Asthma, airways responsiveness and air pollution in two contrasting districts of northern England

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Abstract

Background **– To assess the possible magnitude of differences between normal populations an epidemiological investigation of asthma was conducted in two strongly contrasting districts of northern England – rural West Cumbria on the west coast and urban Newcastle upon Tyne on the east coast.**

Methods **– A cross sectional survey of randomly identified men aged 20–44 years was conducted in two phases: phase 1, a postal survey of respiratory symptoms and asthma medication in 3000 men from each district; and phase 2, a clinical assessment of 300 men from each district comprising investigator administered questionnaires, skin prick tests, spirometry, and methacholine challenge tests.**

Results **– The phase 1 (but not phase 2) study showed a small excess of "ever wheezed" in Newcastle (44% versus 40%), but neither phase showed differences between the two districts for recent wheeze or for other symptoms characteristic of asthma. There were also no differences with regard to diagnosed asthma, current asthma medication, spirometric parameters, or airways responsiveness. The prevalence of quantifiable airways responsiveness ($PD_{20} \leqslant 6400$ µg) was 27·7% in West Cumbria and 28·2% in Newcastle. Regression analyses showed that PD_{20} was negatively associated with atopy and positively with forced expiratory volume in one second (FEV_1); that an association between PD_{20} and current smoking could be explained by diminished FEV_1; and that PD_{20} was not related to geographical site of residence.**

Conclusions **– Neither airways responsiveness nor the other parameters of diagnostic relevance to asthma varied much between the two study populations, despite the apparent environmental differences. The most obvious of these were the levels of outdoor air pollution attributable to vehicle exhaust emissions, the ambient levels of which were 2–10 fold greater in Newcastle. Our findings consequently shed some doubt over the role of such pollution in perceived recent increases in asthma prevalence. It is possible, however, that an air pollution effect in Newcastle has been balanced by asthmagenic effects of other agents in West Cumbria.**

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Keywords: asthma, epidemiology, airways responsiveness, air pollution.

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There is concern at present over reported increases in asthma symptoms, diagnosis, medication, sickness absence, hospital admission, and death.[1–7] These apparent increases in morbidity and mortality have occurred despite advances in the understanding and management of the disease,[8 9] and despite diminishing morbidity and mortality from other diseases amenable to effective preventive and therapeutic intervention.[10] A plausible and popular explanation is that the incidence of asthma is increasing, though trends may have been exaggerated by changes in diagnostic fashion.[11]

Migration and twin studies have shown that asthma is largely an acquired disease determined by environmental factors.[12–14] A logical step towards their elucidation is standardised investigation of populations living under different environmental conditions. Although a number of studies in Britain have reported subjective and objective evidence of asthma prevalence, most have been restricted to single populations and few have used identical methods. Comparisons of prevalence between regions have consequently proved to be difficult, and controversy has arisen over the interpretation of geographical differences and recent time trends in the epidemiology of asthma.

The present investigation was devised to see if there were any differences in the prevalence of asthma in normal populations living in two health districts of the Northern Health Region of England. To provide the greatest opportunity for demonstrating differences several subjective and objective measures of asthma prevalence were included and two strongly contrasting districts – rural West Cumbria on the west coast and urban Newcastle upon Tyne on the east coast – were chosen. These geographical differences confer mild differences in temperature, rainfall, and prevailing wind, considerable differences in the levels of outdoor ambient air pollution from vehicle exhausts and, possibly, qualitative and quantitative differences in airborne aeroallergens. To avoid any confounding effects from sex we chose to study only men.

Methods

Geographical data were obtained from the Ordnance Survey and meteorological data from the Newcastle Meteorological Centre. Pollution data from West Cumbrian town centres were provided by Allerdale and Copeland borough councils. Pollution data from a central site in Newcastle were obtained from the Department of the Environment.[15]

PHASE 1

Phase 1 was a 1992 postal survey of 3000 men aged 20–44 years in each district randomly chosen from Family Health Service Authority (FHSA) registers (a 15% sample of those eligible in West Cumbria and 5% in Newcastle). It was anticipated that symptom prevalences would range between 5% and 40%, and that at least 1500 men in each district would respond. In such circumstances, phase 1 would have 80% power to detect a 5% difference in symptom prevalence at the 5% level of significance. A questionnaire based on the European Community Respiratory Health Survey (ECRHS) screening questionnaire was mailed up to a maximum of three times.[16] It sought demographic details and symptoms/treatment relevant to asthma. Evidence for response bias was sought by comparing replies to the three individual mailings. To clarify reasons for non-response, the names of occupants actually residing at the addresses of a random 10% sample of non-responders were determined by inspection of electoral rolls.

PHASE 2

Phase 2 was a detailed clinical assessment of a sample of phase 1 responders from each district. With an anticipated 30% prevalence of quantifiable airways responsiveness,[17] approximately 300 subjects would be required in each district to provide an 80% chance of detecting a 10% difference at a 5% level of significance. Randomly chosen responders to phase 1 were recruited by mail to participate in phase 2 until the required numbers were obtained. Phase 2 took place concurrently in both districts between October 1992 and March 1993, and comprised an interviewer administered questionnaire, skin prick tests using six common allergens, spirometric tests, and a methacholine challenge test. To clarify phase 2 response bias, responses to the phase 1 postal questionnaire were compared between phase 2 participants and phase 1 responders not invited to participate in phase 2. Socioeconomic and smoking characteristics of phase 2 participants were compared with national statistics.[18,19] Ethical approval was obtained from the West Cumbrian and the Newcastle ethics committees and all participants gave written informed consent.

The study design followed that of an earlier investigation of asthma in shipyard workers.[17] Details of the methods used for spirometric tests, skin prick tests, and methacholine challenge tests have been published previously.[17,20–22] Nebulised methacholine was administered in doubling cumulative doses over the range 3·125–6400 μg and airways responsiveness was expressed as a conventional PD_{20}. Using this methodology, PD_{20} values of <200 μg are almost always associated with active asthma, 200–1000 μg are sometimes associated with active asthma, and >1000 μg are very rarely associated with active asthma.[23]

DATA ANALYSIS

Statistical analyses utilised the STATA Release 3 statistical package (Computing Resource Center, Santa Monica, USA). Adjustment for phase 1 response bias used the method proposed by Drane which assumes linearly decreasing prevalences for those responding to the first, second, and third phase 1 mailings.[24] A linear regression model was fitted to the observed prevalences and the prevalences of non-responders were obtained by extrapolation, enabling adjustment of the observed prevalences for non-response. Phase 2 response bias was quantified by logistic regression of phase 2 participation against age, district of residence, and phase 1 questionnaire responses.

Logistic regression analyses of phase 2 questionnaire responses related the proportions of subjects with a positive response to a given question to age, district of residence, smoking history, social class, and atopic status. Regression analyses of airways responsiveness data related PD_{20} to district of residence, age, smoking habit, atopic status, and baseline ventilatory function as expressed by FEV_1. Regression of airways responsiveness is complicated by "right censoring" of PD_{20} values at the maximum quantifiable level (6400 μg methacholine using our protocol).[25] To utilise all the PD_{20} data we used two multiple regression techniques. Logistic regression assessed the probability of obtaining (i) a PD_{20} of $\leqslant$6400 μg (that is, a positive methacholine test), and (ii) PD_{20} $\leqslant$1000 μg (that is, airways responsiveness with which asthmatic symptoms are usually associated). Regression analysis for censored data used the log transformed values for PD_{20} with values of >6400 μg being identified as "right censored".[26]

Results

The West Cumbrian and Newcastle health districts comprise, respectively, approximately 1200 km^2 adjacent to the west coast and 112 km^2 adjacent to the east coast of northern England. The respective populations are 138 000 and 300 000. The West Cumbrian district is rural, two thirds being within the Lake District national park. Small towns are scattered down the extensive western coastal plain and the local economy depends on light industry, farming, tourism, and nuclear reprocessing. Traffic is spread over a large area with 237 000 vehicles registered in the administrative county of Cumbria (an average of 35/km^2). There is some concentration in the towns of Whitehaven and Workington. The city of Newcastle upon Tyne, and the Tyneside conurbation of which it is a part, is dependent economically on the service industries and light

Table 1 Demographic data for West Cumbria and Newcastle

	West Cumbria	*Newcastle*
Geographical location	West coast	East coast
Mean mid-day temperature	12·4°C	12·0°C
Annual rainfall (mm)	834	618
Predominant wind direction	From the sea	From the land
Locality	Dominantly rural	Urban
Annual average level of air pollutant*		
Nitrogen dioxide (ppb)	10	28
Sulphur dioxide (ppb)	6	7
Particulate PM_{10} ($\mu g/m^3$)	7	29

* West Cumbria, mean of 4–6 sites including Whitehaven and Workington. Newcastle, single site.

Table 2 Results of phase 1 postal questionnaires

	West Cumbria (n=1802)	*Newcastle (n=1368)*
Ever wheezed	39·9%	44·1%*
Woken wheezing, last year	8·1%	8·8%
Woken with chest tightness, last year	17·0%	18·8%
Woken by shortness of breath, last year	8·6%	9·8%
Woken by coughing, last year	23·0%	24·7%
Currently taking asthma medication	7·3%	6·9%

* p = 0·02 (χ^2 test).

Table 3 Socioeconomic characteristics of phase 2 subjects

Social class	*West Cumbrian men*		*Newcastle men*	
	Phase 2	*1991 census*	*Phase 2*	*1991 census*
I	11·4%	5·4%	8·7%	8·8%
II	17·1%	21·9%	26·1%	23·3%
III	53·0%	44·7%	42·3%	45·1%
IV	12·8%	20·3%	12·9%	15·8%
V	5·7%	7·7%	10·0%	7·0%

industry. It attracts a heavy burden of traffic into a small area and at present 353 000 vehicles are registered in the administrative county of Tyne and Wear (an average of 650/km²). Data from the Enhanced Urban Monitoring Initiative suggest that in 1992–3 Newcastle was one of the most polluted of British cities with respect to ambient and peak levels of nitrogen dioxide.[15] Environmental data are summarised in table 1.

PHASE 1

There were 1802 completed questionnaires from West Cumbria and 1368 from Newcastle – apparent response rates of 59% and 45%, respectively. Of the 10% samples of non-responders, only 31 of 112 (28%) in West Cumbria and 26 of 158 (16%) in Newcastle appeared to be living at the addresses to which the questionnaires were sent. We consequently estimate that 2134 questionnaires were delivered appropriately in West Cumbria and 1637 in Newcastle, implying that the true response rates were 84% (95% CI 81% to 89%) in West Cumbria and 84% (79% to 89%) in Newcastle. The mean (SD) age of West Cumbrian respondents was 32·3 (6·8) years and in Newcastle was 32·3 (7·0) years. Table 2 demonstrates that the only significant difference between the two districts was in the prevalence of those who had "ever wheezed", which was higher in Newcastle.

Inspection of symptom prevalences for the three mailings indicated that those from the first mailing were generally the highest and those from the second mailing the lowest. Extrapolation of these observed prevalences to assess response bias suggested that the true prevalences were 92–99% (mean 97%) of those recorded. Response bias was very similar in both districts.

PHASE 2

Recruitment to phase 2 from West Cumbria and Newcastle ceased when 298 and 310 men, respectively, had participated from those responding to the phase 1 study (response rates of 42% and 41%). The mean ages in West Cumbria and Newcastle were 34·1 (95% CI 33·3 to 34·8) and 33·1 (32·3 to 33·9) years which were not significantly different. Socioeconomic profiles (as defined by the Registrar General's classification[27]) were broadly similar (table 3), though the West Cumbrian participants were less closely representative of the parent population.[18]

Bias towards phase 2 participation was associated with increasing age (odds ratio 1·03 per year) and the presence of positive responses to the six phase 1 questions. The estimated prevalences of positive responses to each question among those not invited to participate were 71–96% (mean 80%) of those recorded by the phase 2 participants after allowing for the effect of age. There was no significant effect of district of residence and there were no interactions between district of residence and symptoms, indicating that similar response biases operated in the two districts.

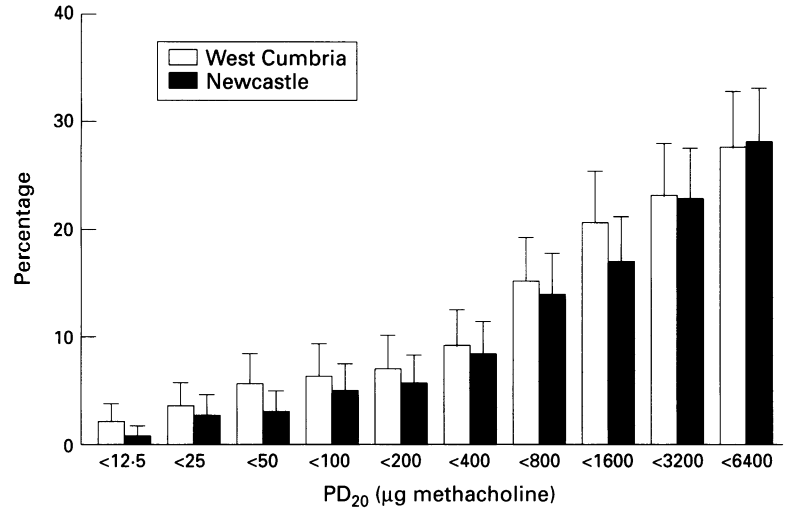
Questionnaires

There were no significant differences between the two districts in the prevalence of symptoms consistent with asthma, diagnosed asthma, and current use of asthma medication (table 4). The subjects from Newcastle had significantly more bronchitic syptoms (regular productive cough) than those from West Cumbria. The prevalence of bronchitic symptoms increased significantly across the social classes I–V, but this was the result of a confounding effect of smoking. Bronchitic symptoms were still more prevalent in Newcastle even after adjustment for age, former smoking, current smoking, and social class. There was no relation, however, between this subjective evidence for chronic

Table 4 Results of phase 2 questionnaire

Symptom	*West Cumbria (n=298)*	*Newcastle (n=310)*	*p*
Ever wheezed	45·3%	43·2%	NS
Wheezed in last year	32·1%	28·5%	NS
Woken wheezing, last year	13·5%	11·3%	NS
Woken with chest tightness, last year	12·0%	11·1%	NS
Woken by shortness of breath, last year	7·4%	7·2%	NS
Woken by coughing, last year	19·9%	23·6%	NS
Ever diagnosed asthmatic	13·0%	11·0%	NS
Medications for asthma, last year	11·5%	9·1%	NS
Usually cough on winter mornings	13·9%	24·5%	<0·01
Usually produce phlegm on winter mornings	14·0%	26·6%	<0·01
Usually cough during rest of day in winter	8·6%	16·5%	<0·001
Usually produce phlegm rest of day in winter	8·2%	21·4%	<0·001

Percentages are given because a few subjects responded "don't know" to some questions.



Cumulative distribution of PD_{20} measurements (with 95% confidence intervals).

bronchitis and the levels of air pollution measured by separate monitoring stations in either West Cumbria or Newcastle.

Men from West Cumbria were less likely to have ever smoked (45·3%) than those from Newcastle (56·5%; p=0·01), but there was no significant difference in the proportion of current smokers (24·5% versus 28·1%), nor in pack year consumption of current smokers (11·4 versus 12·8). The overall prevalence of current smoking of 26% was significantly lower than the 33% reported for 20–49 year olds in England and Wales,[19] suggesting that smokers were reluctant to participate.

Spirometric and skin prick tests

There were no significant differences between the districts in spirometric or prick test reactivity. Mean height was 1·77 m in both West Cumbria and Newcastle, mean FEV_1 was 4·20 l (101% predicted) and 4·28 l (103% predicted), respectively, and mean forced vital capacity (FVC) was 5·14 l (103% predicted) and 5·11 l (103% predicted). At least one positive prick test was obtained in 28·2% of West Cumbrian men and 28·4% of Newcastle men. Skin prick test reactivity was negatively associated with social class, 37·7% of class I, 34·9% of class II, 26·3% of class III, 25·6% of class IV, and 15·4% of class V having at least one positive test.

Airways responsiveness

In West Cumbria 285 men underwent methacholine tests and in Newcastle 302, the remaining 19 being unsuitable or unwilling. Positive tests ($PD_{20} \leqslant 6400$ µg) were obtained in 27·7% and 28·2%, respectively, the corresponding figures for $PD_{20} \leqslant 1000$ µg being 17·5% and 15·6%. There were no significant differences in the distribution of PD_{20} values (figure).

REGRESSION ANALYSES

Logistic regression indicated that the district of residence did not influence the prevalence of wheezing, chest tightness, nocturnal breathlessness, or nocturnal coughing symptoms. The results for wheezing symptoms are detailed in table 5. The symptoms "ever wheezed" and

Table 5 Phase 2: logistic regression analysis, proportion of subjects with wheezing symptoms

Covariate	Odds ratios (95% confidence interval)		
	Ever wheezed	Wheezed, last year	Woken wheezing, last year
West Cumbria vs Newcastle	1·23 (0·86 to 1·75)	1·27 (0·88 to 1·85)	1·15 (0·69 to 1·91)
Age (per year)	0·99 (0·97 to 1·03)	1·01 (0·98 to 1·04)	1·04 (0·99 to 1·08)
Social class, I–V (per class)	1·32* (1·10 to 1·58)	1·33* (1·10 to 1·61)	1·26 (0·98 to 1·63)
Ex-smoker vs never smoker	1·92* (1·23 to 3·01)	1·20 (0·73 to 1·98)	0·70 (0·35 to 1·39)
Current vs never smoker	3·76† (2·44 to 5·79)	3·03† (1·96 to 4·69)	1·05 (0·58 to 1·91)
Atopy (per positive allergen)	2·53† (1·94 to 3·30)	2·05† (1·61 to 2·61)	1·97† (1·50 to 2·59)

*p<0·01; †p<0·001.

Table 6 Logistic regression $PD_{20} \leqslant 6400$ µg and $PD_{20} \leqslant 1000$ µg and regression analysis for censored data, $\log_{10}$ (PD_{20})

Covariate	Odds ratio (95% confidence interval)		Regression coefficient (95% confidence interval)
	$PD_{20} \leqslant 6400$ µg	$PD_{20} \leqslant 1000$ µg	
West Cumbria vs Newcastle	1·00 (0·68 to 1·48)	1·22 (0·75 to 1·98)	−0·050 (−0·35 to 0·249)
Age (per year)	0·97 (0·94 to 1·00)	0·97 (0·94 to 1·00)	0·019 (−0·005 to 0·43)
Social class I–V (per class)	1·07 (0·87 to 1·32)	1·21 (0·93 to 1·56)	−0·088 (−0·246 to 0·07)
Current vs non-current smoking	1·53 (0·99 to 2·36)	1·40 (0·83 to 2·37)	−0·323 (−0·654 to 0·009)
Atopy (per positive allergen)	2·31* (1·79 to 2·99)	2·76* (2·08 to 3·67)	−0·765* (−0·951 to −0·578)
Baseline FEV_1 (per litre)	0·49* (0·36 to 0·66)	0·41* (0·28 to 0·60)	0·646* (0·414 to 0·879)
Constant			1·421

*p<0·001.

"wheezed in last year" were influenced by social class, smoking, and atopy. The more specific symptom of "nocturnal wheeze in the last year" was associated with atopy only.

For airways responsiveness, multiple logistic regression analysis and multiple regression analysis for censored data showed that PD_{20} was positively associated with baseline FEV_1 and negatively with atopic status (table 6). There was no hint of an association with district of residence. A highly significant negative association was found between PD_{20} and current smoking, but adjustment for baseline FEV_1 weakened the relationship to borderline significance, indicating that it resulted largely from the confounding influence of FEV_1. These findings are consistent with previous studies.[28–33] Airways responsiveness was not influenced by "former smoking". There were no significant associations between log (PD_{20}) and interactive terms combining age and smoking, age and atopic status, or smoking and atopic status.

Discussion

We were surprised by the degree of concordance from the various indicators used to assess the prevalence of asthma. These included the symptoms described by the participants themselves, the reported diagnoses (and prescribed medications) of their physicians, and the objective measurements of spirometry and airways responsiveness obtained in the study. Such concordance provides confidence for interpreting the results, particularly as the data were obtained by the same investigators in both districts using the same methods and the same equipment. Although response bias was evident in recruitment of the phase 1 and (particularly) the phase 2 participants, it was similar in both districts and consistent with previous studies.[34 35] We do not think it likely that bias exerted an important influence on the conclusion that there is no important difference between the two districts in the prevalence of asthma.

The absence of such a difference was unexpected because the two districts were chosen for their strongly contrasting environmental characteristics. This implies that the environmental differences were not of much relevance to asthma aetiology, or that relevant factors in one district were balanced by different factors of relevance in the other.

Most prominent among the environmental differences was the contrast between rural and urban settings, and in particular the levels of outdoor air pollution attributable to vehicle exhaust emissions. Although we did not quantify pollutant levels ourselves, contemporary regular monitoring was carried out in both districts for the two pollutants most dependent on vehicle emissions – nitrogen dioxide and small particulates. Both were measured in clear excess in Newcastle compared with West Cumbria, confirming a difference which is intuitively obvious. Current exposures are, of course, less relevant than the exposures that existed when asthma and airways hyperresponsiveness first began in these men, and some of them would not have lived in either district at the relevant time. However, experience with occupational asthma indicates that most affected workers first develop symptoms within one or two years after first exposure, and often within a few months. Furthermore, the mean periods of residence of the participants in West Cumbria and Newcastle were 28 and 25 years, respectively. An important asthmagenic effect attributable to vehicle emissions should consequently have caused an excess prevalence in Newcastle and been readily detectable from the investigation, since marked differences in vehicle use have existed between the two study districts throughout the lifetimes of all the participants.

Our findings consequently suggest that vehicle emissions may not be of major relevance to the aetiology of asthma unless a vehicle emission effect in Newcastle has been balanced by an equal effect from some other factor(s) in West Cumbria. Such a possibility is plausible, though it is not perhaps likely. Of the several other differences between the two districts and the two populations, those associated with climatic, vegetative, socioeconomic, recreational, and occupational variables were of mild or minor degree and hence of doubtful importance unless their effects were all exerted in the same direction. There was, for example, a mild but significant excess of dog keepers among the phase 2 men in West Cumbria, and these subjects were more likely to use rugs in their homes, to use coal or gas fires, and to have double glazing. However, the Newcastle men used gas cookers and gas boilers more commonly and, curiously, kept cats and dogs more commonly in childhood. These variables were not associated with any of the diagnostic parameters of asthma, and their inclusion in the regression analyses did not lead to the emergence of "residential district" as a factor significantly associated with asthma symptoms or airways responsiveness.

Differences in exposure to ozone are less easily dismissed, especially as comprehensive monitoring data were not available to compare the two districts. Ozone generation is greatly enhanced when air pollutants from industrial conurbations are slow to disperse because of atmospheric stagnation (stable high barometric pressure), and when there is excess ultraviolet radiation. The necessary conditions for photochemical interaction are particularly favoured when heavily polluted air drifts slowly to country districts of high altitude in summer, conditions which are relevant in West Cumbria. Within polluted cities themselves ozone levels tend to be lower because the production of nitric oxide readily leads to oxidation reactions with ozone, thereby increasing nitrogen dioxide levels but decreasing the levels of ozone. While these processes may have produced higher cumulative exposures to ozone in West Cumbria than in Newcastle, it should be recognised that exposure peaks occur only sporadically in country districts while excess vehicle emissions occur continuously in urban settings.

We did not address the question of whether air pollution from vehicle emissions exacerbates asthma in subjects already affected. It is important to recognise the difference. The evidence that air pollution may increase morbidity in established asthma is already quite strong,[36-40] though doubts remain as to whether particular measured pollutants such as nitrogen dioxide, ozone, sulphur dioxide, volatile organic compounds, or particulates are truly responsible (whether individually, collectively, or through interactions), or whether they act as markers for additional components of polluted outdoor air.

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