A study of the prevalence of systemic sclerosis in northeast England

R. J. Allcock, I. Forrest, P. A. Corris, P. R. Crook\textsuperscript{1} and I. D. Griffiths\textsuperscript{2}

Objectives. We aimed to obtain an estimate of the prevalence and demographics of systemic sclerosis (SSc) and its subtypes at the turn of the millennium.

Methods. Case finding from multiple sources from a defined geographical area. Diagnosis confirmed by clinical examination.

Results. The crude prevalence of SSc in northeast England was 8.8 (95\% CI: 6.8–10.8) per 100 000. The prevalence when adjusted for the entire UK is 8.2 (95\% CI: 6.2–9.8) per 100 000. The ratio of women to men was 5.2:1. The median age of patients was 57.1 yr. The ratio of limited cutaneous SSc to diffuse cutaneous SSc was 4.7:1. Limited cutaneous SSc is associated with the presence of anticentromere antibodies; diffuse cutaneous SSc is associated with anti-Scl 70 antibodies, but either antibody was found in either form of SSc.

Conclusions. SSc appears to be more common in northeast England than was found in the West Midlands in 1986. This may reflect changes in the diagnostic definition of SSc.

Key words. Systemic sclerosis, Prevalence, Scleroderma, CREST.

Systemic sclerosis (SSc) affects connective tissue and blood vessels. Many organs may be affected including the skin, oesophagus, lungs, kidney and heart. The cause is unknown and the disease is usually progressive, resulting in disability and reduced life expectancy.

Until recently the leading cause of death was due to kidney involvement but now pulmonary complications, particularly pulmonary hypertension, are the leading cause of death [1]. No treatment has yet been shown clearly to change the outcome of SSc [2]. However, treatments for pulmonary hypertension are now emerging, which may help. These treatments can improve the breathlessness on exercise in patients with pulmonary hypertension and may lead to improved survival [3–5].

In 1997 the cost of SSc to the economy of the United States was estimated to be $1.5 billion [6]. New drugs for treating pulmonary hypertension are likely to increase these costs further. Accurate planning to fund treatment for this group of patients requires up to date information on the prevalence of SSc.

Previous data have shown that the prevalence of SSc ranges from 0.4 per 100 000 people [7] to 469 per 100 000 people in a population of Choctaw Native Americans [8]. The annual incidence of new cases of SSc has been reported from less than 1 to 469 per 100 000 people in a resident population of Great Britain [26]. The population living in postcode districts NE1–NE71 but excluded areas NE31–NE38. The study excludes areas in which there is referral overlap with other hospitals. The postcode areas NE31–NE38 were excluded because we anticipated problems in achieving complete acquisition due to proximity to another hospital which was not participating in the study. The area of the study is highlighted on the map in Fig. 1.

Diagnostic criteria for systemic sclerosis

The American College of Rheumatology (ACR) classification system for SSc published in 1980 set out a standard definition for the diagnosis of SSc in order to allow comparisons between patients at different centres [15]. The authors acknowledged that patients with Raynaud’s syndrome and sclerodactyly alone were likely to be excluded from a diagnosis of SSc. Furthermore patients with a history of Raynaud’s disease lasting for more than 2 yr were also excluded from the original registry series. Subsequent authors have argued that the ACR classification system is restrictive [16]. Revisions to the original classification system now more closely reflect clinical practice [17, 18].

Systemic sclerosis is usually subclassified into limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [16]. Patients with thickened skin (scleroderma) affecting only patches of the trunk or limbs are said to have morphea, linea scleroderma or generalized morphea. Patients with Raynaud’s syndrome and autoantibodies compatible with SSc but no other features of SSc are sometimes described as having ‘pre systemic sclerosis’. Neither of the latter groups are considered further here.

Progress in the recognition and understanding of SSc make interpretation of earlier prevalence studies more difficult. In the light of the limitations with the existing data on prevalence, we undertook a study of patients in the northeast of England to establish the prevalence of SSc on 1 January 2000.

Patients and methods

The denominator population was defined by postcode. We included everyone resident in areas with postcode prefixes NE1–NE71 but excluded areas NE31–NE38. The study excludes areas in which there is referral overlap with other hospitals. The postcode areas NE31–NE38 were excluded because we anticipated problems in achieving complete acquisition due to proximity to another hospital which was not participating in the study. The area of the study is highlighted on the map in Fig. 1.

Data from the 1991 National Census includes information on the population subdivided for each postcode district in England and Wales. It is estimated to have covered 97.8 per cent of the resident population of Great Britain [26]. The population living in...
Table 1. Previous studies yielding information on prevalence of SSc. All prevalence/incidence figures are quoted per 100 000

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>Study period</th>
<th>Prevalence date</th>
<th>Acquisition method</th>
<th>Location</th>
<th>Sources of data</th>
<th>Total prevalence</th>
<th>Ratio lcSSc: dcSSc</th>
<th>Ratio women:men</th>
<th>Incidence</th>
</tr>
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<tbody>
<tr>
<td>Silman et al. [13]</td>
<td>128</td>
<td>1986</td>
<td>31 May 1985</td>
<td>Clinicians, patient groups, database, hospital records, some GPs</td>
<td>West Midlands, UK</td>
<td>Multiple overlapping</td>
<td>3.08</td>
<td>1.5:1</td>
<td>3.92:1</td>
<td>0.37</td>
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<tr>
<td>Geirsson et al. [19]</td>
<td>18</td>
<td>1975–1990</td>
<td>1990</td>
<td>Hospital databases, GP records, death certificates, relevant clinicians</td>
<td>Iceland</td>
<td>Multiple</td>
<td>7.1</td>
<td>2.6:1</td>
<td>8.01:1</td>
<td>0.38</td>
</tr>
<tr>
<td>Marin et al. [21]</td>
<td>7 (4)</td>
<td>1987</td>
<td>1987</td>
<td>Nested questionnaire survey with selected review of patients</td>
<td>South Carolina, USA</td>
<td>By extrapolation</td>
<td>11.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Silman et al. [14]</td>
<td>52</td>
<td>1987</td>
<td>1/1/87</td>
<td>Clinicians, patient groups, database, hospital records, some GPs</td>
<td>South and west London, UK</td>
<td>Multiple overlapping</td>
<td>14.6</td>
<td>4.2:1</td>
<td></td>
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<tr>
<td>Tamaki et al. [22]</td>
<td>629</td>
<td>1 Jan 1988</td>
<td></td>
<td>Applicants for free medical care entitlement</td>
<td>Tokyo, Japan</td>
<td>Registration data and questionnaires</td>
<td>5.3</td>
<td>1.9:1</td>
<td>14.5:1</td>
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<tr>
<td>Michet et al. [24]</td>
<td>8</td>
<td>1950–1979</td>
<td>1 Jan 1980</td>
<td>Case records, hospital records</td>
<td>Mayo Clinic, Rochester, USA</td>
<td>-</td>
<td>25.3</td>
<td></td>
<td>8 women</td>
<td></td>
</tr>
<tr>
<td>Arnett et al. [8]</td>
<td>14</td>
<td>1990–4</td>
<td>1994</td>
<td>Records of Indian Health Services</td>
<td>Oklahoma, USA</td>
<td>66</td>
<td></td>
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<tr>
<td>Medsger and Masi [9]</td>
<td></td>
<td></td>
<td></td>
<td>Hospital records of Memphis and Shelby Counties, USA</td>
<td>Tennessee, USA</td>
<td>Hospital database</td>
<td>0.4</td>
<td>2.9:1</td>
<td>0.06</td>
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*a*This study used a questionnaire to identify people with Raynaud’s disease. A sample of those who responded positively were then assessed further with a subset of these being fully assessed clinically. The estimate of prevalence rests on a series of extrapolations and is subject to wide confidence limits.

*b*The prevalence data are based on the national figures (644 patients). The distribution by subtype and gender is based on the subset that were reviewed in the author’s hospital.
the study area at the time of the 1991 census was 931,212. Preliminary data from the 2001 census indicate that the estimated population within the study area on 1 January 2000 was 909,578.

Numerator data
We used the diagnostic definition of SSc as proposed by Leroy et al. in 1988 [16] and further described by Black [2, 27]. Cases were included in the study if they met the following criteria:

- Subjects were alive and resident within the defined postcode area on the first day of January 2000.
- Subjects had SSc that satisfied either (a) the ACR classification criteria [15] or (b) subjects had one major criterion, sclerodactyly, and at least two of the following minor criteria: Raynaud’s phenomenon, oesophageal dysmotility, calcinosis, telangiectasia or an elevated antinuclear antibody titre.

Subject to the agreement of their primary physician, all potential cases were invited to attend an out-patient clinic where the clinical history and examination findings were recorded prospectively on a standardized pro forma. All examinations were performed by the same investigator (RA). Patients with a diagnosis of mixed connective tissue disease or other connective tissue disease and patients with localized scleroderma or morphea were excluded from the study. Autoantibody status was routinely checked in the clinic using the regional immunology laboratory for all assays.

Acquisition strategy
Patients were identified by five overlapping routes in approximately chronological order:

- The Newcastle rheumatology department cumulative database of rheumatology patients was interrogated for patients coded with diagnoses of SSc, scleroderma or CREST syndrome.
- All eight rheumatology consultants practising within the study region were invited to provide details of any patients under their care whom they considered to have definite or possible SSc. If a patient preferred not to be contacted then anonymized information about the patient was requested. All agreed to take part.

- All seven dermatologists in the region were invited to participate in identifying patients in the same way. All agreed to take part.

- The regional immunology laboratory database in Newcastle was interrogated for the names of patients who had been found to have an anticientromere or antitopoisomerase (Scl 70) antibody within the last 12 months. (Due to recent changes in the database system it was not possible to search for patients from earlier than 12 months prior to the prevalence date.)

- All five renal physicians were invited by letter to supply names of patients under their care with SSc. All agreed to take part.

In addition to these formal strategies, opportunities were sought to present interim findings to general medical audiences to raise awareness of the study and to encourage further referrals.

Validation of acquisition
Overlap of referral routes. Case ascertainment was assessed by recording the route by which first notification was made to the project. Subsequent notification of the same patient by another route was also recorded. Where a patient was notified by more than two routes, only the first two were recorded.

Case ascertainment efforts continued for 2 yr after the prevalence date. No further patients were identified who were prevalent cases at 1 January 2000.

Geographical differences in prevalence. Acquisition may tend to be less complete for patients living at the margins of the study area than for patients who live in the centre of the area. The patients were therefore divided into two groups by postcode. Those with a postcode from within the city of Newcastle and those with postcodes outside the city. The prevalence of SSc was then calculated for each subgroup to see if there was a difference.

Ethics
Ethical approval for this study was granted by the Newcastle Local Research Ethics Committee and by the Gateshead Local Ethics Committee. Patients were seen and assessed in clinic as part of a clinical service. Normal clinical consent procedures were used in performing all tests.

Statistical analysis
The 95% confidence intervals were calculated for the estimate of prevalence using the Poisson distribution with Minitab 13. Associations between disease subtype and autoantibody status were assessed using the $\chi^2$ statistic.

Results
One hundred and forty-seven patients were identified using all the acquisition routes described. Of these, 119 had an address within the study area. Twelve patients died prior to the prevalence date of 1 January 2000 and one patient moved out of the area. Twenty-six of the patients from within the study area were found to have a diagnosis other than SSc. In 16 of these 26 patients it was possible to exclude a diagnosis of SSc by review of the clinical notes and/or discussion with the consultant or GP of the patient. Ten of the 26 were judged not to have a diagnosis of SSc after review in the out-patient clinic.

Numerator population
We found 80 patients with SSc. In 75 the diagnosis was confirmed by clinical examination in the out-patient clinic. In the
remaining five patients the diagnosis was made by a consultant rheumatologist but was not confirmed in our study clinic: two of these patients died after the prevalence date but prior to being called to the clinic; three patients declined an invitation to attend the clinic.

Crude prevalence
The 80 cases of SSc were identified in a denominator population of 909,578. The unadjusted prevalence of SSc by each subtype is shown in Table 2.

Acquisition validation
Overlap of referral routes. The initial route of identification was recorded in 145 of the 147 patients. A total of 175 routes of referral were recorded. Sixty-two patients were identified via the rheumatology database at Freeman Hospital. Fifty-one patients were notified first by consultant rheumatologists. Twenty-one patients were notified by hospital physicians who were not rheumatologists, of which three patients were notified first by the dermatology department. Eight patients were identified first from the immunology laboratory database. Of the 80 patients who met the entry criteria for the study, 16 patients were also referred to the study by another separate route.

Geographical referral bias. Using data from the 1991 census adjusted for national demographic changes in the preliminary data from the 2001 census, there were 384,468 people living in the central, urban part of the study area and 561,110 in the surrounding area. The crude prevalence of SSc in these two sub-areas was similar: inner area (Newcastle city) 8.9 (5.8–12.0) per 100,000; outer area (all other postcode areas) 8.7 (6.3–11.2) per 100,000.

Adjusted prevalence
The number of people living in the study area in 1991 for each age range is summarized in Table 3 together with the adjusted population figures for 2000.

The median age of patients with SSc in northeast England was 57.1 yr. Women outnumbered men by a ratio of 5.2:1. The median age of men with SSc was 54.4 yr compared with 58.4 yr for women (Fig. 2). Cases of lcSSc exceeded those of dcSSc by a ratio of 4.7:1. The ratio of limited to diffuse disease in women and men was 4.6:1 and 5.5:1 respectively (Fig. 2).

Age of onset of SSc
The year of diagnosis of SSc was recorded in 71 of the 80 patients. The age at which SSc was diagnosed in our patients is shown in Fig. 3.

Autoantibody status
Twenty-seven patients with lcSSc were positive for anticentromere antibodies; 36 were negative. Anticentromere antibody status was not available in three patients with lcSSc. Two patients with dcSSc were positive for anticientromere antibodies; 12 were negative. There was a strong negative association between the presence of anticientromere antibodies and the dcSSc phenotype ($\chi^2$ test $P<0.001$) but less than half of patients with lcSSc had anticientromere antibodies.

Anti-Scl 70 antibodies
Eleven patients with lcSSc had anti-Scl 70 antibodies; 50 were negative for anti-Scl 70. Scl 70 antibody status was not established in five patients with lcSSc. Five patients with dcSSc were positive for Scl 70 antibodies; none were negative. The presence of anti-Scl 70 antibody was associated with the dcSSc phenotype ($\chi^2$ test $P<0.001$).

Discussion
Data on the prevalence of SSc in the UK are limited. We found a higher prevalence of SSc than the 3.08/100,000 found in the West Midlands in 1986 [13] but not as high as the 14.6/100,000 found in...
south and west London [14]. Studies from Australia and the USA have shown a higher prevalence than the UK studies. How should we explain these differences?

In the present study we used diagnostic criteria that reflect current rheumatological practice. Silman et al. [13] contacted relevant clinicians in the West Midlands area, searched hospital discharge data and contacted patient support groups. Medical records of identified patients were scrutinized to confirm the diagnosis and to decide the diagnostic subtype. Using this strategy, Silman found a prevalence of 3.08 per 100 000, 1.28/100 000 for men and 4.79/100 000 for women. The prevalence of subtypes is reported as 1.88 and 1.2 per 100 000 for dcSSc and lcSSc respectively, but there is a table in their paper which states that the ratios were in fact the other way around, which seems more likely.

In Silman’s study of two areas in south and west London, the prevalence of SSc was 14.6/100 000 (95% CI: 10.6–18.6) [14]. This figure is higher than our findings, but the confidence intervals overlap. The mix of subtypes of disease is not specified, and whilst the diagnosis of SSc was determined by an international expert in SSc, the specific diagnostic criteria used in the study are not specified.

Our study reveals a higher proportion of lcSSc to dcSSc than in the West Midlands study. The clinical features of lcSSc are often more subtle than for in-patients with dcSSc. We may therefore have included patients with more subtle lcSSc than would have been the case according to the usual practice in the West Midlands in 1986. Thus the difference between our findings and those in the West Midlands in 1986 may be due to accepting more mild disease.

Alternatively the difference might reflect a true rise in prevalence of this disease. Several studies suggest that the incidence of SSc may be increasing in the USA [7, 10, 28] and in Australia [20]. Improvements in the management of renal and pulmonary involvement—the two leading fatal complications of SSc—have improved average survival of patients with SSc. Extended survival would be expected to increase the prevalence of a disease if incidence remains constant.
The studies from Chandran et al. in Adelaide [23] and Michet et al. in Rochester, USA [24] both report prevalence figures of more than twice that in the UK. The Rochester study is based on only eight patients so must be regarded with caution. The Adelaide series used an approach based on case records and discharge coding with 25% of patients subsequently being reviewed in a clinic to confirm the diagnosis. Recruitment was over a period of 6 yr. The diagnostic criteria used were similar to the present study. It therefore appears that the prevalence of SSC in Adelaide may be significantly higher than in the UK.

Our data confirm the well-known association between anticientromere antibody status and lcSSc, but we also confirm the observation that the presence of anticientromere or anti-Scl 70 antibodies, or neither, is compatible with a diagnosis of SSC of either subtype. Female patients with SSC outnumbered men by a ratio of 5.2:1. This is consistent with previous observations, although a little higher than other studies [13, 20, 28, 29]. Our finding of an excess of lcSSc to dcSSc in the ratio 4.7:1 is also compatible with other studies. In general the highest prevalence figures have also shown the highest proportion of lcSSc. As discussed above, this most probably reflects changes in the diagnostic criteria for SSC over the last two decades [18].

The accuracy of an estimate of prevalence depends critically on completeness of acquisition. Case identification in SSC is complicated by the insidious onset of the disease combined with the lack of a fully robust disease definition. The transition from Raynaud’s syndrome to oesophageal dysmotility and/or pulmonary vascular involvement may extend over decades. The point during this transition at which a patient ‘earns’ a diagnosis of SSC is variable—a point highlighted in previous studies [20]. Vigorous case searching within a community may therefore reveal patients who meet early criteria for a diagnosis of lcSSc but who would not otherwise come to the attention of a specialist for a decade or more. Offering someone a diagnosis of SSC is not appropriate if the patient has no symptoms and has not noticed any changes in their skin; no treatments have yet been identified that prevent the progression of early SSC.

We did not collect sufficient data on overlapping referral routes to use capture/recapture statistical techniques for formal assessment of completeness of acquisition. Whether capture/recapture techniques are applicable in a study of the prevalence of a rare disease with blurred diagnostic boundaries is in any case debatable. Capture/recapture techniques depend on an assumption that the diverse routes of identification of cases are independent of one another. Interactions between supposedly independent referral routes lead to considerable inaccuracy of estimates of missed cases [30, 31]. We recorded only the first two routes of referral in this study, but these were not fully independent as specialists referring cases were often already aware of which patients might or might not be included on the rheumatology database. Subsequent on-going case searching as part of a clinical screening programme for pulmonary hypertension in patients with SSC after the completion of this study has not revealed further patients who should have been included in this data set.

One hypothetical group of patients who may not have been identified in our study are those cared for by specialist physicians exclusively in private practice. We are not aware of physicians with an interest in SSC who practice exclusively in the private sector in northeast England. Some patients travel to consult national experts but this is usually following referral from within the NHS system and hence such patients would be identified by our ascertainment strategies.

In conclusion we find a higher prevalence of SSC in the UK than was seen in 1986. This increase may reflect changes in diagnostic thresholds but may be a true rise. For the purpose of planning services for these patients, the current prevalence of SSC in the UK is 8.21 (6.35–10.07) per 100 000

Acknowledgements

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<tr>
<th>Rheumatology</th>
<th>Key messages</th>
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<td></td>
<td>• Systemic sclerosis may be becoming more common.</td>
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<td></td>
<td>• Patients with lcSSc outnumber those with dcSSc by 4.7:1.</td>
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<tr>
<td></td>
<td>• Women outnumber men with SSC by 5.2:1.</td>
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References


