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ARTICLE

Biological and behavioural explanations of social inequalities in coronary heart disease: the Whitehall II study

M. G. Marmot · M. J. Shipley · H. Hemingway · J. Head · E. J. Brunner

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Abstract
Aims/hypothesis We determined the degree to which metabolic syndrome components, inflammation and health behaviours account for the social gradient in CHD.
Methods A total of 5312 men, initially aged 39 to 63 years, were followed for 13.1 years for incident coronary death or non-fatal myocardial infarction according to socioeconomic position (employment grade). The contribution of explanatory factors to socioeconomic differences in CHD was assessed by the reduction in hazard ratios computed using Cox models. The effects of measurement error were taken into account.
Results Coronary events were more common in lower employment grades than in higher, with a hazard ratio (relative index of inequality) of 2.2 (95% CI 1.3–3.7), after adjustment for age and ethnic group. Behavioural risk factors (mainly smoking and diet) explained a third of the socioeconomic gradient in CHD incidence. Components of the metabolic syndrome and inflammatory markers predicted CHD incidence and also explained a third of the gradient. Combined, these two groups of predictors, i.e. behavioural and biological, accounted for over half of the socioeconomic gradient in incident CHD. Adding body height as a marker of the effects of early life increased this figure to about 60%.
Conclusions/interpretation A major question has been how someone's socioeconomic position can lead to increased risk of CHD. Socioeconomic differences in components of the metabolic syndrome (and inflammatory markers) provide part of the answer. This was, to an important degree, independent of the contribution of health behaviours to the socioeconomic differentials in CHD.

Keywords Coronary heart disease · Diet · Epidemiology · Inequality · Inflammatory markers · Metabolic syndrome · Physical activity · Smoking · Socioeconomic position

Abbreviations

ATPIII	Adult Treatment Panel III
CRP	C-reactive protein
RII	relative index of inequality

Introduction

There are marked social inequalities in the occurrence of coronary heart disease (CHD) [1, 2]. The first Whitehall study of British Civil Servants showed that these health inequalities were not confined to persons in poverty [3]. Similarly, in the Whitehall II study of white-collar employees in relatively secure employment, the lower the position in the occupational hierarchy, the higher the risk of CHD [4]. In other European countries [5, 6] and the USA [2], there is also a graded relation between socioeconomic position and CHD incidence [7]. The biological mechanisms linking social position and CHD have not been clear [8]. In the first Whitehall study the combination of blood pressure, plasma total cholesterol, body mass index, plasma glucose and a health behaviour (smoking) accounted for less than one-third of the social gradient in CHD mortality rates [9]. In the British Regional Heart Study a slightly different combination of risk factors accounted for 39% of the social class differences in CHD [10].

M. G. Marmot (✉) · M. J. Shipley · H. Hemingway · J. Head · E. J. Brunner
Department of Epidemiology and Public Health,
University College London,
1-19 Torrington Place,
London WC1E 6BT, UK
e-mail: m.marmot@ucl.ac.uk

A central rationale of the Whitehall II study was to extend the range of potential biological and behavioural explanations. The metabolic syndrome is a promising candidate. It predicts CHD in addition to the predictive power of the established risk factors [11]; moreover, components of the metabolic syndrome and inflammatory markers show a social gradient, evidenced by progressively higher levels as the social hierarchy is descended [12, 13]. Here we wished to test the hypothesis that variables associated with the metabolic syndrome, i.e. inflammation (C-reactive protein [CRP], IL-6, fibrinogen) and height, may mediate the relation between socioeconomic position and CHD. We also sought to determine whether this effect was in addition to the role of adult health behaviours.

Methods

Participants The Whitehall II cohort of non-industrial civil servants was first examined between 1985 and 1988 (phase 1) [14, 15]. All men and women aged 35 to 55 years and working in the London offices of 20 departments were invited to participate in this study. The cohort consisted of 10,308 persons with an overall response rate of 73%. Postal questionnaires were administered at six further study phases, with phases 3 (1991–1993), 5 (1997–1999) and 7 (2002–2004) including a screening examination. Written informed consent to follow-up sickness absence and clinical records was obtained from participants.

Phase 3 provides the baseline for the analyses reported here, when the metabolic syndrome variables were first measured. The maximum follow-up from phases 3 to 7 was 13.1 years (median 12.2 years). South Asians and African-Caribbeans together make up less than 10% of the cohort. There is insufficient power to analyse them separately. Ethnic group was included as an adjustment variable in all analyses, which yielded similar results when conducted with whites alone. Analyses were confined to men (n= 5312), as too few incident major coronary events occurred among women during follow-up.

Socioeconomic position Current employment grade within the civil service at phase 3 was used as a measure of socioeconomic position in six categories. For presentation, a three-level variable for grade was used, consisting of clerical and office support staff (low), the three executive officer categories combined (medium) and the two upper administrator categories combined (high).

Behavioural factors Cigarette smoking was assessed at phase 3 and categorised as: never, ex-smoker, pipe/cigar only or current cigarette smoker with the number of cigarettes smoked. Self-reported leisure-time physical activity at phases 1 and 3 was categorised as vigorous (≥1 h of vigorous activity/week), moderate (≥1 h moderate but <1 h vigorous activity/week) and none/mild (<1 h of vigorous and moderate activity/week). Food frequency questionnaires at phase 3, validated against biomarkers and 7 day diet diaries [16], were cluster-analysed to identify dietary patterns (unhealthy, healthy, Mediterranean-type, sweet) [17]. Alcohol consumption (units/week, 1 unit= 10 ml ethanol) was categorised in four levels (0, 1–14, 15–21 and≥22).

Biological factors Waist and hip circumferences and BMI were measured at phase 3 using standard protocols [18]. Systolic and diastolic blood pressure were measured twice after 5 min rest using a Hawksley random zero sphygmomanometer (Hawksley and Sons, Lancing, UK). Oral glucose tolerance tests were administered at phase 3, following an overnight fast or in the afternoon after no more than a light fat-free breakfast taken before 08:00 hours. Known diabetic patients did not participate in this part of the screening. Total cholesterol, HDL-cholesterol and triacylglycerol were measured within 72 h in serum stored at 4°C using enzymatic colorimetric methods [12]. Fibrinogen, factor VIIc and von Willebrand factor were determined in citrated plasma, and CRP and IL-6 were determined in serum; samples were stored at −80°C. Plasma glucose was measured using an electrochemical glucose oxidase method and serum insulin by radioimmunoassay using a polyclonal antiserum [12, 13].

The definition of metabolic syndrome used by the National Cholesterol Education Program Adult Treatment Panel III (ATPIII) is based on waist circumference, HDL-cholesterol, triacylglycerol, blood pressure and fasting plasma glucose. We used these variables but instead of using cut-off points to define caseness, we treated the variables as individual continuous variables.

Follow-up of CHD events About 99.9% of the men were flagged at the NHS Central Registry, who notified us of the date and cause of death. Coronary death was defined by underlying cause (International Classification of Diseases 9, code 410–414) [19]. Potential cases of non-fatal myocardial infarction were ascertained by questionnaire items on chest pain [20], doctors' diagnoses and hospitalisations. Twelve-lead resting ECGs (Mingorec, Siemens Healthcare, Erlangen, Germany) were performed at each clinic phase and assigned Minnesota codes [21]. Details of physician diagnoses and investigation results were sought from clinical records for all potential cases. Based on all available data from questionnaires, study and hospital ECGs, and cardiac enzymes, definite non-fatal myocardial infarction was defined following MONICA criteria [22]. Myocardial infarction was defined as positive, if a

questionnaire or clinical record of diagnosed myocardial infarction was obtained in the presence of an ischaemic ECG; it was defined as negative when self-reported only. Classification of myocardial infarction was carried out independently by two trained coders, who were blind to other study data, with adjudication by a third coder in the rare event of disagreement.

Statistical analysis Continuous variables were log transformed if skewness was >1.0. Least squares regressions were used to produce age-adjusted least squares means (geometric means for log–normal variables) by employment grade using the age at entry distribution (phase 3) of the analysis sample as the standard population. Differences in means across grades were tested using a linear trend term. Tests for trends in age-adjusted proportions across grades were based on the Mantel–Haenszel test.

Mortality follow-up was available to 30 September 2004 and morbidity follow-up to the phase of most recent participation between phases 3 and 7. Tracing through clinical records identified non-fatal CHD events that occurred after the most recent contact. To allow for this and to overcome differential follow-up for mortality and morbidity rates, non-fatal and fatal follow-up was censored on 30 September 2004 for the 81% (of the 5312 men) who attended phase 7 or on the mid-point date of the phase after the last phase of contact for the remaining 19%, whose last contact had been prior to phase 7. For each coronary outcome, we only considered the time to the first event and excluded prevalent cases of myocardial infarction (n=86). Event rates were calculated using person-years at risk and standardised for age at entry by the direct method. The associations of employment grade and other risk factors with incident CHD were analysed using Cox models with the time since phase 3 as the underlying time scale. The proportional hazards assumption was tested by fitting exposure by log follow-up time interaction terms and found to be not violated (all p values>0.25).

The effect of employment grade on CHD incidence was summarised using the relative index of inequality (RII) [23, 24]. The procedure transforms employment grade, a categorical hierarchical variable, into a summary measure scaled from zero (highest socioeconomic position) to one (lowest position), which is weighted to reflect the proportion of the sample in each grade category. We refer to this as the employment grade score. The score is used in a Cox or logistic regression model to estimate the RII: the ratio of instantaneous event rates or log odds between extremes (bottom versus top). The employment grade index was computed within 5-year age strata using six categories of employment grade, since attained grade was associated with age. Using Cox regression, the ability of risk factors to explain grade differences in CHD incidence rates was calculated by computing the proportional (%) change in the RII from models fitted without and with the risk factors of interest. The attenuating effects of traditional risk factors (smoking, blood pressure, serum cholesterol) with respect to the RII for CHD incidence rates were examined, as were those of behavioural factors, metabolic syndrome components and inflammatory markers. Attenuation is calculated as the per cent change in the log hazard ratio or log odds ratio compared with the reference model, controlling for age and ethnic group.

Although data completeness for each individual variable was high, data for one or more variables were missing for approximately one-quarter of participants in the main analysis (Table 3). To retain all participants, multiple imputed values were generated for the missing data from the variables used in the analysis, by means of PROC MI (SAS 8.2, SAS Institute, Cary, NC, USA). Five datasets were randomly selected, and analyses conducted on each of these imputed datasets gave similar results. The mean of these estimates was presented using SAS PROC MIANALYSE. Among the categorical (behavioural) variables, missing values were confined to diet. A complete case analysis of the effect of diet on the social gradient in CHD gave a similar result to that using imputed values.

The impact of measurement error on the contribution of metabolic syndrome variables to the social gradient in CHD was investigated. Within-person variation was estimated using short-term repeat measures obtained at phase 3 (n= 215). This sample size was large enough to ensure that sampling error in the intraclass correlation coefficients estimates would have little impact on the measurement error adjustments. The regression calibration method was used to adjust for measurement error [25]. Since methods for correcting for measurement error in Cox models were not available, logistic regression was used for the measurement error analysis (STATA 8.2, StataCorp, College Station, TX, USA), producing similar results to the Cox models reported in the tables.

Results

In 13.1 years follow-up we documented 201 cases of coronary death or non-fatal myocardial infarction. The overall event rate was 3.3 per 1000 person-years. Figure 1 shows the hazard ratios for CHD across the employment grades, which are well described by a strong linear trend (p<0.001). Using the relative index of inequality method, the hazard ratio (95% CI) for being of low employment grade was 2.43 (1.48–4.00).

Adverse health behaviours and a majority of biological risk factors were inversely associated with employment grade at baseline in 1991 to 1993 (Table 1). Hypotensive

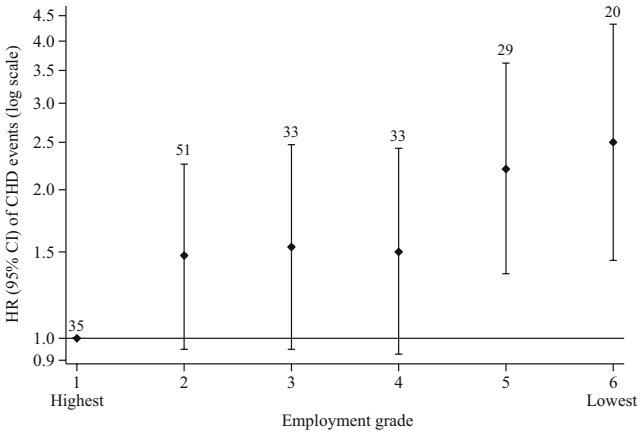

Fig. 1 Age-adjusted HR (95% CI) for coronary death/non-fatal myocardial infarction by employment grade, Whitehall II men. The number of CHD events is shown above error bars for each grade. $p<0.001$ for linear trend; $p=0.63$ for departures from linear trend

medication was related to low employment grade (high 4.9, medium 5.4, low 8.8%, $p=0.02$ for trend), whereas use of lipid-lowering drugs was weakly related to high employment grade (high 0.8, medium 0.6, low 0.0%, $p=0.10$ for trend). Table 2 shows the age-adjusted relation of risk factors to 13 year incidence of major CHD events. For continuous variables, standardised effects (hazard ratio for 1 SD risk factor difference) are presented. Considered singly, all risk factors except factor VIIc showed the expected association with CHD. The contribution of each variable to the social gradient in CHD incidence was calculated using the RII for employment grade, adjusted for age and ethnicity. Although the majority of this population, even in the lowest grade, were non-smokers, current smoking accounted for 19% of the social gradient in incident CHD. Traditional risk factors (smoking, blood pressure, serum cholesterol) explained, statistically, 30% of the CHD gradient—a finding similar to that observed in the first Whitehall study [3]. Based on a logistic model, additional correction for measurement error increased the explanation by a further 8 percentage points.

Diet and physical activity accounted for 15 and 8% of the social gradient in CHD respectively (6 and 6% after adjustment for smoking). A complete case analysis of the effect of diet on the social gradient in CHD gave estimates and standard errors similar to those derived using imputed values. Components of the metabolic syndrome and inflammatory markers contributed substantially to the social gradient in CHD. BMI, which highly correlated with waist circumference, contributed to the gradient (12%). WHR accounted for more of the gradient (24%) than did waist circumference, but we retained waist, following ATPIII. Height contributed 9% to the social gradient in CHD incidence.

Reductions of the social gradient in CHD incidence by adjustments for metabolic syndrome risk factors in logistic models without (and with) adjustment for measurement error were similar: waist −14% (−14%), systolic blood pressure −8% (−10%), diastolic blood pressure −8% (−12%), HDL-cholesterol −13% (−15%), triacylglycerol −18% (−22%) and fasting glucose 0% (0%). Adjustment for measurement error increased the explanatory effect of fibrinogen (24 versus 15%), CRP (27 versus 22%), IL-6 (29 versus 17%), smoking (25 versus 20%) and diet (24 versus 16%). Adjustment for antihypertensive medication, for which no measurement error estimate was available, explained approximately a further 2% of the RII for employment grade in all models. Adjustment for lipid-lowering medication did not change the RII for employment grade in any of the models.

Health behaviours together explained 30% of the employment grade gradient (Table 3). Metabolic syndrome variables explained 27% (model B). Metabolic syndrome and behavioural variables together reduced the social gradient in CHD by 51% (model C), indicating a degree of overlap of the two sets of explanatory effects. Comparison of attenuating effects in models A, B and C showed that about one quarter of the contribution of metabolic syndrome to the disease gradient arises through social differences in health behaviours. If inflammatory markers are treated as components of the metabolic syndrome cluster, the attenuation of the disease gradient is higher (42%, model B1). Based on models A, B1 and C1, where inflammatory mechanisms are assumed to play a causal role in CHD development, the estimate for the overlap in the explanatory effects of health behaviours and metabolic syndrome on the disease gradient was higher.

The two groups of variables, behavioural and biological, together with height as a marker of early life influences, both genetic and environmental, increased the explanation of the social gradient in CHD to about 60%. Using WHR rather than waist circumference, attenuation in the full explanatory model including height was the same.

The contribution to the social gradient in CHD of combinations of risk factors was estimated in analyses based on logistic regression models without (and with) adjustment for measurement error. Compared with the corresponding estimates from Cox models, those derived from logistic models were similar for behavioural factors (−31% [−41%]) and metabolic syndrome variables (−27% [−29%]). The contribution to the gradient increased to −44% (−48%) when inflammatory markers were added to the metabolic variables and to −59% (−61%) when health behaviours were also added. In the final model with health behaviours, biological variables and height, allowance for measurement error added 3% (72 versus 69%) to the explanation.

Table 1 Prevalence and means of demographic factors, health-related behaviours and risk factors in 5,312 men at phase 3 by employment grade

Factors by employment grade	Total (*n*)	Employment grade			Whole sample SD[b]	*p* value for trend
		High	Medium	Low		
Number of men	5,312	2,585	2,393	334		
Demographic factors						
Age (years)	5,312	49.8	48.5	49.7		<0.001
South Asian (%)	5,312	1.0	7.8	15.4		<0.001
African-Caribbean (%)	5,312	0.1	2.7	10.2		<0.001
Health-related behaviours						
Smoking (current) (%)	5,312	7.9	14.4	29.6	–	<0.001
Unhealthy diet (%)	5,040	25.4	43.5	62.5	–	<0.001
Mild or less physical activity (%)	5,312	10.0	14.7	39.5	–	<0.001
Alcohol consumption, >21 units/week (%)	5,312	19.6	17.3	12.8	–	0.003
Biological factors						
Metabolic syndrome factors						
Waist circumference (m)	5,231	0.870	0.876	0.881	0.092	0.04
Systolic blood pressure (mmHg)	5,296	121.5	122.1	122.8	13.0	0.04
Diastolic blood pressure (mmHg)	5,296	80.7	81.2	82.1	9.1	0.003
HDL-cholesterol (mmol/l)	5,257	1.34	1.31	1.32	0.35	0.01
Triacylglycerol (mmol/l)[a]	5,278	1.29	1.37	1.44	0.55	<0.001
Fasting glucose (mmol/l)[a]	5,072	5.26	5.26	5.34	0.10	0.20
Inflammatory markers						
Fibrinogen (g/l)[a,c]	4,930	2.26	2.30	2.40	0.22	<0.001
CRP (mg/l)[a]	5,032	0.79	0.89	1.11	1.16	<0.001
IL-6 (pg/ml)[a]	4,961	1.36	1.50	1.72	0.58	<0.001
Early life factors						
Height (m)	5,298	1.774	1.759	1.725	0.066	<0.001
Other risk factors						
WHR	5,226	0.896	0.906	0.917	0.060	<0.001
BMI (kg/m^2)	5,294	25.0	25.1	25.5	3.1	0.002
Total cholesterol (mmol/l)	5,278	6.46	6.47	6.45	1.12	0.92
LDL-cholesterol (mmol/l)	5,153	4.45	4.44	4.39	1.00	0.52
Apolipoprotein A-I (g/l)	5,278	2.06	2.05	2.05	0.32	0.09
Apolipoprotein B (g/l)	5,278	1.30	1.31	1.32	0.29	0.39
2 h glucose (mmol/l)[a]	5,068	5.16	5.29	5.48	0.31	<0.001
2 h insulin (pmol/l)[a,d]	5,050	207	235	271	6.04	<0.001
Fasting insulin (pmol/l)[a,d]	4,791	36.3	39.1	41.3	4.72	<0.001
von Willebrand factor (IU/ml)[a]	4,792	97.9	101.4	110.3	0.36	<0.001
Factor VII (% of standard)[a]	4,956	85.0	85.3	86.6	0.27	0.27

Prevalences and means are age-adjusted to the age at entry distribution (phase 3) of the whole sample
[a] Age-adjusted geometric means are presented since distributions are log normal
[b] Whole sample SD is for the distribution of logged values
[c] Conversion to SI units: 1 g/l=2.94 μmol/l
[d] Conversion to SI units: 1 mIU/l=6.945 pmol/l

Discussion

Our study set out to determine the extent to which metabolic syndrome variables, inflammatory markers and health behaviours account for the substantial social gradient in incident major coronary events observed in the Whitehall II cohort. We found that, together and without adjustment for measurement error, they account for about half of the social gradient, and indeed more if measurement error is taken into account. The addition of height as a measure of early life influences increased the proportion explained to about 60%, markedly more than that explained by traditional risk factors in the original Whitehall study and consistent with findings from the Kuopio study [26].

Specificity of biological findings A statistical explanation does not necessarily equate with a biological one. It is nevertheless helpful in testing our prior hypotheses. Earlier, based on cross-sectional analysis, we postulated that von Willebrand factor, a marker of endothelial damage, would be

Table 2 Association between phase 3 risk factors and incident CHD, and the effect of adjustment for single risk factors on the relative index of inequality for grade

Risk factors	CHD deaths/non-fatal myocardial infarction (201 events/5,312 men)		
	HR for risk factor[a] (95% CI)	Relative index of inequality adjusted for risk factor (95% CI)	Per cent change in relative index of inequality[b]
Demographic			
South Asian (vs white European)	1.92 (1.19–3.08)	2.17 (1.28–3.67)	Baseline
African-Caribbean (vs white European)	0.87 (0.28–2.72)		
Health related behaviours			
Smoking[c] (current vs never)	2.24 (1.52–3.29)	1.88 (1.10–3.20)	−19
Type of diet[c] (unhealthy vs healthy)	1.55 (1.07–2.23)	1.93 (1.11–3.34)	−15
Physical activity[c] (≤ mild vs active)	1.77 (1.19–2.65)	2.03 (1.20–3.45)	−8
Alcohol[c] (>21 units/week vs none)	0.91 (0.58–1.44)	2.18 (1.28–3.71)	0
Biological factors			
Metabolic syndrome factors			
Waist circumference	1.43 (1.25–1.62)	1.97 (1.16–3.34)	−12
Systolic blood pressure	1.42 (1.25–1.61)	2.05 (1.21–3.47)	−7
Diastolic blood pressure	1.44 (1.26–1.64)	2.05 (1.21–3.47)	−7
HDL-cholesterol	0.66 (0.57–0.76)	1.97 (1.16–3.35)	−12
Triacylglycerol	1.52 (1.34–1.73)	1.90 (1.12–3.23)	−17
Fasting glucose	1.13 (1.00–1.27)	2.16 (1.28–3.66)	0
Inflammatory markers			
Fibrinogen	1.41 (1.23–1.62)	1.96 (1.16–3.33)	−13
CRP	1.62 (1.42–1.86)	1.88 (1.11–3.19)	−18
IL-6	1.39 (1.23–1.56)	1.95 (1.15–3.31)	−14
Early-life factors			
Height	0.82 (0.72–0.94)	2.03 (1.19–3.45)	−9
Other risk factors			
WHR	1.57 (1.37–1.79)	1.81 (1.06–3.07)	−24
BMI	1.38 (1.22–1.56)	1.98 (1.17–3.35)	−12
Total cholesterol	1.49 (1.30–1.70)	2.14 (1.26–3.61)	−2
LDL-cholesterol	1.46 (1.27–1.66)	2.20 (1.30–3.71)	2
Apolipoprotein A-I	0.68 (0.59–0.79)	2.04 (1.21–3.46)	−8
Apolipoprotein B	1.62 (1.42–1.84)	2.13 (1.26–3.60)	−2
2 h glucose	1.19 (1.04–1.37)	2.12 (1.25–3.59)	−3
2 h insulin	1.32 (1.13–1.54)	2.07 (1.22–3.51)	−6
Fasting insulin	1.44 (1.25–1.67)	2.03 (1.20–3.45)	−8
von Willebrand factor	1.23 (1.06–1.42)	2.11 (1.24–3.57)	−4
Factor VII	1.04 (0.91–1.20)	2.16 (1.27–3.65)	−1

[a] Age-adjusted HR associated with a 1 SD increase in the risk factor

[b] Change in the relative index of inequality adjusted for age group and ethnicity after additional adjustment for the risk factor

[c] Multiple-exposure categories were used to adjust for these health behaviours

related to the social gradient in CHD [27]. We found little support for that mechanism. On the other hand, there is support for our previously stated hypothesis that social differentials in metabolic syndrome variables provide an important part of the explanation for the social gradient in CHD incidence [12, 18, 28]. In Whitehall II, serum total and LDL-cholesterol, although strongly related to CHD incidence, are not inversely related to social position and are thus not major explanations of the social gradient in CHD.

The nature of the relation between inflammatory markers and CHD remains unresolved [29–32]. Since it is not certain that IL-6, CRP and fibrinogen are markers of causal processes or measures of disease status, final analyses are presented with and without inclusion of inflammatory markers. When metabolic syndrome and behavioural variables were included in the model, inflammatory markers added modestly to the explanation of the CHD gradient.

Behavioural factors Smoking is important as a cause of CHD. However, more than 85% of participants were non-smokers and 81% (75% after adjustment for measurement

Table 3 Effect of adjustment for phase 3 risk factors on the relationship between incident CHD death/non-fatal myocardial infarction and the relative index of inequality for grade

Adjustments	CHD deaths/non-fatal myocardial infarction (201events/5,312 men)	
	Adjusted relative index of inequality (95% CI)	Per cent change in relative index of inequality[a]
Age	2.43 (1.48–4.00)	–
Age, ethnic group	2.17 (1.28–3.67)	Baseline
Behavioural variables		
Age, ethnic group + smoking	1.88 (1.10–3.20)	−19
Age, ethnic group + smoking + physical activity + alcohol + diet (model A)	1.72 (0.98–3.01)	−30
Biological variables		
Age, ethnic group + metabolic syndrome variables[b] (model B)	1.76 (1.04–2.98)	−27
Age, ethnic group + inflammatory[c]	1.82 (1.07–3.08)	−23
Age, ethnic group + metabolic syndrome variables[b] + inflammatory (model B1)	1.57 (0.92–2.72)	−42
Behavioural + biological variables		
Age, ethnic group + all behavioural + metabolic syndrome variables[b] (model C)	1.46 (0.86–2.48)	−51
Age, ethnic group + all behavioural + metabolic syndrome variables[b] + inflammatory[c] (model C1)	1.41 (0.80–2.47)	−56
Age, ethnic group + all behavioural + metabolic syndrome variables[b] + height	1.37 (0.78–2.41)	−59
Age, ethnic group + all behavioural + metabolic syndrome variables[b] + inflammatory[c] + height	1.34 (0.76–2.35)	−62

[a] Change, compared with the age- and ethnic group-adjusted value, in the relative index of inequality for grade
[b] Metabolic syndrome variables: waist, systolic BP, diastolic BP, HDL-cholesterol, triacylglycerol, fasting glucose
[c] Inflammatory markers: plasma fibrinogen, serum CRP and IL-6

imprecision) of social differences in disease remained after taking account of smoking. Smoking measured at one point in time may be an inaccurate measure of exposure. We therefore repeated the analyses using accumulated pack-years in current and ex-smokers, based on the first three study phases. The degree of attenuation of the social gradient was unchanged. Both physical activity and dietary pattern [17, 33], but not alcohol consumption, made further modest independent contributions to the explanation, after the effect of smoking had been allowed for. Health behaviours overall accounted for just under a third of the socioeconomic differential in CHD. This exceeds the estimate derived from a representative sample of the US population, which found that health behaviours accounted for 12% of the predictive effect of income on total mortality rates [34]. In the latter study, attenuation of the income effect by behavioural factors was similar for cardiovascular and tumour deaths analysed separately.

Relation between behavioural and biological factors If indeed these are the relevant biological pathways, it raises the question of how social gradients in the metabolic syndrome variables and in a marker of inflammation are generated. There may be three types of influence: health behaviours, early life and psychosocial factors. Diet, physical activity, smoking and alcohol may all affect metabolic syndrome variables and fibrinogen [12, 28, 35, 36]. Our multivariate analysis indicates that behaviours, excluding alcohol, account for a part of the social gradient in metabolic syndrome. Moreover, the metabolic syndrome variables appear to mediate the effect of social position in part independently of their association with these health behaviours.

Early life Early life is related to risk of CHD in adulthood [37]. Adult height is inversely related to metabolic syndrome variables [38], plasma fibrinogen [28] and CHD incidence in Whitehall II [39], consistent with an effect of early life on these biological pathways. A further effect of early life is possible, as addition of height to the full model increased the explanation of social differences in CHD.

Psychosocial factors Psychosocial influences are also possible. Activity of the hypothalamic–pituitary–adrenal axis is related to the metabolic syndrome [40]. We have also shown links between metabolic syndrome variables and both sympathoadrenal and cardiac autonomic activity [41, 42]. Psychosocial stress is related to plasma fibrinogen [28] and prospectively to development of central obesity, metabolic syndrome and CHD [43–45]. Among Swedish women [46], a combination of psychosocial and biochemical factors explained much of the social gradient in CHD.

Civil servants and generalisability The scientific challenge is to understand why CHD follows a social gradient in people who are not poor: the lower the position in the hierarchy the higher the risk [1, 2]. Civil servants are an illuminating population to study. They exclude the richest and poorest members of society, as well as manual occupations and the unemployed. They are men and women with higher than average job security. Despite this, there is a marked social gradient in coronary risk [3, 4]. Similar social gradients have been observed in USA [7, 47], Europe [5, 6] and Australasia [48].

Potential limitations Non-responders at the phase 3 examination had higher rates of all-cause mortality than those who attended, but the social gradient in mortality rates was similar (p=0.22). Loss to follow-up may lead to under-identification of non-fatal CHD, but the impact on the grade gradient is likely to be small [49]. Measurement error may lead to underestimation of the contribution of risk factors, particularly of diet, to the social gradient. It had a smaller effect on components of the metabolic syndrome. Furthermore, adjustment for measurement error did not alter our conclusion that health behaviours and biological risk factors make independent contributions to explaining the social gradient in CHD. This observation does not preclude the possibility that explanatory power might be enhanced by multiple measurements of exposure over the life-course. Finally, the analyses here are confined to men; as events accumulate in women, we shall test the degree to which explanations are common across the sexes.

Implications for reducing social inequalities in CHD Our study provides further evidence that differences in traditional risk factors provide a poor explanation for the socioeconomic gradient in CHD. Two implications flow from this observation. First, it adds to our understanding that cardiovascular risk scores such as QRISK, which include an area measure of deprivation, are better discriminators of risk across the socioeconomic hierarchy than those which do not include such a measure [50]. Second, it highlights the possibility that a prevention strategy focusing on smoking cessation and both blood pressure and cholesterol lowering may not be optimal for reducing social inequalities in CHD.

Conclusion Our findings highlight the importance of specific biological pathways involving the metabolic syndrome in mediating the social gradient in CHD.

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