

Chlamydia pneumoniae Serology, Lung Function Decline, and Treatment for Respiratory Disease

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Associations have been reported between *Chlamydia pneumoniae* seropositivity and both acute and chronic obstructive airway diseases. Plasma specimens collected between 1979 and 1983 from 1,773 men 45 to 59 yr of age in Caerphilly, South Wales, were tested for IgG and IgA antibodies to *C. pneumoniae* (TW183) by microimmunofluorescence. Subsequent mortality and medication for obstructive airway disease were ascertained at 5-yr follow-up examinations. Spirometry was performed at the first and second examinations and analyzed both cross-sectionally and longitudinally; 642 men (36%) had IgG antibodies at a titer of 1:16 or above, of whom 362 also had detectable IgA antibodies. No statistically significant associations were found between either IgG titer or IgA titer and any of the outcome measures: inhaler therapy at entry; commencement of inhalers during follow-up; death from respiratory causes; baseline FEV₁, FVC, and FEV₁/FVC ratio; and decline in FEV₁ ($p > 0.1$ throughout). Men with high IgG titers ($\geq 1:64$) had a slower rate of decline of FEV₁ than did seronegative subjects (adjusted mean difference in 5-yr change in FEV₁: +22 ml, 95% confidence interval: -31 ml to +76 ml). Men with high IgA titers ($\geq 1:16$) had a slightly faster rate of decline (-12 ml, -96 ml to +71 ml). This first prospective assessment suggests that chronic *C. pneumoniae* infection is not a major risk factor for progressive airflow obstruction. Strachan DP, Carrington D, Mendall M, Butland BK, Yarnell JWG, Elwood P. *Chlamydia pneumoniae* serology, lung function decline and treatment for respiratory disease.

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Since it was first isolated in students with acute respiratory tract infection in 1986 (1), *Chlamydia pneumoniae* has become established as a cause of acute episodes of both upper and lower respiratory tract illness (2). Its association with chronic lung diseases is less certain (3). Some patients with acute exacerbations of asthma exhibit high or rising convalescent titers of IgG antibodies against *C. pneumoniae* (4-6), suggesting that acute infection or reinfection may trigger bronchospasm in susceptible patients. Other studies have failed to show serologic evidence of acute *C. pneumoniae* infection in exacerbations of asthma, but they have found elevated titers of antibodies to *C. pneumoniae* in chronic asthmatics (7, 8). About 5% of patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) have evidence of acute *C. pneumoniae* infection (9-11). However, the role of chronic, recurrent or persistent *C. pneumoniae* infection in COPD remains unclear. In one study, patients with COPD were no more likely to have IgG antibodies to *C. pneumoniae* than were pa-

tients of a similar age without respiratory disease (9), but such an association was found in another study (10). More recently IgA antibodies, a putative marker of chronic *C. pneumoniae* infection, have been associated with COPD (12), and the severity of this disease has been associated with chronic *C. pneumoniae* infection (13).

The studies to date have been based on case-series, with or without a control group. There has been no prospective investigation of *C. pneumoniae* serology in relation to indicators of COPD such as progressive airflow obstruction, clinical illness, and respiratory mortality. We have previously evaluated *C. pneumoniae* seropositivity as a predictor of ischemic heart disease and cardiovascular mortality among a population-based cohort of middle-aged men (14). We report here on the associations of *C. pneumoniae* antibody titers with lung function, treated airway disease, and mortality from respiratory causes in this cohort.

METHODS

The Caerphilly Prospective Heart Disease Study (15) recruited 2,512 men 45 to 59 yr of age in the Caerphilly area of South Wales between 1979 and 1983. After written consent and with approval of the local research ethics committee, a range of cardiovascular risk factors were measured, including standing height using a Holtain stadiometer. Socioeconomic status was classified according to the Registrar-General's social class of current occupation and father's occupation during childhood (16). Smoking history was ascertained by questionnaire, but, unfortunately, no information on chronic respiratory symptoms was obtained.

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TABLE 1
CHARACTERISTICS AT ENTRY OF MEN WITH AND WITHOUT *Chlamydia pneumoniae* SEROLOGY

	With Serology (n = 1,773)	Without Serology (n = 739)
Mean (SD)		
Age, yr	52.2 (4.6)	52.0 (4.6)
Height, mm	1,712 (65)	1,707 (64)
FEV ₁ , ml	2,750 (762)	2,758 (762)
FVC, ml	3,371 (778)	3,398 (781)
FEV ₁ /FVC, %	0.81 (0.11)	0.81 (0.11)
Percentage (n)		
Ever smoked, %	83 (1,469)	87 (640)
Current smoker, %	54 (962)	58 (425)
Manual occupation, %	67 (1,182)	66 (486)
Prevalent CNSLD, %	2.9 (52)	3.0 (22)

Definition of abbreviation: CNSLD = chronic nonspecific lung disease.

The sample has been followed at intervals of approximately 5 yr, and the fourth round of fieldwork (Phase IV) was completed between 1994 and 1997, an average of 13.7 yr (SD, 0.5 year) after the entry examination. Deaths were classified according to the ninth revision of the International Classification of Diseases (ICD9). In this study we analyzed deaths caused by respiratory illnesses (ICD9 460-519). The prevalence and incidence of obstructive airway disease was estimated from records of medication use that were obtained at each follow-up. Use of β-adrenergic or antimuscarinic bronchodilators, theophyllines, inhaled steroids, cromoglycate, or oxygen was considered evidence of treated airway disease. Because the clinical diagnosis was not recorded, we use the term “chronic nonspecific lung disease” (CNSLD) in this report to refer to subjects receiving one or more of these medications at entry to the study (“prevalent CNSLD”), or reporting such medication for the first time during the follow-up period (“incident CNSLD”).

At entry and 5 yr later, FEV₁ and FVC were measured using a McDermott dry spirometer in the standing position, without noseclips. The measurements were supervised on the first occasion by a physician, and on the second occasion by a nurse. At each examination the maximum value of each spirometric index was used for statistical analysis. Decline in FEV₁ was calculated as the difference between the maximum FEV₁ at entry and the maximum FEV₁ at the 5-yr follow-up, corrected for the interval between examinations. Spirometric measurements were not performed at later follow-ups.

Antibodies to *C. pneumoniae* were measured in plasma that had been stored at -20° C since collection at the entry (Phase I) examination. About one quarter of the specimens were missing because of previous seroepidemiologic studies on this cohort. All available specimens were tested for IgG antibodies to *C. pneumoniae* (TW183 strain) by microimmunofluorescence (MIF) at a dilution of 1:16. Those specimens that were positive at 1:16 were also tested for IgG at dilutions of 1:32 and 1:64, and for IgA antibodies at a dilution of 1:16. Weakly positive reactions at 1:16 were considered “trace positives.” Specimens were available for 1,794 men, but 21 were excluded from the analysis because of the presence of cross-reacting antibodies to *Chlamydia trachomatis* or *Chlamydia psittaci*. Results are thus presented for 1,773 men (71% of the cohort).

Statistical analysis was performed using STATA (17). IgG titer was analyzed as six categories (undetectable, trace, 1:16, 1:32, 1:64, > 1:64) and IgA titer as three categories (undetectable, trace, ≥ 1:16). Samples with IgG titer less than 1:16 (which were not tested for IgA) were considered to have undetectable IgA. The association of seropositivity with prevalent treated CNSLD, incident treated CNSLD, and respiratory mortality was analyzed by tabulations and tests of linear trend in proportions across categories of *C. pneumoniae* antibody titer. Adjustment for potential confounding effects (Table 3) utilized multiple logistic regression models, which included as covariates: age at entry, smoking habit (six categories), own social class (six categories plus unknown) and father’s social class (four categories plus unknown).

The unadjusted relations of *C. pneumoniae* seropositivity to levels of ventilatory function measured at entry, and to 5-yr decline in FEV₁, were analyzed by tabulation and comparisons of means. Multiple regression models were used in Table 5 to evaluate the association of *C. pneumoniae* antibody titers with spirometric indices before and after adjustment for age (linear and quadratic terms), height (linear and quadratic terms), smoking habit (six categories), own social class (six categories plus unknown), and father’s social class (five categories plus unknown). In addition, models with FEV₁ change as the outcome variable included as a covariate the average of the FEV₁ measurements contributing to the change.

RESULTS

The characteristics of men with and without serologic measurements are compared in Table 1. The 1,773 subjects with serology were of similar age, height, smoking habit, and socioeconomic status at entry as the 739 men with cross-reacting seropositivity or no available specimen. The two groups were also similar for baseline lung function and prevalent CNSLD (Table 1).

TABLE 2
NUMBER AND PERCENTAGES OF CASES OF PREVALENT CNSLD, INCIDENT CNSLD, AND RESPIRATORY DEATHS BY *C. pneumoniae* IgG AND IgA TITERS

	Men (n)	Smoking		Mean Age at Entry	Prevalent CNSLD*		Incident CNSLD [†]		Respiratory Deaths	
		Ever (%)	At Entry (%)		(%)	(n/N)	(%)	(n/N)	(%)	(n/N)
IgG										
Zero	821	82	54	52	2.6 (21/821)	10.4 (52/498)	0.61 (5/821)			
Trace	310	85	55	52	2.6 (8/310)	16.0 (29/181)	0.97 (3/310)			
1:16/1:32	268	83	58	53	3.7 (10/268)	10.3 (16/155)	1.49 (4/268)			
≥ 1:64	374	84	52	52	3.5 (13/374)	12.2 (28/230)	0.80 (3/374)			
Test for trend [‡]					p = 0.45	p = 0.77	p = 0.56			
IgA										
Zero [§]	1,411	83	54	52	2.6 (37/1,411)	11.4 (97/853)	0.78 (11/1,411)			
Trace	255	85	55	53	3.9 (10/255)	11.5 (17/148)	1.18 (3/255)			
≥ 1:16	107	85	55	52	4.7 (5/107)	17.5 (11/63)	0.93 (1/107)			
Test for trend					p = 0.12	p = 0.24	p = 0.63			

For definition of abbreviation, see Table 1.

* Using bronchodilator, inhaled steroid, cromoglycate, or oxygen therapy at entry.

[†] Men without prevalent CNSLD at entry who reported inhaled therapy at second, third, or fourth examination: restricted to 1,087 subjects with complete follow-up.

[‡] Chi-square test for trend across six categories: zero, trace, 1:16, 1:32, 1:64, > 1:64.

[§] Includes specimens with IgG titer less than 1:16, not tested for IgA.

TABLE 3

ODDS RATIOS* FOR PREVALENT AND INCIDENT CNSLD BY *C. pneumoniae* IgG AND IgA TITERS, AFTER ADJUSTMENT FOR AGE, SMOKING, AND SOCIOECONOMIC FACTORS

	Prevalent CNSLD [†]	Incident CNSLD [‡]
	(Odds ratio) (95% CI)	(Odds ratio) (95% CI)
IgG		
Zero	1.00 (reference)	1.00 (reference)
Trace	0.96 (0.41–2.22)	1.54 (0.92–2.56)
1:16/1:32	1.37 (0.62–3.02)	0.96 (0.52–1.77)
≥ 1:64	1.26 (0.61–2.58)	1.20 (0.73–1.99)
Test for trend [§]	p = 0.62	p = 0.75
IgA		
Zero	1.00 (reference)	1.00 (reference)
Trace	1.37 (0.67–2.83)	1.04 (0.59–1.83)
≥ 1:16	1.74 (0.65–4.66)	1.70 (0.83–3.48)
Test for trend	p = 0.21	p = 0.23

For definition of abbreviation, see Table 1.

* All odds ratios are adjusted for age, smoking history, own social class, and father's social class. Data are too sparse to present an adjusted analysis of the 18 respiratory deaths.

[†] Using bronchodilator, inhaled steroid, cromoglycate, or oxygen therapy at entry.

[‡] Men without prevalent CNSLD at entry who reported inhaled therapy at second, third, or fourth examination: restricted to 1,087 subjects with complete follow-up.

[§] Chi-square test for trend across six categories: zero, trace, 1:16, 1:32, 1:64, > 1:64.

^{||} Includes specimens with IgG titer less than 1:16, not tested for IgA.

Circulating IgG antibodies against *C. pneumoniae* at a titer of 1:16 or above were detected in 642 (36%) of the 1,773 men. Among these 642 men, 107 (6% of all men) also had IgA antibodies at a titer of ≥ 1:16, and 255 (14% of all men) had a detectable trace of IgA; 280 men (16% of the total) had no detectable IgA, but IgG antibodies were clearly detectable at a dilution of 1:16. IgA antibodies were not tested and presumed to be absent for 821 (46%) men with undetectable IgG and 310 (17%) with a trace of IgG antibodies.

There were 18 respiratory deaths among the 1,773 men during the 13.5 yr follow-up period. These included one coded as pneumonia (ICD9: 486), three as chronic bronchitis (ICD9: 491), two as emphysema (ICD9: 492), two as asthma (ICD9: 493), and seven as chronic airway obstruction (ICD9: 496). Two deaths coded as pneumoconiosis (ICD9: 500) and one as

idiopathic fibrosing alveolitis (ICD9: 516.3) were not considered further in relation to chlamydial serology.

The relations of *C. pneumoniae* IgG and IgA titers to age, smoking history, and respiratory death rate as shown in Table 2. There was no clear relationship of respiratory death rate with either IgG or IgA titer. These patterns were not strongly confounded by age and there were no substantial differences in smoking habits across groups defined by *C. pneumoniae* IgG or IgA titers.

Also shown in Table 2 is the association of *C. pneumoniae* IgG and IgA titers with use of inhaled bronchodilators, inhaled steroids, cromoglycate, or oxygen therapy at entry (prevalent CNSLD) and new reports of such therapy at the second, third, or fourth examinations (incident CNSLD). The analysis of incident disease is restricted to 1,064 subjects who attended all four examinations and reported none of the inhaled medications at entry. The prevalence of treated CNSLD at entry was higher in men with higher IgG or IgA titers, although in neither case was the trend statistically significant. In contrast to the pattern of respiratory mortality, the incidence of treated CNSLD was more strongly related to IgA titer than to IgG titer, although neither trend was statistically significant. Similar patterns emerged after adjustment for age, smoking history, and socioeconomic status (Table 3).

Baseline lung function was related (cross-sectionally) to prevalent CNSLD at entry. For instance, mean FEV₁ was 1,256 ml (95% CI, 1,079 to 1,433 ml) lower in the treated group, and mean FEV₁/FVC ratio was 13 (10 to 17) percentage points lower in that group. Longitudinally, there was a nonsignificantly faster rate of decline in FEV₁ among those in the group who developed incident CNSLD: 60 ml (95% CI, -6 to 126 ml) greater decline over the first 5 yr, compared with men without incident CNSLD.

The relationship of *C. pneumoniae* IgG and IgA titers to measures of ventilatory function at the entry examination and to change in FEV₁ over the first 5 yr of follow-up are shown in Table 4. Baseline spirometry was performed by 1,703 (96%) of the 1,773 men with serologic data, of whom 1,503 provided three acceptable spirograms. Measures of change in FEV₁ were available for 1,315 men (74% of 1,773). There were no statistically significant correlations between *C. pneumoniae* antibody titers and any of the unadjusted measures of ventila-

TABLE 4
UNADJUSTED SPIROMETRIC INDICES AT ENTRY AND DURING 5 yr OF FOLLOW-UP, BY *C. pneumoniae* IgG and IgA ANTIBODY TITERS

	Entry Examination						Five-year Follow-up			
	Subjects Tested (n)	FEV ₁ (ml)		FVC (ml)		FEV ₁ /FVC		Subjects Tested (n)	dFEV ₁ (ml)*	
		Mean	(SD)	Mean	(SD)	Mean	(SD)		Mean	(SD)
IgG										
Zero	784	2,777	(727)	3,397	(744)	0.813	(0.102)	610	-16	(377)
Trace	304	2,723	(819)	3,338	(852)	0.808	(0.105)	241	-11	(388)
1:16/1:32	257	2,715	(752)	3,324	(787)	0.811	(0.105)	188	-1	(324)
≥ 1:64	358	2,739	(794)	3,377	(778)	0.803	(0.124)	276	+8	(408)
Test for trend [†]		p = 0.25		p = 0.41		p = 0.18			p = 0.21	
IgA										
Zero [‡]	1,357	2,759	(754)	3,380	(772)	0.811	(0.106)	1,056	-5	(375)
Trace	241	2,725	(801)	3,340	(804)	0.808	(0.115)	175	-19	(375)
≥ 1:64	105	2,690	(775)	3,327	(790)	0.800	(0.119)	84	-17	(431)
Test for trend		p = 0.29		p = 0.35		p = 0.33			p = 0.64	

* Maximum FEV₁ at 5-yr examination minus maximum FEV₁ at entry, corrected for the interval between tests, and restricted to 1,315 men attending both examinations.

[†] Chi-square test for trend across six categories: zero, trace, 1:16, 1:32, 1:64, > 1:64.

[‡] Includes specimens with IgG titer less than 1:16, not tested for IgA.

TABLE 5
FEV₁ AT ENTRY AND CHANGE IN FEV₁ DURING 5 yr OF
FOLLOW-UP BY *C. pneumoniae* IgG AND IgA TITERS,
AFTER ADJUSTMENT FOR OTHER RISK FACTORS*

	FEV ₁ at Entry (ml) [†]	FEV ₁ Change (ml) [†]
	Difference (95% CI)	Difference (95% CI)
IgG		
Zero	0 (reference)	0 (reference)
Trace	+2 (-84-+88)	0 (-56-+57)
1:16/1:32	-23 (-115-+69)	+19 (-43-+81)
≥ 1:64	-21 (-102-+61)	+22 (-31-+76)
Test for trend [§]	p = 0.37	p = 0.22
IgA		
Zero	0 (reference)	0 (reference)
Trace	-3 (-92-+86)	-11 (-72-+50)
≥ 1:16	-65 (-193-+63)	-12 (-96-+71)
Test for trend	p = 0.41	p = 0.68

* All results are adjusted for age, height, smoking habit, own social class, and father's social class.

[†] Model restricted to 1,669 men with information on all covariates.

[‡] Maximum FEV₁ at 5-year examination minus maximum FEV₁ at entry, corrected for interval between tests, and restricted to 1,290 men attending both examinations with complete covariate information.

[§] Chi-square test for trend across six categories: zero, trace, 1:16, 1:32, 1:64, > 1:64.

^{||} Includes specimens with IgG titer less than 1:16, not tested for IgA.

tory function shown in Table 4, and the differences between group means were generally small.

The results of multiple regression models with, in turn, baseline FEV₁ and change in FEV₁ as the outcome variable are shown in Table 5. The patterns shown in the unadjusted data are not altered greatly by adjustment for age, height, average level of FEV₁, smoking history, or socioeconomic factors. Men with high IgG titers experienced a slower rate of decline in FEV₁ during the 5 yr of follow-up than did those with no detectable *C. pneumoniae* IgG antibodies, whereas the opposite appeared to be the case for IgA titers. Again, none of the trends or group comparisons are statistically significant.

DISCUSSION

This is the first study to relate serologic markers of *C. pneumoniae* infection prospectively to prevalent, incident, and fatal respiratory disease. It is also the largest population sample to date that has been assessed for both IgG and IgA antibodies to *C. pneumoniae*. Nevertheless, our study has limited statistical power to evaluate rare outcomes such as respiratory mortality. Cross-sectional associations with continuous outcome measures such as spirometric indices can be assessed with much greater confidence. The effects of *C. pneumoniae* infection on lung function decline are somewhat less precisely measured because 5 yr is a rather short period during which to monitor long-term progression of airflow obstruction.

Serologic markers of *C. pneumoniae* infection at a single time point can be difficult to interpret, particularly if there have been local outbreaks of *C. pneumoniae* infection shortly beforehand. Reinfection or reactivation of chlamydial infection is followed by elevated IgG antibody levels that persist for months or years, whereas IgA levels decay much more rapidly. For this reason, IgA antibodies are considered a more reliable marker of chronic chlamydial infection. It is unlikely that the antibody titers in our study were influenced to any great extent by recent epidemics because during the years 1980 to 1982, when 90% of our subjects were recruited, the prevalence of elevated IgG titers and detectable IgA antibodies remained consistently low (ranging from 18 to 23% for detectable IgA).

We therefore believe that the IgA we detected reflects an immune response to chronic *C. pneumoniae* infection.

Smoking has been proposed as a potential confounder in epidemiologic studies of *C. pneumoniae* infection (18, 19). In common with another large prospective study (20), we found no evidence of any association of current smoking habit with either IgG or IgA titer. Associations with age and socioeconomic status were weak or nonexistent (14). Results from adjusted and unadjusted analyses of prevalent and incident CNSLD were generally similar. For these reasons, we consider it unlikely that our findings are substantially affected by confounding from these major risk factors for chronic respiratory disease.

Our study has greatest power to detect associations of *C. pneumoniae* with lung function indices. Cross-sectionally, the relationships were weak and unlikely to be of clinical or epidemiologic significance. The rate of decline of FEV₁ among men with the highest IgG titers was about 4 ml/yr slower compared with men with undetectable *C. pneumoniae* titers. This is the opposite of what might be expected if repeated episodes of this infection were implicated in the etiology of COPD. The association of FEV₁ decline with detectable IgA antibodies was in the "correct" direction, but the estimated effects were very weak (an extra 2 ml/yr loss in men with detectable IgA, with wide 95% confidence intervals).

Previous studies based on patients with COPD have reported inconsistent results, with one finding no association of COPD with *C. pneumoniae* IgG antibodies (9), one showing an association with IgG titer (10) and a third reporting an association with IgA titer, but not with IgG seropositivity (12). Elevated IgG titers have also been found among younger adults (mean age, 36 yr) with chronic asthma (8). Our results for prevalent and incident CNSLD are based on use by middle-aged men of medications that are relatively specific for asthma, chronic bronchitis, emphysema or COPD rather than clinical diagnoses. They are more consistent with an association of COPD with IgA antibodies than with IgG titer, although neither association is statistically significant. On the other hand, we cannot exclude a threefold increase in risk of chronic respiratory disease among the small proportion of men with high IgA titers (≥ 1:16). Future studies of *C. pneumoniae* serology in patients with airflow obstruction should assess both IgG and IgA antibodies.

Although there were too few incident cases to draw direct conclusions from this cohort regarding the association of *C. pneumoniae* infection with clinically severe COPD and related mortality, our cross-sectional and longitudinal spirometric findings suggest that chronic *C. pneumoniae* infection is unlikely to be a strong risk factor for impaired lung function in British adults. We therefore consider it unlikely that repeated or persistent episodes of *C. pneumoniae* infection play a major role in the development of progressive airflow obstruction, which is the main cause of death and disability from chronic obstructive pulmonary disease. However, our study did not evaluate how often acute *C. pneumoniae* infection is responsible for short-term exacerbations of COPD (9-11), or the possibility that these acute episodes may account for some respiratory deaths.

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