Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors

P Patel, M A Mendall, D Carrington, D P Strachan, E Leatham, N Molineaux, J Levy, C Blakeston, C A Seymour, A J Camm, T C Northfield

Abstract

***Objective*—To investigate the relation between seropositivity to chronic infections with *Helicobacter pylori* and *Chlamydia pneumoniae* and both coronary heart disease and cardiovascular risk factors.**

***Design*—Cross sectional study of a population based random sample of men. Coronary heart disease was assessed by electrocardiography, Rose angina questionnaire, and a history of myocardial infarction; serum antibody levels to *H pylori* and *C pneumoniae* were measured, risk factor levels determined, and a questionnaire administered.**

***Setting*—General practices in Merton, Sutton, and Wandsworth, south London.**

***Subjects*—388 white south London men aged 50-69.**

***Main outcome measures*—Evidence of coronary risk factors and infection with *H pylori* or *C pneumoniae*.**

***Results*—47 men (12·1%) had electrocardiographic evidence of ischaemia or infarction. 36 (76·6%) and 18 (38·3%) were seropositive for *H pylori* and *C pneumoniae*, respectively, compared with 155 (45·5%) and 62 (18·2%) men with normal electrocardiograms. Odds ratios for abnormal electrocardiograms were 3·82 (95% confidence interval 1·60 to 9·10) and 3·06 (1·33 to 7·01) in men seropositive for *H pylori* and *C pneumoniae*, respectively, after adjustment for a range of socioeconomic indicators and risk factors for coronary heart disease. Cardiovascular risk factors that were independently associated with seropositivity to *H pylori* included fibrinogen concentration and total leucocyte count. Seropositivity to *C pneumoniae* was independently associated with raised fibrinogen and malondialdehyde concentrations.**

***Conclusions*—Both *H pylori* and *C pneumoniae* infections are associated with coronary heart disease. These relations are not explained by a wide range of confounding factors. Possible mechanisms include an increase in risk factor levels due to a low grade chronic inflammatory response.**

St George's Hospital Medical School, Tooting, London SW17 0RE
P Patel, *research fellow in gastroenterology*
M A Mendall, *lecturer in gastroenterology*
D Carrington, *senior lecturer in virology*
D P Strachan, *senior lecturer in public health sciences*
E Leatham, *research fellow in cardiology*
N Molineaux, *research nurse*
J Levy, *research assistant*
C Blakeston, *research assistant*
C A Seymour, *professor of clinical biochemistry and metabolism*
A J Camm, *professor in cardiology*
T C Northfield, *professor in gastroenterology*

Correspondence to:
Dr Mendall, division of biochemical medicine.

BMJ 1995;311:711-4

Introduction

Recent studies have suggested that chronic infections with *Chlamydia pneumoniae* and *Helicobacter pylori* may be associated with the risk of coronary heart disease.[1-5] In a case-control study we found that seropositivity to *H pylori* conferred a twofold risk of coronary heart disease.[5] However, this finding may have been biased by the method of case selection and by residual confounding,[6] as both *H pylori*[7] and coronary heart disease[8] have been linked to childhood poverty.

The possible mechanisms by which *H pylori* and *C pneumoniae* may influence cardiovascular risk are unknown. We postulated that these chronic infections, which are accompanied by a persistent inflammatory response, may contribute to the risk of coronary heart disease by increasing the concentrations of acute phase reactants such as fibrinogen[9,10] and sialic acid,[11] which are predictors of coronary heart disease. Only part of the variation in fibrinogen concentration has been explained,[12] and in a preliminary report we described an independent association between fibrinogen concentration and *H pylori* or *C pneumoniae* infection.[13] Factor VII is not an acute phase protein but has been linked to coronary heart disease.[10] Factor VII antigen is responsible for most of factor VII coagulant activity and can now be measured directly.[14] We postulated that chronic infections could activate factor VII antigen via a tissue factor dependent process, inducing a procoagulant state and thereby influencing the risk of coronary heart disease.

We performed a cross sectional survey to confirm the relation between seropositivity to *H pylori* and *C pneumoniae* and coronary heart disease ascertained objectively by electrocardiography and chest pain questionnaire. We also investigated the relation of each infection to plasma fibrinogen concentration and other cardiovascular risk factors.

Subjects and methods

General practices in the Merton, Sutton, and Wandsworth district health authority area, south London, referring one or more patients to the St George's Hospital cardiology clinic over the one year study period participated. A random sample of male patients with European sounding names, aged 50-69, on the general practitioners' lists were recruited by taking six consecutive patients from each practice based on their surnames.

All subjects were interviewed by means of a structured questionnaire for general demographic details, history of myocardial infarction, symptoms of angina according to the Rose angina questionnaire,[15] social circumstances, smoking habit, and drug treatment. A positive history of angina was deemed to be present if chest pain in any location was related to exercise and relieved by rest.[16]

Fasting blood samples were drawn for *H pylori* and *C pneumoniae* serological tests and for measurement of plasma fibrinogen, factor VII antigen, sialic acid, C reactive protein, glucose, cholesterol, and triglyceride concentrations and other lipid fractions. Measurements of total leucocyte count and malondialdehyde concentration, a marker of lipid peroxidation, were included in the second half of the study.

H pylori specific IgG titres were measured by a commercial enzyme linked immunosorbent assay (ELISA; Helico-G test). The manufacturer's recom-

mended cut off point is 10×10^3 U/l, which in a white population provides a sensitivity of 92% and a specificity of 94%.[17] *C pneumoniae* IgG titres were measured by microimmunofluorescence,[18] as described,[3] elementary bodies of *C pneumoniae* strain IOL 207 being used as a representative *C pneumoniae* strain type. Cross reactions with *Chlamydia psittaci* and *Chlamydia trachomatis* were assessed. IgG titres of 64 or greater were considered as positive.

Fibrinogen concentrations were measured by the Clauss clotting assay.[19] Factor VII antigen concentrations were measured by a modification of the method of Morrissey *et al*,[14] sialic acid concentrations by an enzymatic assay (Boehringer Mannheim), and malondialdehyde concentrations by a modification of the Yagi method.[20]

A 12 lead resting electrocardiogram was recorded supine, the same machine (Mac PC, Marquette Electronics) being used in all cases. Electrocardiograms were interpreted blind by two observers using the Minnesota coding system.[21] Electrocardiograms indicating coronary heart disease were taken to be those with any of the following: Q waves, ST segment depression, left bundle branch block, or T wave inversion.

STATISTICAL ANALYSIS

Results were analysed by multiple logistic regression using generalised linear interactive modelling[22] and multiple regression using the generalised linear modelling procedure in the SAS statistical analysis system.[23] All models included as explanatory variables age (50-54, 55-59, 60-64, 65-69); smoking habit (never, former, current); years of smoking; years since last smoked; current daily cigarette consumption; social class (registrar general's classification I, II, IIINM (non-manual), IIIM (manual), IV, V); current housing tenure (owned or rented); father's social class (I, II, IIINM, IIIM, IV, V, unclassified); housing density at age 8 (persons per room in four equal groups); hot water supply at age 8 (sole use, shared use, none); and seropositivity to *H pylori* and *C pneumoniae*.

The relation between each infection and coronary heart disease was assessed by logistic regression models with the outcome variables being taken in turn as history of angina or myocardial infarction, electrocardiographic evidence of ischaemia or infarction, and prevalent coronary heart disease (defined as either a positive history or electrocardiographic evidence). The models included history of hypertension, history of hyperlipidaemia, and history of diabetes as explanatory variables, in addition to the risk factors listed above.

The relation between each infection and risk factors for coronary heart disease was assessed by Gaussian error models with each risk factor in turn being taken as the outcome variable. These models included body mass index (weight (kg) divided by height (m^2)) as an explanatory variable, in addition to those listed above. Risk factors with positively skewed distributions (white cell count, malondialdehyde concentration, triglyceride concentration, Lp(a) lipoprotein concentration) were transformed by taking natural logarithms before modelling. Models for triglyceride, glucose, and lipoprotein concentrations were restricted to fasting samples.

TABLE I—*Characteristics of survey participants by seropositivity to H pylori and C pneumoniae. Figures are numbers (percentages) of subjects*

Characteristic	*H pylori*		*C pneumoniae*		All subjects (n=388)
	Seropositive (n=191)	Seronegative (n=197)	Seropositive (n=80)	Seronegative (n=308)	
Age ≥ 60	94 (49)	88 (45)	38 (48)	144 (47)	182 (47)
Ever smoked	150 (79)	150 (76)	69 (86)	231 (75)	300 (77)
Current smoker	52 (27)	56 (28)	31 (39)	77 (25)	108 (28)
Manual occupation	119 (62)	82 (42)	41 (51)	160 (52)	201 (52)
Current housing rented	58 (30)	43 (22)	20 (25)	81 (26)	101 (26)
Father manual worker	152 (80)	120 (61)	60 (75)	212 (69)	272 (70)
Housing at age 8:					
Shared or absent hot water	119 (62)	81 (41)	46 (58)	154 (50)	200 (52)
1 person/room	108 (57)	79 (40)	52 (65)	135 (44)	187 (48)
History of:					
Hypertension	58 (30)	62 (31)	28 (35)	92 (30)	120 (31)
Hyperlipidaemia	17 (9)	6 (3)	4 (5)	19 (6)	23 (6)
Diabetes	23 (12)	24 (12)	7 (9)	40 (13)	47 (12)
On treatment for:					
Hypertension	49 (26)	47 (24)	23 (29)	73 (24)	96 (25)
Hyperlipidaemia	7 (4)	3 (2)	1 (1)	9 (3)	10 (3)
Diabetes	13 (7)	5 (3)	3 (4)	15 (5)	18 (5)
Seropositive to:					
H pylori	191 (100)	0	42 (53)	149 (48)	191 (49)
C pneumoniae	42 (22)	38 (19)	80 (100)	0	80 (21)

TABLE II—*Numbers and percentages of subjects seropositive to H pylori and C pneumoniae by presence or absence of electrocardiographic abnormalities and history of angina or myocardial infarction*

	No (%) seropositive to:				
	Neither	*H pylori*	*C pneumoniae*	Both	Total
History:					
No coronary heart disease	145 (44)	120 (36)	33 (10)	33 (10)	331 (100)
Angina alone	8 (25)	15 (47)	3 (9)	6 (19)	32 (100)
Myocardial infarction alone	2 (25)	4 (50)	1 (13)	1 (13)	8 (100)
Angina and myocardial infarction	4 (24)	10 (59)	1 (6)	2 (12)	17 (100)
Electrocardiographic abnormalities†:					
None	154 (45)	125 (37)	32 (9)	30 (9)	341 (100)
Infarction	1 (4)	16 (62)	3 (12)	6 (23)	26 (100)
Ischaemia	4 (19)	8 (38)	3 (14)	6 (29)	21 (100)
All prevalent coronary heart disease‡:					
None	140 (46)	110 (36)	30 (10)	25 (8)	305 (100)
Any	19 (23)	39 (47)	8 (10)	17 (20)	83 (100)

†Infarction (Q wave) and ischaemia (ST depression, left bundle branch block, or T wave inversion).
‡Electrocardiographic abnormalities or history of angina or myocardial infarction.

Results

Of 612 patients invited to St George's Hospital for examination, 413 (67·5%) attended. This report is restricted to 388 white male patients. A total of 191 (49·2%) were seropositive to *H pylori* and 80 (20·6%) seropositive to *C pneumoniae*. Table I shows the characteristics of men who were seropositive for each infection. *H pylori* was strongly related to socioeconomic status in childhood. *C pneumoniae* was related less strongly to social factors but more strongly to smoking. Neither infection was associated with a history of hypertension, hyperlipidaemia, or diabetes, nor with seropositivity to the other infection (table I).

Forty seven men (12·1%) had electrocardiographic evidence of coronary heart disease, 49 (12·6%) gave a history of angina, and 25 (6·4%) gave a history of myocardial infarction on the chest pain questionnaire. Altogether 83 (21·4%) men had evidence of prevalent coronary heart disease. Table II shows the relation between *H pylori* and *C pneumoniae* infections and each of these disease outcomes. The associations of each infection with electrocardiographic abnormalities were stronger than with symptomatic coronary heart disease. Compared with men with neither infection the prevalence of all past or present coronary heart disease was significantly increased among those with one infection (odds ratio 2·47; 95% confidence interval 1·38 to 4·43) and further increased among men seropositive for both infections (odds ratio 5·01; 2·30 to 10·94). The associations of each infection with all prevalent coronary heart disease and with electrocardiographic abnormalities were statistically significant and virtually unaltered by adjustment for a wide range of potential confounding variables (table III).

Tables IV and V show the association of *H pylori* and *C pneumoniae* infections with risk factors for atheroma and thrombosis. With two exceptions the number of subjects included in each regression model ranged from 289 for fasting triglyceride concentrations to 379 for total cholesterol concentrations; the exceptions were the regression models for white cell count and malondialdehyde concentration, which included 137 and 92 patients respectively. In view of the multiple

TABLE III—*Association of seropositivity to H pylori and C pneumoniae with prevalent coronary heart disease before and after adjustment for other risk factors. Odds ratios expressed with 95% confidence interval in parentheses*

Outcome variables	*H pylori*		C pneumoniae	
	Odds ratio	χ^2 (df=1)	Odds ratio	χ^2(df=1)
All prevalent coronary heart disease				
Unadjusted	2·80 (1·67 to 4·69)	16·3***	1·96 (1·13 to 3·40)	5·45*
Adjusted†	2·76 (1·43 to 5·31)	9·63**	2·25 (1·11 to 4·58)	4·93*
History of angina or myocardial infarction:				
Unadjusted	2·33 (1·29 to 4·18)	8·25**	1·31 (0·68 to 2·53)	0·61
Adjusted†	1·87 (0·87 to 4·02)	2·60	1·41 (0·60 to 3·30)	0·61
Electrocardiographic abnormalities:				
Unadjusted	3·93 (1·94 to 7·95)	16·7***	2·79 (1·46 to 5·33)	8·95**
Adjusted†	3·82 (1·60 to 9·10)	10·2**	3·06 (1·33 to 7·01)	6·84**

†Adjusted for age, smoking history, duration of smoking, years since last smoked, current daily cigarette consumption, history of hypertension, history of diabetes, history of hyperlipidaemia, social class, father's social class, housing tenure, housing density in childhood, hot water supply in childhood, and seropositivity to other infection.
*P<0·05. **P<0·01.
***P<0·001.

comparisons presented, greater attention should be paid to the relative size and significance of differences than to absolute P values.

Fibrinogen concentrations were significantly raised, to a similar degree, in association with each infection. In addition, *H pylori* but not *C pneumoniae* was associated with a significant increase in total leucocyte count, whereas *C pneumoniae* but not *H pylori* was associated with higher concentrations of factor VII antigen and malondialdehyde. The relation of *C pneumoniae* with factor VII antigen concentration was weakened slightly but rendered non-significant (at the 5% level) by adjustment for all confounding variables considered. Raised concentrations of C reactive protein (>4 mg/l) were present in 54% of specimens (43/80) seropositive for *C pneumoniae* and 37% (114/308) of seronegative specimens (adjusted odds ratio 1·55; 1·07 to 3·51). Forty six per cent of specimens (88/191) seropositive for *H pylori* contained raised C reactive protein concentrations as compared with 34% (67/197) of seronegative specimens (adjusted odds ratio 1·55; 0·87 to 2·57).

Neither infection was associated with raised concentrations of cholesterol, triglycerides, or glucose (tables IV and V). The adjusted mean difference in fibrinogen concentrations between normal subjects and those with coronary heart disease was 0·2 g/l. The effect of each infection on mean fibrinogen concentration was equivalent to currently smoking 10-15 cigarettes a day.

Discussion

These results confirm that both *H pylori* and *C pneumoniae* are independently associated with the prevalence of ischaemic heart disease. The association with each infection was stronger when objective evidence of coronary heart disease on electrocardiography was used as the outcome. The relations persisted virtually unchanged after adjustment for a wide range of possible confounding factors. These observations argue strongly against a spurious relation arising from chance or from confounding factors. This could have resulted in bias only if the association of each infection with coronary heart disease differed in attenders and non-attenders. As neither *H pylori* nor *C pneumoniae* status was known, this is unlikely.

Concern has been expressed that our observations of an association of *H pylori* infection with coronary heart disease might be explained by residual confounding by conventional risk factors or socioeconomic circumstances in childhood or adult life.[6] Risk factors such as smoking, hypertension, and hyperlipidaemia can be discounted as confounders only in follow up studies. Nevertheless, our findings make it unlikely that they are major confounders and showed strong associations that were virtually unchanged by controlling for a wide range of factors, including five separate measures of current and childhood socioeconomic status. In this setting any residual confounders would have to be very strongly related both to coronary heart disease and to *H pylori* infection to explain a relative risk of 3·0 or more. It is more likely that the relation is causal, and the associations that we detected between *H pylori* infection and fibrinogen concentration and total leucocyte count point to possible mechanisms.

The systemic effects of *H pylori* infection on fibrinogen concentration and total leucocyte count parallel those seen in chronic dental infection,[24] which has also been linked to coronary heart disease.[25] This effect of *H pylori* gastritis on markers of inflammation such as

TABLE IV—*Effect of seropositivity to H pylori on cardiovascular risk factors before and after adjustment for other risk factors*

Risk factor	Mean (SD)		Difference (95% confidence interval)			
	Seropositive	Seronegative	Unadjusted	*t* Value	Adjusted†	*t* Value
Fibrinogen (g/l)	2·842 (0·594)	2·606 (9·617)	0·237 (0·104 to 0·406)	3·48***	0·175 (0·039 to 0·311)	2·52*
Sialic acid (g/l)	0·721 (0·124)	0·691 (0·103)	0·030 (0·005 to 0·082)	2·37*	0·014 (−0·012 to 0·040)	1·03
Factor VII antigen (μg/l)	8·112 (2·498)	7·858 (2·823)	0·254 (−0·334 to 0·842)	0·85	0·283 (−0·342 to 0·908)	0·89
Log_e leucocyte count (×10⁹/l)	1·971 (0·247)	1·871 (0·210)	0·100 (0·022 to 0·178)	2·52*	0·123 (0·041 to 0·205)	2·93**
Log_e malondialdehyde (μmol/l)	−0·985 (0·415)	−1·024 (0·315)	0·039 (−0·112 to 0·190)	0·51	−0·018 (−0·198 to 0·162)	−0·19
Cholesterol (mmol/l)	5·953 (1·071)	5·937 (1·089)	0·016 (−0·202 to 0·234)	0·14	0·046 (−0·185 to 0·277)	0·39
Log_e triglyceride (mmol/l)‡	0·443 (0·485)	0·352 (0·483)	0·091 (−0·020 to 0·202)	1·59	0·068 (−0·046 to 0·182)	1·17
Log_e Lp(a) lipoprotein‡	5·141 (1·050)	5·100 (1·030)	0·141 (−0·094 to 0·376)	1·18	0·109 (−0·147 to 0·365)	0·83
Apolipoprotein A I (g/l)‡	1·593 (0·321)	1·637 (0·307)	−0·044 (−0·115 to 0·027)	−1·22	−0·045 (−0·120 to 0·030)	−1·18
Apolipoprotein B (g/l)‡	1·474 (0·351)	1·446 (0·376)	0·028 (−0·054 to 0·110)	0·67	0·037 (−0·051 to 0·125)	0·83
Glucose (mmol/l)‡	5·633 (1·761)	5·409 (1·541)	0·224 (−0·116 to 0·584)	1·29	0·166 (−0·193 to 0·525)	0·91

†Adjusted for age, smoking history, duration of smoking, years since last smoked, current daily cigarette consumption, social class, father's social class, housing tenure, housing density in childhood, hot water supply in childhood, body mass index, and seropositivity to other infection.
‡Fasting values only. *P<0·05. **P<0·01. ***P<0·001.

TABLE V—*Effect of seropositivity to C pneumoniae on cardiovascular risk factors before and after adjustment for other risk factors*

Risk factor	Mean (SD)		Difference (95% confidence interval)			
	Seropositive	Seronegative	Unadjusted	*t* Value	Adjusted†	*t* Value
Fibrinogen (g/l)	2·922 (0·524)	2·669 (0·629)	0·253 (0·105 to 0·401)	3·36***	0·180 (0·015 to 0·345)	2·14*
Sialic acid (g/l)	0·728 (0·116)	0·700 (0·114)	0·028 (−0·002 to 0·058)	1·83	0·009 (−0·021 to 0·039)	0·60
Factor VII antigen (μg/l)	8·654 (2·989)	7·800 (2·542)	0·854 (0·076 to 1·632)	2·15‡	0·710 (−0·031 to 1·451)	1·88
Log_e leucocyte count (×10⁹/l)	1·927 (0·213)	1·917 (0·241)	0·010 (−0·074 to 0·094)	0·23	0·010 (−0·079 to 0·099)	0·22
Log_e malondialdehyde (μmol/l)	−0·882 (0·421)	−1·067 (0·327)	0·185 (0·01 to 0·355)	2·13*	0·207 (0·036 to 0·378)	2·37*
Cholesterol (mmol/l)	6·000 (1·102)	5·931 (1·074)	0·069 (−0·206 to 0·344)	0·49	0·026 (−0·257 to 0·309)	0·18
Log_e triglycerides (mmol/l)‡	0·444 (0·512)	0·387 (0·478)	0·057 (−0·087 to 0·201)	0·78	0·004 (−0·132 to 0·140)	0·05
Log_e Lp(a) lipoprotein (mg/l)‡	4·883 (0·996)	5·192 (1·051)	−0·309(−0·575to−0·043)	−2·28*	−0·255 (−0·559 to 0·049)	−1·65
Apolipoprotein A I (g/l)‡	1·592 (0·260)	1·620 (0·329)	−0·028 (−0·103 to 0·047)	−0·73	−0·031 (−0·120 to 0·058)	−0·68
Apolipoprotein B (g/l)‡	1·487 (0·347)	1·453 (0·368)	0·034 (−0·061 to 0·129)	0·70	0·009 (−0·095 to 0·113)	0·17
Glucose (mmol/l)‡	5·727 (2·106)	5·466 (1·519)	0·261 (−0·253 to 0·775)	1·00	0·263 (−0·180 to 0·706)	1·16

†Adjusted for age, smoking history, duration of smoking, years since last smoked, current daily cigarette consumption, social class, father's social class, housing tenure, housing density in childhood, hot water supply in childhood, body mass index, and seropositivity to other infection.
‡Fasting values only. *P<0·05. **P<0·01. ***P<0·001.

Key messages

- *H pylori* is a common chronic bacterial infection of the stomach and *C pneumoniae* is a common chronic bacterial infection of the lungs
- Both infections are associated with electrocardiographic abnormalities indicating myocardial infarction or ischaemia, independent of a wide range of confounders
- These associations may be explained in part by the effects of long term inflammation, including increases in plasma fibrinogen concentration and other inflammatory markers
- These relations need confirming in prospective and interventional studies

fibrinogen concentration, circulating leucocyte count, and C reactive protein and sialic acid concentrations may be mediated via certain cytokines, including tumour necrosis factor α and interleukin 6, whose concentrations are increased in the gastric mucosa of *H pylori* infected patients.[26]

This study confirms the reported association of *C pneumoniae* with coronary heart disease, which is independent of confounding by smoking and socioeconomic factors.[3] A reverse causal relation may apply, as *C pneumoniae* titres reportedly rise after acute myocardial infarction.[4] Reverse causality is unlikely to be an issue for *H pylori*, as this infection is acquired largely in childhood[7] and there was no difference in antibody titre (above the cut off for positivity) between subjects with and without a history of previous myocardial infarction. On the other hand, an important argument in favour of a direct causal role for *C pneumoniae* in coronary heart disease is its effect on several cardiovascular risk factors, which we found in this study.

Though *C pneumoniae* seropositivity is related to fibrinogen concentration, it could also be acting via other immune related mechanisms to cause coronary heart disease. The organism has been found in macrophages[27] and necrotic smooth muscle cells in atherosclerotic plaques.[28] Stimulated macrophages expressing procoagulant activity have been isolated from aortic plaques.[29] Infected macrophages may express tissue factor, activate factor VII antigen, and thus increase the risk of local or distant thrombosis. However, though epidemiological studies, including ours, have shown a relation between high *C pneumoniae* titre and coronary heart disease, postmortem studies have detected *C pneumoniae* in plaques predominantly from subjects with a low antibody titre.[27]

The situation may parallel that of trachoma caused by *C trachomatis* (a closely related organism), in which disease is found in patients with few bacteria in the lesion but high antibody titres,[30] suggesting that hypersensitivity is important. Persisting immunological responses to *C pneumoniae* may raise the fibrinogen concentration as part of an inflammatory response through release of the cytokine tissue necrosis factor α and interleukin 6.[31] Raised malondialdehyde concentrations due to release of oxidative free radicals suggests another possible mechanism whereby *C pneumoniae* may influence coronary heart disease.

The risk factors measured in this study do not explain all the increased risk of coronary heart disease associated with *H pylori* and *C pneumoniae*. These chronic infections may have other effects on the cellular immune system. One such example may include the possible role of cross reactivity between bacterial heat shock proteins and heat shock proteins expressed in atherosclerotic lesions.[32]

We have shown an association of the prevalence of coronary heart disease with potentially treatable infections which are common in the general population. Our figures imply that between one third and half of current coronary heart disease in this population was statistically attributable to either or both infections. What are required now are well conducted prospective studies and eradication trials to evaluate the causal relation of these infections to haemostatic function, progression of atherosclerosis, and cardiovascular morbidity and mortality.

Funding: The British Heart Foundation.
Conflict of interest: None.

1 Saikku P, Mattila K, Nieminen MS, Huttunen JK, Leinonen M, Eckman MR, *et al.* Serological evidence of an association of a novel chlamydia, TWAR, with chronic coronary heart disease and acute myocardial infarction. *Lancet* 1988;ii:983-6
2 Thom DH, Grayston JT, Siscovick DS, Wang SP, Weiss NS, Daling JR. Association of prior infection with Chlamydia pneumoniae and angiographically demonstrated coronary heart disease. *JAMA* 1992;**268**:68-72
3 Mendall M, Carrington D, Strachan D, Patel P, Molineaux N, Levy J, *et al.* Chlamydia pneumoniae: risk factors for seropositivity and association with coronary heart disease. *J Infect* 1995;**30**:121-8.
4 Saikku P, Leiononen M, Tenkanen L, Linnanmaki E, Ekman M, Manninen M, *et al.* Chronic Chlamydia pneumoniae infection as a risk factor for coronary heart disease in the Helsinki heart study. *Ann Intern Med* 1992;**116**:273-7.
5 Mendall M, Goggin P, Levy J, Molineaux N, Strachan D, Camm A, *et al.* Relation of Helicobacter pylori infection and coronary heart disease. *Br Heart J* 1994;**71**:437-9.
6 Glynn J. Helicobacter pylori and the heart. *Lancet* 1994;**344**:146.
7 Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan DP, *et al.* Childhood living conditions and Helicobacter pylori seropositivity in adult life. *Lancet* 1992;**339**:896-7.
8 Elford J, Whincup P, Shaper AG. Early life experience and adult cardiovascular disease: longitudinal and case-control studies. *Int J Epidemiol* 1991;**20**:833-44.
9 Yarnell JW, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, *et al.* Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. *Circulation* 1991;**83**:836-44.
10 Meade TW, Brozovic M, Chakrabarti RR, Haines AP, Imeson JD, Mellows S, *et al.* Haemostatic function and ischaemic heart disease: principal results of the Northwick Park heart study. *Lancet* 1986;ii:533-7.
11 Lindberg G, Eklund GA, Gullberg B, Rastam L. Serum sialic acid concentration and cardiovascular mortality. *BMJ* 1991;**302**:143-6.
12 Lee WCS, Lowe GDO, Tunstall-Pedoe AB. Plasma fibrinogen and coronary risk factors: the Scottish heart health study. *J Clin Epidemiol* 1990;**43**:913-9.
13 Patel P, Carrington D, Strachan D, Leatham E, Goggin P, Northfield T, *et al.* Fibrinogen: a link between chronic infection and coronary heart disease. *Lancet* 1994;**343**:1634.
14 Morrissey JH, Macik BG, Neuenschwander PF, Comp PC. Quantitation of activated factor VII levels in plasma using a tissue factor mutant selectively deficient in promoting factor VII activation. *Blood* 1993;**81**:734-44.
15 Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962;**27**:645-58.
16 Shaper A, Cook D, Walke M, Macfarlane P. Prevalence of ischaemic heart disease in middle aged British men. *Br Heart J* 1984;**51**:595-605.
17 Mendall MA, Goggin PM, Marrero JM, Molineaux, Levy J, Badve S, *et al.* Helicobacter pylori screening prior to endoscopy. *European Journal of Gastroenterology and Hepatology* 1992;**4**:713-7.
18 Wang SP, Grayston JT. Human serology in Chlamydia trachomatis infection with microimmunofluorescence. *J Infect Dis* 1994;**130**:388-97.
19 Clauss A. Gerinnungsphysiologische schnellmethode zur bestimmung des fibrinogens. *Acta Haematol* 1957;**17**:237-46.
20 Hendricks T, Assman RF. On the fluorometric assay of circulating lipoperoxides. *Clin Chim Acta* 1988;**174**:263-70.
21 Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular survey methods* 2nd ed. Geneva: World Health Organisation,1982:123-43. (WHO Monograph Series, No 56.)
22 Baker RJ, Nelder JA. *The GLIM system manual, release 3.* Oxford: Numerical Algorithms Group, 1978.
23 SAS Institute Inc. *SAS user's guide (statistics version).* 5th ed. Cary, North Carolina: SAS Institute, 1985.
24 Kweider M, Lowe GDO, Murray GD, Kinane DF, McGowan DA. Dental disease, fibrinogen and white cell count: links with myocardial infarction? *Scott Med J* 1993;**38**:73-4.
25 Mattila KJ, Neiminen MS, Valtonen W, Rasi VP, Kesaniemi YA, Syrjala SL, *et al.* Association between dental health and acute myocardial infarction. *BMJ* 1989;**298**:779-81.
26 Crabtree JE, Shallcross TM, Heatley RV, Wyatt JI. Mucosal tumour necrosis factor and interleukin-6 in patients with Helicobacter pylori associated gastritis. *Gut* 1991;**32**:1473-7.
27 Kuo CC, Shor A, Campbell LA, Fukushi H, Patton DL, Grayston JT. Demonstration of Chlamydia pneumoniae in atherosclerotic lesions of coronary arteries. *J Infect Dis* 1993;**167**:841-9.
28 Tipping PG, Malliaros J, Holdsworth SR. Procoagulant activity expression by macrophages from atheromatous vascular plaques. *Atherosclerosis* 1989;**79**: 237-43.
29 Puolakkainen M, Kuo CC, Shor A, Wang SP, Grayston JT, Campbell LA. Serological response to Chlamydia pneumoniae in adults with coronary arterial fatty streaks and fibrolipid plaques. *J Clin Microbiol* 1993;**31**: 2212-4.
30 Darougar S, Jones B. Trachoma. *Br Med Bull* 1983;**39**:117-22.
31 Williams D, Bonewald L, Roodman G, Schacter J, *et al.* Tumor necrosis factor alpha is a cytotoxin induced by murine Chlamydia trachomatis infection. *Infect Immun* 1989;**58**:1351-5.
32 Xu Q, Willet J, Marosi M, Kleindeinst R, Oberhollenzer F, Klechl S, *et al.* Association of serum antibodies to heat shock protein 65 with carotid atherosclerosis. *Lancet* 1993;**341**:255-9.

(Accepted 15 June 1995)