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ORIGINAL ARTICLE

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Hospitalizations due to systemic connective tissue diseases: Secular trends and regional disparities in Sweden, 1998-2016

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Abstract

Aim: To investigate secular trends and regional disparities in hospitalizations due to systemic connective tissue diseases (SCTD) in Sweden from 1998 to 2016.

Method: We identified all hospital admissions with a principal diagnosis of SCTD (ICD-10 codes: M30-M36) from the Swedish National Patient Register. Joinpoint regression was used to assess secular trends in age-standardized hospitalization rates (ASHR) and proportions of SCTD from all and musculoskeletal disorders hospitalizations. We also assessed the secular trends in the absolute and relative regional disparities of SCTD hospitalizations.

Results: We identified 89 333 SCTD hospitalizations (0.3% of all hospitalizations), of these about 69% were for women and 49% of patients were aged 15-64 years. Polyarteritis nodosa and related conditions (PANRC) and systemic lupus erythematosus (SLE) were the most frequent SCTD among those aged <10 years and 10-54 years, respectively. Joinpoint regression suggested that both rates and proportions of SCTD hospitalizations declined over time. These trends persisted among sex, age and diagnosis subgroups except for PANRC in patients aged 0-19 years who observed an average annual increase of 3.4% (95% CI: 1.8, 5.1) over the study period. There were 2.4-fold (95% CI: 2.3-2.5) difference between the regions with the highest and lowest mean ASHR. There was no statistically significant secular trend in the relative regional disparities, whereas the absolute regional disparity declined over time.

Conclusion: There were substantial decreases in the absolute and relative burden of SCTD hospitalizations reflecting possible improvements in disease management in Sweden. The rising trend in PANRC among the youngest children warrants further investigation.

KEYWORDS
epidemiology, Sjögren's syndrome, soft tissue rheumatism and regional pain syndromes, systemic lupus erythematous, vasculitides

1 | INTRODUCTION

The systemic connective tissue diseases (SCTD) including systemic vasculitis, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren syndrome, polymyositis and dermatomyositis are a group of chronic inflammatory systemic autoimmune disorders associated with disability, pain, deterioration in quality of life, morbidity and excess mortality.[1-4] These disorders are also associated with substantial health care costs and productivity losses (work disability, early retirement) imposing significant economic burden on patients, healthcare systems and societies.[3-7] For instance, there was a 3-fold difference in total costs for SLE in an incipient cohort

compared with matched population controls in southern Sweden.[8] Hospitalizations are a key driver of healthcare costs among people with SCTD.[3,4,9] A recent study estimated that 58% of total healthcare costs of Swedish patients with SLE were attributed to hospitalization.[10] Despite this, very few studies investigated secular trends in hospitalization for a specific SCTD (eg, SLE,[11,12] SSc,[13,14] granulomatosis with polyangiitis [GPA][15]) and to our knowledge, no study has assessed secular trends of hospitalizations for SCTD and its sub-diagnoses in a single study using the same data source and uniform methodology. Considering improvements in management of SCTD in recent decades, such analysis can assist evaluating the effectiveness of these improvements, helping to understand changes in burden and management of the disease, and aid informed healthcare planning. To address this knowledge gap, we evaluated secular trends in SCTD hospitalizations and its sub-diagnoses in Sweden from 1998 to 2016 using the Swedish National Patient Register. We also quantified the absolute and relative regional disparities in SCTD hospitalizations and assessed secular trends in these disparities over the study period.

2 | METHOD

2.1 | Data sources

This study was performed using the public data from 1998 to 2016 on the principal diagnoses of almost all hospital admissions in Sweden by age, sex, region and year from the National Board of Health and Welfare's Patient Register (NPR) (http://www.socialstyrelsen.se/). The principal diagnoses are coded according to the International Classification of Diseases, 10th revision (ICD-10). We identified SCTD hospitalizations as principal diagnoses with the ICD-10 codes of M30-M36. We also identified the following SCTD sub-diagnoses: polyarteritis nodosa and related conditions (PANRC, ICD-10 code: M30), other necrotizing vasculopathies (ICD-10 code: M31), SLE (ICD-10 code: M32), dermatomyositis/polymyositis (ICD-10 code: M33), SSc (ICD-10 code: M34), other systemic involvement of connective tissue (ICD-10 code: M35). Due to low numbers of hospital admissions from ICD-10 code M36 (n = 13) we did not conduct subgroup analysis for this sub-diagnosis. Furthermore, we identified hospitalizations of musculoskeletal (MSK) disorders as principal diagnoses with the ICD-10 codes of M00-M99. The data on population by sex, age, region and year were obtained from Statistics Sweden (http://www.scb.se).

2.2 | Temporal trend analysis

We used joinpoint regression to evaluate the secular trends in age-standardized hospitalization rates (computed by means of direct standardization using the Swedish population in the year 2016 as standard), in proportions of SCTD hospitalizations from MSK disorders hospitalizations, in proportions of SCTD hospitalizations from all hospitalizations, and in proportions of each SCTD sub-diagnosis from total SCTD hospitalizations. We used the Joinpoint Regression Program version 4.2.0.2 from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint). This program applies a series of permutation tests to calculate the number of joinpoints to best fit the data and estimate an annual percentage change (APC) for each joinpoint. The average annual percent change (AAPC) is calculated as the weighted average of APCs to provide a summary measure of the trend for the whole time period. These analyses were also performed across sex and age subgroups (0-19, 20-49, 50-64, 65-79 and 80+ years).

2.3 | Regional disparity

The absolute weighted mean difference from overall mean was used to assess the absolute regional disparities. This was calculated as the sum of the absolute difference in each region age-standardized hospitalization rate from the national rate, weighted by the region's proportion of the Swedish population.[16] We quantified the relative regional disparities using the index of disparity, calculated as the average of the absolute differences between age-standardized hospitalization rate in each region and the national rate, divided by the national rate and expressed as a percentage.[17] The secular trends in the regional disparities were assessed using the non-parametric Mann Kendall trend test.[18]

3 | RESULTS

3.1 | Absolute numbers

There were 89 333 hospital admissions with a principal diagnosis of SCTD during 1998-2016; 68.6% of these were for women and 48.5% of patients were aged 15-64 years. In all age groups but those patients <10 years of age, hospitalizations frequencies and rates were higher in women than men (Figure 1). Overall, SCTD constituted 0.3% of all hospitalizations and 5.6% of MSK disorders hospitalizations, with substantial variations across sex and age subgroups (Figure S1). Across SCTD sub-diagnoses, other systemic involvement of connective tissue was most common (30.5%), followed by other necrotizing vasculopathies (28.1%), SLE (18.3%) and SSc (14.0%). The distribution of SCTD sub-diagnoses varied by sex and age subgroups (Figure S2). Women had higher age-standardized hospitalization rates compared with men for all SCTD sub-diagnoses but PANRC.

3.2 | Temporal trends

The mean age-standardized hospitalization rate for SCTD declined from 66.4 (95% CI: 65.4-67.4) in 1998-2000 to 37.7 (37.0-38.4) in 2014-2016 per 100 000 persons, representing 43.2% (41.8-44.5) reduction. Across SCTD sub-diagnoses, the greatest reduction was seen for SLE which declined by 57% (54.4-59.4) from 13.1 to 5.6 per 100 000 persons between 1998-2000 and 2014-2016. At the same time, the proportions of SCTD from all (MSK disorders) hospitalizations decreased from 0.39% (7.38%) to 0.26% (4.19%).

Joinpoint regression revealed that the annual age-standardized hospitalization rate for SCTD declined by 5.5% (95% CI: 3.0-8.0) per

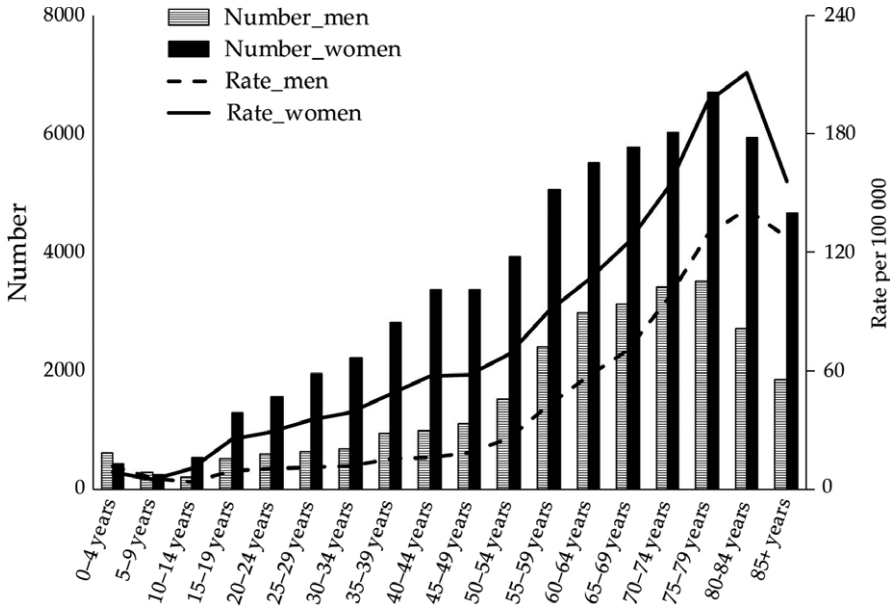

FIGURE 1 The absolute number and hospitalization rates per 100 000 persons for systemic connective tissue diseases from 1998 to 2016, by sex and age subgroups

year from 1998 through 2003, remained stable during 2003-2008, and declined by 6.1% (4.7, 7.5) per year thereafter (Figure 2), resulting in an average annual reduction of 3.9% (2.6-5.1) for the whole study period (Table 1). Similar declining trends were seen for the proportions of SCTD from all and MSK disorders hospitalizations. These trends persisted among sex and age subgroups (Table 1).

Age-standardized hospitalization rates for all SCTD sub-diagnoses declined over the study period (Table 2). Hospitalization rates were either declining or stable across sex and age subgroups except for PANRC among persons aged 0-19 years which rose, on average, by 3.4% (1.8-5.1) per year over the study period. There were changes in composition of SCTD with statistically significant increases in proportions of other necrotizing vasculopathies and SSc from SCTD hospitalizations and declines in proportions of SLE and other systemic involvement of connective tissue (Table 2, Figure 3).

3.3 | Regional disparities

The absolute weighted mean difference from overall mean ranged from 6.7 to 23.5 per 100 000 persons with a statistically significant declining trend ($Z = -3.2$, $P = .001$, Table S1). In overall, there were 2.4-fold (95% CI: 2.3-2.5) difference between the regions with the highest and lowest mean age-standardized SCTD hospitalization rates (in 13 out of 19 study-years, this ratio was ≥3.0). The index of disparity ranged from 16.9% to 32.6% with no statistically significant trend over the study period ($Z = -0.6$, $P = .53$).

4 | DISCUSSION

There were substantial reductions in SCTD hospitalization rates and proportional burden in Sweden during the 2 most recent decades. Hospitalization rates peaked in the 80-84 years age group and was higher in women than men in all age groups but in the youngest children (<10 years of age). While there were generally declining secular trends in hospitalization rates for SCTD sub-diagnoses across sex and age subgroups, rates for PANRC in the youngest children were rising. It was notable that about half of SCTD hospitalizations occurred in the working-age population (aged 15-64 years), and this age group was responsible for 82.5% of SLE hospitalizations. There were changes in composition of SCTD hospitalizations over the study period. The absolute regional disparity in SCTD hospitalizations declined, whereas there were no statistically significant changes in the relative regional disparity.

Very few studies have investigated secular trends in a specific SCTD and the findings have been mixed. For instance, hospitalizations for SSc were reported as declining in the USA between 1999 and 2011[14] but rose in Sardinia (Italy) from 2001 to 2012.[13] Furthermore, hospitalizations for SLE were stable among people aged 2-21 years in the USA during 2000-2009,[11] but declined in Sardinia (Italy) between 2001 and 2012.[12] In our study, hospitalization rates for SCTD and its sub-diagnoses statistically significantly declined from 1998 through 2016. In addition, we found significant regional disparities in SCTD hospitalizations in Sweden. These between-study differences in secular trends and regional disparities in SCTD hospitalizations might be due to differences in incidence and prevalence of SCTD, in diagnostic procedures and reporting, in clinical practices, in environmental exposures (eg, sunlight exposure, UV levels), in social and living conditions, in lifestyle habits, in the distribution of SCTD risk factors, in population genetic predisposition, in healthcare systems including the availability of and access to treatments, in a population's health-seeking behaviour, and in hospital coding practices including ICD versions (eg, ICD-9 in previous studies *vs.* ICD-10 in our study).[5,19-23] Furthermore, while the presence of national health insurance with universal access to health care in Sweden implies that affordability cannot explain the observed regional

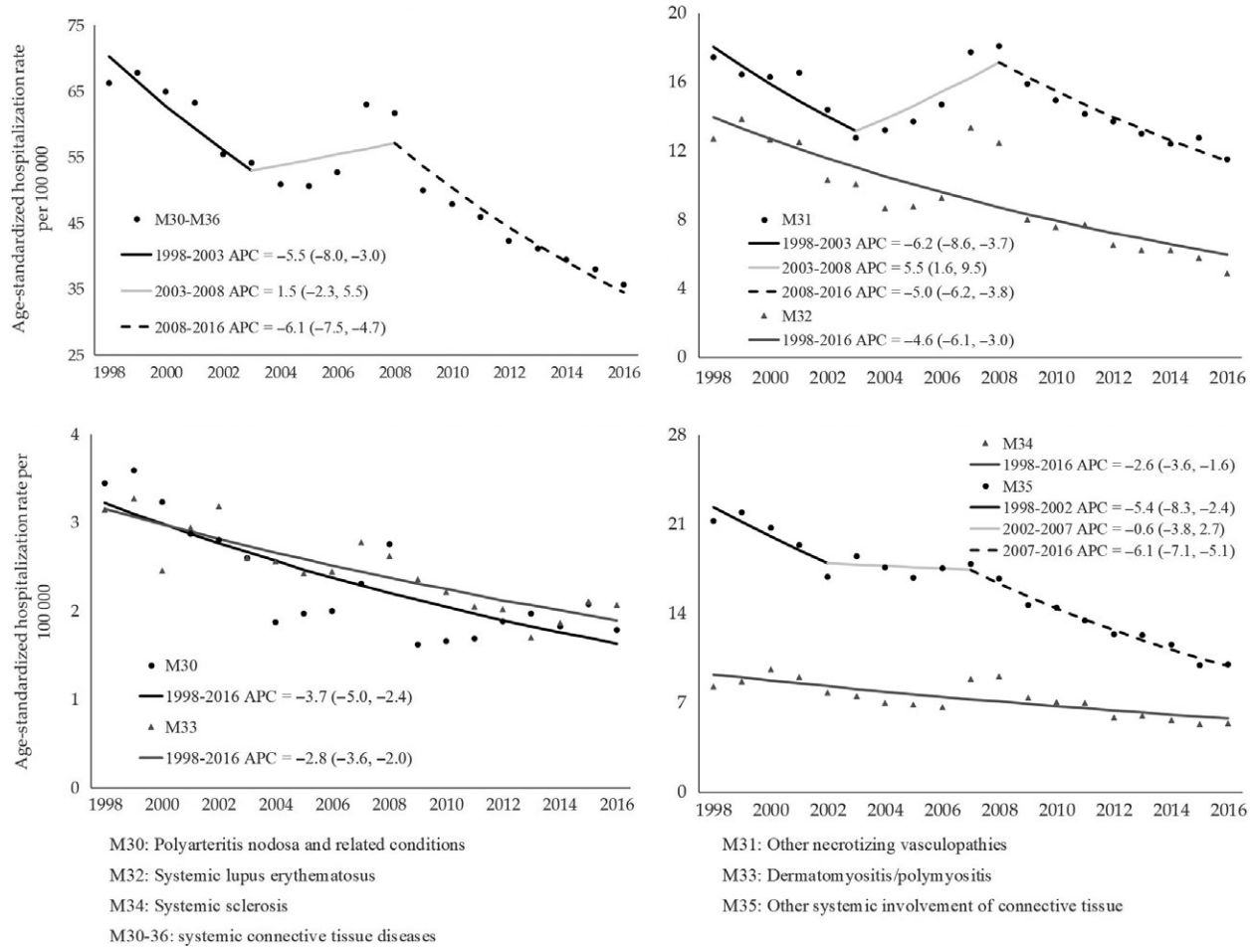

FIGURE 2 Secular trends in age-standardized hospitalization rates per 100 000 persons for systemic connective tissue diseases, 1998-2016. Symbols display the observed values and solid lines indicate fitted values using joinpoint regression. For each joinpoint, the annual percentage change (APC) and its 95% confidence interval are reported

TABLE 1 Secular trends in hospitalizations with principal diagnosis of systemic connective tissue diseases in Sweden by sex and age, 1998-2016

	% Change (95% CI) between 1998-2000 and 2014-2016	Average annual percent change (95% CI), 1998-2016		
	Rate[a]	Rate[a]	Proportion from all hospitalizations	Proportion from MSK disorders hospitalizations
All	**−43.2 (−44.5, −41.8)**	**−3.9 (−5.1, −2.6)**	**−2.5 (−3.3, −1.7)**	**−3.6 (−4.4, −2.7)**
Men	**−41.0 (−43.5, −38.5)**	**−3.6 (−5.3, −1.8)**	**−2.0 (−2.9, −1.1)**	**−3.5 (−4.4, −2.6)**
Women	**−44.0 (−45.6, −42.4)**	**−4.0 (−5.1, −2.9)**	**−2.8 (−3.6, −2.0)**	**−3.4 (−4.2, −2.6)**
Age groups, years				
0-19	**−23.5 (−31.1, −15.1)**	**−1.4 (−2.5, −0.3)**	−0.4 (−1.6, 0.7)	−0.9 (−2.6, 0.9)
20-49	**−47.1 (−49.8, −44.3)**	**−3.5 (−4.8, −2.2)**	**−3.5 (−4.8, −2.1)**	**−2.4 (−3.8, −1.0)**
50-64	**−52.8 (−55.2, −50.3)**	**−4.4 (−6.2, −2.7)**	**−3.2 (−4.3, −2.1)**	**−5.0 (−6.1, −3.8)**
65-79	**−44.4 (−46.6, −42.0)**	**−3.5 (−5.7, −1.3)**	−1.6 (−3.9, 0.8)	**−3.7 (−4.5, −3.0)**
80+	**−29.1 (−33.1, −24.9)**	**−2.6 (−4.5, −0.6)**	**−1.7 (−2.2, −1.3)**	**−2.8 (−3.2, −2.4)**

Statistically significant changes ($P < .05$) are in bold.

CI, confidence interval; MSK, musculoskeletal.

[a]In the joinpoint regression analysis, we used age-standardized rates per 100 000 population for overall and sex-stratified analyses, and age-specific rates per 100 000 population for age-stratified analyses.

TABLE 2 The average annual percent change (95% CI) in hospitalizations from sub-diagnoses of systemic connective tissue diseases in Sweden by sex and age, 1998-2016

	Sex			Age groups, years				
ICD-10 code	All	Men	Women	0-19	20-49	50-64	65-79	80+
Hospitalization rate[a]								
M30	**−3.7 (−5.0, −2.4)**	**−3.2 (−4.5, −1.9)**	**−4.3 (−5.9, −2.7)**	**3.4 (1.8, 5.1)**	−2.1 (−4.9, 0.7)	**−5.5 (−8.1, −2.9)**	**−9.5 (−11.5, −7.4)**	**−9.6 (−12.4, −6.7)**
M31	**−2.5 (−3.7, −1.3)**	**−2.9 (−4.7, −1.1)**	**−2.2 (−3.9, −0.5)**	−1.2 (−5.2, 3.1)	**−3.8 (−6.8, −0.8)**	**−3.3 (−6.3, −0.2)**	**−2.5 (−3.8, −1.1)**	−0.0 (−0.9, 0.9)
M32	**−4.6 (−6.1, −3.0)**	**−5.0 (−7.2, −2.9)**	**−6.0 (−7.9, −4.0)**	**−4.3 (−6.8, −1.8)**	**−4.5 (−6.1, −2.8)**	**−5.7 (−7.3, −4.0)**	**−5.6 (−8.6, −2.4)**	**−3.9 (−5.9, −1.9)**
M33	**−2.8 (−3.6, −2.0)**	**−2.5 (−3.7, −1.3)**	**−2.9 (−4.0, −1.9)**	−2.8 (−5.6, 0.2)	**−4.1 (−6.2, −2.0)**	−3.6 (−7.6, 0.7)	**−2.5 (−4.1, −0.8)**	0.2 (−4.2, 4.7)
M34	**−2.6 (−3.6, −1.6)**	**−3.6 (−5.7, −1.4)**	**−2.4 (−3.4, −1.3)**	NE	**−3.3 (−4.4, −2.2)**	**−4.2 (−5.4, −3.0)**	−1.6 (−3.7, 0.5)	−0.6 (−6.2, 5.4)
M35	**−4.5 (−5.5, −3.4)**	**−3.5 (−4.1, −2.9)**	**−4.3 (−5.3, −3.4)**	**−4.8 (−6.5, −3.1)**	**−2.9 (−5.0, −0.7)**	**−6.0 (−7.8, −4.2)**	**−5.1 (−6.8, −3.3)**	**−3.6 (−5.5, −1.6)**
Proportions from systemic connective tissue diseases hospitalizations								
M30	0.3 (−1.5, 2.2)	0.6 (−2.0, 3.3)	−0.9 (−3.0, 1.3)	**4.8 (3.5, 6.2)**	1.6 (−1.1, 4.4)	−1.6 (−3.9, 0.7)	**−6.6 (−8.2, −4.9)**	**−8.0 (−10.9, −5.1)**
M31	**1.4 (0.5, 2.3)**	0.8 (−0.3, 1.8)	**2.0 (1.5, 2.5)**	−2.6 (−8.7, 3.9)	0.2 (−1.9, 2.4)	1.8 (−0.4, 4.1)	**1.2 (0.3, 2.0)**	**1.5 (0.9, 2.2)**
M32	**−1.8 (−2.5, −1.0)**	**−2.6 (−4.1, −1.1)**	**−1.5 (−2.3, −0.7)**	**−2.8 (−4.6, −1.0)**	**−1.1 (−1.6, −0.6)**	**−1.8 (−2.8, −0.9)**	−1.6 (−4.0, 0.9)	**−2.3 (−4.1, −0.5)**
M33	0.5 (−0.5, 1.4)	0.3 (−1.0, 1.7)	1.6 (−1.3, 4.6)	−1.2 (−3.8, 1.5)	−0.6 (−2.9, 1.9)	1.9 (−0.7, 4.5)	1.6 (−1.8, 5.1)	2.3 (−2.4, 7.2)
M34	**0.5 (0.1, 1.0)**	−1.2 (−2.9, 0.5)	**1.0 (0.5, 1.6)**	NE	0.4 (−0.7, 1.6)	−0.2 (−0.8, 0.5)	**2.5 (0.7, 4.4)**	1.5 (−3.6, 6.8)
M35	**−0.9 (−1.4, −0.4)**	**−0.8 (−1.4, −0.1)**	**−0.9 (−1.5, −0.3)**	**−3.3 (−5.7, −1.0)**	0.7 (−0.4, 1.8)	**−1.6 (−2.5, −0.8)**	**−1.9 (−2.5, −1.2)**	**−0.8 (−1.2, −0.3)**

Statistically significant changes ($P < .05$) are in bold.

M30, Polyarteritis nodosa and related conditions; M31, Other necrotizing vasculopathies; M32, Systemic lupus erythematosus; M33, dermatomyositis/polymyositis; M34, Systemic sclerosis; M35, Other systemic involvement of connective tissue; SCTD, systemic connective tissue diseases.

[a]In the joinpoint regression analysis, we used age-standardized rates per 100 000 population for overall and sex-stratified analyses, and age-specific rates per 100 000 population for age-stratified analyses.

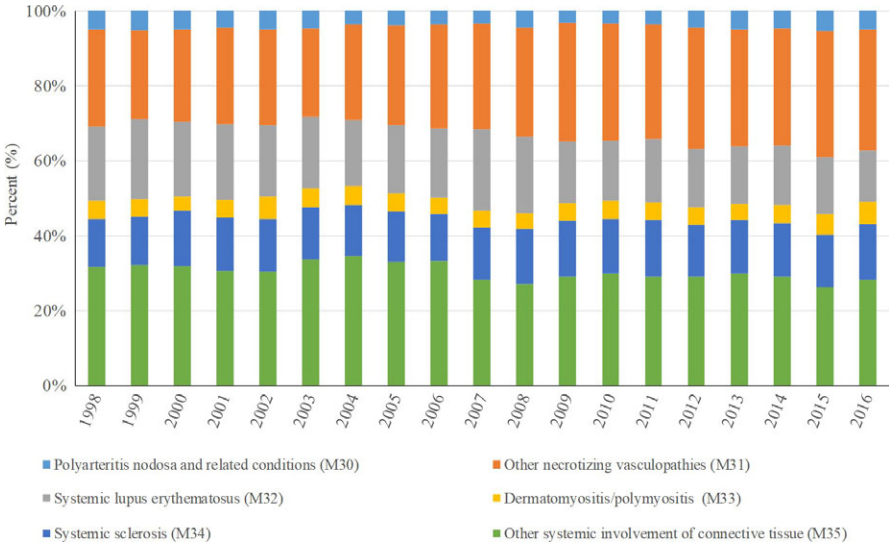

FIGURE 3 Changes in composition of hospitalizations for systemic connective tissue diseases from 1998 through 2016

disparities, regional differences in availability of rheumatology specialists and hospital beds (eg, lower threshold for hospital admission if more beds are available) should not be overlooked.

The declining trends in SCTD hospitalizations in our study is encouraging, suggesting possible improvements in SCTD management including earlier diagnosis and treatment, improved availability of new treatments, better management of comorbidities, and reduction in prevalence of SCTD risk factors.[11,12] It should be noted that the reduction in SCTD hospitalizations does not necessarily imply reduction in the disease burden, but it might reflect a shift toward outpatient care, including day-care clinics. In addition, possible impact of the reduction in the number of hospital beds over the study period should not be overlooked. Potential increases in incidence of PANRC including Kawasaki disease (partly due to increased awareness of the disease) and possible increased immigrations from countries with high incidence and prevalence of PANRC (eg, those of Asian descent) might partially explain the observed rise in PANRC hospitalizations among people aged <20 years.[24] This rising trend suggests the need for improvement in PANRC management, particularly among children 0-9 years, since the majority (89%) of PANRC hospitalizations in those aged <20 years occurred among children aged 0-9 years.

Several limitations of the current study should be acknowledged. We used physicians' diagnostic coding which may be prone to misclassification. Despite low level of absence in the principal diagnosis (about 1% of hospital admissions in the NPR), potential variations by regions is a source of concern. Due to lack of data, we were unable to investigate severity of SCTD, treatment administered, and associated comorbidities over the study period. Furthermore, since ICD-10 codes up to 3 digits were publicly available, we could not assess SCTD sub-diagnoses in more details. Due to lack of data, specialized outpatient care (including day surgeries) and primary care visits were not included, meaning that our estimates are not generalizable to these healthcare visits. This is a descriptive aggregate-level study, and all given explanations for the findings are speculative, and no causal inference can be made.

5 | CONCLUSION

This study suggests substantial reductions in the absolute and relative burden of SCTD hospitalizations in Sweden over the past 2 decades. We found significant variations in SCTD hospitalizations by sex, age and sub-diagnoses groups. While declining trends generally persisted for SCTD sub-diagnoses across sex and age subgroups, hospitalization rates for PANRC in the youngest children were rising and warrant further investigation.

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AUTHOR CONTRIBUTIONS

AA Kiadaliri participated in the design, acquisition of data, analysis and interpretation of results and drafting the manuscript. AJ Mohammad and M Englund participated in interpretation of results, and revision of the manuscript for important intellectual content.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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