

## *Chlamydia pneumoniae* and asthma

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### Abstract

**Background**—This study was designed to test the association of *Chlamydia pneumoniae* infection with asthma in a multi-racial population, after adjustments for several potential confounding variables.

**Methods**—Antibodies to *C pneumoniae* were measured by microimmunofluorescence in 123 patients with acute asthma, 1518 control subjects admitted to the same hospital with various non-cardiovascular, non-pulmonary disorders, and 46 patients with severe chronic asthma, including some with “brittle” asthma. Acute infection or reinfection was defined by titres of IgG of  $\geq 512$  or IgM  $\geq 8$  or a fourfold rise in IgG, and previous infection by IgG 64–256 or IgA  $\geq 8$ . Logistic regression was used to control for likely confounders, including ethnic origin, age, sex, smoking habit, steroid medication, diabetes mellitus and social deprivation, on antibody levels.

**Results**—Antibody titres consistent with acute *C pneumoniae* infection were found in 5.7% of patients with acute asthma and 5.7% of control patients, while 14.6% of patients with acute asthma and 12.7% of control patients had titres suggesting previous infection. These two groups did not differ significantly. However, titres suggesting previous infection were found in 34.8% of patients with severe chronic asthma: the difference between this group and the control group was statistically significant with an adjusted odds ratio of 3.99 (95% confidence interval 1.60 to 9.97).

**Conclusions**—These data raise important questions about the previously demonstrated association of *C pneumoniae* infection with asthma, and suggest that future studies of this association should give particular attention to the presence or absence of a history of severe chronic asthma.

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Keywords: *Chlamydia pneumoniae*; serology; asthma

*Chlamydia pneumoniae*, previously designated the TWAR agent, was first described in 1986.<sup>1</sup> Serological studies indicate that it is one of the most prevalent infectious agents worldwide<sup>2–4</sup> with a wide range of clinical manifestations including pneumonia,<sup>5</sup> exacerbations of chronic obstructive pulmonary disease,<sup>6</sup> and chronic asthma.<sup>7</sup> There is also evidence that coronary and cerebral vascular disease are associated with serological evidence of this infection.<sup>8</sup>

This study was designed to test the association of *C pneumoniae* infection with asthma in

a hospital serving the multiracial inner city population of north and west Birmingham, UK, adjusting for several potential confounding variables.

### Methods

#### STUDY SUBJECTS AND INVESTIGATIONS

Approval for this project was obtained from the hospital ethical committees at the City and Heartlands Hospitals, Dudley Road, Birmingham. All subjects gave informed consent to participation.

#### Hospital admissions (acute asthma and controls)

Patients with acute asthma and control subjects were admitted to Birmingham City Hospital via the Accident and Emergency Department. All patients were initially considered to be eligible; recruitment was prospective and continued at a steady rate so that those who were eventually included in the study were admitted consecutively throughout a 24 month period (March 1993 to March 1995). Exclusion criteria were known or suspected immunodeficiency, hypergammaglobulinaemia, connective tissue disease, and other autoimmune disease.

Patients with acute asthma were recruited on the basis of episodes of wheezing requiring immediate treatment with nebulised bronchodilators, on which all showed rapid clinical improvement. Further requirements for inclusion in this group were the absence of chronic bronchitis or emphysema (either from the patient's testimony or from the hospital case records) and the absence of a history of chronic sputum production. Where the responsible physician was in doubt about the diagnoses of asthma, the patient underwent formal measurements of forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC), and peak expiratory flow (PEF); the criteria for inclusion were then FEV<sub>1</sub>/FVC ratio  $< 0.7$  with an improvement of  $\geq 15\%$  in FEV<sub>1</sub>, FVC, or PEF (or 0.2 litre in FEV<sub>1</sub> alone) after nebulised  $\beta_2$  agonist. Cases in which the diagnosis was uncertain, or which were complicated by active cardiovascular disease, were excluded from the study. Control subjects were selected randomly from all admissions to the Accident and Emergency Department with acute non-pulmonary, non-cardiovascular disorders, provided that there was no evidence of coexisting active cardiac, vascular, or pulmonary disease; thus there is no reason to suspect that they were predisposed to acquire *C pneumoniae* infection.

Blood was taken from the patients with acute asthma and controls by the admitting physician on arrival in hospital (or within 12–24 hours where immediate venepuncture was impossible). All patients were asked to attend the out-

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Table 1 Demographic characteristics of acute asthma, chronic asthma, and control groups

	Acute asthma (n=123)	Chronic asthma (n=46)	Controls (n=1518)
Ethnic origin			
Caucasian	67 (54.5%)	45 (97.8%)	1061 (69.9%)
Asian	39 (31.7%)	0	290 (19.1%)
Afro-Caribbean	17 (13.8%)	1 (2.2%)	167 (11.0%)
Age (years)			
Range	16–82	15–62	16–88
Mean (SD)	45.5 (16.2)	36.2 (11.4)	56.5 (18.0)
Sex			
Male	47 (38.2%)	14 (30.4%)	844 (55.6%)
Female	76 (61.8%)	32 (69.6%)	674 (44.4%)
Mean (SD) Townsend score	5.1 (3.1)	1.1 (3.8)	4.6 (3.5)
Smoking habit			
Current	27 (22.0%)	13 (28.3%)	448 (29.5%)
Previous (>3 months)	12 (9.8%)	6 (13.0%)	264 (17.4%)
Never	82 (66.6%)	21 (45.7%)	689 (45.4%)
Steroid use			
Inhaled only	44 (35.8%)	43 (93.5%)	61 (4.0%)
Systemic	25 (20.3%)	3 (6.5%)	52 (3.4%)
None	53 (43.1%)	0	1393 (91.8%)
Diabetes mellitus			
Insulin dependent	1 (0.8%)	NA	54 (3.6%)
Non-insulin dependent	10 (8.1%)	NA	86 (5.7%)
Unknown	10 (8.1%)	NA	58 (3.8%)

NA = not available.

patients' department 2–3 months after discharge for convalescent blood sampling. Demographic characteristics, medical history, smoking habit, drug therapy, and physical signs were recorded by the admitting medical staff; ethnic origin, smoking habit, and use of steroid medication were later confirmed by postal questionnaires. Townsend scores of socioeconomic deprivation were assigned to those subjects who lived in the West Midlands conurbation by linking postcode sectors to census enumeration districts.

#### Outpatients (severe chronic asthma)

In an attempt to compare patients with acute and severe chronic asthma, *C pneumoniae* antibody titres were measured in outpatients, all of whom were regularly attending asthma clinics at a neighbouring hospital (also serving the North Birmingham Health District) for type 1 or type 2 "brittle" asthma, or stable severe chronic asthma on high dose inhaled steroids (without wide PEF variability and therefore not meeting the criteria for diagnoses of "brittle" asthma). For type 1 "brittle" asthma these criteria were  $\geq 40\%$  daily variation in PEF (measured by the patient) for  $\geq 50\%$  of the time over a period of at least 150 days on high dose inhaled steroids. For type 2 "brittle" asthma the criteria were two or more life threatening exacerbations of otherwise stable asthma resulting in loss of consciousness, or type II respiratory failure with onset over less than 30 minutes and recovery within four hours of admission to hospital, despite intensive bronchodilator and steroid therapy. Blood samples were taken at routine outpatient appointments. Subjects were recruited to this part of the study during a 30 month period (March 1991 to September 1993).

Information on the presence of diabetes mellitus was not available for patients with chronic asthma. This potential confounding variable was therefore not included in the logistic regression analysis.

#### SEROLOGICAL TESTING

For each subject 2–5 ml of serum was obtained by centrifugation within six hours and stored at  $-20^{\circ}\text{C}$  until analysis; testing of serum samples obtained on admission and during convalescence was deferred until both specimens were available. Each blood sample was labelled only with a serial number so the investigator was blind to all patient data at the time of testing and remained so until statistical analysis of the results.

Serum samples were tested by one investigator (PC) using Maxiscreen *Chlamydia* microimmunofluorescence (MIF) slides (IO International Ltd, London, UK) and FITC conjugated anti-human immunoglobulins. Only an even pattern of elementary body fluorescence was regarded as positive. In every batch of slides tested two control serum preparations known to be positive for this organism and two negative controls were each applied to two slides. All serum samples were screened at a dilution of 1:8; thereafter, positive samples were tested at dilutions of 1:8 to 1:1024.

Acute infection or reinfection just prior to entry into the study was presumed to be indicated by titres of IgG  $\geq 512$ , IgM  $\geq 8$  or, in patients who provided convalescent samples, IgG rising fourfold between initial and convalescent sampling. Titres indicating previous infection without recrudescence were presumed to be IgG 64–256 or IgA  $\geq 8$  provided that IgM could not be detected and there was no significant rise in IgG. Because patients with chronic asthma were not acutely ill when blood samples were taken, we did not expect to find evidence of acute *C pneumoniae* (re)infection and were primarily interested in comparing frequencies of previous infection in this group.

Rheumatoid factor was assayed in patients in whom connective tissue diseases were suspected on clinical grounds despite insufficient evidence to exclude them from the study. *C pneumoniae* IgM antibodies were discounted for serological classification where it was present because of its non-specific IgM reactivity.

#### ANALYSIS OF DATA

The raw frequencies of acute (re)infection and previous infection were compared in patients with acute asthma, chronic asthma, and controls by simple univariate analyses using  $\chi^2$  tests. A logistic regression modelling method, as implemented in the EGRET statistical package, was used to explore possible influences of broad ethnic origin (Caucasian, Asian or Afro-Caribbean), age ( $\pm 10$  years), sex, smoking habit (current or previous versus never), steroid use, and social deprivation on any association of antibody levels with asthma. Hence we derived odds ratios expressing the associations of acute asthma with acute *C pneumoniae* (re)infection and previous infection and of chronic asthma with previous infection, adjusted for potential confounding factors.

Table 2 IgG titres and serological classification of acute asthma, chronic asthma, and control groups

	Acute asthma (n=123)	Chronic asthma (n=46)	Controls (n=1518)
IgG titres			
Range	0–512	0–256	0–512
Median	0	16	0
Mean	24.3	33.7	19.6
Acute (re)infection	7 (5.7%)	2 (4.3%)	87 (5.7%)
Unadjusted odds ratio (95% CI)	1.02 (0.46 to 2.25)	1.02 (0.24 to 4.34)	1.00
Adjusted odds ratio (95% CI)	0.81 (0.32 to 2.05)	1.07 (0.13 to 8.65)	1.00
Previous infection	18 (14.6%)	16 (34.8%)	193 (12.7%)
Unadjusted odds ratio (95% CI)	1.18 (0.70 to 1.99)	3.66 (1.95 to 6.90)	1.00
Adjusted odds ratio (95% CI)	0.92 (0.49 to 1.70)	3.99 (1.60 to 9.97)	1.00
No infection	98 (79.7%)	28 (60.9%)	1238 (81.6%)

## Results

### STUDY SUBJECTS AND INVESTIGATIONS

Twenty seven patients with acute asthma and 312 potential controls were excluded from the study by the criteria stated above, and seven and 53 subjects, respectively, refused to participate. A total of 1687 patients were recruited and their demographic characteristics are shown in table 1; 123 (7.3%) had been admitted with acute asthma, in four of whom the responsible physicians were uncertain about the diagnosis and referred them for formal pulmonary function tests which confirmed the presence of asthma by the criteria stated above. Forty six (2.7%) were assigned to the chronic asthma group; 17 (four men) had type 1 “brittle” asthma, 11 (four men) had type 2 “brittle” asthma, and 18 (four men) were stable severe chronic asthmatics. Many of these patients had important co-morbidities including diabetes mellitus.

The remaining 1518 patients (90.0%) were assigned to the control group. In these patients the primary indications for admission to hospital were abdominal pain (n = 460) for which causes were established in 403 cases; chest pain not suggestive of myocardial ischaemia and for which no cause was found (n = 91); malignant disease (n = 85); fractures of various bones (n = 77); urinary obstruction (n = 64); complications of diabetes mellitus (n = 44); and other miscellaneous medical and surgical diagnoses (n = 697).

Approximately 4% of control patients were taking inhaled steroids at the time of admission to hospital. However, these patients had no evidence of active pulmonary disease and therefore lacked standard indications for inhaled steroids. Control patients who were taking systemic steroids all did so for non-pulmonary, non-cardiovascular diseases.

Twenty nine patients with acute asthma and 282 control patients (23.6% and 18.5%, respectively) attended for convalescent blood sampling within 160 days at a mean (SD) of 98.2 (37.6) days following admission. After 160 days the serum samples were no longer considered to be convalescent samples and they were discarded.

All patients known to have connective tissue or other autoimmune disease were excluded, after which there remained in the study 13 patients with acute asthma and 133 controls in whom connective tissue diseases were suspected on clinical grounds and who were therefore tested for the presence of rheumatoid factor. Where this test was positive (in four

patients with acute asthma and 24 controls) the finding of IgM antibodies was discounted for the diagnosis of acute *C pneumoniae* infection.

Acute infection was diagnosed solely on the basis of IgM titres in two patients with acute asthma and 30 controls, of whom both of the patients with acute asthma and 22 of the controls would otherwise have been defined by their IgG titres as previously infected. Eleven of the controls, but none of the patients with acute asthma, were older than 60 years and therefore were within the age group that has been associated with unsuspected rheumatoid factor production.<sup>9</sup>

### C PNEUMONIAE AND ACUTE ASTHMA

Immunoglobulin titres and serological classifications are shown in table 2. On  $\chi^2$  analysis there was no significant difference in the distributions of the three possible serological outcomes (acute (re)infection, previous infection, and no infection) between the acute asthma and control groups. The odds ratios for acute and previous *C pneumoniae* infection in patients with acute asthma compared with control subjects, unadjusted and adjusted by logistic regression for ethnic origin, sex, smoking habit, age and Townsend score, are shown in table 2 with 95% confidence intervals (CI). There was no evidence of an interaction between these potential confounding factors and acute asthma or *C pneumoniae* infection.

Ignoring IgM antibody titres from the 11 control patients over 60 years of age, not tested for rheumatoid factor, in whom we detected acute *C pneumoniae* infection solely on the basis of IgM would have made no difference to this lack of association between acute asthma and either acute *C pneumoniae* (re)infection or previous infection.

### C PNEUMONIAE AND SEVERE CHRONIC ASTHMA

The results from this group are also shown in table 2. Two of the patients with type 2 “brittle” asthma appear to have had acute (re)infection at or shortly before the time of sampling. On  $\chi^2$  analysis the distributions of the three possible serological outcomes (acute (re)infection, previous infection, and no infection) differed significantly between the patients with chronic asthma and controls ( $p < 0.05$ ), this difference being attributable to previous infection. There was no evidence of an interaction between the potential confounding factors and chronic asthma or *C pneumoniae* infection.

These numbers are too small to permit a rigorous comparison of the subgroups of chronic severe asthma.

## Discussion

### C PNEUMONIAE AND ASTHMA

Asthma is a chronic inflammatory disorder<sup>10</sup> in which eosinophils appear to play a major part, irrespective of the presence or absence of an atopic diathesis,<sup>11</sup> but the relevance of pulmonary infection to this condition remains uncertain.<sup>12</sup> Chronic infection with *C pneumoniae* has been documented<sup>13</sup> and, since chlamydial lung infections commonly cause wheezing,<sup>14</sup> it is plausible that chronic infection would produce a tendency to chronic asthma.

In a study of 365 adults with acute respiratory illness acute *C pneumoniae* infection was diagnosed serologically in 19 patients (5.2%), of whom nine (47.3%) reported wheezing.<sup>7</sup> A polyvalent *C pneumoniae* antibody titre of  $\geq 64$  conferred a high risk of wheezing, and there was a clear dose-response relationship between antibody titre and the presence of wheezing. Later diagnoses of asthmatic bronchitis were made within six months of the presenting illness in 29.6% of patients with antibody titres of  $\geq 64$  at recruitment, and in only 7% of matched controls ( $p < 0.05$ ). Antibodies to this organism were more likely to be found in adults with late onset asthma but no atopy (as judged by negative skin tests) than in those who were atopic or whose asthma started in childhood.<sup>15</sup>

Several other groups have also shown a serological association with this organism in chronic adult asthma.<sup>16-17</sup> Furthermore, population based longitudinal data from Helsinki suggest that increasing *C pneumoniae* seroprevalence is associated with increasing incidence of asthma attacks in all age groups.<sup>18</sup>

Our data support an association of previous *C pneumoniae* infection with severe chronic asthma in the absence of exacerbations. The lack of outpatient controls might be criticised, but the comparison with inpatients (for previous infection only) can be justified on the grounds that blood samples were taken from them within 24 hours of admission to hospital and there was therefore insufficient time to acquire any infections nosocomially. However, the number of patients with chronic asthma recruited to this study was small and further investigation is therefore warranted.

Our results do not support an association between *C pneumoniae* antibody titres and the incidence of acute asthma attacks. This is in agreement with a small study by Simon *et al.*<sup>19</sup> The apparent conflict with other studies<sup>7,16</sup> might be due to the small numbers of patients returning for convalescent blood sampling, or to the fact that the power of our study to detect such an association was limited by the relatively small number of subjects with acute asthma. However, in other studies it is not clear how many subjects had chronic asthma. In our study the 123 patients recruited to the acute asthma group included only 13 with documented reversible airflow obstruction prior to the onset of the presenting illness. It is possible

that an association between *C pneumoniae* infection and asthma was merely masked by the heterogeneity of this group. Furthermore, asthma is not a homogeneous condition and exacerbations may be provoked by a wide range of infectious and non-infectious factors. Any effect of *C pneumoniae* infection in promoting the development of asthma could therefore have been obscured by other factors, at least during the period of the study.

Strategies to take account of potential confounding variables are essential in studies of *C pneumoniae* antibodies, which have been associated with Afro-Caribbean origin,<sup>20</sup> the use of steroid medication,<sup>21</sup> increasing age,<sup>22</sup> and male sex.<sup>22</sup>

Few previous studies of *C pneumoniae* infection have addressed the smoking habits of the subjects.<sup>23</sup> However, smokers have in general a higher risk of respiratory infection than non-smokers.<sup>24,25</sup> Evidence that they may also be more susceptible to *C pneumoniae* infection was published in 1992.<sup>26,27</sup> A greater propensity among smokers to acquire *C pneumoniae* infection might create a spurious association between this infection and pulmonary disease. This hypothesis is supported by a reported association between smoking and seroconversion to *C pneumoniae* as detected by microimmunofluorescence.<sup>26,28</sup>

Socioeconomic deprivation must also be considered as a potential confounding variable. In the UK social deprivation is clearly correlated with overall morbidity<sup>29</sup> but not with asthma or chronic bronchitis. (Obstructive lung diseases may more readily be labelled "bronchitis" than "asthma" when they afflict people from lower socioeconomic groups.) Asthma is rare in developing countries<sup>30,31</sup> and less common in rural than in urban districts, so it might be considered a disease of affluence in such countries. In developed countries, where urban dwelling has no clear association with income, asthma appears to have a higher prevalence in towns. These observations suggest that environmental factors are more important than poverty.

Townsend scores, which include items that reflect predominantly personal and family income, may be considered to reflect the socioeconomic status of people living within a particular locality.<sup>32</sup> They include items that reflect predominantly personal and family income and were therefore considered to be superior to the Jarman score (developed as a predictor of the demand for primary medical care) for an assessment of the effects of living standards on health. In our study Townsend scores showed no correlation with asthma or with serological evidence of *C pneumoniae* infection.

By logistic regression analysis we found no noteworthy statistical interactions—that is, effect modifications in different subgroups—of ethnic origin, age, sex, steroid use, smoking habit, or Townsend score with the *C pneumoniae*/asthma associations. Furthermore, where data on diabetes mellitus were available—that is, in the acute asthma and

control groups—we detected no interaction with diabetes.

#### SEROLOGICAL TESTING

Various techniques are available to detect *C pneumoniae* antibodies.<sup>33</sup> The best and most widely used is the MIF assay which is sensitive and species-specific and reliably detects IgG, IgM, and IgA.<sup>34</sup> The kit which we used has been employed in several studies.<sup>2 35</sup>

Because only a small proportion of patients in each group gave convalescent serum samples within 160 days, the acute (re)infection rate ascertained by a fourfold rise in IgG should be considered to represent a minimum for each group. In a single serum specimen an IgG titre of  $\geq 512$  can also be interpreted as evidence of acute primary infection<sup>36</sup> or, particularly in older subjects, reinfection or recrudescence of chronic or latent infection.<sup>37</sup> IgG titres of  $\leq 256$  have generally been accepted (in a single serum specimen) as evidence of previous infection<sup>6</sup> provided that there are no IgM antibodies. Many authors have employed these serological criteria<sup>38–45</sup> and a large study combining serological data with an examination of pharyngeal swabs by polymerase chain reaction has provided evidence in support of them.<sup>46</sup> Our decision to include IgA is justified by evidence that it persists for more than three weeks in chronic infection.<sup>47 48</sup>

IgM is generally considered to signify acute primary infection.<sup>49</sup> A threshold titre of  $\geq 16$  has been proposed with titres of 8 indicating “probable acute infection”,<sup>40</sup> but we found no difference in the proportions of patients with IgM antibodies at these two titres in a large pilot study and therefore saw no merit in drawing a distinction between such low levels of antibody production. It has been suggested<sup>50</sup> that rheumatoid factor may make the measurement of IgM antibodies unreliable, particularly in elderly patients.<sup>9</sup> We therefore excluded from this study all patients known to have connective tissue or other autoimmune diseases and measured rheumatoid factor in a further 146 cases in which such diseases were considered less probable, discounting IgM antibodies in the 28 cases in which it was present. As shown above, ignoring IgM titres from the 11 remaining patients over 60 years of age would not have significantly altered the relationships of acute and chronic asthma to acute and chronic *C pneumoniae* infections.

We conclude that these data do not support an association between the seroprevalence of *C pneumoniae* in the general population and acute asthma, but they do suggest that there may be an association with severe chronic asthma. In future studies researchers should specify whether subjects were previously asthmatic (particularly whether they had “brittle” or other severe chronic asthma), and their ethnic origin and medication.

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## ***Chlamydia pneumoniae* and asthma**

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