


Direct and indirect costs of systemic sclerosis and associated interstitial lung disease: A nationwide population-based cohort study

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Abstract

Background and objective: The study aimed to evaluate the direct and indirect costs of systemic sclerosis (SSc) in cases with and without interstitial lung disease (ILD).

Methods: Cases diagnosed with SSc (2002–2015) were identified in the Danish National Patient Registry. Cases were matched 1:4 with non-SSc controls from the general population. Data on costs were obtained from national databases. Excess cost was estimated as the annual cost per case subtracting the costs of the control.

Results: We identified 1869 cases and 7463 controls. Total excess cost (direct healthcare, elderly care and indirect costs) in the SSc-ILD cohort was €29,725, and €17,905 in the non-ILD SSc cohort. In- and out-patient contacts and forgone earnings were the key drivers of costs in both cohorts. Healthcare costs were higher before and after the diagnosis compared with the controls. Men incurred higher excess healthcare costs than women. Hospitalization and outpatient services were the key drivers of the gender-associated differences. Income from employment decreased more rapidly after diagnosis in the SSc-ILD cohort than in the non-ILD SSc cohort. Public transfer income increased after diagnosis, with the most pronounced difference in the SSc-ILD cohort. Disability pension was the key driver of public transfer income.

Conclusion: SSc is associated with a significant individual and societal burden that is evident several years before and after the diagnosis. Total excess costs are higher in SSc-ILD than in the non-ILD SSc underlining the severity of pulmonary involvement. Initiatives to maintain work ability and to reduce hospital admissions may reduce the economic burden of SSc.

KEYWORDS

cost of illness, direct healthcare cost, healthcare cost, indirect costs, systemic sclerosis-associated interstitial lung disease

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by fibrosis of the skin and internal organs and vasculopathy.¹ SSc is a rare disease with an annual prevalence of 4–44 per 100,000 and associated with high morbidity, premature death and loss of productivity.^{1–3} SSc is mostly diagnosed in women between 30 and 50 years.^{4,5} Pulmonary involvement with interstitial lung

disease (SSc-ILD) is a prevalent complication and clinically significant ILD is seen in up to 40% of patients.⁶ SSc-ILD onset is usually within the first 5 years after diagnosis^{1,7,8} and ranges from subclinical to severe pulmonary fibrosis with reduced lung function and respiratory failure. Moreover, SSc-ILD is associated with a higher mortality than non-ILD SSc.^{4,6,9}

Few studies have evaluated direct healthcare costs related to SSc-ILD and they all find higher annual healthcare

costs related to SSc-ILD (€5855–€33,072) compared with non-ILD SSc (€4406–€5206).^{10–12}

SSc is associated with high working disability and the rate of patients unable to work increases with disease severity.^{3,13,14} Given that SSc mostly affects patients in their working age, loss of productivity imposes an economic burden on both the affected individuals and society. There is a lack of studies evaluating the economic impact of foregone earnings due to lost working ability and public transfer income (i.e., indirect costs) associated with SSc as such information is sparsely available. The majority of studies evaluating indirect costs of SSc are cross-sectional and unable to assess how costs vary with disease severity (Table S1 in the Supporting Information). Only one study¹² has evaluated indirect costs of SSc-ILD. However, the study was small (52 cases) and included only cases, who were insured and employed, thus limiting the generalizability of the results.

In our nationwide registry-based cohort study with matched controls, we evaluated the excess direct healthcare costs and indirect costs associated with SSc in patients with and without ILD 5 years before and 4 years after the diagnosis.

The aims of the study were (1) to evaluate the annual average direct healthcare costs, elderly care costs and indirect costs in patients with SSc with or without ILD and in matched controls without SSc and (2) to evaluate the change in societal burden of SSc-ILD and non-ILD SSc in comparison with matched controls without SSc before and after the diagnosis.

METHODS

Study setting

In Denmark, all citizens have access to tax-funded universal health care. A unique 10-digit Civil Registration System (CPR) number is assigned to all Danish citizens upon birth or immigration, enabling precise, individual-level record linkage across all Danish registries.¹⁵

Data source

The Danish National Patient Registry (DNPR) is an administrative registry that has achieved complete nationwide coverage on all non-psychiatric admissions since 1978 and outpatient clinic contacts since 1995.¹⁶ Registration is mandatory and submitted by the treating physician. Diagnoses are classified according to the International Classification of Diseases and Related Health problems 10th Revision (ICD-10).

The National Income Statistics Registry (ISR) holds information on income composition of the entire Danish population¹⁷ Information on vital status, migration and cohabitation was obtained from the CPR.¹⁸

SUMMARY AT A GLANCE

In a cohort of 1869 cases and 7463 matched controls, we found a significant individual and societal burden of systemic sclerosis that is evident several years before and after the diagnosis. Total excess costs were highest in cases with concomitant interstitial lung disease, which underlines the severity of pulmonary involvement.

Study population

Patients ≥ 18 years of age diagnosed with SSc (ICD-10: M34) from 1 January 2002 to 31 December 2015 were identified in the DNPR and included as incident cases. Prevalent cases would bias the results and therefore a 2-year washout period was applied (2000–2001) excluding patients diagnosed before the inclusion period. Cases diagnosed with ILD (ICD-10: J84) any time before or after SSc diagnosis were included in the SSc-ILD cohort and cases with no ILD diagnosis were included in the non-ILD SSc cohort.

Cases were individually matched on the date of the first SSc diagnosis to controls without SSc randomly selected from the background population using the CPR registry. Cases and controls were matched 1:4 by sex, birth year, cohabitating status and municipality.

The Deyo–Charlson Comorbidity Index (DCCI) included comorbidities from the DNPR 3 years before the index date (Table S2 in the Supporting Information).^{19–21} The DCCI includes both separate comorbidities and SSc-related conditions as these cannot be accurately separated using only the ICD-10 coding system.

The DCCI has a positive predictive value (PPV) of 98% in the DNPR.²²

Socioeconomic status (SES) was defined by source of income in SSc cases and controls as high if employed or enrolled in an educational programme and low if receiving public transfer payment. Cases receiving age pension were not included in either SES group as a universal public pension is paid to all retired Danish citizens above 65 years of age.

Patients and controls were followed up until death, migration or end of follow-up in 2016. Controls were excluded if the matched case died or migrated and cases were excluded if all four controls died or migrated before the end of follow-up.

Costing methodology

Cohort studies can measure the costs and work productivity from the time of diagnosis and onwards and thereby display the burden of disease at different disease stages. The present study used an excess cost approach (including costs related

to SSc and comorbidities)²³ by estimating the mean annual cost per case compared with the costs of the controls.

Healthcare costs included the average costs of hospital admissions, outpatient care (including emergency department contact), primary care visits and medication. Hospital-related costs were calculated based on data from the Diagnosis-Related Groups/Danish Ambulant Grouping System codes. Costs of medication were obtained from the Danish Register of Medicinal Product Statistics, which includes data on all prescription drugs collected in the Danish community pharmacies since 1995.²⁴ Frequencies and costs of consultations with general practitioners and other specialists were obtained from the National Health Service Register.²⁵ Psychiatric costs were available from 2007.

Indirect costs were estimated as the differences in earning between cases and controls based on earned income and various social security compensation.

Costs of elderly care and retirement home were available from 2009. Costs were measured annually and adjusted to 2020 prices in euros (€1: DKK 7.45).

Statistical analysis

Costs are presented as annual means for cases and controls. Statistical significance of the cost estimates and DCCI was assessed by non-parametric bootstrap analysis. A significance level of 0.05 was assumed for all tests. In the before

and after analysis, only cases with at least a 5-year follow-up period prior to diagnosis were included. A Generalized Estimating Equation (two-step model) for gamma regression was used to compare healthcare costs, income from employment and public transfer income in female cases and controls with male cases and controls within age groups and to assess gender differences in healthcare costs (adjusted for age). The two-step model takes individuals with no costs or income (= 0) into account. Statistical analyses were performed using SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA).

RESULTS

We identified and extracted data for 1869 SSc cases and 7463 matching controls from the DNPR. Matching was successful in more than 99% of cases. Female cases were over-represented (75.5%) and the age-associated incidence peak was 51–70 years. SSc-ILD was diagnosed in 275 cases (14.7%). The proportion of men was higher in the SSc-ILD cohort (30.9%) than in the non-ILD SSc cohort (23.4%). DCCI was higher in cases than in controls ($p < 0.01$) (Table 1). SES did not differ between the SSc cohort and controls from 5 to 3 years before diagnosis, whereas the SSc cohort had lower ($p < 0.01$) SES from 2 years before until 4 years after the diagnosis compared with controls (Table S3 in the Supporting Information).

TABLE 1 Baseline characteristics of the SSc cases (all), SSc-ILD cases, non-SSc cases and matched controls

	SSc-all		Controls		ILD-SSc		Controls		Non-ILD SSc		Controls	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Total (<i>n</i>)	1869		7463		275		1098		1594		6365	
Age												
18–30	116	6.2	464	6.2	9	3.3	36	3.3	107	6.7	428	6.7
31–40	176	9.4	702	9.4	18	6.5	71	6.5	158	9.9	631	9.9
41–50	316	16.9	1264	16.9	56	20.4	224	20.4	260	16.3	1040	16.3
51–60	462	24.7	1848	24.8	70	25.5	280	25.5	392	24.6	1568	24.6
61–70	455	24.3	1815	24.3	73	26.5	292	26.6	382	24.0	1523	23.9
>70	344	18.4	1370	18.4	49	17.8	195	17.8	295	18.5	1175	18.5
Sex												
Male	458	24.5	1831	24.5	85	30.9	340	31.0	373	23.4	1491	23.4
Female	1411	75.5	5632	75.5	190	69.1	758	69.0	1221	76.6	4874	76.6
Cohabiting	1179	63.1	4699	63.0	183	66.5	731	66.6	996	62.5	3968	62.3
CCI score ^a												
0	1172	62.7	6430	86.2	167	60.7	951	86.6	1005	63.0	5479	86.1
1	352	18.8	556	7.5	60	21.8	80	7.3	292	18.3	476	7.5
2	188	10.1	299	4.0	28	10.2	43	3.9	160	10.0	256	4.0
3+	157	8.4	178	2.4	20	7.3	24	2.2	137	8.6	154	2.4
Mean CCI score (SD)	0.7 (1.2)		0.3 (0.9)		0.7 (1.2)		0.3 (1.0)		0.7 (1.3)		0.3 (0.9)	

Abbreviations: CCI, Charlson comorbidity index; ILD, interstitial lung disease; SSc, systemic sclerosis.

^aChi-square test for difference in CCI between cases and controls: $p < 0.001$ in all three groups.

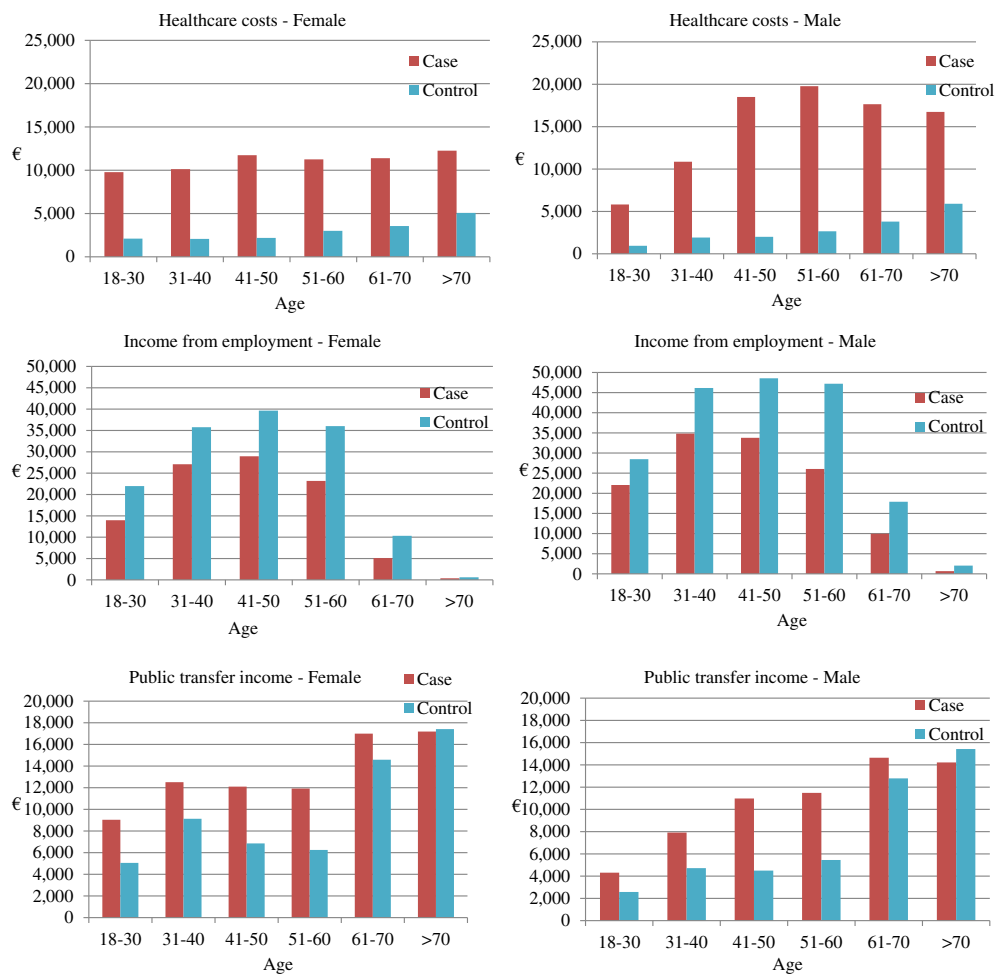


FIGURE 1 Healthcare costs, income from employment and public transfer income in euros (€) of all systemic sclerosis cases and matched controls distributed by age and sex

Healthcare costs were markedly higher in both genders within all age groups in the total SSc cohort compared with the controls (Figure 1).

Males aged 41–70 years incurred higher healthcare costs compared with controls than women compared with controls (Table S4 in the Supporting Information). Males aged 41–70 years incurred significantly higher healthcare costs than women compared with the controls in the non-ILD cohort, whereas a difference in costs between genders was only seen from 51 to 60 years in the SSc-ILD cohort (Table S4 in the Supporting Information). The differences in costs related to hospitalization and outpatient services were significantly higher in men compared with women for the SSc and non-ILD cohorts, whereas no gender differences were seen in the ILD-SSc cohort (Table S5 in the Supporting Information).

Income from employment was lower in all age groups and income from public transfers higher compared with the controls (Figure 1).

Both cohorts had higher healthcare and indirect costs compared with the controls. The total excess cost in the SSc-ILD cohort was €29,725, and €17,905 in the non-ILD SSc cohort. Healthcare costs and forgone earnings were key drivers of excess costs in both cohorts (Table 2).

The total healthcare costs were higher in both cohorts before and after the diagnosis compared with the controls with a peak around the time of diagnosis (Figure 2). Three years after diagnosis, healthcare costs seemed to increase again in the SSc-ILD, whereas healthcare cost continued to decrease in the non-ILD SSc cohort. Income from employment was lower in both cohorts compared with the controls 5 years before diagnosis, although this did not reach statistical significance until 2 years after diagnosis in the SSc-ILD cohort (Figure 2 and Table S6 in the Supporting Information). Income from employment decreased more rapidly after diagnosis in the SSc-ILD cohort than in the non-ILD SSc cohort (Figure 2). Income from public transfer was higher in both cohorts before diagnosis compared with the controls, although not statistically significant until the year of diagnosis (Table S6 in the Supporting Information). After diagnosis, public transfer income increased markedly with the most pronounced difference in the SSc-ILD cohort (Figure 2)

DISCUSSION

Our study is the first European study to evaluate indirect costs associated with SSc-ILD in a follow-up study. We saw

TABLE 2 Mean annual healthcare costs, income from employment, social transfer payments and home care costs after SSc diagnosis in (A) SSc-ILD cases and matched controls and (B) non-ILD SSc cases and matched controls

(A)		SSc-ILD	Controls	Difference	<i>p</i> -value
Number of persons (<i>N</i>)		275	1098		
Healthcare costs					
Outpatient services	€	5398	935	4463	<0.001
Inpatient admissions	€	11,215	1522	9693	<0.001
Prescription drugs	€	1384	484	900	<0.001
Primary health sector	€	917	413	504	<0.001
Psychiatric outpatient services	€	37	41	−4	1.000
Psychiatric inpatient admissions	€	98	99	−1	1.000
Healthcare costs total	€	19,050	3495	15,555	<0.001
Home care costs					
Home care—care	€	1007	607	400	0.126
Home care—practical help	€	218	85	133	<0.001
Home care total	€	1225	692	533	0.015
Earned income	€	14,922	24,685	−9763	<0.001
Public transfer income					
Unemployment insurance	€	237	442	−206	0.020
Social security benefit	€	1318	498	819	<0.001
Age pension	€	4782	5385	−604	0.046
Early retirement	€	1307	1087	220	0.748
Disability pension	€	4931	1731	3200	<0.001
Sick pay (public funded)	€	693	242	451	<0.001
Housing benefits	€	551	483	68	0.692
Childs benefits	€	280	355	−75	0.161
Public transfer income total	€	14,097	10,223	3873	<0.001
SSc-ILD excess costs					
Excess direct healthcare costs	€			15,555	
Excess home care costs	€			533	
Excess foregone earnings from employment	€			9763	
Excess social transfer payments	€			3873	
Excess costs, total	€			29,725	
(B)		Non-ILD SSc	Control	Difference	<i>p</i> -value
Number of persons (<i>N</i>)		1594	6365		
Healthcare costs					
Outpatient services	€	4433	1021	3411	<0.001
Inpatient admissions	€	5435	1600	3835	<0.001
Prescription drugs	€	975	427	547	<0.001
Primary health sector	€	746	419	326	<0.001
Psychiatric outpatient services	€	35	36	−1	1.000
Psychiatric inpatient admissions	€	96	96	0	1.000
Healthcare costs total	€	11,719	3599	8119	<0.001
Home care					
Home care—care	€	914	535	379	<0.001
Home care—practical help	€	206	100	105	<0.001
Home care total	€	1120	635	485	<0.001

(Continues)

TABLE 2 (Continued)

(B)		Non-ILD SSc	Control	Difference	p-value
Earned income	€	15,111	21,715	-6604	<0.001
Public transfer income					
Unemployment insurance	€	266	448	-182	<0.001
Social security benefit	€	1043	655	389	<0.001
Age pension	€	5370	5855	-485	<0.001
Early retirement	€	974	1148	-174	0.019
Disability pension	€	4518	1661	256	<0.001
Sick pay (public funded)	€	541	326	215	<0.001
Housing benefits	€	733	606	127	<0.001
Childs benefits	€	420	470	-49	0.014
Public transfer income total	€	13,864	11,167	2697	<0.001
Non-ILD SSc excess costs					
Excess direct healthcare costs	€			8119	
Excess home care costs	€			485	
Excess foregone earnings from employment	€			6604	
Excess social transfer payments	€			2697	
Excess costs, total	€			17,905	

Note: p-value from t-test and bootstrapping.
Abbreviations: ILD, interstitial lung disease; SSc, systemic sclerosis.

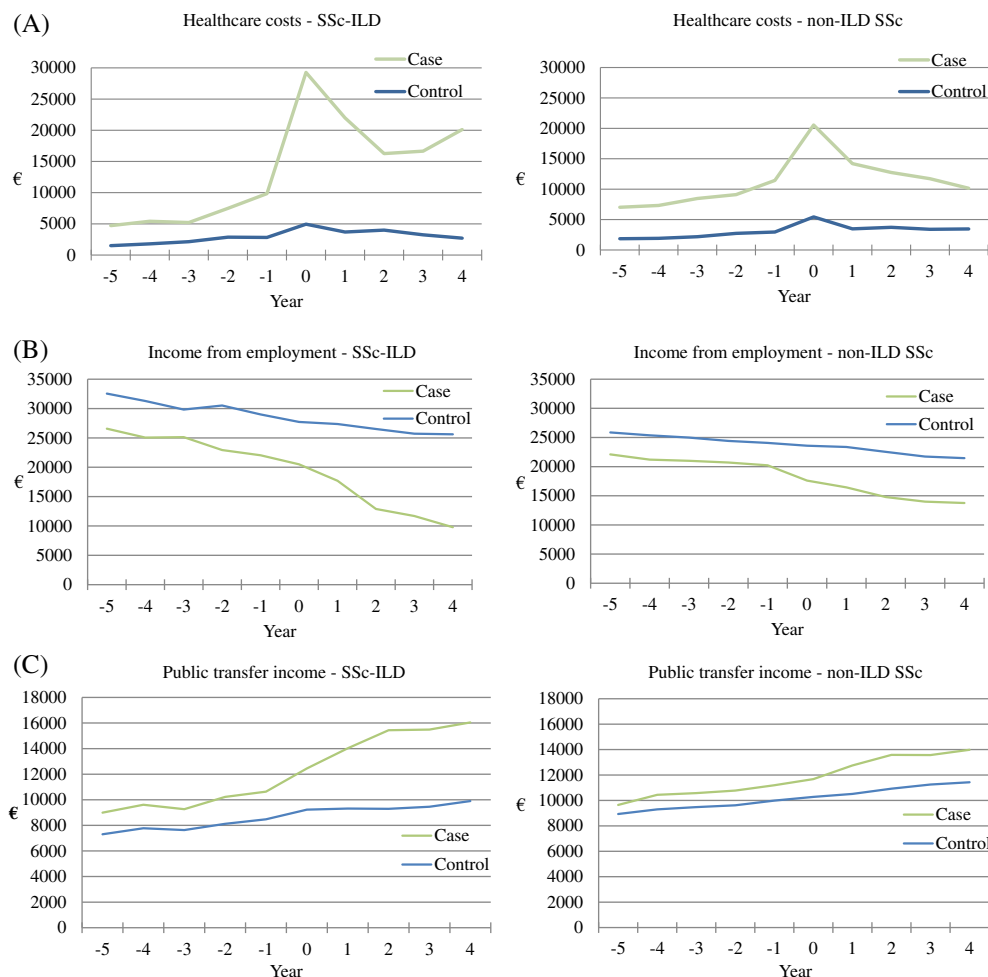


FIGURE 2 (A) Total healthcare costs, (B) income from employment and (C) public transfer income in euros (€) before and after the diagnosis of systemic sclerosis (SSc) in the SSc-interstitial lung disease (SSc-ILD) and non-ILD SSc cohorts compared with the matched controls. Year 0 = year of SSc diagnosis

that SSc-ILD was associated with a 40% higher total excess cost than non-ILD SSc compared with the controls (€29,725 vs. €17,905). The study provides important information on the individual and societal impact of SSc with and without ILD, not only at the time of diagnosis, but also in the years before and after the initial diagnosis of SSc.

With regard to direct healthcare costs, we found considerably higher healthcare costs among SSc cases compared with the controls in all age groups and both genders. Healthcare costs for both the SSc-ILD and the non-ILD SSc cohorts were largely driven by hospitalizations and outpatient visits. Noteworthy, the excess costs due to inpatient admissions were vastly higher in the SSc-ILD cohort (€9693) than in the non-ILD SSc cohort (€3835) indicating the severity of this complication. Two previous cohort studies also found higher excess healthcare costs in SSc-ILD compared with non-ILD SSc, with costs driven by outpatient pharmacy claims and services,¹¹ hospitalization and increasing ILD severity.¹⁰ An American study found healthcare costs to be significantly higher in an SSc-ILD cohort (\$37,505/€33,072) compared with non-SSc controls (\$4997/€4406) during 12 months of follow-up.¹²

Interestingly, we find that although healthcare costs decline after diagnosis in the non-ILD cohort, healthcare costs seem to increase in the 3 years following diagnosis in the SSc-ILD cohort. This is in concordance with Fischer et al.¹¹ who found healthcare cost to increase in cases with SSc-ILD 5 years after diagnosis. This likely reflects the high morbidity and progressive course of SSc-ILD seen in a high proportion of patients.

Because of the low prevalence and heterogeneous presentation of SSc, the time to diagnosis is often prolonged²⁶ which might be reflected in our data by the higher healthcare costs several years before diagnosis in both cohorts compared with the controls. Moreover, comorbidity 3 years prior to SSc diagnosis was higher in SSc cases than in the controls, which likely contributes to the observed excess healthcare costs. Two years prior to diagnosis, we also observed lower SES in SSc cases compared with the controls. Low SES is associated with poor health, and poor health is vice versa a risk factor for low SES.²⁷ It is unclear from our data to what extent comorbidities contribute to this socioeconomic disadvantage and low SES in the SSc cases. Future research is needed to detangle this interaction between SES and comorbidities and the impact on SSc.

Excess healthcare costs in the total SSc cohort were considerably higher in men compared with women. Surprisingly, the difference in costs between genders could not be explained by the high share of men with SSc-ILD (Figure 2 and Table S4 in the Supporting Information). The gender-associated difference in costs was related to hospitalization and outpatient services, whereas we saw no difference in costs related to medication and primary health care (Table S5 in the Supporting Information). These findings might reflect that men suffer more severe disease than women, which is supported by several studies that find worse prognosis among men.²⁸

To our knowledge, this is the first study to evaluate indirect costs associated with SSc-ILD in a population-based nationwide cohort. We find that indirect costs contributed markedly to the total costs associated with both ILD-SSc and non-ILD SSc, which is in line with previous cross-sectional studies on productivity loss associated with SSc that found annual costs from €5500 to €10,500.^{29–32} A cohort study from the United States evaluated insured and working SSc cases and matched non-SSc controls and found excess costs of \$3103 (€2736) due to productivity loss in the first year following diagnosis.³³ In a subset cohort from the study, a difference of \$5846 (€5155) was found between SSc-ILD cases ($n = 52$) and matched non-SSc controls during 6 months of follow-up.¹² This is in line with our study where we saw reduced earned income in both cohorts compared with the matched controls, with the largest difference in the SSc-ILD cohort (€9763) compared with the non-ILD SSc cohort (€6604). Importantly, our results reflect foregone earnings of not only working cases, but also the entire Danish SSc population.

Public transfer income after diagnosis was higher and increased in both cohorts compared with the controls, with the most significant difference seen in the SSc-ILD cohort. Disability pension was the key driver of excess public transfer income in both cohorts after diagnosis, which is in line with Sandqvist et al. who found increasing rates of working disability after SSc onset.¹³

As expected, the difference in earned income and public transfer income levelled out in the age groups >70 years because of the universal public pension (Figure 2).

The strengths of the present study are the large and nationwide study population and the 17-year study period. The population-based study design, within a tax-funded, uniformly organized healthcare system and virtually complete follow-up on all cases, reduces the risk of selection bias.¹⁸ The population-based matched control cohort enabled us to control for some important demographic confounders. We expect the risk of SSc misclassification to be minimal as SSc have a PPV of 94% in the DNPR.³⁴ Importantly, most cases with SSc and ILD are diagnosed in the hospital settings; hence, we expect our data to be highly representative of the entire Danish SSc population and our findings to be generalizable to populations with similar standard of medical care as in Denmark.

The study has several limitations. The DNPR does not provide information on disease severity, BMI or smoking; thus, we were not able to evaluate the impact of these important factors.

Low SES may contribute to the excess costs found in this study. We partly accounted for socioeconomic factors by matching on cohabitation and residency. Furthermore, stratification analysis showed no difference in SES between SSc cases and controls 5 to 3 years before diagnosis, whereas the observed low SES 2 years before diagnosis in the SSc cohorts is likely influenced by increased morbidity prior to SSc diagnosis hindering cases to maintain their job.

We cannot dismiss that other markers of SES (e.g., highest achieved educational level and occupational type) are associated with SSc and thus affect income level.

ILD is not validated in the DNPR which could lead to misclassification and an over- or under-estimation of the share of cases with SSc-ILD. However, validation studies of the DNPR generally show a high PPV, particularly for diseases that are primarily followed in specialized departments such as ILD; thus, we expect this information bias to be limited.²²

In conclusion, we found that SSc is associated with a significant individual as well as societal burden that is evident several years before and after the diagnosis. SSc-ILD is associated with 40% higher total excess costs compared with non-ILD SSc, thus underlining the severity of pulmonary involvement. Importantly, we find that men impose higher excess healthcare-related costs than women, and hospitalization and outpatient services are the key drivers of gender differences in healthcare costs.

Given that the key driver of healthcare costs in SSc-ILD was inpatient admissions, initiatives to reduce admissions could potentially reduce costs associated with SSc-ILD. Furthermore, since the majority of patients are diagnosed with SSc in their working age, the decrease in working ability and increasing costs due to public transfer income underline the importance of timely diagnosis and treatment in order to maintain employment for patients.

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CONFLICT OF INTEREST

Ole Hilberg has received an unrestricted grant from Boehringer Ingelheim A/S for the current work. Outside the current work, Malene Knarborg has received a fee from AstraZenica A/S. Melina Gade Sikjær, Anders Løkke and Rikke Ibsen declare no competing interests.

AUTHOR CONTRIBUTION

Malene Knarborg: Conceptualization (equal); methodology (lead); project administration (lead); visualization (equal); writing – original draft (supporting); writing – review and editing (equal). **Anders Løkke:** Conceptualization (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (lead). **Ole Hilberg:** Conceptualization (equal); methodology (equal); project administration (supporting); supervision (lead); writing – review and editing (equal). **Rikke Ibsen:** Conceptualization (equal); data curation (lead); formal analysis (lead); methodology (equal); software (lead); validation (lead); visualization (equal); writing – review and editing (supporting). **Melina Gade Sikjær:** Conceptualization (equal); methodology (equal); project administration (equal); visualization (equal); writing – original draft (lead).

DATA AVAILABILITY STATEMENT

Data were anonymized from the national databases and are not publicly available.

HUMAN ETHICS APPROVAL DECLARATION

The study was approved by the Danish Data Protection Agency as the research only involved register-based data and therefore human research ethical approval was not required.

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REFERENCES

- Denton CP, Khanna D. Systemic sclerosis. *Lancet*. 2017;390(10103):1685–99.
- Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. *Clin Epidemiol*. 2019;11:257–73.
- Hudson M, Steele R, Lu Y, Thombs BD, Baron M. Work disability in systemic sclerosis. *J Rheumatol*. 2009;36(11):2481–6.
- Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis*. 2010;69(10):1809–15.
- Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum*. 2003;48(8):2246–55.
- Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med*. 2020;8(3):304–20.
- Benan M, Hande I, Gul O. The natural course of progressive systemic sclerosis patients with interstitial lung involvement. *Clin Rheumatol*. 2007;26(3):349–54.
- Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moynadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol*. 2014;66(6):1625–35.
- Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. *Am J Respir Crit Care Med*. 2019;200(10):1258–66.
- Morrisroe K, Stevens W, Sahhar J, Ngian GS, Ferdowsi N, Hansen D, et al. The clinical and economic burden of systemic sclerosis related interstitial lung disease. *Rheumatology (Oxford)*. 2020;59(8):1878–88.
- Fischer A, Kong AM, Swigris JJ, Cole AL, Raimundo K. All-cause healthcare costs and mortality in patients with systemic sclerosis with lung involvement. *J Rheumatol*. 2018;45(2):235–41.
- Zhou Z, Fan Y, Thomason D, Tang W, Liu X, Zhou ZY, et al. Economic burden of illness among commercially insured patients with systemic sclerosis with interstitial lung disease in the USA: a claims data analysis. *Adv Ther*. 2019;36(5):1100–13.
- Sandqvist G, Hesselstrand R, Petersson IF, Kristensen LE. Work disability in early systemic sclerosis: a longitudinal population-based cohort study. *J Rheumatol*. 2015;42(10):1794–800.
- Sharif R, Mayes MD, Nicassio PM, Gonzalez EB, Draeger H, McNearney TA, et al. Determinants of work disability in patients with systemic sclerosis: a longitudinal study of the GENISOS cohort. *Semin Arthritis Rheum*. 2011;41(1):38–47.
- Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 Suppl):22–5.

16. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30–3.
17. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39(7 Suppl):103–5.
18. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541–9.
19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613–9.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–83.
21. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004;57(12):1288–94.
22. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.
23. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. *Pharmacoeconomics*. 2011;29(8):653–71.
24. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38–41.
25. Andersen JS, Olivarius Nde F, Krasnik A. The Danish National Health Service Register. *Scand J Public Health*. 2011;39(7 Suppl):34–7.
26. Delisle VC, Hudson M, Baron M, Thombs BD, Canadian Scleroderma Research Group A. Sex and time to diagnosis in systemic sclerosis: an updated analysis of 1,129 patients from the Canadian scleroderma research group registry. *Clin Exp Rheumatol*. 2014;32(6 Suppl 86):S-10-4.
27. Hoffmann R, Kröger H, Geyer S. Social causation versus health selection in the life course: does their relative importance differ by dimension of SES? *Soc Indic Res*. 2019;141(3):1341–67.
28. Poekerbux MR, Giovannelli J, Dauchet L, Mouthon L, Agard C, Lega JC, et al. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. *Arthritis Res Ther*. 2019;21(1):86.
29. Chevrel K, Brigham KB, Gandré C, Mouthon L. The economic burden and health-related quality of life associated with systemic sclerosis in France. *Scand J Rheumatol*. 2015;44(3):238–46.
30. Bernatsky S, Hudson M, Panopalis P, Clarke AE, Pope J, Leclercq S, et al. The cost of systemic sclerosis. *Arthritis Rheum*. 2009;61(1):119–23.
31. López-Bastida J, Linertová R, Oliva-Moreno J, Posada-de-la-Paz M, Serrano-Aguilar P. Social economic costs and health-related quality of life in patients with systemic sclerosis in Spain. *Arthritis Care Res (Hoboken)*. 2014;66(3):473–80.
32. Kawalec PP, Malinowski KP. The indirect costs of systemic autoimmune diseases, systemic lupus erythematosus, systemic sclerosis and sarcoidosis: a summary of 2012 real-life data from the Social Insurance Institution in Poland. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(4):667–73.
33. Zhou Z, Fan Y, Tang W, Liu X, Thomason D, Zhou ZY, et al. Economic burden among commercially insured patients with systemic sclerosis in the United States. *J Rheumatol*. 2019;46(8):920–7.
34. Butt SA, Jeppesen JL, Fuchs C, Mogensen M, Engelhart M, Torp-Pedersen C, et al. Trends in incidence, mortality, and causes of death associated with systemic sclerosis in Denmark between 1995 and 2015: a nationwide cohort study. *BMC Rheumatol*. 2018;2:36.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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