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Original Contribution

No Rise in Incidence but Geographical Heterogeneity in the Occurrence of Primary Biliary Cirrhosis in North East England

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In this study, we examined temporal changes in the incidence of primary biliary cirrhosis (PBC) and investigated associations between PBC incidence and sociodemographic factors and spatial clustering. We included 982 patients aged ≥40 years from North East England with incident PBC diagnosed during 1987–2003. Age-standardized incidence rates with 95% confidence intervals were calculated. Negative binomial regression was used to analyze incidence and socioeconomic deprivation. Clustering analysis was performed using point process methods, testing the null hypothesis that disease risk does not vary spatially and that PBC cases occur independently. The age-standardized incidence rate was 53.50 per million persons per year (95% confidence interval: 48.65, 58.35) in 1987–1994 and 45.09 per million persons per year (95% confidence interval: 41.10, 49.07) in 1995–2003. Risk of PBC increased in areas with higher levels of socioeconomic deprivation ($P = 0.035$). More specifically, risk increased in areas with higher levels of overcrowded homes ($P = 0.040$), higher levels of households without cars ($P < 0.001$), and higher levels of non-owner-occupied homes ($P < 0.001$). Overall, there was evidence of spatial clustering ($P = 0.001$). The findings confirm that overall incidence of PBC did not rise over time, but sociodemographic variations suggest that certain aspects of deprivation are involved in its etiology.

England; environment; etiology; geographic factors; incidence; primary biliary cirrhosis; spatial clustering

Abbreviations: ASR, age-standardized incidence rate; CI, confidence interval; PBC, primary biliary cirrhosis.

We previously reported an apparent increase in the incidence of primary biliary cirrhosis (PBC) in North East England (1). However, it was uncertain whether this was due to a true rise in case numbers or was an artifact of better case ascertainment. The etiology of PBC is not clear (2). A real increase would suggest the involvement of a widespread environmental agent. However, both genetic (3–5) and environmental factors are likely to be involved. We also previously reported evidence of spatial clustering among PBC cases in a defined geographical population in North East England (6). This finding suggested that one or more spatially heterogeneous environmental agents may play a role in the etiology of PBC. Putative agents include infections, smoking, hair dyes, and xenobiotics (4, 7–10).

In the present study, we were concerned with examining temporal trends in PBC incidence and analyzing the geographical distribution of incident PBC cases among persons aged 40 years or more at the time of diagnosis in North East England. One aspect of the study focused on determining whether cases exhibited an irregular distribution of PBC occurrence. An overall irregular spatial distribution of cases not limited to one specific small area is termed "spatial clustering." This type of distribution could result from a small number of areas with highly raised incidence or a large number of areas with moderately raised incidence. Furthermore, we sought to identify the locations of any particular clusters found.

We had 4 aims: to determine 1) whether the incidence of PBC has remained constant; 2) the association between PBC incidence and sociodemographic factors; 3) whether spatial clustering was present during an extended period within the same well-defined geographical region of North East England as the one studied previously (6); and 4) the location of specific spatial clusters.

The following prior hypotheses were tested:

1. There has been an increase in the incidence of PBC.
2. A primary factor influencing geographical heterogeneity of PBC incidence is modulated by differences between environmental exposures occurring in 1) less and more densely populated residential areas and 2) less and more socioeconomically deprived residential areas.
3. A primary factor influencing geographical heterogeneity of PBC is exposure to a spatially varying environmental agent occurring close to the place of residence at the time of diagnosis.

METHODS

Cases

Case definition. For this study, we included both cases defined as "definite PBC" and cases defined as "probable PBC" in our original case-finding study (1). "Definite PBC" is all 3 of the following: antimitochondrial antibody-positive titer greater than or equal to 1 in 40, cholestatic liver blood tests, and diagnostic or compatible liver histology. "Probable PBC" is any 2 of the above 3 criteria (usually antimitochondrial antibody-positive titer greater than or equal to 1 in 40 and cholestatic liver blood tests in the absence of liver biopsy). These criteria are now widely accepted (2). For this reason, we refer to all cases meeting the above criteria—either "definite" or "probable"—as cases. We defined "symptomatic" patients as those with pruritus, persistent fatigue, or signs and symptoms of cirrhosis. Patients with none of these were regarded as "asymptomatic" for liver disease at diagnosis.

Time frame and study area. The study included all persons with incident PBC diagnosed during 1987–2003 who resided in North East England (Northumberland, Sunderland, North Durham, South Durham, Newcastle upon Tyne, North Tyneside, South Tyneside, and Gateshead), as defined by postal code. The total population of the area at the time of the 2001 United Kingdom census was less than 2.05 million (11). Population density varies markedly, from the sparsely populated rural area of Northumberland to the densely populated urban areas of Newcastle upon Tyne and Gateshead. The entire region includes some of the most socioeconomically deprived areas of the United Kingdom—areas that have suffered economic decline as a result of the demise of traditional industries such as coal mining and shipbuilding (12).

Case-finding. Our case-finding methods have been described previously (13). Briefly, requests were made to all gastroenterologists and hepatologists in the region to identify all PBC patients under their care. There were 30 gastroenterologists and hepatologists in the region, all working within the United Kingdom's socialized health care system, which ensures full population coverage. Thereafter, we examined hospital admission data in regional information systems for all 13 hospitals in the region using *International Classification of Diseases*, Ninth Revision, code 571.6 (up to April 1994) and *International Classification of Diseases*, Tenth Revision, code K74.3 (thereafter). All hospital immunology laboratory data for patients with antimitochondrial antibody-positive titers greater than or equal to 1 in 40 by indirect immunofluorescence (over 500,000 laboratory records) were examined. Finally, we examined all Office for National Statistics listings of deaths within the region and study period in which PBC (above *International Classification of Diseases* codes) appeared anywhere on the death certificate.

Case selection was approved by local ethical committees. After initial identification, hospital records of all cases were reviewed.

Location at diagnosis. We assigned United Kingdom Ordnance Survey grid references to each case using the centroid of the postcode of the patient's residential address at the time of diagnosis. In the United Kingdom there are approximately 1.7 million postcodes, which are unique identifiers used for mail delivery. Each postcode usually represents 15–20 houses, fewer multiple-occupancy residences, or a single commercial location (14). This enabled us to georeference patients' addresses to the nearest 0.1 km.

Population data

In the study region, the hierarchy of geographical areas for which population data are available is as follows (largest to smallest): local authority district (population aged ≥40 years ranges from 13,383 to 132,837; median, 42,834) and census ward (population aged ≥40 years ranges from 341 to 8,518; median, 2,318). Analyses were performed at the small-area census ward level. There were 2 censuses conducted during the study period (11, 15). There were also widespread boundary changes throughout this time span, especially at the small-area level. Unless the same geographical units are used at different time points, comparisons cannot be made, so we used the method of Norman et al. (16, 17) to derive population estimates using the small-area boundaries that applied at the time of the 2001 census.

Demographic data

Small-area (census ward) demographic characteristics were derived from the census data (11, 15). These characteristics were population density (number of persons per hectare) and level of socioeconomic deprivation. We calculated Townsend scores (12) for deprivation at the small-area level (and not the individual level). The Townsend score is a combination of 4 census measures: unemployment, households with no car or van, non–home ownership, and household overcrowding (12). We constructed a time series of Townsend deprivation by apportioning these 4 constituent measures from the 1991 and 2001 censuses (applied to 1987–1995 and 1996–2003 data, respectively) to the 2001 census geography (16, 17). Increasingly negative Townsend deprivation scores represent lower levels of area deprivation. Increasingly positive scores represent higher levels of deprivation. Population density was apportioned similarly.

Control selection for overall spatial clustering analyses

Control locations were randomly selected from postcodes within the study region. Random selection of control locations was performed using a list of all postcodes that

pertained within the study region. The probability of choosing each postcode was weighted by the number of addresses in the postcode area and the population (all ages) of the postcode area. Approximately 2 control locations were generated per case.

Statistical methods

Calculation of rates. Age-specific incidence rates per million persons per year were calculated based on annual midyear population estimates for the study region obtained from the Office for National Statistics. Comparisons of age-standardized incidence rates (ASRs) are only meaningful if they are standardized in a similar fashion. ASRs were calculated using the standard world population (18–21). ASRs between the two periods were compared using the Z test.

Demographic analyses. For the small-area analysis, there was evidence of extra-Poisson variation: 90% of cells (each ward consists of 4 age bands by sex) had counts of zero. Therefore, PBC incidence was modeled at the census small-area level using negative binomial regression in STATA (22). The number of cases observed in each small area was the dependent variable, and the logarithm of the underlying population was used as the offset. The ecological (independent) variables were the census-derived small-area characteristics. A series of multivariable models was fitted including the following independent variables: sex, age, population density, and Townsend score (as a composite). In supplementary analyses, the following components of the Townsend score were included in separate models that did not include the composite score: percentage of households overcrowded, percentage without a car, percentage with residents unemployed, and percentage owner-occupied. Each variable was removed in turn, and results were compared using a likelihood ratio test. Thus, the effect of each variable was assessed by comparing differences in residual deviances with a χ^2 distribution with degrees of freedom equal to the difference in residual degrees of freedom. Model fit was assessed using both the residual deviance and the Akaike Information Criterion. Significant effects are reported as relative risks and associated 95% confidence intervals.

Overall spatial clustering analyses. Overall spatial clustering was tested using the method of Diggle and Chetwynd (23). The method tests the null hypothesis that the risk of disease does not vary spatially and that cases occur independently of one another. The technique uses case-control methodology to account for heterogeneity in the distribution of the population at risk. Controls are randomly selected from the underlying "at risk" population. Thus, they reflect the spatial structure of the underlying population, so there will be a concentration in urban areas with high population density. The spatial distribution of the controls will be consistent with the null hypothesis.

Under the null hypothesis that there is no difference between the probability densities for cases and controls, the K-function is defined by $K_{ij}(s) = \lambda_j^{-1} E$ (number of events j

Table 1. Demographic and Socioeconomic Characteristics of Primary Biliary Cirrhosis Patients Aged ≥40 Years and the Total Study Population in North East England, 1987–2003

Characteristic	All Persons		Males		Females	
	No.	%	No.	%	No.	%
		Cases				
Age ≥40 years	982	100	95	9.7	887	90.3
Median age, years	65		64		65	
Household without car or van						
Rented accommodations						
Major urban population						
Socioeconomic deprivation[a]						
Quintile 1		14.5		14.7		14.5
Quintile 2		20.7		25.3		20.2
Quintile 3		21.3		21.1		21.4
Quintile 4		22.4		23.2		22.3
Quintile 5		21.1		15.8		21.7
		Study Population[b]				
Age ≥40 years	1,228,000	100	576,000	46.9	652,000	53.1
Median age, years	58		57		59	
Household without car or van		35.9				
Rented accommodations		36.4				
Major urban population		35.0				

[a] Census wards ranked by quintile of Townsend score (12), based on 2001 United Kingdom census data.
[b] Midyear estimates from the United Kingdom Office for National Statistics.

Table 2. Incidence of Primary Biliary Cirrhosis Among Persons Aged ≥40 Years in North East England During 1987–1994

Age Group, years	All Persons				Males				Females			
	No.	Population	ASR	95% CI	No.	Population	ASR	95% CI	No.	Population	ASR	95% CI
40–59	149	4,908,900	30.81	25.84, 35.77	18	2,448,600	7.49	4.43, 11.85	131	2,460,300	53.96	44.69, 63.24
60–74	216	2,916,600	74.53	64.58, 84.47	21	1,399,100	15.08	9.33, 23.07	195	1,517,500	128.57	110.52, 146.62
≥75	117	1,072,700	111.60	90.85, 132.36	6	425,400	13.35	4.71, 29.42	111	647,300	178.80	144.39, 213.21
≥40	482	8,898,200	53.50	48.65, 58.35	45	4,273,100	10.38	7.30, 13.46	437	4,625,100	91.01	82.33, 99.69

Abbreviations: ASR, age-standardized incidence rate; CI, confidence interval.

within distance s of an arbitrary type i event), and λ_j is the intensity of j events: $i = 1$ for cases and $i = 2$ for controls.

The degree of clustering was assessed by looking at the function $D(s) = K_{11}(s) - K_{22}(s)$, which can be interpreted as the number of excess cases within distance s of a given case that are expected when there is clustering.

Under the null hypothesis, the expected value of D was zero ($E(D) = 0$). Following the method of Diggle and Chetwynd (23), we calculated

$$T = \sum_{k=1}^{m} \hat{D}(s_k) / \sqrt{\mathrm{Var}\{\hat{D}(s_k)\}}$$

as a measure of the clustering. We then tested the null hypothesis of no clustering by using bootstrapping to simulate the distribution of T. We used control data as the source for bootstrapped samples of both cases and controls. The significance level for m bootstrap simulations $T_1, T_2 \ldots T_m$ is given by the P value, $p = (k + 1)/(m + 1)$, where k is the number of $T_j > T$.

Detection of individual clusters. Kulldorff's scan statistic, based on a Bernoulli model, was used to identify individual clusters (24, 25). The complete study region was scanned by construction of a moving circle. The diameter of this circle varies so that it includes at most 25% of the entire geographical area. The variable circle is centered on the postcode centroid of each case.

Statistical assessment. Where appropriate, significant effects are reported as relative risks and 95% confidence intervals. All P values are 2-sided, and statistical significance was taken as $P < 0.05$.

RESULTS

Rates

The study analyzed the dates of diagnosis of 482 PBC patients aged ≥40 years at diagnosis who were diagnosed during 1987–1994 and 500 patients who were diagnosed during 1995–2003 within the specified region and whose details were extracted from the population-based register. Demographic and socioeconomic characteristics of the cases and the study population are presented in Table 1.

The ASR during the first period (1987–1994) was 53.50 per million persons per year (95% confidence interval (CI): 48.65, 58.35). For males and females, the overall ASRs were 10.38 (95% CI: 7.30, 13.46) and 91.01 (95% CI: 82.33, 99.69) per million persons per year, respectively. The ASR during the second period (1995–2003) was 45.09 per million persons per year (95% CI: 41.10, 49.07). For males and females, the overall ASRs were 9.49 (95% CI: 6.85, 12.14) and 76.68 (95% CI: 69.47, 83.89) per million persons per year, respectively. Thus, rates had fallen between the earlier and later time periods for females but not for males (all persons: $P = 0.009$; males: $P = 0.668$; females: $P = 0.013$). Full details are given in Tables 2 and 3.

Demographic analyses

For cases diagnosed during 1987–2003, analysis of deviance and the Akaike Information Criterion showed that, after allowing for sex and age, population density was not significant ($P = 0.157$). However, the Townsend score (as a composite) was significant ($P = 0.035$). The risk of PBC increased in more socioeconomically deprived areas (for a

Table 3. Incidence of Primary Biliary Cirrhosis Among Persons Aged ≥40 Years in North East England During 1995–2003

Age Group, years	All Persons				Males				Females			
	No.	Population	ASR	95% CI	No.	Population	ASR	95% CI	No.	Population	ASR	95% CI
40–59	190	5,955,400	32.07	27.50, 36.63	15	2,961,000	5.03	2.82, 8.30	175	2,994,400	58.83	50.11, 67.55
60–74	220	3,302,800	66.39	57.59, 75.18	30	1,551,000	19.15	12.29, 26.01	190	1,751,800	108.39	92.91, 123.87
≥75	90	1,639,100	58.11	45.73, 70.50	5	582,100	8.76	2.77, 20.60	85	1,057,000	89.03	69.27, 108.80
≥40	500	10,897,300	45.09	41.10, 49.07	50	5,094,100	9.49	6.85, 12.14	450	5,803,200	76.68	69.47, 83.89

Abbreviations: ASR, age-standardized incidence rate; CI, confidence interval.

1-unit increase in the deprivation score, relative risk = 1.026, 95% CI: 1.002, 1.050).

Additional analyses showed that risk increased in areas with higher levels of overcrowded homes ($P = 0.040$), higher levels of carless households ($P < 0.001$), and higher levels of non-owner-occupied homes ($P < 0.001$). The best-fitting model contained the variable "percentage of homes that are not owner-occupied" (residual deviance = 2,548.02; Akaike Information Criterion = 0.63748; per 1% increase in areas with higher levels of non-owner-occupied homes, relative risk = 1.008, 95% CI: 1.004, 1.012).

Overall spatial clustering analyses

During the period 1987–2003, there were 982 cases (Figure 1) and 968 controls inside the study area boundary. For distances within 15 km, there was evidence of clustering of cases in comparison with controls (based on 1,000 simulations, $P = 0.001$). Within the urban area, there was also evidence of clustering ($P = 0.006$). Similar evidence of clustering was seen for the 887 females within the range ≤15 km ($P = 0.005$) and within the urban area ($P = 0.011$). However, only weak evidence was seen for the 95 males in the range ≤15 km ($P = 0.066$) and within the urban area ($P = 0.056$), possibly because of lack of statistical power.

Detection of individual clusters

For cases diagnosed during 1987–2003, using at most 25% of the entire geographical area, Kulldorff's scan statistic indicated no evidence of any clusters, either for all cases together or separately for males and females.

DISCUSSION

This study revealed 2 highly novel findings. First, the incidence of PBC in North East England did not rise between the earlier and later time periods. Secondly, the incidence of PBC was higher in areas that had greater levels of socioeconomic deprivation. Furthermore, overall spatial clustering was confirmed in the extended time period, both over the entire study region and within urban areas. The previous study of spatial variation only considered clustering (6). Our new study was fully comprehensive and included analyses of demographic factors as well as analyses of identification of specific clusters.

The finding of no rise in incidence indicates that the overall influence of environmental factors has remained constant, and suggests that the widely reported apparent rise in PBC incidence and prevalence in the 1980s and early 1990s is likely to have been due to improvements in recognition of

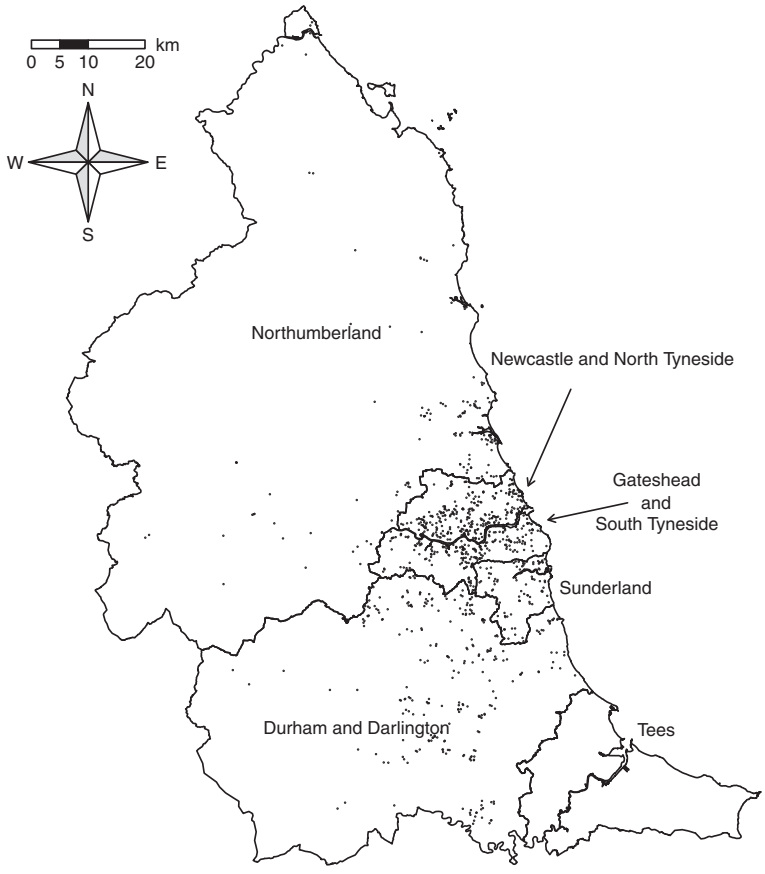

Figure 1. Distribution of primary biliary cirrhosis patients aged ≥40 years in North East England, 1987–2003.

PBC and its ascertainment (1). It also confirms the reliability of ascertainment during the study period. However, results suggest that geographical heterogeneity of PBC incidence is modulated by differences in environmental exposures in areas with greater or lesser levels of some aspect of socioeconomic deprivation. The association with the overall Townsend deprivation score was also confirmed by additional analyses of its component variables. There was no support for prior hypothesis 1, since PBC incidence did not increase between periods. There was also no support for the first part of prior hypothesis 2, as area-level population density was not associated with geographical variation in incidence of PBC. However, there was support for the second part of prior hypothesis 2, since socioeconomic deprivation was associated with differences in PBC incidence. Higher Townsend deprivation scores conferred greater risk. Furthermore, there was support for prior hypothesis 3, as there was evidence of spatial clustering.

The study had particular strengths. Rigorous statistical methods were used to analyze high-quality population data. However, 3 methodological caveats should be noted. First, census-ward population density and deprivation measures may not necessarily be related to the attributes of individual patients. They are ecological proxies. Caution should be used when making inferences concerning individuals from this type of analysis. It is possible that unknown confounding factors exhibit the same sort of geographical variation (26). Secondly, PBC case, census population, and demographic data were analyzed using 2001 United Kingdom census boundaries. The methodology did not consider the putative effects of migration. This could have diluted the results. However, other published data have shown that the region has very low rates of inward and outward migration (11, 15). Thus, migration is likely to have had little or no effect on the results, and if it had any effect it would have diluted rather than inflated the significant findings. Thirdly, there could still have been additional overdispersion or clustering between neighboring census areas that was not accounted for.

Previous studies have explored geographical and temporal patterning in PBC occurrence in North East England. In a previous prevalence study, Prince et al. (6) found overall spatial variation. This was interpreted as providing support for an environmental etiology. A study of the same data set as that used in the current analysis showed space-time clustering of incident cases diagnosed during 1987–2003 (27). These findings suggested that transient environmental agents may be involved. A further study found marked seasonal variation in occurrence, with a June peak (28). This indicated the possible involvement of a seasonally varying environmental agent.

The present findings are consistent with the involvement of spatially heterogeneous environmental agents in PBC etiology. These include infections such as *Mycobacterium gordonae*, *Escherichia coli*, and *Novosphingobium aromaticivorans* (29–41). Other environmental factors that may display spatial variation include xenobiotics, which are present in pollutants (10). Lifestyle factors may also vary by social community and residential area. Smoking and use of hair dyes have been linked with increased risk of PBC (4). The prevalence of smoking is known to be linked with socioeconomic status and so varies geographically (42). Other putative lifestyle factors, involving xenobiotics, could conceivably include use of perfumes, lipstick, and food flavorings (43).

In conclusion, we found that PBC incidence has not risen over a 17-year time period in a well-defined geographical area. We also found evidence of spatial variation and clustering in the incidence of PBC, supporting an etiological role for geographically varying environmental factors. Living in an area of greater socioeconomic deprivation was associated with greater incidence of PBC. This was also confirmed by analyses of the components of deprivation. These findings confirm that spatially varying environmental factors are involved in the development of PBC and suggest that certain aspects of deprivation may be implicated in the etiology of PBC.

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