.001	0.97
CHD mortality	1.09 (0.86–1.38), 0.47	1.34 (1.20–1.51), <0.001	0.06
Stroke mortality	2.17 (1.70–2.75), <0.001	1.69 (1.37–2.09), <0.001	0.18
Cancer mortality	1.03 (0.84–1.26), 0.80	0.98 (0.85–1.14), 0.80	0.67
Respiratory mortality	1.05 (0.77–1.43), 0.77	1.02 (0.83–1.26), 0.83	0.97
	Total Cholesterol		p-value for sex interaction
	HR** (95% CI), p-value	HR** (95% CI), p-value	
	WOMEN	MEN	
All cause mortality	1.22 (1.08–1.37), <0.001	0.98 (0.91–1.06), 0.68	0.007
CVD mortality	1.39 (1.16–1.66), 0.001	1.09 (0.98–1.21), 0.11	0.05
CHD mortality	1.40 (1.09–1.80), 0.008	1.10 (0.96–1.25), 0.17	0.14
Stroke mortality	1.53 (1.11–2.11), 0.01	1.15 (0.89–1.49), 0.28	0.21
Cancer mortality	1.10 (0.88–1.37), 0.41	0.86 (0.74–0.99), 0.04	0.06
Respiratory mortality	1.20 (0.83–1.73), 0.34	0.91 (0.75–1.10), 0.33	0.25
	2-hour glucose†		p-value for sex interaction
	HR*** (95% CI), p-value	HR*** (95% CI), p-value	
	WOMEN	MEN	
All cause mortality	1.06 (0.96–1.17), 0.25	1.15 (1.07–1.23), <0.001	0.17
CVD mortality	1.10 (0.95–1.27), 0.20	1.21 (1.10–1.33), <0.001	0.23
CHD mortality	1.05 (0.85–1.30), 0.66	1.25 (1.12–1.40), <0.001	0.12
Stroke mortality	1.25 (0.97–1.61), 0.08	1.06 (0.83–1.35), 0.65	0.38
Cancer mortality	1.03 (0.86–1.25), 0.73	1.11 (0.97–1.27), 0.13	0.94
Respiratory mortality	1.11 (0.85–1.45), 0.46	1.21 (1.00–1.47), 0.05	0.55

* Hazard ratio associated with a 1 SD increase in Systolic BP (20.4 mmHg women; 21.4 mmHg men)

** Hazard ratio associated with a 1 SD increase in cholesterol (1.14 mm/L women; 1.16 mm/L men)

*** Hazard ratio associated with a 1 SD increase in 2-hour glucose (0.68 mm/L women; 0.87 mm/L men)

† 2-hr glucose adjusted for time since glucose load (see statistical methods)

Table 3

Hazard ratios for mortality associated with categories of body mass index

		HR(95% CI), p-value	HR* (95% CI), p-value	
	Body Mass Index categories (kg/m^2)	**WOMEN**	**MEN**	**p-value for sex interaction***
All cause mortality	<18.5	1.78 (0.91–3.49), 0.09	1.72 (0.99–2.99), 0.06	0.83
	18.5 – 24.9	1.0	1.0	
	25.0 – 29.9	0.84 (0.66–1.06), 0.14	0.97 (0.84–1.11), 0.65	0.20
	≥ 30.0	1.53 (1.11–2.12), 0.01	1.22 (0.92–1.61), 0.17	0.41
CVD mortality	<18.5	0.97 (0.24–3.95), 0.09	0.26 (0.04–1.86), 0.18	0.34
	18.5 – 24.9	1.0	1.0	
	25.0 – 29.9	0.91 (0.64–1.31), 0.63	1.02 (0.84–1.25), 0.82	0.58
	≥ 30.0	2.23 (1.42–3.49), <0.001	1.32 (0.90–1.94), 0.16	0.15
CHD mortality	<18.5	0.0	0.40 (0.06–2.86), 0.36	0.97
	18.5 – 24.9	1.0	1.0	
	25.0 – 29.9	1.13 (0.69–1.86), 0.63	1.07 (0.83–1.37), 0.61	0.94
	≥ 30.0	1.90 (0.97–3.74), 0.06	1.59 (1.02–2.49), 0.04	0.85
Stroke mortality	<18.5	0.0	0.0	-
	18.5 – 24.9	1.0	1.0	
	25.0 – 29.9	0.72 (0.36–1.42), 0.34	0.97 (0.60–1.55), 0.90	0.53
	≥ 30.0	2.42 (1.12–5.24), 0.02	1.02 (0.36–2.88), 0.97	0.21
Cancer mortality	<18.5	2.60 (0.94–7.19), 0.07	3.05 (1.33–6.96), 0.008	0.72
	18.5 – 24.9	1.0	1.0	
	25.0 – 29.9	0.72 (0.45–1.14), 0.15	0.93 (0.71–1.23), 0.62	0.24
	≥ 30.0	1.19 (0.64–2.22), 0.58	1.18 (0.67–2.06), 0.57	0.99
Respiratory mortality	<18.5	7.14 (0.86–58.9), 0.07	5.16 (1.84–14.5), 0.002	0.40
	18.5 – 24.9	1.0	1.0	
	25.0 – 29.9	0.67 (0.17–2.60), 0.56	1.12 (0.76–1.64), 0.57	0.32
	≥ 30.0	1.74 (0.36–8.38), 0.49	0.71 (0.25–1.97), 0.51	0.59

* p-values are for separate BMI categories in order to assess sex interactions in underweight, overweight and obese participants separately

Table 4

Standardized hazard ratios for mortality associated with smoking, ECG ischaemia and a one standard deviation increase in FEV_1

	FEV_1		
	HR* (95% CI), p-value	**HR* (95% CI), p-value**	
	WOMEN	**MEN**	**p-value for sex interaction**
All cause mortality	0.88 (0.79–0.99), 0.03	0.81 (0.75–0.88), <0.001	0.19
CVD mortality	0.94 (0.79–1.12), 0.48	0.82 (0.73–0.92), <0.001	0.12
CHD mortality	0.96 (0.74–1.23), 0.72	0.86 (0.74–0.99), 0.04	0.37
Stroke mortality	0.84 (0.61–1.15), 0.27	0.93 (0.70–1.24), 0.62	0.69
Cancer mortality	0.97 (0.79–1.20), 0.80	0.99 (0.84–1.17), 0.94	0.84
Lung cancer	0.81 (0.46–1.41), 0.46	0.74 (0.55–0.99), 0.04	0.68
Respiratory mortality	0.68 (0.50–0.92), 0.01	0.53 (0.42–0.66), <0.001	0.17
		Smoking	p-value for sex interaction
	HR** (95% CI), p-value	HR** (95% CI), p-value	
	WOMEN	MEN	
All cause mortality	1.74 (1.37–2.22), <0.001	1.40 (1.13–1.74), 0.002	0.23
CVD mortality	1.62 (1.11–2.35), 0.01	1.21 (0.90–1.62), 0.21	0.29
CHD mortality	2.55(1.45–4.50), 0.001	1.24 (0.86–1.80), 0.25	0.05
Stroke mortality	0.81 (0.41–1.61), 0.55	0.96 (0.49–1.87), 0.90	0.71
Cancer mortality	1.46 (0.95–2.24), 0.08	1.53 (0.98–2.39), 0.06	0.89
Lung cancer	3.39§ (0.43–26.4), 0.24	2.29§ (1.08–4.86), 0.03	0.75
Respiratory mortality	3.26 (1.56–6.81), 0.002	2.39 (1.15–4.97), 0.02	0.57
		ECG ischaemia	p-value for sex interaction
	HR (95% CI), p-value	HR (95% CI), p-value	
	WOMEN	MEN	
All cause mortality	1.65 (0.90–3.01), 0.10	2.21 (1.63–2.99), <0.001	0.27
CVD mortality	2.83(1.38–5.79), 0.005	2.63 (1.77–3.92), <0.001	0.85
CHD mortality	2.85(1.04–7.86), 0.04	3.05 (1,94–4.80), <0.001	0.73

* Hazard ratio associated with a 1 SD increase in FEV_1 (0.50 L women; 0.76 L men)

** Hazard ratios and p-values for current smokers v never smokers, except

§ current smokers v ex-smokers