Annual Medical Costs and Healthcare Resource Use in Patients with Systemic Sclerosis in an Insured Population

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ABSTRACT. ***Objective.*** Systemic sclerosis (SSc) is a chronic autoimmune disease. The objective of our study was to estimate the medical costs and healthcare resource use of subjects with SSc in a large US managed care plan.

Methods. Subjects at least 18 years of age and with claims-based evidence of SSc (ICD-9-CM code 710.1x) were identified from a health plan database from 2003 through 2008. Subjects were matched to unaffected controls, based on index date, age, sex, geographic region, time on insurance, and comorbidity score. Costs and resource use were identified during the 12-month postindex period. A generalized linear model (GLM) was used to estimate costs, controlling for demographic and clinical characteristics.

Results. In this study, 1648 subjects with SSc were matched to 4944 controls. Mean overall annual medical costs were higher among SSc subjects than controls ($17,365 vs $5,508; $p < 0.001$). A GLM model supported these results. Evidence of lung disease, gastrointestinal bleeding, or renal disease increased costs (all $p < 0.001$). Compared to controls, significantly higher proportions of SSc subjects had postindex ambulatory visits, emergency department visits, and inpatient hospital stays (all $p < 0.001$).

Conclusion. Our findings suggest that the medical costs and resource use associated with treating SSc are high (compared to matched controls), and as expected, subjects with serious disease complications experience the highest costs. (First Release Oct 1 2012; J Rheumatol 2012;39:2303–9; doi:10.3899/jrheum.120600)

Key Indexing Terms:
SYSTEMIC SCLEROSIS COSTS RESOURCE USE DATABASE CLAIMS

Systemic sclerosis (SSc) is a chronic connective tissue disease thought to result from immune system abnormalities and defects in endothelial cells and fibroblasts[1]. SSc can affect the skin and/or internal organs, and damage of blood vessels, inflammation, thickening of the skin, and fibrosis may occur[2]. The 2 main subsets of SSc are limited SSc (lSSc) and diffuse SSc (dSSc). In lSSc, fibrosis progresses slowly, and the affected skin is primarily limited to the hands, feet, and face; in dSSc, fibrosis progresses more rapidly and large areas of skin are affected[3]. Subjects with SSc often experience internal organ complications, including cardiac problems, pulmonary arterial hypertension (PAH), renal crisis, pulmonary fibrosis, and esophageal dysmotility[3,4]. Patients with SSc have reported a significant emotional burden due to disruption in their social lives, concerns with appearance, and low self-esteem[5].

The 10-year survival rate for SSc has been estimated at 66% to 82%, and subjects with dSSc have a higher mortality than those with lSSc[6,7,8]. Risk factors for SSc include female sex, family history, African American ethnicity, and exposure to silica or organic solvents[1,9,10,11,12,13]. Genetic variations involving a number of genes have also been linked to SSc susceptibility[14,15,16]. Studies have reported the prevalence of SSc in the US at 28 per 100,000 individuals or higher, and the annual incidence of SSc in the US has been reported at slightly under 2 cases per 100,000 individuals[17,18,19]. Recently, we reported the 2008 prevalence of SSc at 18.38 per 100,000 individuals and the overall age- and sex-adjusted incidence rate of SSc at 5.61 cases per 100,000 person-years (2003–2008) in the United States[20].

There is currently no widely accepted pharmacotherapy for treating the underlying disease of SSc, and most drugs taken by subjects with SSc are for treatment of specific symptoms or organ complications[21]. Pharmacotherapy for vascular complications of SSc may include endothelin-1 receptor blockers (bosentan, ambrisetan), phosphodiesterase type-5 inhibitors (sildenafil and tadalifil), and prostacyclin

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analogs (epoprostenol, treprostinil, iloprost)[22]. Renal involvement may be treated with angiotensin-converting enzyme inhibitors plus beta-blockers, pulmonary fibrosis may be treated with cyclophosphamide or mycophenolate mofetil, skin manifestations may be treated with methotrexate, and proton pump inhibitors may be used to treat gastrointestinal (GI) complications such as gastroesophageal reflux disease[21,23].

Studies from multiple countries have investigated the economic burden associated with SSc[24,25,26,27,28]. In this study, we used a national healthcare claims database to provide a current estimate of the burden of SSc on the US healthcare system. Previous studies of SSc costs in the United States are over 10 years old, and therefore may not account for the effects of newer medications to treat complications of SSc. We matched subjects with SSc to control individuals unaffected by SSc in order to determine the costs and resource use associated with SSc in the United States.

MATERIALS AND METHODS

Study design and subject identification. Eligible enrollees were from a national managed care organization (MCO) consisting of roughly 35 million commercially insured members with medical and pharmacy benefits during the study period from 2003 to 2008 (and about 14 million total covered lives per year). The MCO provided full insurance coverage for physician, hospital, and pharmacy services. Individuals covered by the health plan were from geographically diverse regions of the US. Previous studies have validated the use of claims-based algorithms to identify disease in a database affiliated with this MCO[29].

Claims were submitted by physicians, facilities, and pharmacies for payment of services (such as specialty, preventive, and office-based treatments) rendered to covered health plan members. Claim forms included multiple diagnoses recorded with *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) standard diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT) codes, or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); and paid amounts. Claims for ambulatory services submitted by individual providers used the Health Care Financing Administration-1500 format, and claims for facility services submitted by institutions used the Uniform Bill (UB)-82 or UB-92 format. Typically, medications administered in hospital were not included in facility claims. Roughly 6 months following the delivery of services is required for complete medical data.

SSc subjects were required to have a medical claim with a diagnosis code for SSc from January 1, 2003, through December 31, 2008, that satisfied the following inclusion criteria: (1) the subject was at least 18 years of age on the date of service; (2) the subject was continuously enrolled with medical and pharmacy benefits for 12 months prior to and following the date of service; and (3) in the 12 months following the date of service the subject had either (3a) evidence of at least 1 inpatient claim with an SSc diagnosis (ICD-9-CM code 710.1x) or (3b) 2 or more office or emergency room visits (combinations allowed) at least 30 days apart, but not more than 365 days apart, with a diagnosis code for SSc (where the first visit occurred during the same calendar year as the date of service). An index date for subjects with SSc was assigned randomly from all qualifying service dates that met the above criteria between 2003 and 2008.

Age, sex, and geographic region (Northeast, South, West, or Midwest) were identified from enrollment data based on the SSc claim associated with the earliest of all qualifying service dates. Comorbidities were identified based on the presence of codes on medical claims during the 1 year prior to (but not including) the index date. A Quan-Charlson comorbidity score was calculated using preindex comorbidities[30].

Matching. SSc subjects were matched to controls, who consisted of commercial health plan enrollees without evidence of SSc. To be eligible for selection, controls were required to be age 18 years or older as of the year of index date, to have at least 1 office visit from January 1, 2003, through December 31, 2008, to have continuous enrollment with medical and pharmacy benefits for at least 24 months during 2003 through 2008, and to have no diagnosis claims for SSc (ICD-9-CM 710.1x), or for other connective tissue disorders such as systemic lupus erythematosus (ICD-9-CM 710.0x) or myositis (ICD-9-CM 710.3, 710.4, 728.81) during the continuous enrollment period. The other connective tissue disorders were excluded to avoid a confounding effect on the results, as they tend to overlap with SSc and can be misclassified. An index date was selected randomly from within each subject's enrollment period to ensure that the subject would have at least 1 year of preindex and postindex enrollment. For example, consider a control subject with a 30-month enrollment period. The index date for this subject would be randomly chosen from the "middle" 6 months of their 30-month enrollment period. This process would guarantee that a subject would be continuously enrolled for 12 months pre- and post-index, and hence maximized the number of case-control matched pairs that satisfy the enrollment criterion. SSc subjects were matched to eligible controls in a 2-step process. In the first step, SSc subjects were matched to controls using a ratio of 1:5 based on the following criteria: index date (± 6 months); age (± 5 years); sex; geographic region; and length of time on insurance (± 5 years). In the second step, SSc subjects were matched to the subset of controls selected in the first step using a ratio of 1:3, based on the preindex Quan-Charlson comorbidity score (± 2.0). Matching was conducted to maximize the probability of retaining all SSc subjects. Bivariate comparisons of comorbid conditions (between SSc subjects and controls) were performed using logistic regression. Also, we performed an empirical comparison between all SSc patients identified and those that we were able to match, and we found that characteristics between the groups were similar.

Resource use and costs. Healthcare resource utilization and costs were measured for a fixed 1-year postindex period (including the index date). Healthcare resource use was operationalized as the numbers of the following: ambulatory visits (office and outpatient), emergency department visits, and inpatient admissions. The average total length of inpatient stays was also calculated. Evidence of services rendered by specific physician specialists (rheumatologist, dermatologist, or nephrologist) during ambulatory visits was extracted. Evidence of use of selected procedures (diagnostic services or durable medical equipment) was determined. Pharmacy claims were used to determine average counts of medications that could be used to treat SSc. Healthcare costs were computed as the combined health plan and patient-paid amounts; in addition, payments from Medicare (or other payers) were estimated based on coordination of benefits information obtained by the health plan, and these estimates were incorporated into the total paid amount. The following cost variables were calculated: total, pharmacy, ambulatory, emergency services, inpatient, and others. Any costs that could not be assigned to pharmacy, ambulatory, emergency services, or inpatient categories were included by default in the "other costs" category. Costs were adjusted to 2009 US$ using the annual medical care component of the Consumer Price Index.

Bivariate comparisons of costs and resource use were compared between SSc subjects and controls using logistic regression for binary variables and a general linear model for continuous variables. The correlated expression of the matched data was accounted for by using generalized estimating equations with an exchangeable correlation matrix. Reported p values for both types of variables are based on Wald tests. In addition to the bivariate comparison, overall total healthcare costs were also modeled with a generalized linear model (GLM) using a gamma distribution. The natural logarithm of the mean overall total healthcare cost was modeled as a linear function of indicator variables for cohort (case vs control), sex (male vs female), and evidence of any of the following: Raynaud's syndrome, lung

disease, pulmonary hypertension, GI bleeding, and renal disease. Other variables were evidence of use of any of these: methotrexate, steroids, bosentan, ambrisentan, epoprostenol, treprostinil, or sildenafil. Also noted were categorical index year, age, and region.

RESULTS

Initially, 2739 subjects were selected for the SSc cohort based on study inclusion criteria, and 1648 of these were retained after matching to controls (Figure 1). In both cohorts about 87% of the individuals were female, and the majority of subjects were between 45 and 64 years of age (Table 1). The average age of SSc subjects was 50.78 years (SD 12.32) and the average age of controls was 50.79 years (SD 12.28).

Overall mean annual medical costs were significantly higher among subjects with SSc compared to matched controls ($17,365 vs $5508; $p < 0.001$; Figure 2). Ambulatory costs accounted for the largest portion of overall healthcare costs among SSc subjects (mean annual costs $6713; 38.7% of total costs), followed by inpatient costs (mean annual costs $5390; 31.0% of total costs), pharmacy costs (mean annual costs $3856; 22.2% of total costs), other medical costs (mean annual costs $1229; 7.1% of total costs), and emergency services costs (mean annual costs $177; 1.0% of total costs; Figure 2). Overall mean annual medical costs predicted by a GLM were similar to unadjusted costs. SSc subjects had mean annual predicted healthcare costs of $18,396, compared to $5316 among controls (Table 2). When clinical and demographic characteristics were adjusted for using a GLM, the cost ratio of SSc subjects to controls was 1.988 ($p < 0.001$; Table 2).

A GLM was used to investigate whether selected demographic or clinical characteristics were associated with increased costs in SSc subjects and matched controls (Table 2). Compared to individuals with an index year in 2003, individuals with an index year in 2006 had significantly higher mean annual medical costs (cost ratio = 1.161; $p = 0.046$; Table 2). However, no significant difference in costs was observed for individuals with an index year in 2004, 2005, 2007, or 2008, when compared to individuals with an index year in 2003 (Table 2). Individuals aged 45–64 years had significantly higher costs than individuals aged 18–44 (cost ratio = 1.317; $p < 0.001$), but no statistically significant difference in costs was observed between individuals aged 18–44 and individuals aged 65 years and up (Table 2). Mean annual healthcare costs were significantly lower among

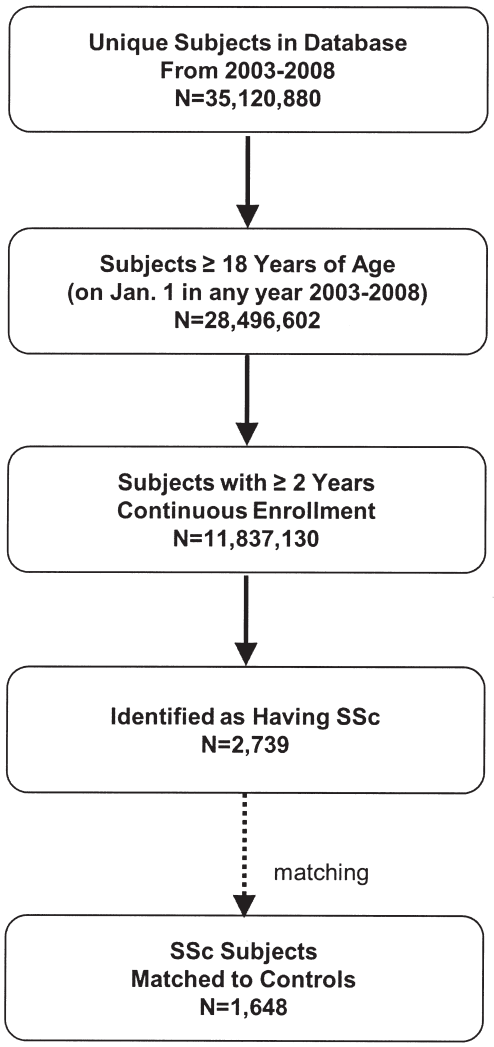

Figure 1. Selection of subjects with systemic sclerosis (SSc; 2003-2008).

Table 1. Demographic characteristics of subjects with systemic sclerosis (SSc) and matched controls (2003–2008).

Characteristics	SSc Subjects n = 648		Controls n = 4944	
	n	(%)	n	(%)
Index year				
2003	253	(15.35)	765	(15.47)
2004	236	(14.32)	710	(14.36)
2005	236	(14.32)	700	(14.16)
2006	270	(16.38)	812	(16.42)
2007	284	(17.23)	857	(17.33)
2008	369	(22.39)	1100	(22.25)
Age, yrs				
18–44	459	(27.85)	1377	(27.85)
45–64	1027	(62.32)	3081	(62.32)
65+	162	(9.83)	486	(9.83)
Sex				
Male	215	(13.05)	645	(13.05)
Female	1433	(86.95)	4299	(86.95)
US Region				
Northeast	191	(11.59)	573	(11.59)
Midwest	494	(29.98)	1482	(29.98)
South	726	(44.05)	2178	(44.05)
West	237	(14.38)	711	(14.38)
	mean	SD	mean	SD
Length of time on insurance, days	1079	(688)	1046	(586)

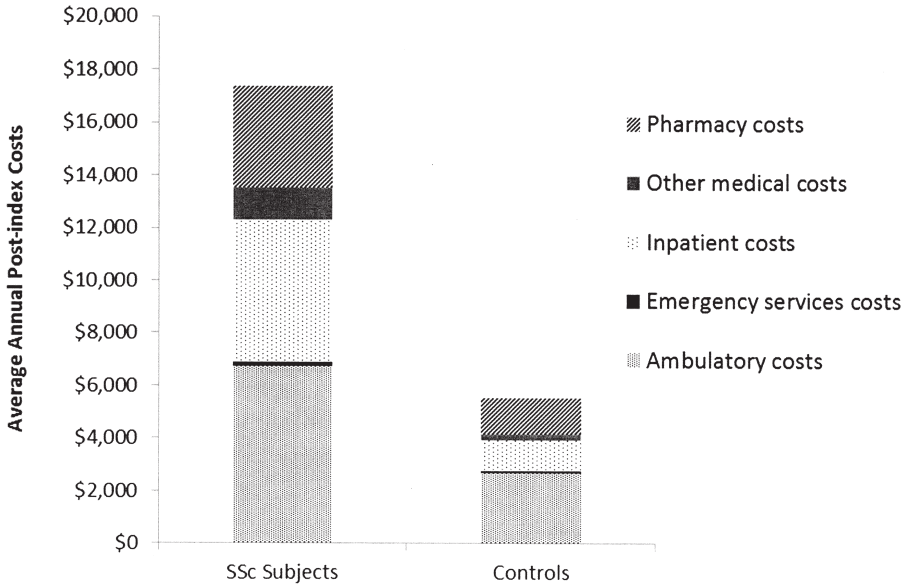

Figure 2. Average annual component costs of systemic sclerosis (SSc) subjects and matched controls (2003–2008).

Table 2. Generalized linear model of annual costs (2003–2008).

Factor	Cost Ratio	(95% CI)	p
SSc (control patients as Ref.)	1.988	(1.773–2.230)	< 0.001
Year (2003 as Ref.)			
2004	1.100	(0.954–1.268)	0.191
2005	1.075	(0.927–1.247)	0.339
2006	1.161	(1.002–1.346)	0.046
2007	1.083	(0.943–1.245)	0.260
2008	1.129	(0.985–1.295)	0.082
Age (18–44 yrs as Ref.)			
45–64	1.317	(1.200–1.444)	< 0.001
> 65	1.013	(0.889–1.154)	0.849
Male (female as Ref.)	0.861	(0.749–0.989)	0.035
Geographic region (South as Ref.)			
Midwest	1.116	(0.952–1.307)	0.175
Northeast	0.959	(0.875–1.052)	0.379
West	0.972	(0.864–1.092)	0.626
Organ involvement (post-index)			
Raynaud's syndrome	0.948	(0.831–1.082)	0.427
Lung disease	2.298	(2.021–2.614)	< 0.001
Pulmonary hypertension	0.907	(0.743–1.107)	0.335
GI bleeding	1.894	(1.577–2.273)	< 0.001
Renal disease	3.074	(2.406–3.927)	< 0.001
Medications			
Methotrexate	1.263	(1.021–1.562)	0.032
Systemic corticosteroids	1.650	(1.484–1.834)	< 0.001
PAH drugs (Bosentan, Ambrisentan, epoprostenol, treprostinil, sildenafil)	2.599	(1.969–3.430)	< 0.001
Mean predicted costs, US $			
SSc patients			18,395.66
Controls			5,316.05

GI: gastrointestinal; PAH: pulmonary arterial hypertension; SSc: systemic sclerosis.

males compared to females (cost ratio = 0.861; p = 0.035). No significant associations were observed between the geographic region where services were received (North, South, West, or Midwest) and healthcare costs (Table 2). Several SSc-related conditions (diagnosed within 1 year following the index date) were associated with increased costs, including lung disease (cost ratio = 2.298; p < 0.001), GI bleeding (cost ratio = 1.894; p < 0.001), and renal disease (cost ratio = 3.074; p < 0.001). Additionally, evidence of pharmacy claims for methotrexate (cost ratio = 1.263; p = 0.032), corticosteroids (cost ratio = 1.650; p < 0.001), or drugs used to treat PAH (cost ratio = 2.599; p < 0.001) was associated with higher costs.

Annual postindex healthcare resource use was compared between subjects with SSc and matched controls (Table 3). Subjects with SSc, compared to controls, had on average higher counts of ambulatory visits (23.98 vs 11.15; p < 0.001), emergency department visits (1.00 vs 0.54; p < 0.001), and inpatient hospital stays (0.33 vs 0.09; p < 0.001; Table 3). The average length of an inpatient stay was significantly higher among SSc subjects than matched controls (2.19 days vs 0.44 days; p < 0.001). Also, average counts of visits to specialists were significantly higher among SSc subjects than matched controls (nephrologists, p = 0.003; rheumatologists, p < 0.001; dermatologists, p < 0.001). A greater proportion of SSc subjects than controls had pharmacy claims for systemic corticosteroids, methotrexate, mycophenolate mofetil, cyclophosphamide, bosentan, epoprostenol, and sildenafil (Table 3). Additionally, a greater proportion of SSc subjects had claims for each of durable medical equipment and diagnostic services, compared to controls (both p < 0.001).

Table 3. Annual (postindex) healthcare resource use of subjects with systemic sclerosis (SSc) and matched controls (2003–2008).

Resource	SSc Subjects, n = 1648		Controls, n = 4944		p
	n	(%)	n	(%)	
Postindex resource use					
Ambulatory visits	1642	(99.64)	4696	(94.98)	< 0.001
Visit to primary care physician	1495	(90.72)	4117	(83.27)	< 0.001
Visit to nephrologist	39	(2.37)	27	(0.55)	< 0.001
Visit to rheumatologist	1203	(73.00)	97	(1.96)	< 0.001
Visit to dermatologist	413	(25.06)	797	(16.12)	< 0.001
Emergency department visits	507	(30.76)	855	(17.29)	< 0.001
Inpatient hospital stays	394	(23.91)	346	(7.00)	< 0.001
Diagnostic services (laboratory and radiology)	1618	(98.18)	4222	(85.40)	< 0.001
Durable medical equipment[1]	265	(16.08)	428	(8.66)	< 0.001
Postindex medications					
Systemic corticosteroids[2]	638	(38.71)	883	(17.86)	< 0.001
Methotrexate	155	(9.41)	23	(0.47)	< 0.001
Mycophenolate mofetil	55	(3.34)	2	(0.04)	< 0.001
Cyclophosphamide	25	(1.52)	5	(0.10)	< 0.001
Cyclosporine	2	(0.12)	4	(0.08)	0.640
Bosentan	26	(1.58)	0	(0.00)	< 0.001
Ambrisentan	1	(0.06)	0	(0.00)	0.250
Epoprostenol	3	(0.18)	0	(0.00)	0.016
Trepostinil	0	(0.00)	0	(0.00)	1.000
Sildenafil	38	(2.31)	28	(0.57)	< 0.001
	Mean[3]	(SD)	Mean[3]	(SD)	
Postindex resource use					
Count of ambulatory visits	23.98	(19.70)	11.15	(12.44)	< 0.001
Visit to primary care physician	5.16	(5.19)	3.36	(3.50)	< 0.001
Visit to nephrologist	0.10	(1.06)	0.01	(0.34)	0.003
Visit to rheumatologist	2.96	(3.12)	0.06	(0.61)	< 0.001
Visit to dermatologist	0.78	(3.40)	0.32	(1.10)	< 0.001
Count of emergency department visits	1.00	(3.66)	0.54	(2.60)	< 0.001
Count of inpatient hospital stays	0.33	(0.76)	0.09	(0.35)	< 0.001
Total length of inpatient stay, days	2.19	(7.92)	0.44	(2.71)	< 0.001
Postindex pharmacy claims					
Systemic corticosteroids[2]	1.44	(2.90)	0.33	(1.09)	< 0.001
Methotrexate	0.60	(2.19)	0.03	(0.45)	< 0.001
Mycophenolate mofetil	0.20	(1.25)	0.00	(0.04)	< 0.001
Cyclophosphamide	0.06	0.58	0.01	(0.20)	< 0.001
Cyclosporine	0.00	(0.12)	0.00	(0.15)	0.957
Bosentan	0.12	(1.10)	0.00	(0.00)	< 0.001
Ambrisentan	0.00	(0.15)	0.00	(0.00)	0.317
Epoprostenol	0.03	(0.64)	0.00	(0.00)	0.083
Trepostinil	0	—	0	—	1.000
Sildenafil	0.12	(1.02)	0.03	(0.45)	< 0.001

[1] Medical equipment included spirometer, exercise equipment, enteral nutrition infusion pump, parenteral nutrition infusion pump, automatic external defibrillator, orthotic procedures and devices, prosthetic procedures and implants; and enuresis alarm, including medical equipment delivery, setup, and/or dispensing service component of another HCPCS code. [2] Systemic corticosteroids included betamethasone, corticotropin, dexamethasone, methylprednisolone, prednisolone, prednisone, or triamcinolone. [3] Mean values are per patient per year.

DISCUSSION

In our study we used a national managed care database to estimate the medical costs and healthcare resource use of subjects with SSc in the United States. This approach allowed us to obtain a relatively large sample of SSc subjects with geographic diversity throughout the country. During the period 2003-2008, average annual postindex costs of subjects with SSc were $17,365 (SD $34,674). Without adjustment for other factors, average annual costs of SSc subjects were more than 3-fold higher than the average annual costs of matched control individuals unaffected by SSc. When adjusting for clinical and demographic char-

acteristics (including comorbid conditions), the cost ratio of SSc subjects to controls was 1.988 (95% CI 1.773–2.230). Ambulatory costs appeared to be the largest driver of overall medical costs in this study population. Among SSc subjects, average postindex ambulatory costs totaled $6713 (39% of yearly costs). The second-largest driver of overall medical costs was inpatient costs (31% of costs), followed by pharmacy costs (22% of costs). We did not assess indirect costs, which may also add to the economic burden associated with SSc.

Most statistics of healthcare resource use were higher among SSc subjects than controls, including average counts of ambulatory visits, primary care physician visits, specialist visits, emergency department visits, and inpatient hospital stays. The percentage of SSc subjects with a rheumatologist visit was about twice as high as the percentage of subjects with a nephrologist visit or a dermatologist visit. Average counts of pharmacy claims for many of the selected medications evaluated here were higher among SSc subjects compared to their respective matched controls, including claims for systemic corticosteroids, methotrexate, mycophenolate mofetil, cyclophosphamide, bosentan, and sildenafil. Of these, systemic corticosteroids were the most frequently prescribed medication among subjects with SSc. Additionally, evidence of pharmacy claims for systemic corticosteroids, as well as for methotrexate and PAH medications, was associated with significantly higher overall medical costs. Although evidence of use of PAH medication was associated with higher overall costs, evidence of pulmonary hypertension was not associated with higher overall costs. Possible reasons for this could be that presence of a single pulmonary hypertension diagnosis could mean presence of disease or use of diagnosis code as a rule-out criterion. In the latter case this means using the presence of a single diagnosis to identify comorbidities could result in some misclassified cases. Another explanation could be that diagnosis alone may have included patients with milder disease who did not need treatment, or alternatively, evidence of use of PAH medication could be a better proxy for a confirmed condition severe enough to require therapy.

Several studies have investigated the economic burden of SSc. A study using community hospital discharge data from 1995 in the United States reported that subjects with SSc had an average charge per hospitalization of $14,948 and an average length of stay of 7.5 days[24]. Another US study, which used multiple databases, reported that subjects with SSc had average annual direct costs of $4731 in 1994 and that overall annual direct and indirect costs for the disease amounted to $1.5 billion[25]. A Canadian study using a disease registry found that average annual direct costs of SSc were $5038 (2007 Can$) per subject and that total average indirect costs due to productivity losses were $13,415 (2007 Can$) per subject[26]. Studies in Europe have reported average total (direct and indirect) annual costs for SSc ranging from €9619 to €11,073.99 per subject[27,28]. Multiple studies have found that costs for subjects with dSSc are higher than costs for those with lSSc[26,27,28].

Our estimate of mean annual direct healthcare costs for subjects with SSc ($17,365) is substantially higher than the estimate from Wilson ($4731)[25]. However, compared to the present study, the estimates from Wilson are not as recent (Wilson used data from 1994), and the sample of SSc subjects used by Wilson for the direct cost estimates was relatively small and not geographically diverse throughout the country. Wilson obtained cost data from the Medi-Cal claims database in California, and from the American Rheumatism Association Medical Information System (ARAMIS) databank, which contains data collected by questionnaire from patients in major SSc centers; in contrast, data from our study were from a large national MCO database. Nietert, *et al* studied the average length of hospitalization among SSc subjects in the United States[24]. They reported an average length of stay of 7.5 days, higher than the average length of stay reported in our study (2.19 days). Although the cause for this difference is not clear, differences in claims-based patient identification algorithms and/or time periods between the studies may have been contributing factors. Nietert, *et al* reported that SSc subjects had an average charge per hospitalization of $14,948. The average inpatient costs reported in our study ($5390 among SSc subjects) were calculated per year, not per visit, and cannot be directly compared to those of Nietert, *et al*. In another study, Bernatsky, *et al* estimated average direct costs of SSc subjects in Canada at $5038 (2007 Can$)[26], which is lower than the estimates reported in the present study. However, as differences exist between the US and Canadian healthcare systems, comparisons between our study and that of Bernatsky, *et al* should be made with caution. If we compare our results to other related chronic connective tissue disorders, our estimates appear to be lower than estimates for lupus ($19,502 per year) and higher than those for rheumatoid arthritis ($10,716 per year)[31,32]. However, no direct statistical comparisons were involved and no definite conclusions can be drawn.

Limitations related to claims data should be considered when interpreting these results. The presence of a diagnosis code on a medical claim could either indicate presence of the disease or could be a marker for a rule-out criterion (rather than actual disease). Also, for an individual to be counted in our study, a diagnosis of SSc was required; therefore, subjects (especially those with milder disease) who may not have been diagnosed correctly or who did not seek help from a healthcare provider would have been overlooked. However, individuals were eligible to enter the study on the basis of an outpatient diagnosis without requiring an inpatient diagnosis, which may have led to selection of some subjects with milder disease. Future studies in which subjects' medical charts are reviewed could help val-

idate the claims-based patient identification algorithm used here. Also, at the time of our study there were no ICD-9-CM codes available that could differentiate between limited and diffuse disease, so we could not determine separate cost and resource use estimates for these subgroups. The presence of a pharmacy claim does not necessarily mean a medication was taken as prescribed, and medications given as samples would not have been recorded in our study. Finally, subjects from the study were from a managed care plan, and these results may not be generalizable to other populations.

Subjects with SSc in this US managed care population had high annual medical costs and resource use, in comparison to individuals without the disease. Ambulatory costs were the single largest component of overall costs in this population of subjects with SSc. Also, as expected, presence of several SSc-related conditions (GI bleeding, renal disease, and lung disease) was associated with increased costs. Given the chronic expression of SSc, these findings demonstrate a need to develop more effective therapeutic strategies to manage this disease.

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