Socioeconomic status, pathogen burden and cardiovascular disease risk

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Objective: Socioeconomic status (SES) is inversely associated with coronary heart disease (CHD) risk. Cumulative pathogen burden may also predict future CHD. The hypothesis was tested that lower SES is associated with a greater pathogen burden, and that pathogen burden accounts in part for SES differences in cardiovascular risk factors.

Methods: This was a cross-sectional observational study involving the clinical examination of 451 men and women aged 51–72 without CHD, recruited from the Whitehall II epidemiological cohort. SES was defined by grade of employment, and pathogen burden by summing positive serostatus for *Chlamydia pneumoniae*, cytomegalovirus and herpes simplex virus 1. Cardiovascular risk factors were also assessed.

Results: Pathogen burden averaged 1.94 (SD) 0.93 in the lower grade group, compared with 1.64 (0.97) and 1.64 (0.93) in the intermediate and higher grade groups ($p=0.011$). Pathogen burden was associated with a higher body mass index, waist/hip ratio, blood pressure and incidence of diabetes. There were SES differences in waist/hip ratio, high-density lipoprotein-cholesterol, fasting glucose, glycated haemoglobin, lung function, smoking and diabetes. The SES gradient in these cardiovascular risk factors was unchanged when pathogen burden was taken into account statistically.

Conclusions: Although serological signs of infection with common pathogens are more frequent in lower SES groups, their distribution across the social gradient does not match the linear increases in CHD risk present across higher, intermediate and lower SES groups. Additionally, pathogen burden does not appear to mediate SES differences in cardiovascular risk profiles.

There is a socioeconomic gradient in coronary heart disease (CHD) mortality and cardiovascular disease risk in the USA, UK and many other countries.^{1,2} Lower socioeconomic status (SES) is associated with a range of cardiovascular risk factors including smoking, adverse lipid profiles, abdominal adiposity, glucose intolerance and inflammatory markers.^{3–7} Both early life SES and adult socioeconomic position appear to contribute to the social gradient.^{5,8}

A history of infection may contribute to cardiovascular disease risk by stimulating sustained vascular inflammation. Evidence concerning the relevance of individual pathogens is mixed, but the cumulative pathogen burden, defined by positive serostatus for a range of pathogens, has been associated with coronary artery disease and carotid atherosclerosis in case-control^{9–11} and longitudinal cohort studies.^{12–14} Pathogen burden is also related to cardiovascular risk markers such as endothelial dysfunction,¹⁵ low high-density lipoprotein (HDL)-cholesterol¹⁶ and insulin resistance,¹⁷ in some but not all studies.^{9,18}

It is plausible that pathogen burden could contribute to SES differences in cardiovascular disease risk. Exposure to infection is greater in lower SES groups, particularly in early life,¹⁹ and childhood infection is associated with endothelial dysfunction.²⁰ We therefore tested the hypothesis that lower SES is associated with greater cumulative pathogen burden in healthy middle-aged and older adults. Seropositivity was measured for three pathogens, *Chlamydia pneumoniae*, cytomegalovirus (CMV) and herpes simplex virus 1 (HSV-1), that have been associated with cardiovascular disease risk,^{21–23} and have contributed to studies of cumulative pathogen burden.^{10,12,14,15} We also determined whether variations in pathogen burden accounted for SES differences in cardiovascular risk factors.

METHODS

Participants

Data were collected from 451 members of the Whitehall II epidemiological cohort. The Whitehall II cohort consists of 10 308 London-based civil servants originally recruited in 1985–1988 to investigate psychosocial, biological and demographic risk factors for CHD.²⁴ Participants were recruited from different grades of employment within the civil service in order to study the social gradient in CHD. The sample were selected at random from a larger group of 860 consecutive attendees at a medical screening session in whom plasma heat shock protein 60 (not presented here) was assessed. These 860 participants were all the cohort members invited for physical examinations during a 3-month period in the summer of 2003. Forty-six were excluded from the analysis because they had a history of CHD or stroke, or were prescribed cardiovascular medication including antihypertensives, anti-coagulants and nitrates. The final sample of 405 consisted of 263 men and 142 women ranging in age from 51 to 72 years. Participants were defined as higher, intermediate and lower SES on the basis of grade of employment. We calculated that with this sample size, we had 80% power ($p<0.05$) to detect a pathogen burden effect size ≥ 0.30 across SES groups.

Measures

Participants underwent a physical examination during which fasting blood samples were obtained. Height, weight and waist and hip circumference were measured using standard methods,

Abbreviations: AU, arbitrary unit; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CMV, cytomegalovirus; FEV₁, forced expiratory volume in 1 s; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HSV-1, herpes simplex virus 1; IgG, immunoglobulin G; SES, socioeconomic status

Table 1 Characteristics of participants

	Men (n = 263)	Women (n = 142)
Age, years	60.7 (5.6)	60.0 (5.4)
Grade of employment, n (%)		
Higher	77 (29.3)	18 (12.7)*
Intermediate	152 (57.8)	57 (40.1)
Lower	34 (12.9)	67 (47.2)
Current smokers, n (%)	25 (9.5)	10 (7.0)
BMI, kg/m ²	26.7 (3.8)	26.4 (5.5)
Waist/hip ratio	0.968 (0.064)	0.860 (0.094)*
HDL-cholesterol, mmol/l	1.46 (0.36)	1.85 (0.50)*
Total/HDL ratio	4.04 (1.2)	3.35 (1.1)*
Fasting glucose, mmol/l	5.47 (1.2)	5.22 (0.90)*
HbA1c, %	5.22 (0.63)	5.30 (0.59)
Systolic BP, mm Hg	128.5 (15.6)	124.3 (17.6)*
Diastolic BP, mm Hg	75.2 (10.5)	72.1 (10.4)*
FEV ₁ , litres	3.12 (0.72)	1.95 (0.59)*
Positive serostatus, n (%)		
<i>C. pneumoniae</i> (n = 392)	174 (68.8)	72 (51.8)*
CMV (n = 399)	123 (47.1)	85 (61.6)*
HSV-1 (n = 403)	149 (57.1)	92 (64.8)
Pathogen burden, n	1.69 (0.96)	1.75 (0.94)

Results are expressed as n (percentage) and mean (SD).

BMI, body mass index; BP, blood pressure; CMV, cytomegalovirus; FEV₁, forced expiratory volume in 1 s; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HSV-1 herpes simplex virus 1.

*p < 0.05 difference between men and women.

from which body mass index (BMI) and waist/hip ratio were derived. Two blood pressure (BP) readings were taken with the participant seated, and these were averaged to generate systolic and diastolic BP. Three spirometric measures were taken, from which forced expiratory volume in 1 s (FEV₁) was computed. Current or most recent occupational grade in the civil service was used to index SES, and participants were divided into higher, intermediate and lower grade of employment groups.

Laboratory methods

Fasting HDL cholesterol, the total/HDL-cholesterol ratio, fasting glucose and glycated haemoglobin (HbA1c) were analysed from samples obtained during the physical examination. The serostatus for *C. pneumoniae*, CMV and HSV-1 was assayed at the University of Umeå. *Chlamydia pneumoniae* immunoglobulin G (IgG) was measured with the *Chlamydia* microtitre indirect immunofluorescence (MIF) test (Focus technologies, Cypress, CA, USA) used according to the manufacturer's instructions. Each slide was read in a fluorescence microscope (Zeiss axioplan) by two independent investigators with congruent results. The antigen for the CMV IgG ELISA was derived from CMV strain Ad 169 cultured in human fibroblasts. The antigen was extracted by sonication in 0.1 M glycine buffer at pH 9.5. A control antigen was prepared from uninfected cells in the same manner. Sera were diluted 1/440 and incubated for 2 h at 37°C. The conjugate (alkaline phosphatase) was incubated for 1 h and the substrate for 30 min. The antibody activity was expressed in arbitrary units (AU)—that is, as the net absorbance of the sample as a percentage of the net absorbance of the high positive control. A value of ≥10 AU was considered positive for the presence of IgG and <5 AU as negative. A grey zone area was defined in the range between 5 and 9 AU, but participants who fell into this range were classified conservatively as seronegative. The antigen for the HSV-1 IgG ELISA was a local HSV-1 strain cultured in GMK cells. The antigen was a lysate of the infected cells prepared as reported previously.¹¹ A control antigen was included. The ELISA procedure was as for CMV.

Statistical analysis

Cardiovascular risk factors were compared in men and women using analysis of variance for continuous variables and χ^2 tests for categorical variables. Cumulative pathogen burden was defined as the number of pathogens for which the individual was seropositive, so could range from 0 to 3. Pathogen burden was compared across the three SES groups (higher, intermediate and lower grade of employment) using analysis of covariance, adjusting for age and gender. The relationship between pathogen burden and cardiovascular risk factors was assessed using analysis of covariance, and p values for linear trends across levels of seropositivity are presented. Continuous cardiovascular risk factors (BMI, waist/hip ratio, HDL-cholesterol, total/HDL ratio, fasting glucose, HbA1c, BP and FEV₁) were compared across grade of employment groups using analysis of covariance, adjusting for age and gender. We also tested whether the gradient was modified by including pathogen burden as an additional covariate. Smoking and diabetes incidence were compared across grade of employment groups using logistic regression with the higher grade group as the reference category. Odds ratios with 95% CI are presented.

RESULTS

The characteristics of the participants are shown in table 1. Men were more likely to be of higher grade of employment than women, and had greater waist/hip ratios, lower HDL-cholesterol and total/HDL-cholesterol ratios, and higher fasting glucose, systolic and diastolic BP (p < 0.05). Between 52.1 and 62.8% of participants were seropositive for each of the pathogens. The pathogen burden was 0 in 11.6%, 1 in 28.9%, 2 in 35.8% and 3 in 23.7%, with a mean of 1.72 (0.95).

The pathogen burden was significantly greater in the lower grade compared with the higher and intermediate grade participants after adjustment for age and gender (p = 0.027, table 2). Of the individual pathogens, only CMV showed an SES gradient, with higher rates of seropositivity in the lower grade of employment group (p = 0.011).

The association between pathogen burden and cardiovascular risk is summarised in table 3. After adjustment for age and gender, a higher pathogen burden was related to greater BMI (p = 0.008), higher waist/hip ratio (p = 0.055), a greater prevalence of diabetes (p = 0.024) and higher systolic and diastolic BP (p = 0.04). There were no differences in lipids, fasting glucose, HbA1c or FEV₁.

Lower SES was associated with significantly greater waist/hip ratio (p = 0.004), lower HDL-cholesterol (p < 0.001), a higher total/HDL-cholesterol ratio (p = 0.025), elevated fasting glucose (p = 0.006) and HbA1c (p < 0.001), and a lower FEV₁ (p = 0.014, table 4). Lower SES participants were also more likely to be smokers (odds ratio 4.41, 95% CI 1.45 to 13.5), and to suffer from diabetes (odds ratio = 5.93, 95% CI 1.52 to 23.2). We tested whether pathogen burden contributed to these SES differences by adding it to the regression models (table 4). Cardiovascular risks associated with SES were virtually unchanged after pathogen burden had been taken into account. For example, the difference in waist/hip ratio between higher and lower grade of employment groups fell by 5.3% after pathogen burden had been included in the regression models, while the difference in fasting glucose was reduced by 4%. The odds ratios for smoking and diabetes in participants of lower compared with higher SES fell slightly to 4.28 (95% CI 1.39 to 13.1) and 5.28 (95% CI 1.33 to 21.0), respectively, with pathogen burden added to the logistic models. These results indicate that pathogen burden made little contribution to the SES gradient in cardiovascular risk factors.

Table 2 Socioeconomic status and pathogen burden

	Grade of employment			p Grade difference*
	Higher	Intermediate	Lower	
Positive serostatus:				
<i>C. pneumoniae</i> (n = 399)	59 (62.1%)	125 (62.8%)	62 (63.3%)	0.16
CMV (n = 392)	41 (43.6%)	100 (48.8%)	67 (67.0%)	0.011
HSV-1 (n = 403)	56 (59.6%)	118 (56.7%)	67 (66.3%)	0.58
Total pathogen burden (n = 405)	1.64 (0.93)	1.64 (0.97)	1.94 (0.93)	0.027

CMV, cytomegalovirus; HSV-1 herpes simplex virus 1.

Results expressed as n (percentages) and means (SD).

*Adjusted for age and gender.

DISCUSSION

We hypothesised that lower SES would be associated with a greater pathogen burden in this sample of middle-aged and older men and women without evident cardiovascular disease. SES was defined on the basis of grade of employment, since this has been shown in both the original Whitehall and later Whitehall II studies to predict CHD risk.^{24–25} Grade of employment is strongly associated with the other markers of SES—for example, 64% of the higher grade of employment participants had a college degree, compared with 33% of the intermediate and 12.3% of the lower grade of employment groups. Our primary hypothesis was partly confirmed, in that pathogen burden was greater in the lower SES group. Interestingly, the association with SES was non-linear, since the higher and intermediate grade groups did not differ. The mean pathogen burden was 1.94 in the lower grade group compared with 1.64 in the other two SES categories; 76.3% of the lower grade group were seropositive for two or more pathogens, compared with 53.7% and 55.0% in the higher and intermediate groups, respectively. This indicates that high pathogen burden is a characteristic of more deprived individuals in the population, but is not proportional to social position across the socioeconomic spectrum. Since the gradient in CHD risk is continuous, the result casts doubt on the contribution of pathogen burden to SES differences in risk. The association with SES was stronger for the measure of combined pathogen burden than individual pathogens, as has been found in studies relating serostatus with coronary artery disease.^{10–14}

Increased pathogen burden was related to greater BMI, waist/hip ratio, BP and incidence of diabetes. Previous studies have related pathogen burden to adverse lipid profile, impaired vascular function and insulin resistance.^{16–17, 26} Lower SES was also associated with several cardiovascular risk factors, including prevalence of smoking and diabetes, greater central adiposity, lower HDL-cholesterol, elevated fasting glucose and HbA1c, and lung function. Similar findings have been reported in the full Whitehall II cohort.^{5–7, 24} It is notable that for all these

factors, apart from fasting glucose and HbA1c, the trend across SES groups was continuous, with the intermediate grade group falling between the higher and lower grade groups. However, pathogen burden had a negligible effect on SES differences in cardiovascular risk. As shown in tables 4 and 5, the differences between grade of employment groups were virtually unchanged after pathogen burden had been taken into account.

These findings suggest that although pathogen burden is associated with SES, it does not mediate SES differences in cardiovascular disease risk. However, there are alternative explanations of the results. *Chlamydia pneumoniae*, CMV and HSV-1 may not be appropriate pathogens, and other infectious organisms could be more relevant. *Helicobacter pylori* has been associated with cardiovascular disease, though the evidence is inconsistent.^{27–28} In an earlier unpublished analysis from the Whitehall II cohort, only a weak association between grade of employment and *H. pylori* infection was observed. Other research has focused on periodontal infections.^{11–16} This study was exploratory in nature, so we selected pathogens that have contributed to measures of cumulative burden that related to cardiovascular disease in previous studies.^{10–12, 14} Further investigation of a wider range of pathogens in a larger sample would be desirable. A second possibility is that pathogen burden mediated SES differences in cardiovascular disease through other risk factors that were not measured in this study. For example, markers of inflammation are elevated in lower SES groups.³ The lack of association between pathogen burden and inflammatory markers in other studies argues against this possibility, but it cannot be ruled out.^{9–18, 29} We therefore conclude that although serological signs of infection with common pathogens are more frequent in lower SES groups, their distribution across the social gradient does not match the linear increase in cardiovascular disease risk present between higher, intermediate and lower SES groups. Additionally, pathogen burden does not appear to mediate SES differences in cardiovascular risk profiles. It is therefore likely that other pathways are responsible for translating the SES gradient into differences in CHD incidence.³⁰

Table 3 Pathogen burden and cardiovascular risk factors

	Pathogen burden				p Trend*
	0	1	2	3	
Current smokers, n (%)	2 (4.3)	11 (9.6)	12 (8.3)	10 (10.4)	0.32
Body mass index	25.9 (0.68)	25.6 (0.45)	26.7 (0.38)	27.7 (0.48)	0.008
Waist/hip ratio	0.900 (0.01)	0.909 (0.08)	0.916 (0.01)	0.926 (0.01)	0.055
Diabetes, n (%)	1 (2.1)	2 (1.7)	12 (8.3)	8 (8.3)	0.024
Systolic BP, mm Hg	123.5 (2.4)	124.7 (1.6)	126.6 (1.3)	129.1 (1.7)	0.044
Diastolic BP, mm Hg	71.7 (1.6)	72.2 (1.0)	74.1 (0.9)	75.2 (1.1)	0.040

BP, blood pressure.

Results expressed as means (SE) and n (percent).

*Adjusted for age and gender.

Table 4 Socioeconomic status, cardiovascular risk factors and pathogen burden

	Grade of employment, adjusted for age and gender				Grade of employment, adjusted for age, gender and pathogen burden			
	Higher	Intermediate	Lower	p Trend	Higher	Intermediate	Lower	p Trend
Body mass index	26.4 (0.58)	26.3 (0.35)	26.8 (0.47)	0.60	26.3 (0.59)	26.3 (0.35)	27.0 (0.47)	0.36
Waist/hip ratio	0.898 (0.01)	0.904 (0.01)	0.933 (0.01)	0.004	0.899 (0.01)	0.904 (0.01)	0.932 (0.01)	0.008
HDL-cholesterol, mmol/l	1.84 (0.05)	1.68 (0.03)	1.53 (0.04)	0.001	1.83 (0.05)	1.68 (0.03)	1.54 (0.04)	0.001
Total/HDL-cholesterol ratio	3.48 (0.15)	3.63 (0.09)	3.91 (0.12)	0.025	3.49 (0.15)	3.63 (0.09)	3.90 (0.12)	0.034
Fasting glucose, mmol/l	5.26 (0.14)	5.25 (0.09)	5.76 (0.11)	0.006	5.27 (0.14)	5.25 (0.09)	5.75 (0.12)	0.009
HbA1c, %	5.15 (0.08)	5.16 (0.05)	5.62 (0.06)	0.001	5.16 (0.08)	5.16 (0.05)	5.61 (0.06)	0.001
Systolic BP, mm Hg	126.2 (2.1)	126.0 (1.3)	124.5 (1.7)	0.53	126.5 (2.1)	126.1 (1.2)	124.2 (1.7)	0.39
Diastolic BP, mm Hg	74.2 (1.4)	73.1 (0.8)	72.6 (1.1)	0.38	74.4 (1.4)	73.2 (0.8)	72.4 (1.1)	0.26
FEV ₁ , litres	2.65 (.09)	2.55 (.05)	2.35 (.08)	0.014	2.65 (.09)	2.55 (.05)	2.35 (.08)	0.017

BP, blood pressure; FEV₁, forced expiratory volume in 1 s; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein. Results are expressed as means (SE) and n (percent).

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