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Relation of *Chlamydia pneumoniae* serology to mortality and incidence of ischaemic heart disease over 13 years in the Caerphilly prospective heart disease study

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Abstract

Objectives To investigate the effect of *Chlamydia pneumoniae* infection on future development of ischaemic heart disease and mortality.
Design Prospective longitudinal study.
Setting Caerphilly, South Wales.
Subjects Plasma specimens were collected during 1979-83 from 1773 men aged 45-59 years. These were tested for IgG and IgA antibodies to *C pneumoniae* (TW183) by microimmunofluorescence.
Outcome measures 13 year mortality and incident ischaemic heart disease events were ascertained from death certificates, hospital records, and electrocardiographic changes at follow up every 4 to 5 years.
Results 642 men (36.2%) had IgG antibodies at a titre of ≥1 in 16, of whom 362 (20.4% of all men) also had detectable IgA antibodies. The prevalence of ischaemic heart disease (a history of past or current disease) at entry was similar at all IgG antibody titres but was positively related to IgA antibody titre. IgA antibody titre was positively correlated with plasma viscosity but not with other cardiovascular risk factors. Incidence of ischaemic heart disease was not associated with either IgG antibody titre or IgA antibody titre, but there were stronger and significant relations of IgA antibodies with all cause mortality and fatal ischaemic heart disease, which persisted after adjustment for conventional cardiovascular risk factors. The odds ratios associated with detectable IgA antibodies were 1.07 (95% confidence interval 0.75 to 1.53) for all incident ischaemic heart disease, 1.83 (1.17 to 2.85) for fatal ischaemic heart disease, and 1.50 (1.10 to 2.04) for all cause mortality.
Conclusion This is the first prospective demonstration of an association between IgA antibodies to *C pneumoniae*, a putative marker of chronic infection, and subsequent risk of death from ischaemic heart disease. In contrast to earlier case-control studies, IgG antibodies were not associated with either prevalent or incident ischaemic heart disease.

Introduction

Since the first report of increased concentrations of IgG and IgA antibodies to *Chlamydia pneumoniae* in patients with acute myocardial infarction or chronic coronary heart disease,[1] evidence has accumulated of an association between serological markers of this infection and clinically significant atheroma or manifestations of ischaemic heart disease.[2] The detection, both by polymerase chain reaction or immunocytochemistry[3] and by culture,[4] of *C pneumoniae* in atheromatous plaques lends biological plausibility to a causal link. Although there seems to be preferential localisation of this organism in cardiovascular tissue,[5] its role in the pathogenesis of atheroma and clinical ischaemic heart disease remains controversial.[2 6] In addition to possible local effects, it has been suggested that persistent *C pneumoniae* infection may result in altered lipid metabolism, increased fibrinogen concentrations, and low grade systemic inflammation, as shown by increased C reactive protein concentrations.[7–10]

Most published epidemiological studies have been of cross sectional or case-control design,[2] in which a spurious association could arise from antigenic cross reactivity between *C pneumoniae* and damaged cardiac

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tissue. Prospective investigations are less prone to this reverse causality phenomenon but only three such studies have been published.[7 11 12] None of these distinguished fatal from non-fatal outcomes. We report findings from a longitudinal study relating *C pneumoniae* seropositivity prospectively to the incidence of ischaemic heart disease and, for the first time, to mortality from ischaemic heart disease and all causes.

Subjects and methods

The Caerphilly prospective heart disease study

The Caerphilly prospective heart disease study recruited 2512 men aged 45-59 years in the Caerphilly area of South Wales during 1979-83.[13] Symptoms and electrocardiographic abnormalities suggestive of past or current ischaemic heart disease were ascertained, and a range of cardiovascular risk factors were measured: smoking habit, standing height, body weight, blood pressure, forced expiratory volume in one second (FEV_1), plasma viscosity, leucocyte count, and concentrations of total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and fibrinogen.[14 15] Socioeconomic status was derived from each man's current occupation and his father's occupation during childhood according to the registrar general's social classes.[16]

The sample has been followed up at intervals of around 5 years, and the fourth round of fieldwork (phase IV) was completed during 1994-97, an average of 13.7 (SD 0.5) years after the entry examination. Deaths were classified according to ICD-9 (international classification of diseases, 9th revision) as due to ischaemic heart disease (ICD-9 codes 410-414) or other causes. Incident ischaemic heart disease (new cases arising during follow up) were ascertained from death certificates, review of hospital notes, and electrocardiographic changes, using the same conventions as in previous prospective analyses of this cohort.[14 15 17] Three groups were thus included as incident cases of ischaemic heart disease: fatal ischaemic heart disease (410-414); clinical myocardial infarction (hospitalised episodes meeting WHO criteria of combinations of serial electrocardiographic changes, increased concentrations of cardiac enzymes, and acute symptoms); and development of new Q or QS waves (Minnesota codes 1-1-1 to 1-2-5, or 1-2-7). Follow up for mortality is considered complete. Over 98% of survivors were seen at the 5 year examination, 95% at 10 years, and 93% at 13.7 years.

Serology

Frozen plasma specimens banked at the entry (phase I) examination were available for 1794 (71.4%) of the 2512 men. The specimens had been stored at −20°C since collection in 1979-83, with one thaw cycle. The main reason for specimens not being available was depletion of material during previous seroepidemiological studies of about one quarter of the cohort. All available specimens were tested for IgG antibodies to *C pneumoniae* by microimmunofluorescence at a dilution of 1 in 16. Those specimens that were positive for IgG antibodies to *C pneumoniae* at a dilution of 1 in 16 were also tested for IgG antibodies at dilutions of 1 in 32 and 1 in 64, and for IgA antibodies at a dilution of 1 in 16. Weakly positive reactions at a dilution of 1 in 16 were considered "trace positives." Twenty one specimens were excluded from the analysis owing to the presence of cross reacting antibodies to *Chlamydia trachomatis* or *Chlamydia psittaci*. Results are thus presented for 1773 men (70.6% of the cohort).

Most of the microimmunofluorescence tests used elementary bodies of the TW183 strain of *C pneumoniae*, but confirmatory testing by microimmunofluorescence with the IOL207 strain was carried out on a sample of 156 cases of incident ischaemic heart disease and 198 controls (selected for other seroepidemiological studies[18]). These samples were also tested by an in-house enzyme linked immunosorbent assay for IgG antibodies to mycobacterial heat shock protein. C reactive protein was also measured using an in-house ELISA as previously described.[13]

Statistical analyses

Statistical analysis was performed using STATA.[19] IgG antibody titre was analysed as six categories (undetectable, trace, 1 in 16, 1 in 32, 1 in 64, and >1 in 64) and IgA antibody titre as three categories (undetectable, trace, and ≥ 1 in 16). Samples with IgG antibody titres <1 in 16 (which were not tested for IgA antibodies) were considered to have undetectable IgA antibodies. The cross sectional relations of *C pneumoniae* seropositivity to concentrations of cardiovascular risk factors measured at entry were analysed by tabulations and comparisons of means, testing for trends across antibody titres by multiple regression, rank correlation, or tests for linear trend in proportions. We used tabulations and multiple logistic regression to analyse the associations of *C pneumoniae* IgG antibody titre and IgA antibody titre with prevalent ischaemic heart disease (history of severe chest pain or angina or electrocardiographic abnormalities at entry), incident ischaemic heart disease (fatal and non-fatal cases arising during follow up), and all cause mortality. Odds ratios for incident ischaemic heart disease, fatal ischaemic heart disease, and all cause mortality comparing men with and without detectable IgA antibodies were derived both before and after adjustment for laboratory batch, age, body mass index, systolic blood pressure, total cholesterol concentration, height, and FEV_1 (all as continuous variables); and for smoking history (six categories), own social class (six categories), and father's social class (five categories).

Results

Overall, 642 of the 1773 men (36.2%) had IgG antibody titres ≥ 1 in 16, of whom 107 (6.0% of all men) also had IgA antibody titres ≥ 1 in 16. A further 255 (14.4%) had a trace of IgA antibody and IgG antibody titres of ≥ 1 in 16, and 280 (15.8%) had no detectable IgA antibodies, but IgG antibodies were clearly detectable at a dilution of 1 in 16. IgA antibodies were not tested in, and were presumed to be absent for, 821 (46.3%) men with undetectable IgG antibodies and 310 (17.5%) men with a trace of IgG antibodies.

Table 1 shows the numbers of prevalent and incident cases of ischaemic heart disease and deaths in relation to IgG antibody and IgA antibody titres both

for the men in this study and for the 739 men not included in this study. IgG antibody titres for *C pneumoniae* were not significantly related to prevalent ischaemic heart disease, incident ischaemic heart disease, or fatal ischaemic heart disease. There was an association of borderline significance between IgG antibody titres and mortality from all causes (P = 0.048). In contrast, there was a highly significant association between IgA antibody titres with prevalent ischaemic heart disease at entry (odds ratio for detectable versus undetectable IgA antibody 1.49, 95% confidence interval 1.16 to 1.92), but not with all incident ischaemic heart disease (1.14, 0.84 to 1.56). Detectable IgA antibody was, however, associated with a significantly increased risk of mortality (1.47, 1.12 to 1.94) including fatal ischaemic heart disease (1.68, 1.15 to 2.46). The association of fatal ischaemic heart disease with detectable IgA antibody was apparent among men with past or prevalent ischaemic heart disease at entry (1.40, 0.80 to 2.48) and among those men without ischaemic heart disease at entry (1.69, 1.00 to 2.84). Among the men who developed new ischaemic heart disease events, the proportion who died of ischaemic heart disease was greater among those with detectable IgA antibodies (42/62, 68%) than the rest (102/216, 47%), a highly significant difference (odds ratio 2.35, 1.29 to 4.26).

Table 2 shows the relation of IgA antibody titres to *C pneumoniae* to major cardiovascular risk factors. There was no evidence of associations of IgA antibody titres with either smoking or social class. Differences in age, body mass index, systolic blood pressure, leucocyte count, and concentrations of total cholesterol, high density lipoprotein cholesterol or low density lipoprotein cholesterol, and fibrinogen were small and non-significant, but there was a significantly higher plasma viscosity among men with detectable IgA antibodies, equivalent to about 0.15 SD of the viscosity index. IgG antibody titre, and to a lesser extent IgA antibody titre, were positively related to C reactive protein concentration (P = 0.004 and P = 0.075 respectively) but inversely associated with concentrations of heat shock protein antibody (P = 0.042 for IgG antibody, P = 0.072 for IgA antibody). In addition there were weak but statistically significant positive associations of IgG antibody titre with age (P = 0.026) and body mass index (P = 0.029).

Table 3 shows the effect of adjustment for major cardiovascular risk factors upon the associations of detectable IgA antibody with all incident ischaemic heart disease, fatal ischaemic heart disease, and all cause mortality. These analyses are based on 1692 men with complete information on the cardiovascular risk factors. The odds ratios were little changed by adjustment for multiple covariates (table 3). Additional adjustment for prevalent ischaemic heart disease and plasma viscosity (possible intermediates in the relation of IgA antibody titre to incident events) reduced the odds ratios slightly for fatal ischaemic heart disease and total mortality.

Table 1 Number (percentage) of cases of prevalent ischaemic heart disease, incident ischaemic heart disease, and deaths, by titres of *Chlamydia pneumoniae* IgG antibody and IgA antibody, and availability of specimens from entry examination

Antibody titre	No of men	Prevalent ischaemic heart disease*	Incident ischaemic heart disease		All deaths
			Non-fatal†	Fatal	
Not tested	739	193 (26.1)	59 (8.0)	74 (10.0)	158 (21.4)
Tested	1773	438 (24.7)	134 (7.6)	144 (8.1)	341 (19.2)
IgG antibody titre:					
Zero	821	194 (23.6)	65 (7.9)	62 (7.6)	135 (16.4)
Trace	310	74 (23.9)	27 (8.7)	23 (7.4)	68 (21.9)
1 in 16	268	69 (25.7)	19 (7.1)	27 (10.1)	61 (22.8)
⩾1 in 64	374	101 (27.0)	23 (6.1)	32 (8.6)	77 (20.6)
IgA antibody titre:					
Zero‡	1411	326 (23.1)	114 (8.1)	102 (7.2)	253 (17.9)
Trace	255	80 (31.4)	15 (5.9)	28 (11.0)	62 (24.3)
⩾1 in 16	107	32 (29.9)	5 (4.7)	14 (13.1)	26 (24.3)

*History of severe chest pain, angina, or electrocardiographic abnormalities suggestive of ischaemic heart disease at entry.
†Men developing myocardial infarction who did not subsequently die of ischaemic heart disease.
‡Includes specimens with IgG antibody titres <1 in 16; not tested for IgA antibody.

Table 2 Mean levels of cardiovascular risk factors at entry by *Chlamydia pneumoniae* IgA antibody titre. Values are number (percentage) unless stated otherwise

Risk factor	IgA antibody titre			P value (trend)
	Zero (n=1411)	Trace (n=255)	⩾1 in 16 (n=107)	
Age (years)	52.1	52.7	52.2	0.17
Standing height (m)	1.71	1.71	1.72	0.32
$FEV_1/height^2$ (l/m^2)	0.90	0.89	0.88	0.28
Body mass index (kg/m^2)	26.1	26.5	26.3	0.18
Systolic blood pressure (mm Hg)	139.9	140.5	141.4	0.40
Total cholesterol (mmol/l)	5.72	5.74	5.55	0.30
High density lipoprotein cholesterol (mmol/l)	1.12	1.09	1.14	0.88
Low density lipoprotein cholesterol (mmol/l)	3.84	3.86	3.71	0.41
Fibrinogen (g/l)	3.78	3.89	3.81	0.31*
Leucocytes ($\times 10^9$/l)	6.94	6.97	7.11	0.52*
Viscosity (cP)	1.705	1.719	1.722	0.009*
C reactive protein (g/l)	2.58	3.08	3.48	0.08*
Heat shock protein antibody†	0.82	0.77	0.71	0.07*
Current smokers	763/1405 (54.3)	140/254 (55.1)	59/107 (55.1)	0.79
Manual worker	940/1385 (67.9)	170/247 (68.8)	72/103 (69.9)	0.66‡
Father manual worker	1101/1257 (87.6)	201/223 (90.1)	81/96 (84.4)	0.93‡

Column totals vary slightly owing to missing data for each variable.
*Significance test based on log transformed data.
†Optical density, measured in 230 men with undetectable IgA antibodies and 68 men with detectable IgA antibodies.
‡Based on Spearman's rank correlation between social class and IgA antibody titre.

Discussion

This is the first study to relate serological markers of *C pneumoniae* infection prospectively to risk of mortality, independent of conventional cardiovascular risk factors. Over more than 13 years of follow up, six extra deaths occurred among every 100 men with IgA antibodies detectable at entry, compared with men with undetectable IgA antibodies. This increased risk was mainly due to fatal ischaemic heart disease and attributable to differential case fatality rather than an excess of incident ischaemic heart disease. In contrast to earlier case-control studies and cross sectional surveys,[2] we found no association of past or current ischaemic heart disease at the entry examination with IgG antibody titre, although there was a significant association of IgA antibody titre with prevalent ischaemic heart disease at entry.

Although different strains of *C pneumoniae* share a common outer membrane protein, antigenic differences have been identified by western blotting.[20] Our earlier work showing associations between *C pneumoniae* seropositivity and past or prevalent ischaemic

Table 3 Odds ratio (95% confidence interval) for incident ischaemic heart disease and mortality comparing men with and without detectable IgA antibodies to *Chlamydia pneumoniae*, before and after adjustment for cardiovascular risk factors

Model No	Risk factors adjusted for:	All incident ischaemic heart disease	Fatal ischaemic heart disease	Total mortality
1	No adjustments	1.20 (0.87 to 1.64)	1.76 (1.19 to 2.60)**	1.56 (1.18 to 2.07)**
2	Laboratory batch	1.13 (0.80 to 1.58)	1.84 (1.21 to 2.78)**	1.59 (1.19 to 2.13)**
3	Batch, age, smoking, body mass index, total cholesterol concentration, systolic blood pressure, current social class†, father's social class‡, height, and FEV_1§	1.07 (0.75 to 1.53)	1.83 (1.17 to 2.85)**	1.50 (1.10 to 2.04)*
4	Model 2 plus past or prevalent ischaemic heart disease at entry	1.01 (0.70 to 1.44)	1.74 (1.11 to 2.73)*	1.41 (1.03 to 1.93)*
5	Model 3 plus plasma viscosity at entry	0.98 (0.68 to 1.41)	1.69 (1.06 to 2.68)*	1.36 (0.99 to 1.87)

Significance tests for detectable *v* undetectable IgA antibodies: *P<0.05, **P<0.01.
Trend in risk of total mortality with increasing IgA antibody titre (zero, trace, ⩾1 in 16) was not significant at 5% level in models 3-5.
Trend in risk of fatal ischaemic heart disease with increasing IgA antibody titre was not significant in model 5.
†Modelled as six levels: I and II; III non-manual; III manual; IV; V; missing.
‡Modelled as five levels: I and II; III non-manual; III manual; IV and V; missing or unemployed.
§Subjects with missing FEV_1 retained in model by use of dummy variable representing missing data.

heart disease[9 21] used elementary bodies of the IOL207 strain, whereas other studies have used either the TW183[1 7 22] or Kajaani 6 strain[8 11] of *C pneumoniae*. We confirmed that the relation of IgG antibody titre to incident ischaemic heart disease in the present study was similar using TW183 and IOL207 strains (data not shown), suggesting that strain specificity does not explain our "negative" results.

Our analyses were based on serological markers of *C pneumoniae* infection at a single time point, and these can be difficult to interpret particularly if there have been local outbreaks of *C pneumoniae* infection shortly beforehand. After reinfection or reactivation of latent chlamydial infection, increased IgG antibody concentrations persist for months or years, whereas IgA antibody concentrations decay much more rapidly. It is unlikely that the antibody titres in our study were influenced by recent epidemics, because during 1980-82, when 90% of our subjects were recruited, the prevalence of increased IgG antibody titres and detectable IgA antibodies remained consistently low (ranging from 18% to 23% for detectable IgA antibodies). We therefore have greater confidence that the IgA antibody concentrations we detected reflect an immune response to chronic *C pneumoniae* infection.

Our study investigated several biological mechanisms proposed as links between *C pneumoniae* and ischaemic heart disease. Only plasma viscosity emerged as a likely candidate, but this could be a false positive result arising from multiple significance tests. We did not confirm earlier findings of an association of IgG antibody titre with increased fibrinogen concentration.[9] Previous studies have been inconsistent regarding effects of *C pneumoniae* infection on circulating lipid concentrations.[7–9] Our results suggest that this is an unlikely mechanism linking this infection with ischaemic heart disease. Smoking has been proposed as both a confounder and an effect modifier of the association between *C pneumoniae* and ischaemic heart disease.[7 22–24] In common with another large prospective study,[11] we found no evidence of any association of current smoking habit with either IgG antibody titre or IgA antibody titre, nor of effect modification by smoking (data not shown, test for interaction, P = 0.36). We found no support for the hypothesis that cross reactivity between chlamydial and human heat shock proteins might be of relevance in the pathogenesis of ischaemic heart disease.[25 26]

The relation between titres of circulating antibody and the presence of *C pneumoniae* in arterial tissue remains uncertain. One recent study found no association of either IgG antibody titre or IgA antibody titre with viable *C pneumoniae* infection in coronary arteries that had been surgically removed.[27] Another study found that *C pneumoniae* detected in coronary arteries at postmortem examination was related to IgG antibody titre, but not IgA antibodies, in sera collected 1-26 years before death.[28] In contrast, our longitudinal study shows a stronger relation of prevalent and fatal ischaemic heart disease with IgA antibodies. A possible explanation for this paradox could be that it is the immune response and local inflammation induced by *C pneumoniae* that is more important than the presence of the organism in arterial walls. IgA antibody titres may be a better marker of this persistent immune response, which may increase the risk of rupture in atheromatous plaques but reduce the viability of *C pneumoniae* in arterial tissue.

Early results from intervention studies in patients with established ischaemic heart disease suggest some short term benefit from antichlamydial treatment.[29 30]

Key messages

- Middle aged men with circulating IgA antibodies against *Chlamydia pneumoniae* had increased mortality over a 13 year period, mainly due to an excess of fatal ischaemic heart disease
- This association was largely independent of conventional cardiovascular risk factors and attributable to increased case fatality of ischaemic heart disease among men with detectable IgA antibodies
- No association was found between *C pneumoniae* IgA antibody titre and incident ischaemic heart disease (fatal and non-fatal combined), nor between *C pneumoniae* IgG antibody titre and incident ischaemic heart disease
- This is the first study to suggest an association between persistent *C pneumoniae* infection and subsequent mortality

Our observational data raise the possibility that treatment of this infection may influence survival in the longer term.

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Contributors: DPS, DC, MAM, PCE, and PMS designed the study. PCE and PMS initiated and maintained the Caerphilly cohort. DC, MAM, LB, and JM developed and carried out the laboratory analyses. DPS and BKB performed the statistical analyses. DPS and DC are guarantors for the paper, vouching for the epidemiological and virological aspects respectively.

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Commentary: *Chlamydia pneumoniae* infection and ischaemic heart disease

The story so far

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Strachan and colleague's paper adds to the epidemiological evidence of an association between *Chlamydia pneumoniae* infection and ischaemic heart disease. Antibodies to *C pneumoniae*, a marker for infection, were found to be associated with ischaemic heart disease in a 13 year follow up of middle aged men in the Caerphilly cohort study.

Since the times of Jenner and Koch, the infections hypothesis for disease has influenced medical thinking and repeatedly re-emerged to challenge constitutional or lifestyle hypotheses. It was not long after the identification of *C pneumoniae* (then called TWAR) that links were drawn between infections with this organism and ischaemic heart disease, influenced perhaps by the recognised role of infections in the formerly more common rheumatic valve disease.[1]

The first reports were of case-control studies. Saikku et al reported increased concentrations of IgG and IgA antibodies to *C pneumoniae* associated with a fourfold increase in risk of myocardial infarction or angina combined.[2] A twofold increase was reported by Cook et al in a larger study,[3] and an overview suggested a pattern of significant association in case-control studies between markers of chronic infection with *C pneumoniae* and various manifestations of ischaemic heart disease (angina, electrocardiographic abnormali-

ties, coronary stenosis, unstable angina, or myocardial infarction).[4] There were fewer reports of cohort studies—the preferred methodology for examining association—and those suggested a weaker and non-significant association.[5 6] The present study is unusual in that it was undertaken retrospectively, which was possible because of the foresight of laying down stores of frozen plasma when the cohort was established.[7]

This study, in 70% of the original Caerphilly cohort, found that IgA antibodies, the marker for active or chronic infection with *C pneumoniae*, were significantly associated with prevalent ischaemic heart disease, fatal (but not non-fatal) myocardial infarction, and all cause mortality. In contrast with some previous reports,[4] the study found no association with IgG antibodies, a marker of any prior infection with *C pneumoniae* and thus more commonly present. Previous concerns over reproducibility of the microimmunofluorescence test, even in expert hands, were addressed by retesting 350 samples using other methods, but it is not clear whether the threshold of seropositivity for IgA antibodies was selected before or after analysis of outcomes. In general in cohort studies, it is preferable to measure exposure on more than one occasion in case it changes. IgA antibodies are a marker for active (or recent) as well as chronic infection and it may be that association with ischaemic heart disease was not found in Helsinki,[5] because the prevalence of antibody was unusually high owing to recent infection. If we accept that presence of these antibodies at one point in time is a marker for chronic *C pneumoniae* infection, the present study confirms an association between chronic infection and fatal myocardial infarction and total mortality. The only established risk factor for ischaemic heart disease to show association was viscosity and therefore statistical adjustment for most risk factors had little effect on the findings. After adjustment for risk factors including viscosity, however, the association with total mortality just failed to achieve statistical significance. One anomaly in the present study lies with the finding for non-fatal myocardial infarction, where seropositivity for IgA antibodies (chronic *C pneumoniae* infection) conferred a lower risk (relative risk for survivors 0.68) that almost balanced the increased risk for fatal myocardial infarction (1.60). This may simply be a statistical anomaly but it weakens the overall association. Pooling these findings with those of previous cohort studies[5 6] raises the likelihood of the association with fatal myocardial infarction being real.

Association is not causation and, as both *C pneumoniae* infection and atherosclerosis have early origins, chronic *C pneumoniae* infection could be an "innocent bystander." *C pneumoniae* is, however, commonly found in monocytes and macrophages within atheromatous plaque, but not in circulating monocytes, implying that plaque somehow attracts or facilitates multiplication of *C pneumoniae* within macrophages.[8] The presence of macrophages implies an inflammatory response, and it is recognised that inflammatory changes could weaken the plaque cap predisposing it to rupture and thrombosis.[9] These mechanisms could underlie a role for chronic *C pneumoniae* infection in precipitating acute coronary events and in the stepwise progression towards coronary stenosis consequent upon incorporation of thrombi. The Caerphilly study must be counted among those supporting an association between *C pneumoniae* infection and clinical ischaemic heart disease but more persuasive evidence for a causal explanation lies with clinical trials. Early results of a trial of roxithromycin in 202 patients with established heart disease reported no events on treatment compared with two cases of myocardial infarction and two deaths among patients on placebo.[10]

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Corrections and clarifications

Only half of GPs in study knew that advance directives carry legal force in UK
This letter by Kevin Stewart and colleagues (9 January 1999, p 123) wrongly referred to the Sidaway case when making the point that patients detained under the Mental Health Act can make a valid directive concerning treatment that is not covered by the terms of their detention. A more suitable reference would have been to Re C. (Adult: Refusal of Treatment) [1994] 1 All ER 819.

When I use a word: Homogenous/homogeneous
A typesetting error in this article by Jeff Aronson (6 February 1999, p 376) led to the Greek letter υ (upsilon) being wrongly used instead of ν (nu) in several words such as γένεσις (genesis) and γένος (genos).

Communicating risk reductions
Because of an editorial error, the letter by D J Galton and M Seed (27 February 1999, pp 602-3) stated that statins act through "powerful inhibition of the enzyme 3-hydroxy-3-methylglutamyl coenzyme A reductase." This should have read "the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase."