Depósito de investigación de la Universidad de Sevilla

https://idus.us.es/

Table 1. Age-adjusted mortality rates (ASMR) per 100,000 inhabitants and trend analysis of annual average percentage change according to age and sex.

	1980-1984	2015-2019	Total 1980-2019	JP	Periods	
	ASMR (95% CI)	ASMR (95% CI)	AAPC (95% CI)		Years	APC (95% CI)
Both genders						
All ages	1.9 (1.0; 3.0)	2.5 (1.7; 3.0)	0.9 (-0.2; 2.0)	2	1980-1994 1994-2002 2002-2019	1.9 (0.1; 3.8)* -3.8 (-7.5; 0.1) 2.3 (1.2; 3.4)*
35-64 years	1.3 (0.5; 2.4)	1.6 (0.9; 2.6)	1.0 (0.4; 1.5)*	0	-	-
>64 years	6.8 (4.1; 10.9)	9.3 (7.3; 11.7)	0.3 (-0.2; 0.8)	0	-	-
Men						
All ages	1.6 (0.7; 3.8)	1.1 (0.3; 2.0)	-1.5 (-2.2; -0.8)*	0	-	-
35-64 years	0.7 (0.1; 2.0)	1.0 (0.2; 2.1)	4.9 (-4.2; 14.9)	2	1980-1982 1982-1999 1999-2019	132.6 (-57.8; 1180.5) -4.8 (-10.8; 1.6) 5.2 (1; 9.7)*
>64 years	6.6 (2.7; 16.8)	3.6 (1.9; 6.4)	-2.3 (-3.1; -1.4)*	0		
Women						
All ages	2.1 (1.1; 3.6)	3.5 (2.6; 4.5)	1.0 (0.5; 1.4)*	0	-	-
35-64 years	1.8 (0.6; 3.3)	2.1 (1.2; 3.3)	0.5 (0.0; 1.1)	0	-	-
>64 years	6.8 (3.4; 12.4)	13.4 (10.4; 17.2)	1.2 (0.7; 1.7)*	0	-	-

95% CI: 95% confidence interval; APC: annual percent change; ASMR: Age Standardized Mortality Rate; AAPC Annual Average percentage change; JP: joinpoint.
* = p < 0.05.

Table 2. Goodness-of-fit test for different age-, period- and cohort specific models of systemic sclerosis in Spain, 1980-2019

Model	df	Deviance	p	AIC
Both genders				
Age-Model	98	239.85	**<0.001**	762.35
Age-Drift Model	97	219.53	**<0.001**	744.02
Age-Period Model	91	207.01	**<0.001**	743.50

Table 1. Goodness-of-fit test for different age-, period- and cohort specific models of systemic sclerosis in Spain, 1980-2019.

Age-Period-Cohort Model	72	102.92	0.010	677.41
Age-Cohort Model	78	122.08	0.001	684.58
Men				
Age-Model	98	165.74	**<0.001**	526.66
Age-Drift Model	97	162.11	**<0.001**	525.02
Age-Period Model	91	152.56	**<0.001**	527.46
Age-Period-Cohort Model	72	85.87	0.126	498.80
Age-Cohort Model	78	89.04	0.185	489.95
Women				
Age-Model	98	268.12	**<0.001**	752.75
Age-Drift Model	97	222.65	**<0.001**	709.27
Age-Period Model	91	212.68	**<0.001**	711.31
Age-Period-Cohort Model	72	124.34	**<0.001**	660.96
Age-Cohort Model	78	144.37	**<0.001**	668.99

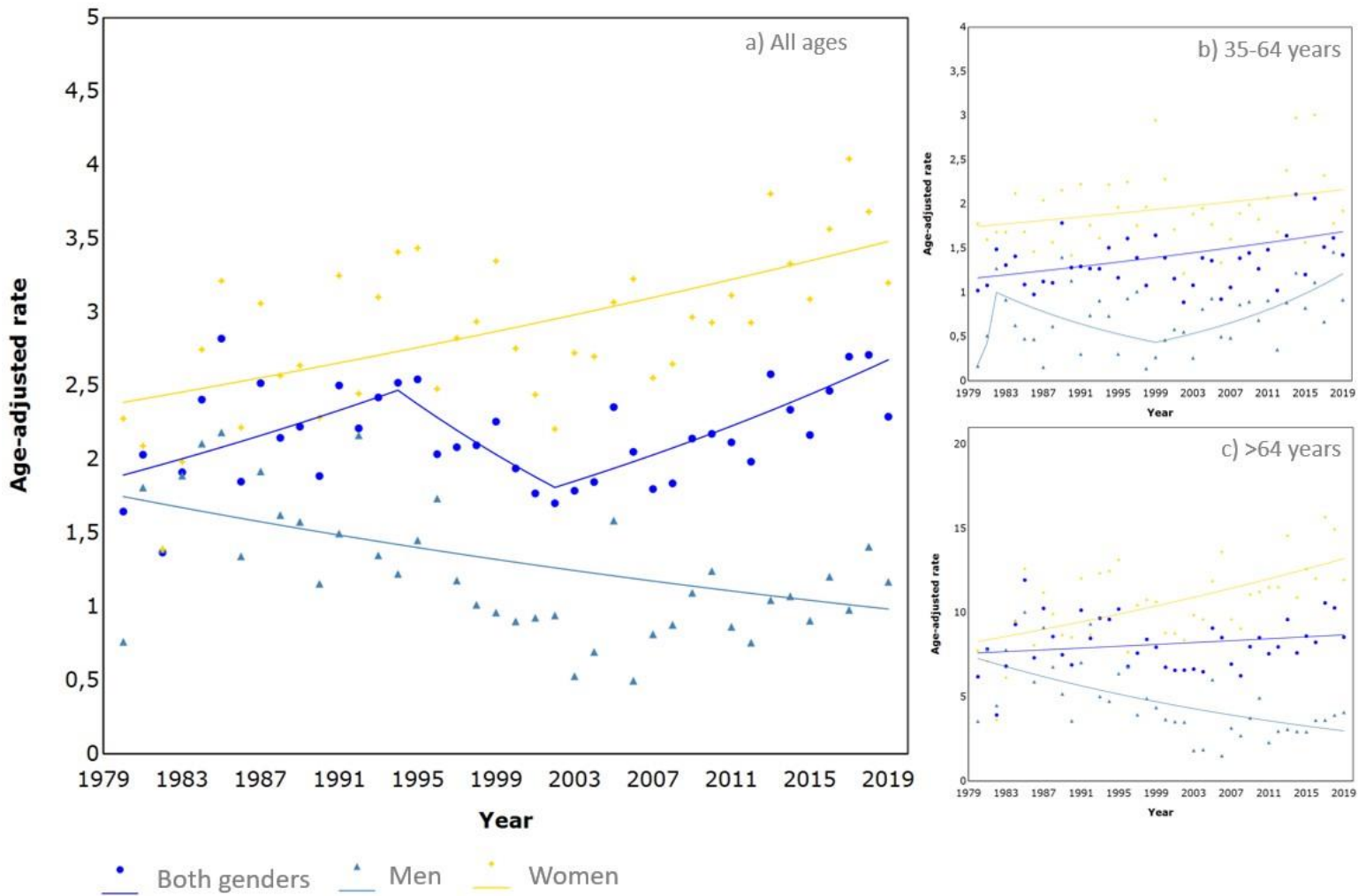df: degrees of freedom; AIC: Akaike information criteria

Figure 1. Joinpoint regression analysis (years 1980-2019) for all ages (a), between 35 and 64 years (b) and over 65 years (c).
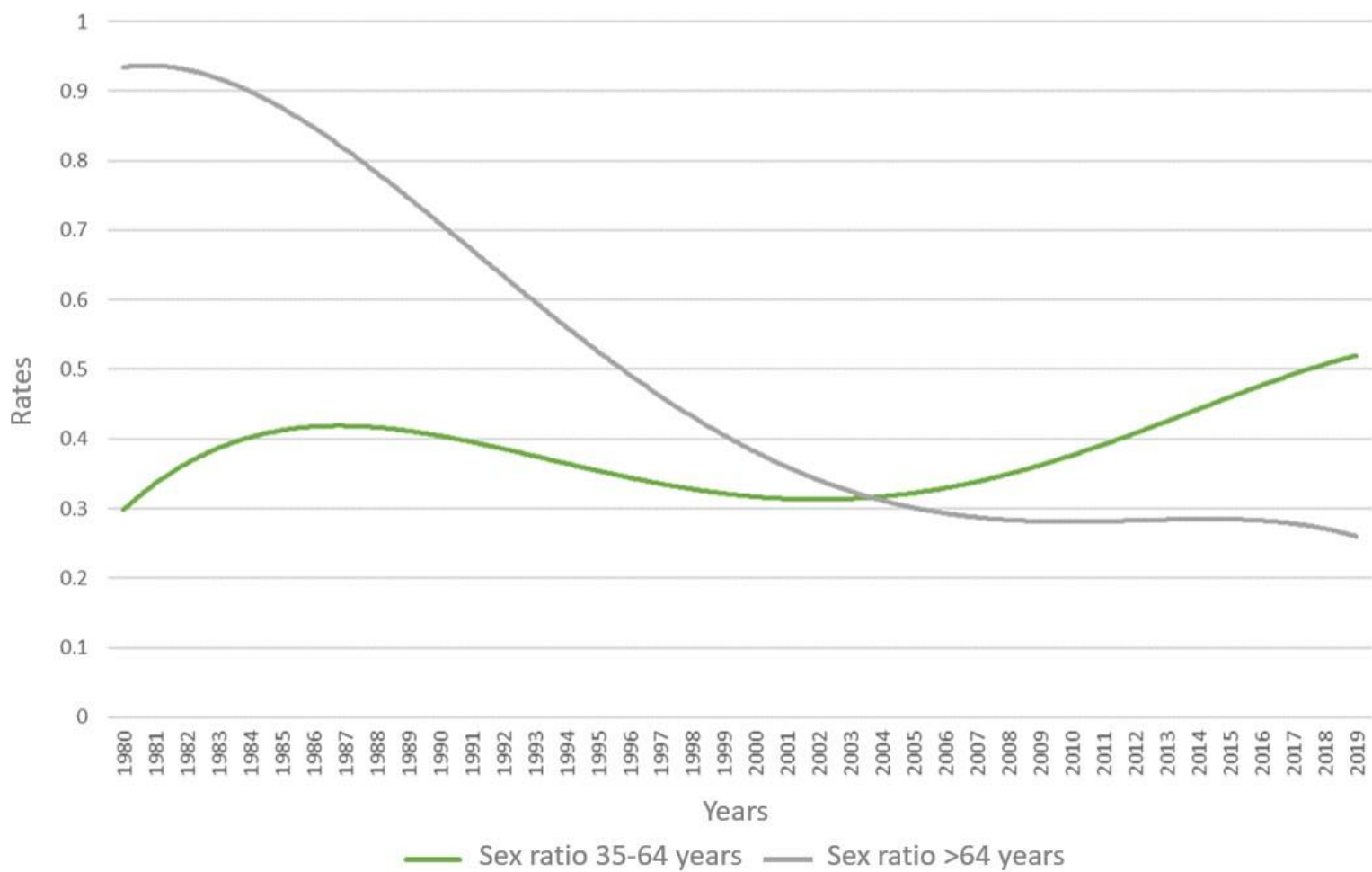
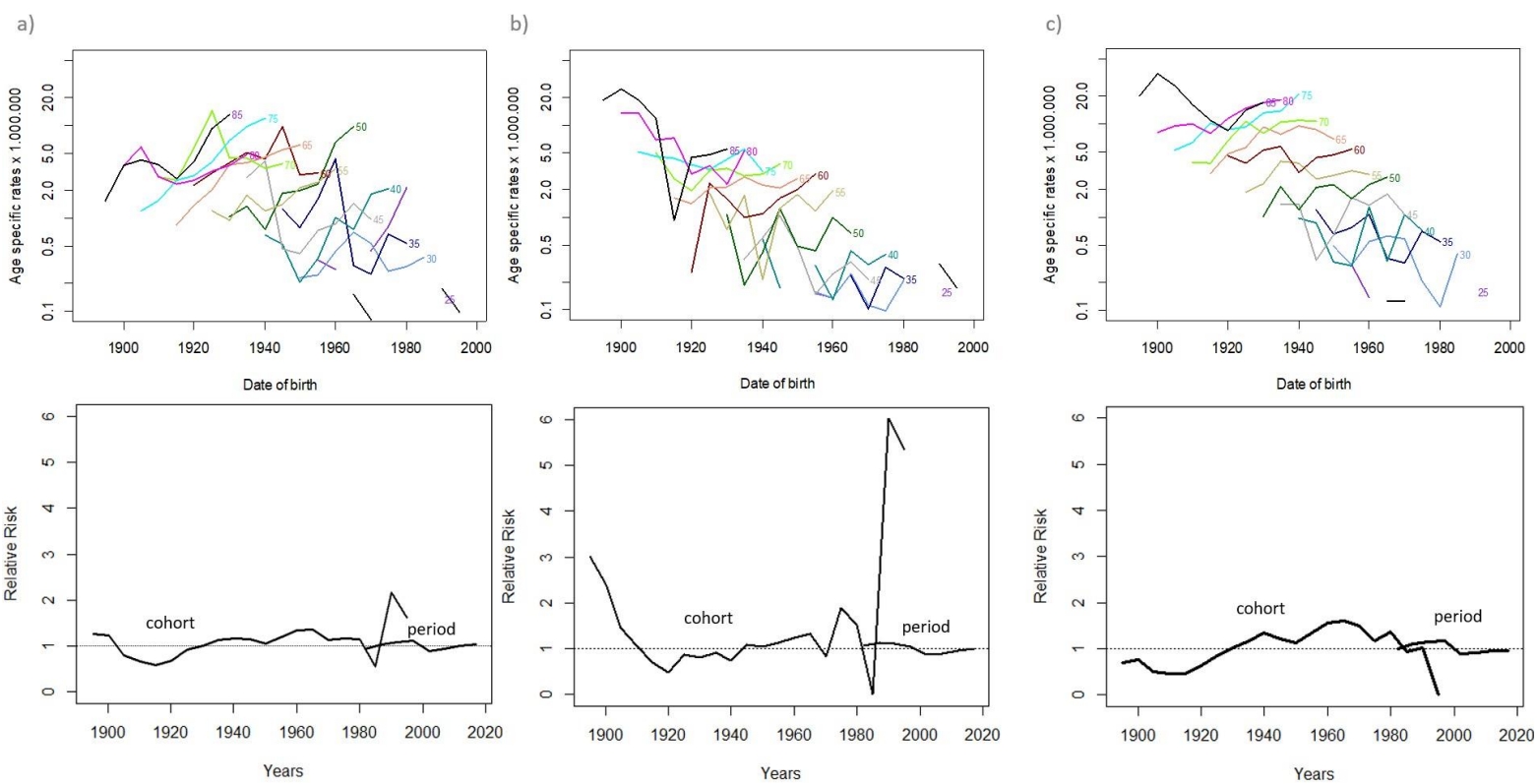Figure 2. Trend in the sex ratio (men / women) over the years 1980-2019 by age group.

Figure 3. Analysis of the age-period-cohort effect for both sexes (a), men (b) and women (c). The upper graph shows the mortality rates for each five-year age; the lower graph shows the variation of the relative risk for the different cohorts and period.
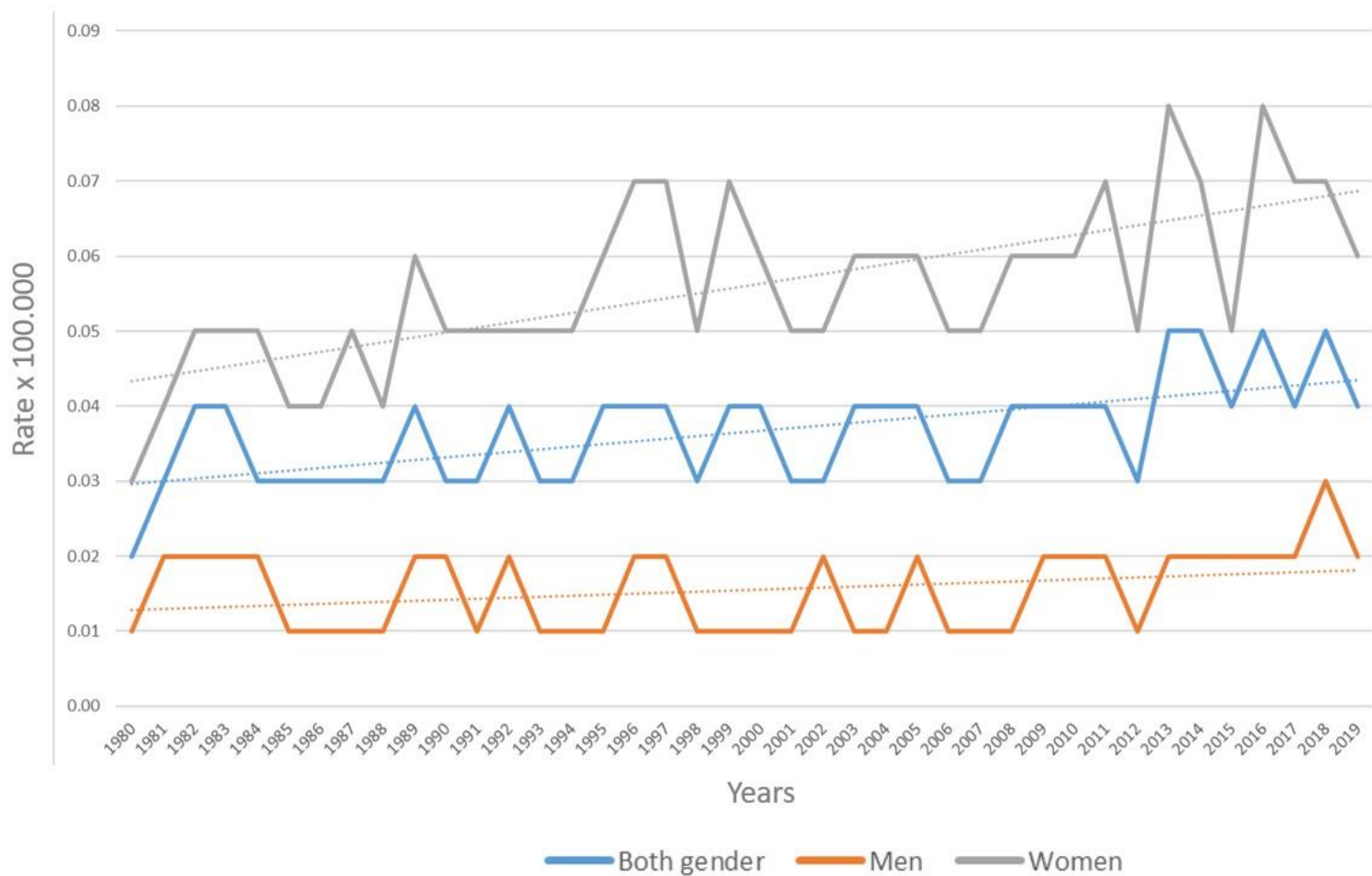
Figure 4. Rates of potential years lost per 100,000 persons-year.

Authors: Juan-Carlos Hernández-Rodríguez[1], Mercedes Sendín-Martín[1], Antonio-José Durán-Romero[1], Juan Ortiz Álvarez[1], Julián Conejo-Mir[1, 2], José-Juan Pereyra-Rodríguez[1, 2].

1. Department of Dermatology. Virgen del Rocío University Hospital, Seville, Spain.
2. Medicine Department. Universidad de Sevilla, Seville, Spain.

Correspondence to:

Juan-Carlos Hernández-Rodríguez.

Department of Dermatology

Virgen del Rocío University Hospital.

Av. Manuel Siurot S/N. 41013 Seville, Spain.

Email: j.carlos.her.rod@gmail.com

OrcidID:

- Juan-Carlos Hernández-Rodríguez: 0000-0003-2525-4069
- Mercedes Sendín-Martín: 0000-0003-0156-381X
- Antonio José Durán Romero: 0000-0001-8203-3057
- Juan Ortiz-Álvarez: 0000-0003-2134-3902
- Julián Conejo-Mir: 0000-0001-9108-9538
- José-Juan Pereyra-Rodríguez: 0000-0001-6843-5877

Type of manuscript: Original article

Bulleted statements:

What is already known about this topic?

- Few studies has assessed the mortality of the Spanish SSc mortality, analysing only a particular region of the country or limiting the sample size to the RESCLES register.

What does this study add?

- We analysed a period of thirty-nine years of SSc mortality trends through the independent effect of sex, age, period, and cohort.
- The overall SSc ASMR increased from 1.87 to 2.47 deaths per 1,000,000 inhabitants from 1980 to 2019 in Spain.
- The employment of 2013 Standard European Population will allow a suitable comparison with future studies that analyse SSc mortality.

Abstract:

Background: Systemic sclerosis (SSc) is an autoimmune chronic rheumatic disease with notable mortality that continues to be a challenge for clinicians today.

Objective: To assess changes in mortality trends in the Spanish SSc population between 1980 and 2019, considering the independent effect of sex, age, period and birth cohort.

Patients and Methods: SSc death records and mid-year population data were collected from the National Statistics Institute. Age-standardized mortality rates were calculated for the overall population and for each sex and age group. Significant changes in mortality trends were identified by Joinpoint regressions. Similarly, an age-period-cohort (APC) and potential years of life lost (PYLL) analysis were performed to know the burden of SSc.

Results: Age-standardized mortality rates due to SSc increased from 1.87 (95% CI: 1.00; 3.02) per 1,000,000 inhabitants between 1980 and 1984, to 2.47 (95% CI: 1.74; 3.02) per 1,000,000 inhabitants between 2015 and 2019. The relative risk of mortality fell in cohorts born after 1990 in all groups. The PYLL rates registered a gradual rise in both sexes.

Conclusions: Mortality due to SSc in Spain Spain experienced a rise in overall mortality trend during the 39 years of study evaluated, although the male group showed a progressive drop.

Background:

Systemic sclerosis (SSc) is an autoimmune chronic rheumatic disease whose main clinical manifestations are fibrosis of the skin and internal organs, and vascular injury [1].

The pooled prevalence of SSc has recently been estimated at 17.6 cases per 100,000 inhabitants and the pooled incidence rate at 1.4 per 100,000 inhabitants [2]. In the Spanish context, the prevalence of SSc points is 27.7/100,000 inhabitants and the incidence 2.3 per 100.000 inhabitants per year [3]. Despite a greater understanding of the pathogenesis of SSc and better complications management, the mortality of these patients continues to overcome the rates of the general population, as states the 2.72 deaths per 100,000 inhabitants [4].

In Spain, few studies have been conducted to assess the mortality of the target disease, analysing only a particular region of the country [3,5] or limiting the sample size to the RESCLE registry [6], a prospective registry unveiled in 2006 by the Spanish Internal Medicine Society. For these reasons, we propose an ecological study with the longest period and cases analysed in Europe, based on reliable SSc mortality data from the Spanish National Statistics Institute. Therefore, the objective of this study is to assess changes in mortality trends in the SSc population in Spain between 1980 and 2019, considering the independent effect of sex, age, period, and cohort of birth.

Materials and methods:

In this study, data on the annual number of deaths due to SSc from 1980 to 2019 in Spain were collected from the Spanish National Statistics Institute. To obtain reliable SSc mortality data in Spain, we draw on death certificates. SSc mortality cases were coded as 734 and 710.1 according to the 8th and 9th revision of the International Classification of Diseases (ICD), respectively. Furthermore, M34 was the code used in ICD-10. Intrinsic to the methodology, only cases coded as SSc as the main cause of death were included. Neither toxic-oil syndrome (coded as 710.5 in ICD-9) nor systemic sclerosis induced by drug and chemical (M34.2 in ICD-10) were analysed. A statistical analysis of age-specific mortality rates was performed by age groups of 5 years. Annual age-standardized mortality rates (ASMR) stratified by sex and age group (<35, 35–64,>64) were calculated using the direct method and the revised European Standard Population 2013 [7]. All computed rates were expressed as 1,000,000 inhabitants. Furthermore, the sex ratio was estimated as the proportion of male mortality rates relative to female mortality rates. Data management and statistical analysis were performed using Epidat 4.2®, Microsoft® Excel and SPSS Statistics 25® statistical software.

Joinpoint regression models were performed through the Joinpoint software [8] to assess points of significant trend changes in mortality rates, stratified by the sex and age groups mentioned before (<35, 35–64,>64). Additionally, this method computed the Annual Average Percent Change

(AAPC). The maximum of joinpoint allowed in the analysis was five. The number of periods reflects in one more than the number of registered joinpoint (periods = JP + 1). Note that if there is any joinpoint it is equal to 0.

The assessment of mortality rates for the APC effect was carried out using penalty functions [9]. The APC model evaluates the trend fluctuations through time and its graphic representation and interpretation. The APC models were calculated using the Poisson regression based on the Osmond and Garner models [10]. These authors provided Generalized Linear Interactive Modeling (GLIM) macros to perform the calculation using the R® software (APC package Age-Period-Cohort Analysis version 1.3 for R®). Assuming the Poisson distribution all joinpoints would represent a significant change in mortality trends. Data were divided into 5-year periods and the quinquennial age to make these estimates. Due to the number of periods must be multiple of five, the search of registers was enlarged until 1980 with the aim to include the maximum of years as possible into the analysis. The goodness-of-fit of possible APC models was also compared.

One measure that provides information on the burden disease and allows one to quantify premature mortality disease is Potential Years of Life Lost (PYLL). Crude and standardized by age and sex, PYLL was computed taken as reference the 2013 Standard European Population.

Results:

2914 deaths from SSc were identified between 1980 and 2019. The ASMR between 1980 and 1984 was 1.87 per 1,000,000 inhabitants, reaching 2.47 cases between 2015 and 2019. Similarly, female ASMR rose from 2.10 to 3.52 cases. However, male ASMR showed a drop from 1.59 to 1.13. (Table 1).

The studied population underwent two trend changes, getting 3 different periods (Figure 1a). A first period with a significant mortality ascent from 1980 to 1994 (AAPC = 1.9). A second with a drop reaching the minimum in 2002 (AAPC = -3.8). The last period experienced a significant sustained ascent until 2019 (AAPC = 2.3). The stratification by sex groups revealed an opposite pattern and neither the female nor the male curve presented any joinpoint.

Specific data and mortality trends standardized by ages are shown in Figure 1 (b and c) and Table 1. Age group analysis could not be executed in those cases whose annual rates were equal to 0 (both gender, males, and females under the age of 35).

Regarding sex ratio a slight increase was observed in the 35-64 year old group. Furthermore, a sharp fall was observed in the over 64 years old group until the beginning of the twentieth century from that moment it levelled off (Figure 2).

In the APC analysis, the effect of age showed higher mortality rates in older subjects (Figure 3). Linked to the cohort effect, a decrease in the relative risk of death from SSc is observed until the beginning of 20's, being more notable in men. From 1980 a brief but outstanding ascent in relative risk of mortality happened even in both genders and in the male group.

For the period effect, the three curves seem to overlap, drawing a small descent in 2000 to level-off hereinafter. Table 2 (supplemental material S2) shows the goodness of fit to examine the calculation of APC effects in each possible regression model that has been performed. Due to the Akaike information criteria being lower and the deviation narrower, the 3-factors model fits better for the overall population and women than those that contemplated just two.

Both genders lost 5,215 years of potential life throughout the period. PYLL rate values were higher in women, although both genders experienced a gradual upward trend (Figure 4). For each study year, a detailed summary of the total number of deaths, crude and age-standardized mortality rates, and PYLL is provided in Appendix S1.

Discussion:

The main objective of this study was to assess the evolution of mortality trends in the Spanish population with SSc between 1980 and 2019. During the studied period, the overall ASMR gradually increased in both the combined gender curve and the female curve separately, compared to the descent recorded by the male group.

These results are in line with Kernéis et al. [11], who obtained a similar ascent in female mortality trends for the French and US SSc population between 1980 and 1998. Furthermore, mortality trends in men tended to level off in both countries compared to our data. In contrast, mortality trends in an American [12] and a Danish [13] population-based studies disagree with our outcomes with a steady fall from the beginning of 21st century until 2015 in both genders. The mentioned studies employed the 1976 European Standard Population [11], US population in 2000 [12], and a background population not specified [13], so comparisons may be done with caution. We took as a reference the 2013 Standard European Population to achieve a homogeneous comparison with current and future studies that evaluate SSc mortality rates.

In the stratified by sex over 64 years old group, it stands out that mortality trends of women and men are opposite, that could influence the overall population. Furthermore, the mortality increase in 1999 for the overall population, met in time with the ascent observed in males between 35-64 years old. Thus, the latter group appears to induce changes in mortality trend for the group of all ages. This could be related to a higher proportion of men over 50 years of age when examining the age of SSc onset in a Spanish cohort [14]. Additionally, diffuse cutaneous SSc is a more common

phenotype in male [15]. Considering deaths from the onset of SSc symptoms, diffuse cutaneous SSc and a later age of onset of symptoms have been reported to be the main prognostic factors [4,14].

Focusing on sex ratio, our results agree with the concurrent statement that mortality rates registered by women are significantly higher than in males [16]. But in younger cohorts' men, it presents a higher rate, ergo, a premature mortality exists [17].

In line with previous SSc mortality studies, the age effect showed higher mortality rates as age progressed. The SSc cases that onset in ages over 60 are associated with a shorter survival [5,18].

First, according to the cohort effect, we observed a progressive fall in the relative risk of mortality until 1920, followed by an ascent until 1980. Therefore, this risk experimented an ascension in the male group, but not in the female group. Ranque et al. [19] supports this fact determining that SSc incidence increases between the 1950s and 1980s, related to a greater awareness of physicians and an accurate diagnosis. A higher compliance to 1980 ACR criteria diagnosis of a prospective Spanish men cohort has been reported. Nonetheless, high compliance has been found for both sexes in the 2013 ACR diagnosis criteria [14,20,21]. Therefore, we could elucidate that the cohort effect occurred in men born from 1980, might be caused by a larger number of diagnosed cases after the establishment of 1980 ACR criteria. Bairkdar et al. [2] declared the ascension of the overall SSc mortality rates could be related to a higher number of diagnosed cases, estimated incidence rates, and prevalence recorded in recent observational studies compared to old ones.

Second, it should be noted that both genders suffered from a decrease in the relative risk of mortality from the 1990s. At this time, angiotensin-converting enzyme inhibitors started to be used as a treatment against hypertension associated with renal crisis, achieving an improvement of SSc prognosis and survival [22,23].

The outcomes of PYLL have been found to be more pronounced in patients with SSc than in other autoimmune diseases like rheumatoid arthritis [24]. Female rates were higher than male, in contrast with previous studies [17,25]

We hypothesize that the trend fall recorded in younger cohorts from 1990 might indicate a stabilization of the Spanish mortality rates of SSc. This is supported by previous studies in which despite SSc mortality overtaking mortality of the general population, trends have been falling in the last decades [4,12].

Strengths and limitations:

We present the largest period assessed of SSc mortality trends through the independent effect of sex, age, period, and cohort. The 2013 Standard European Population allows comparison with future studies that analyze mortality of SSc. The use of a national mortality register enhances data

reliability and allows handling a higher number of deaths along larger periods in comparison to population-based cohort studies.

An intrinsic limitation is that APC methods do not explain the reason for trends changes. According to previous APC studies, in our research it was not possible to make a distinction on how the different SSc phenotypes could influence mortality trends. This issue is because ICD does not recognize these clinical SSc cases. In low-prevalence diseases a not suitable coding on death certificates could underestimate the real burden of disease, it being possible the presence of bias during the collection of mortality data based on death certificates.

Conclusions:

This study addresses the mortality trends of SSc in the past thirty-nine years in the Spanish population. The overall SSc ASMR experimented a raise from 1980 to 2019. However, the male group recorded a trend fall. The joinpoint occurred in 1999 and was met in time for overall and male patients with SSc between 35 and 64 years of age, preceding a maintained ascendance. The curve of women in all ages, 35-64 and over 65 years of age showed a progressive ascent of mortality trends throughout the analysed period and recorded higher rates than male.

A cohort effect appeared in 1980, with a rise in overall and male relative mortality risk. All groups showed a steady decrease in relative risk of mortality in young cohorts since 1990. This outcome could explain a future stabilization of the mortality rates of SSc in Spain, although an upcoming monitoring is required to confirm these findings.

References:

1.   Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017; 390 (10103): 1685–99 https://doi.org/10.1016/S0140-6736(17)30933-9

2.   Bairkdar M, Rossides M, Westerlind H, Hesselstrand R, Arkema EV, Holmqvist M. Incidence and prevalence of systemic sclerosis globally: A comprehensive systematic review and meta-analysis. Rheumatol. 2021; 60 (7): 3121–33. https://doi.org/10.1093/rheumatology/keab190

3.   Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, et al. Systemic sclerosis in northwestern Spain: A 19-year epidemiologic study. Medicine. 2008; 87(5): 272–80. https://doi.org/10.1097/MD.0b013e318189372f

4.   Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: Systematic review and meta-analysis. Semin Arthritis Rheum. 2014; 44(2): 208–19. https://doi.org/10.1016/j.semarthrit.2014.05.010

5.   Simeon CP, Armadans L, Fonollosa V, Solans R, Selva A, Villar M, et al. Mortality and

prognostic factors in Spanish patients with systemic sclerosis. Rheumatol. 2003; 42(1): 71–5. https://doi.org/10.1093/rheumatology/keg033

6. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Campillo-Grau M, Ramos-Casals M, et al. Registry of the Spanish network for systemic sclerosis: Survival, prognostic factors, and causes of death. Medicine (Baltimore). 2015; 94(43): 1–9. https://doi.org/10.1097/MD.0000000000001728

7. Eurostat. Revision of the European Standard Population. 2013. 128 p.

8. Joinpoint Regression Program, Version 4.8.0.1 – April 2020. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.

9. Decarli A, Vecchia C La, Malvezzi M, Micciolo R. An R package for fitting age, period and cohort models. Epidemiol Biostat Public Heal. 2014;11(4):1–12. https://doi.org/10.2427/9977

10. Osmond C, Gardner MJ. Age, period and cohort models applied to cancer mortality rates. Stat Med. 1982;1(3):245–59. https://doi.org/10.1002/sim.4780010306

11. Kernéis S, Boëlle PY, Grais RF, Pavillon G, Jougla E, Flahault A, et al. Mortality trends in systemic sclerosis in France and USA, 1980-1998: An age-period-cohort analysis. Eur J Epidemiol. 2010; 25(1): 55–61. https://doi.org/10.1007/s10654-009-9403-2

12. Yen E, Singh DR, Singh RR. Trends in Systemic Sclerosis Mortality Over Forty-Eight Years, 1968–2015: A US Population–Based Study. Arthritis Care Res (Hoboken) 2020. https://doi.org/10.1002/acr.24411.

13. 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(1): 1–11. https://doi.org/10.1186/s41927-018-0043-6

14. Freire M, Rivera A, Sopeña B, Tolosa-Vilella C, Guillén-Del Castillo A, Colunga-Argüelles D, et al. Clinical and epidemiological differences between men and women with systemic sclerosis: a study in a Spanish systemic sclerosis cohort and literature review. Clin Exp Rheumatol. 2017; 35 Suppl 106 (4): 89–97.

15. Peoples C, Medsger TA, Lucas M, Rosario BL, Feghali-Bostwick CA. Gender differences in systemic sclerosis: relationship to clinical features, serologic status and outcomes. J Scleroderma Relat Disord. 2016; 1(2): 204–12. https://doi.org/10.5301/jsrd.5000209

16. Hughes M, Pauling JD, Armstrong-James L, Denton CP, Galdas P, Flurey C. Gender-

related differences in systemic sclerosis. Autoimmun Rev. 2020; 19: 102494. https://doi.org/10.1016/j.autrev.2020.102494

17. Hao Y, Hudson M, Baron M, Carreira P, Stevens W, Rabusa C, et al. Early Mortality in a Multinational Systemic Sclerosis Inception Cohort. Arthritis Rheumatol. 2017; 69(5): https://doi.org/1067–77. 10.1002/art.40027

18. Moinzadeh P, Kuhr K, Siegert E, Mueller-Ladner U, Riemekasten G, Günther C, et al. Older age onset of systemic sclerosis - Accelerated disease progression in all disease subsets. Rheumatology (Oxford). 2020; 59(11): 3380–9. https://doi.org/10.1093/rheumatology/keaa127

19. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev. 2010; 9(5): A311–8. https://doi.org/10.1016/j.autrev.2009.11.003

20. Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23:581–90. https://doi.org/10.1002/art.1780230510

21. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: An American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013; 72(11): 1747–55. https://doi.org/10.1136/annrheumdis-2013-204424

22. Woodworth TG, Suliman YA, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol. 2016; 12(11): 678–91. https://doi.org/10.1038/nrneph.2016.124

23. Chrabaszcz M, Małyszko J, Sikora M, Alda-Malicka R, Stochmal A, Matuszkiewicz-Rowinska J, et al. Renal Involvement in Systemic Sclerosis: An Update. Kidney Blood Press Res. 2020; 45(4): 532–48. https://doi.org/10.1159/000507886

24. Yen E, Singh D, Wu M, Singh R. OP0248 Premature mortality burden for systemic sclerosis: nationwide population-based study. Ann Rheum Dis 2020. https://doi.org/10.1136/annrheumdis-2020-eular.2270.

25. Morrisroe K, Stevens W, Huq M, Prior D, Sahhar J, Ngian GS, et al. Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. Arthritis Res Ther. 2017; 19(1):122. https://doi.org/10.1186/s13075-017-1341-x

Figure legends:

Figure 1. Joinpoint regression analysis (years 1980-2019) for all ages (a), between 35 and 64 years (b) and over 65 years (c).

Figure 2. Trend in the sex ratio (men / women) over the years 1980-2019 by age group.

Figure 3. Analysis of the age-period-cohort effect for both sexes (a), men (b) and women (c). The upper graph shows the mortality rates for each five-year age; the lower graph shows the variation of the relative risk for the different cohorts and period.

Figure 4. Rates of potential years lost per 100,000 persons-year.

Table captions:

Table 1. Trend analysis on annual average percentage change (AAPC) global and stratified by age and sex.

Table 2. Goodness-of-fit test for different age-, period- and cohort specific models of systemic sclerosis in Spain, 1980-2019.