Estimating the Burden of Scleroderma Disease in Spain

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ABSTRACT. ***Objective.*** Scleroderma (systemic sclerosis) is a rare disease that results in great suffering. We estimated the burden of disease posed by scleroderma and its relative importance in the health of the Spanish population.

Methods. We estimated scleroderma-based burden of disease following procedures developed for the Global Burden of Disease study to ensure comparability.

Results. Despite its low prevalence, scleroderma generated 1732 disability-adjusted life-years (DALY) in Spain in 2001, comprising 562 (32%) years of life lost and 1170 (68%) years lived with disability. Most scleroderma-related DALY (73%) occurred in the population aged 15–54 years. Estimated DALY accounted for 0.59% of other musculoskeletal disorder-related DALY in the European A subregion (countries with low mortality rate in both adults and children in the World Health Organization classification), a significant value in the overall burden of disease.

Conclusion. The burden of scleroderma in Spain was high, with disability being the major contributing factor. Burden of disease is an important measure in rare diseases, and may be an important indicator to be considered as a health unit in developed countries. (First Release Oct 1 2007; J Rheumatol 2007;34:2236–42)

Key Indexing Terms:

SCLERODERMA | SYSTEMIC SCLEROSIS | RARE DISEASES
DISABILITY | BURDEN OF DISEASE | EPIDEMIOLOGY

Rare diseases are those that have a prevalence, in terms of the prevailing European threshold, of fewer than 5 cases per 10,000 population and that are life-threatening or chronically debilitating. The importance of studying these diseases has been well established since the introduction of the Orphan Drug Act in the United States in 1983[1]. They are diseases whose low frequency usually implies difficulty and delay in diagnosis and problems with appropriate and continuous treatment. There are thousands of rare diseases and their prevalences range between less than 1/100,000 to 5/10,000 people. The prevalence of scleroderma (systemic sclerosis, SSc) is estimated to range between 0.5 and 2/10,000. This prevalence provides a better starting point for researchers in order to investigate and to gain experience than other rare diseases with a lower prevalence. Thus scleroderma is a good model for developing specific research methods for rare diseases whose prevalence is in the middle range of the definition. Enhancing existing knowledge about rare diseases leads to ensuring equity in access to diagnosis, treatment, and care.

SSc is a chronic and heterogeneous disease of unknown etiology, although it is believed to have an autoimmune component. It is characterized by vascular alterations and overproduction and accumulation of collagen and other extracellular matrix macromolecules in skin and visceral organs[2-7].

The natural history of SSc is highly variable, but according to the pattern of skin manifestations, it is possible to identify 2 main subsets with different clinical manifestations and prognosis[2-4,8-10]. Limited SSc, the most frequent subset of the disease[11,12], has a much better prognosis, and diffuse SSc, with generalized skin thickening, presents with more severe damage to the visceral organs earlier in the disease course, occasionally with a devastating clinical course. There is no cure for the disease, which has a high mortality and morbidity[13].

While the epidemiology of SSc displays a worldwide distribution, certain ethnic groups nevertheless register a higher prevalence and other different features. Other risk factors are age (peak incidence in the third to fifth decade of life, usually sparing children) and female sex, with average incidence in women being 3-fold that of men. There are environmental risk factors, such as professional exposure to certain chemical agents and the toxic oil syndrome, which occurred in Spain in 1981, a multisystem disease resembling SSc that emerged

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after ingestion of aniline-adulterated cooking oil[14]. There is suspicion that other environmental factors might be acting on persons genetically predisposed to SSc[15-17].

In rare diseases, there is a lack both of indicators and of adequate quantification. Quality-adjusted life-years (QALY) and disability-adjusted life-years (DALY) are the only 2 health measures that combine in just one figure death and non-death consequences due to disease. QALY measurements were designed to quantify results of health interventions and DALY to define the health status of a population (burden of disease); other differences between QALY and DALY can be seen in Table 1[18,19].

Burden of disease as a summary measure of population health estimated on the basis of DALY has never been applied to rare diseases. We feel it may be a useful tool for characterizing SSc, which severely affects relatively young persons and thus leads to a major shortening of life expectancy. Burden of disease depends both on frequency (incidence) and on ensuing mortality and disability. The usefulness of this type of summary measure is well established for monitoring health changes in a population, assessing the relative contribution of different diseases to the total disease burden in a population, comparing health between different populations, analyzing the benefits of health interventions, and other purposes[20-23].

Our aim was to estimate SSc-related burden of disease, and describe the disease's quantitative importance. This article is intended to be the first of a series in which estimation of rare disease-related burden of disease and its relative importance in global burden of disease in developed countries will be evaluated.

MATERIALS AND METHODS

To estimate SSc-related burden of disease in the Spanish population, we followed the procedures used in the Global Burden of Disease study described by Murray and Lopez, to ensure comparability with other studies using the same methodology[24]. DALY are obtained from the addition of 2 components, namely, years of life lost (YLL) and years lived with disability (YLD) (DALY = YLL + YLD).

Study population. The total Spanish population in 2001 comprised 41,116,842 inhabitants (20,165,514 men and 20,951,328 women). The population distribution was provided by the National Statistics Institute (NSI; Instituto Nacional de Estadística)[25].

Calculation of YLL. The general formula for calculating YLL is YLL = $\sum^{1}_{0} D_i \times E_i$, where D_i is the number of deaths related to SSc as primary cause and E_i is the standard life expectancy at each year of age. Data required to quantify YLL were as follows.

(1) SSc deaths during the period studied, by cause of death, age group, and sex. This was calculated using Spanish 2001 death certificate information on SSc as the primary cause of death, furnished by the NSI[26]. For study purposes, SSc was defined as all causes of death listed under the M34 code of the *International Classification of Diseases*, 10th revision, in which every death is ascribed a single cause. This M34 code includes these terms: M34 Systemic sclerosis; includes: scleroderma, excludes: scleroderma: circumscribed and neonatal. M34.0, Progressive systemic sclerosis. M34.1, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia). M34.2, Systemic sclerosis induced by drugs and chemicals. M34.8, Other forms of systemic sclerosis: Systemic sclerosis with: lung involvement; myopathy. M34.9, Systemic sclerosis, unspecified[27].

(2) Life expectancy for each age. This was obtained from the Princeton Model Life Table with Level West 26 modified (80 and 82.5 years of life expectancy for men and women, respectively) "The word 'modified' following the 'Princeton table West 26' shows that while the level 26 of the table is taken for life expectancy estimate in women, a lower level (level 25) is taken for men. Women have a greater life expectancy than men for biological reasons and this difference is estimated in 2 years."[28]

Calculation of YLD. The general formula for quantifying YLD is YLD = $\sum^{1}_{0} N_i \times I_i \times T_i \times D_i$, where N_i is the population susceptible to SSc at each age, I_i is SSc incidence for each age group (i), T is the average duration for each age group, and D is the level of disability. To calculate YLD, the following were therefore needed.

(1) SSc incidence by age group and sex. Because there was neither a population registry in Spain nor a specific bibliography for this disease, incidence data

Table 1. Properties of DALY and QALY.

Features	DALY	QALY
Type of measures	Both are health outcome measurement units that combine duration and quality of life	
Meaning	Measures health differences due to disease clinical course	Measures health expectation of the disease
Significance	Differences between health status and a situation of full health Disability years saved	Differences between quality and quantity of life that can be improved after an intervention Quality years gained
Range	1 = full disability, 0 = no disability	1 = full health, 0 = death
Designed for measuring	Burden of diseases estimates in populations and for results after interventions (mortality and disability reduction)	Results after interventions (clinical trials, cost-utility analysis, etc) QALY accepted as the reference standard in cost-effectiveness analysis
Method	World Health Organization method	No unique standard method
Age weighting	Yes	No
Discount rate	3%	3% to 5%
Disease starts in the very early years of life and is of short duration	QALY gained exceed DALY saved	
Disease starts in later years, up to young adulthood	DALY saved exceed QALY gained	
Disease starts in late adulthood and in older ages	QALY gained exceed DALY saved	

DALY: disability-adjusted life-years; QALY: quality-adjusted life-years.

were collected from the study conducted by Silman, *et al* in the West Midlands (United Kingdom)[29], after a comprehensive review of the literature[11,16,30-33].

(2) Disease model (average duration and age at onset of SSc for the different age groups by sex, and disability weight). The natural history of SSc was drawn up using the formulation in Medsger[34] as well as Spanish expert opinion (personal communication) and survival described by Roberts-Thomson, *et al*[16]. Duration by sex, age group, and age at onset were estimated using DisMod II, a software program designed by the World Health Organization (WHO) and Harvard University to perform epidemiologic estimates (incidence, prevalence, etc.) within the context of burden of disease[35]. SSc was modeled as a progressive condition, with 75% of patients having limited and 25% diffuse SSc[3,11,12,33] and passing through the 3 stages described by Medsger[34]. In order to determine the severity of disabilities associated with each stage, we used stage-weighting from the Disability Weights for Diseases in The Netherlands[36]. To estimate these, a group of experts weighted the severity of several disabling conditions from 0 (perfect health) to 1 (death), using a person-tradeoff methodology. SSc disability weights were then constructed on the assumption that SSc was similar to rheumatoid arthritis (RA). From the above studies, we assumed that in limited SSc, 73% of total SSc duration was spent in the moderate stage, with a disability weight of 0.37, and the remainder in the mild and severe stages, with disability weight levels of 0.21 and 0.94, respectively. The intermediate stage of diffuse SSc represents 42% of total disease duration, with an associated disability weight of 0.65, the mean of the disability weights from the initial and late stages. The overall disability weight was 0.48 and mean duration of SSc was 23 years (Figure 1).

To calculate DALY, we applied the same age-weighting and discounting factors used in the WHO Global Burden of Disease study (a 3% discount rate and an age-weighting modulation factor of k = 1)[22]. A sensitivity analysis using several disability weights taken from the diseases model (Figure 1) is presented. Health quality measures are also considered for disability weights estimates based on the following general formula: D = 1 – Q, where D = disability weight and Q = quality of life related to health[18,37,38]. Analyses were performed using GesMor[39], a software tool for calculating DALY developed by the International Health Department, Carlos III Institute of Public Health, Madrid.

RESULTS

In 2001, the total number of estimated new SSc cases in Spain was 115 for women and 24 for men (Table 2). There were no deaths in the population under 15 years of age, and incidence in this group was negligible. Accordingly, only subjects aged over 15 years in 2001 were used for estimate purposes, a population totaling 35,266,970 (18,104,727 women and 17,162,243 men).

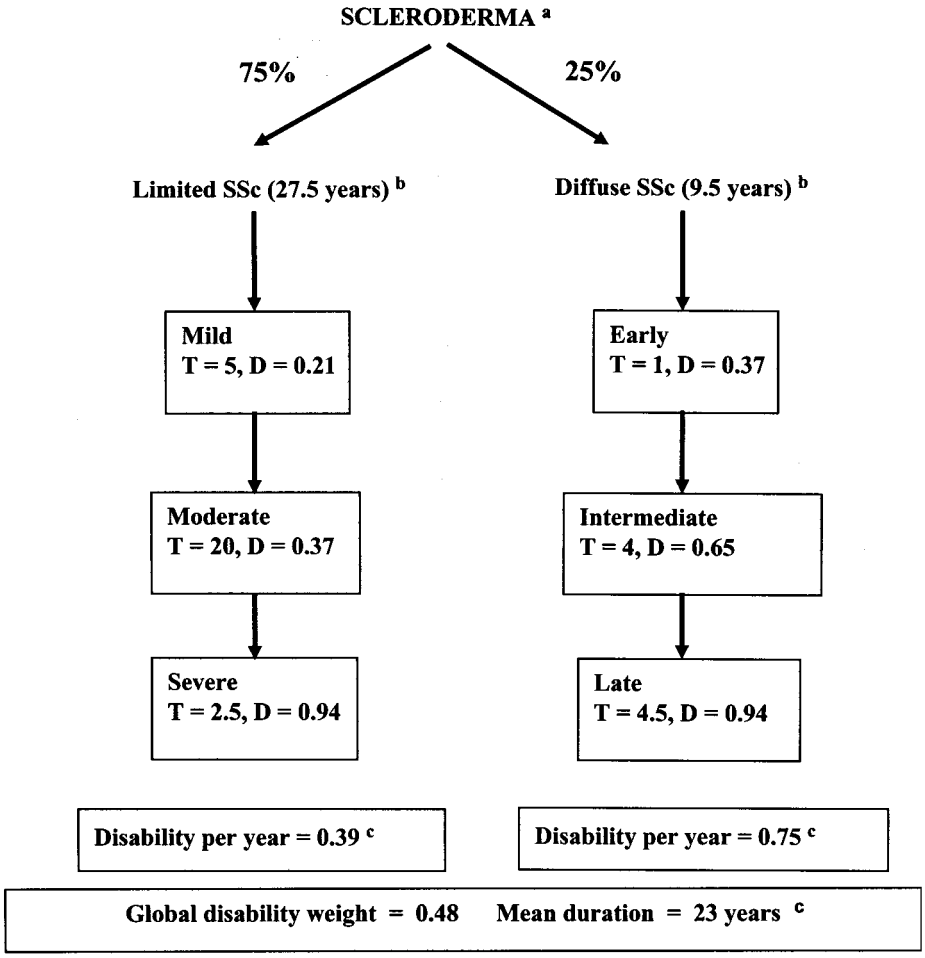

Figure 1. Scleroderma disease model. T: time (yrs) in the different disease stages described by Medsger[34] and expert opinion; D: disability weight in the different disease stages[36]. a: 75% of patients having limited SSc and 25% diffuse SSc[3,16,18,33,44,45]. b: Survival data[16]. c: The weighted-disability weight from the following formula, calculating the percentages of time in different disease stages: limited: [(0.21 × 0.18) + (0.37 × 0.73) + (0.94 × 0.09)]; diffuse: [(0.37 × 0.11) + (0.65 × 0.42) + (0.94 × 0.47)]; global weighted-disability weight: [(0.39 × 0.75) + (0.75 × 0.25)]; mean duration: [(27.5 × 0.75) + (9.5 × 0.25)].

Table 2. Data used for calculations.

Age group, yrs	Age of SSc Onset[a]		SSc Duration, yrs[b]		Population Size, Spain 2001[d]		SSc Incidence*[f]		Estimated No. of Incident SSc cases[c]		No. of SSc Deaths[e]	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
15–34	25.67	27.09	36.84	41.88	6,525,177	6,244,297	0.8	4.6	5	26	0	1
35–44	40.15	40.25	23.28	34.08	3,169,266	3,136,034	0.9	9.4	3	28	0	5
45–54	50.47	49.86	16.87	27.42	2,510,808	2,531,949	2.8	13.7	5	29	1	4
55–64	59.63	59.43	13.69	19.94	1,995,297	2,116,588	2.2	5.8	5	14	3	4
65–74	69.57	69.59	8.73	12.94	1,817,596	2,146,179	2.2	5.7	4	11	4	16
75+	80.88	81.81	4.36	7.07	1,144,099	1,929,680	1.4	3.2	2	7	5	19
Total					17,162,243	18,104,727			24	115	13	49

[a,b,c] Estimations with DisMod II with the reference data[35]. [d,e] National Statistics Institute[25,26]. [f] Silman, *et al*[29]. * Crude rate × million population.

Spanish SSc mortality was 0.17 per thousand deaths. There were 62 deaths with diagnosis of SSc (49 women, 13 men). The overall SSc mortality rate was 1.75 per million population over the age of 15 years (2.70 for females, 0.75 for males). The number of SSc deaths was higher among females than among males across all age groups. In all, 71% of SSc deaths were registered by the over-65 age group.

SSc-related DALY totaled 1732 (1474 for women, 258 for men), with most (73%) being accounted for by the population aged 15–54 years (Table 3 shows the variables used for SSc-related DALY calculations in 2001). The major contributory factor to SSc-related DALY was YLD (68%). YLL, in contrast, accounted for just 32% of total DALY (Table 3). Older groups had an increasing percentage of DALY due to mortality (YLL). Among the under-65 age group, the most important component of DALY was morbidity (Figure 2). The sensitivity analysis shows a range between 1515 and 2393 DALY for disability weights from 0.39 to 0.75, respectively. When the general rule $D = 1 - Q$[37] and the Q value 0.37 obtained from the Medical Outcomes Study Short Form-36 Health Survey (SF-36) in subjects with SSc[38] is applied, the estimated disability weight is 0.63, resulting in 2100 DALY.

In 2000, SSc-related YLL in Spain accounted for 4.5% of total YLL caused by musculoskeletal diseases, while the total burden of disease due to SSc accounted for 0.035% (0.031%–0.049%) of overall DALY in Spain for the disability weights of 0.48 (0.39; 0.75), respectively[40,41].

Comparison showed that, in 2000, DALY due to SSc estimated for Spain accounted for 0.59% (0.52%–0.72%) of DALY due to "other musculoskeletal disorders" (which include SSc) calculated by the WHO for the European-A subregion — countries with low mortality rate in both adults and children — as a whole (Table 4). In Spain, estimated SSc-related DALY represented 0.73% (0.64%–1.01%) of total DALY due to musculoskeletal diseases.

DISCUSSION

Our study represents the first approach to estimating SSc-related burden of disease, and the results show that despite its low frequency in the population, SSc accounts for an important loss of health in the total of diseases and disorders, mainly through YLD, because of the severity with which it affects relatively young people. Estimating cost of illness in the USA, Wilson observed that the greatest importance was that of morbidity and concluded that the high cost of SSc, despite its low prevalence, suggested that the cost burden of rare chronic diseases could nevertheless be high[42]. Smyth, *et al* indicated that with improved SSc survival rates over the past few decades, morbidity rather than mortality appeared to be the more relevant issue in many patients[43]. Further, in their 2003 study addressing the cost of illness of SSc in a cohort of 106 patients, Belotti Masserini, *et al* confirmed the "extremely high costs for total and single patients caused by systemic sclerosis"[44].

To calculate YLL, we used death certificate mortality data for 2001 furnished by the NSI[26]. Although diagnoses reported in death certificates may be erroneous or incomplete[45], we

Table 3. Estimated scleroderma-related DALY in Spain in 2001.

Age Group, yrs	YLL		YLD		DALY		
	Men	Women	Men	Women	Men	Women	Total
15–34	0	38	69	369	69	407	476
35–44	0	117	27	295	27	412	439
45–54	19	72	30	228	49	300	349
55–64	39	47	21	75	60	122	182
65–74	27	124	9	35	36	159	195
75+	15	64	2	10	17	74	91
Total	100	462	158	1012	258	1474	1732

YLL: years of life lost; YLD: years lived with disability; DALY: disability-adjusted life-years.

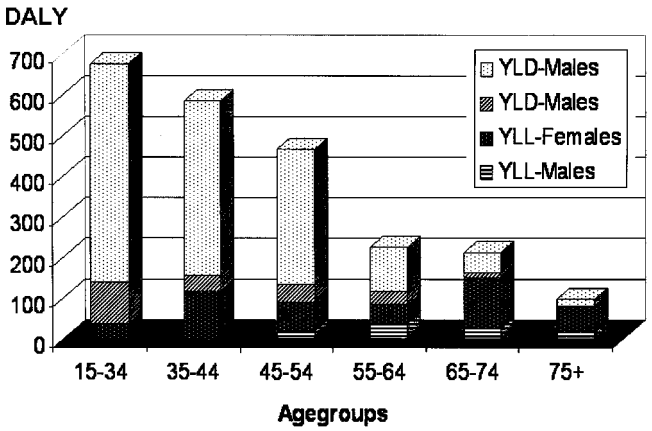

Figure 2. Contribution to DALY by years of life lost (YLL) and years lived with disability (YLD), by age group, Spain, 2001.

nonetheless feel that the possibility of committing a mistake is remote because of the NSI's system of establishing cause of death, due to the clinical relevance of SSc and the NSI's definition of cause of death as being the lesion or disease that started the pathologic events that led directly to death. In our opinion, the possibility of committing a mistake would be higher if one sought to estimate percentages of other causes of death partially due to this low-prevalence disease. It is important to note the relevant information that mortality rates alone can provide in a rare disease such as SSc through epidemiologic consideration of changes across time[46].

The most difficult calculation posed by our study was that of YLD. As with many other rare diseases, there is no SSc-specific epidemiologic register. The need for epidemiologic studies and the creation of a register for a better understanding of the nature of SSc have been suggested[16,30,47]. The absence of data for Spain made it necessary to base our estimate on data for the West Midlands, UK, an area that has an SSc pattern similar to that of Spain, by applying the incidence rate reported by Silman, *et al*[29] to the Spanish population in 2001. We regard this epidemiologic estimate as the most accurate to date for SSc in Europe, with results comparable to those from Spanish studies[5,48], bearing in mind that incidence rates seem to have remained stable over the last 20 years[49]. With respect to duration of SSc, we estimated this on the basis of age at onset and mortality using the DisMod II program[35], which allows for an estimate by sex and age group, and the weighted duration proved similar to that observed by Roberts-Thomson, *et al* in 2001[16]. Another complex aspect of burden of disease studies entails the estimation of a disease model and assignment of a disability weight.

Insofar as calculating disability weight is concerned, there is no consensus as to the best procedure for drawing up a severity scale capable of assessing health status and establishing equivalence with the loss of life due to premature death. The WHO Burden of Disease method describes how the disability weight should be taken from the literature review and then discussed among experts. This consensus can be reached using several strategies. In our case, we started by taking the disability weight from the general consensus for osteomuscular and connective tissues diseases (included in the general burden of disease study carried by the WHO). Then a specific literature review on scleroderma and a national expert consultation were used for adjusting that weight to the scleroderma clinical course[19].

Both SSc and RA belong to the group of musculoskeletal and connective tissue diseases with a likely autoimmune etiopathogenic origin and similar clinical manifestations (with overlapping forms in some patients) and can be severely disabling. Using the Health Assessment Questionnaire, which essentially measures basic activities of daily living subjectively in a range from 0 to 3, patients with RA and SSc registered similar values, i.e., 0.82 and 0.92, respectively[34,50]; similarly, no differences were seen when the health-related quality of life (HRQOL) test was administered[51]. Despite absence of agreement as to the best way of measuring the physical, psychological, and social implications of a disease, we feel that, in agreement with the opinion voiced by the

Table 4. Comparison between scleroderma-related disability-adjusted life-years (DALY) in Spain and WHO "Other musculoskeletal disorders" burden of disease data for 2001[†].

	Total Population	Musculoskeletal Diseases*, DALY	Other Musculoskeletal Disorders[†], DALY	Scleroderma, DALY
Spain[40,41]	41,116,842	238,299	NA	1732 (1515; 2393)
Europe A Subregion	411,889,100	3,343,707	291,127	NA
World	6,045,017,327	33,596,292	3,722,892	NA

* Musculoskeletal diseases (ICD-10 codes): rheumatoid arthritis (M05–M06); osteoarthritis (M15–M19); gout (M10); low back pain (M45–M48, M54, minus M54.2).

[†] Other musculoskeletal disorders (ICD-10 codes): pyogenic arthritis; direct infections of joint in infectious and parasitic diseases classified elsewhere; reactive arthropathies (M00–M02); juvenile arthritis (M08); other crystal arthropathies; other specific arthropathies (M11–M13); other joint disorders (M20–M29); systemic connective tissue disorders (M30–M36); deforming dorsopathies (M40–M43); other dorsopathies (minus dorsalgia) (M50–M53); cervicalgia (M54.2); soft tissue disorders, osteopathies and chondropathies (minus dorsalgia) (M50–M53); cervicalgia (M54.2); soft tissue disorders, osteopathies and chondropathies (M55–M99).

NA: not available.

experts we consulted, an average weight disability value of 0.48 can be regarded as a "soft" picture of the real implication of having a serious disease such as SSc, in which depressive symptoms alone have been estimated to be present in as many as 46% of patients[52]. A sensitivity analysis including some limits to the estimated disability weight has been used. The limits used were taken from the model of the diseases used for the general burden of disease estimate (Figure 1). Other measures taken from quality of life studies were also considered, but the disability weights obtained by this method were included among the limits we used[38]. As reported, differences in burden of disease estimation based on different disability weights can be substantial[53], so SSc-related burden of disease could be even higher. Nevertheless, burden of disease based on the same measures is a useful unit of comparison.

Despite the above limitations affecting estimation of DALY, we feel that our results represent an approach to understanding the real health status of the SSc population. Moreover, these limitations are the same as those found in other burden of disease studies: the absence or reduced reliability of the epidemiologic data used in the calculation; the absence of consensus on the severity — the disability weight — associated with each disease[20]; and, in addition, the debate about the age limits employed to calculate YLL, the application of discount rates, and the weighting of years based on age[18,19,54]. Yet we feel that the DALY's ability to synthesize disease frequency and lethal and nonlethal health outcomes, enable quantification of the ensuing health loss in the population, and allow comparison between different populations has served to retain interest in these types of indicators, as shown by the WHO Global Burden of Disease and other studies[20,22,55-57]. In addition, DALY allow statistical changes due to different etiopathogenic factors to be identified, something that can be especially interesting in the case of rare diseases in general and SSc in particular, in which genetic as well as unknown environmental factors could contribute to the origin of the disease[15,17].

Comparison between our results and those reported by the WHO for the European-A subregion as a whole establish SSc's relative importance and, indeed, show it to be high, although account must be taken of the differences in the disability weights and natural history of the disease when studied within the global context of "other musculoskeletal disorders" rather than the context of an individual study. Direct comparison with SSc-related DALY was not possible because, as with most rare diseases, there is no SSc-specific analysis in the WHO Global Burden of Disease Study[55].

Despite its limitations, the results of our study confirm the need for keener public health interest in rare diseases, particularly in developed countries, in which the relative quantitative importance of the associated burden of diseases could be considerable. With respect to monitoring health trends by studying and measuring variables in different populations, ranging from life expectancy or child mortality to others that are more sensitive, such as DALY, which address mortality as well as disability, suffering, and quantitative loss of health, we feel that in rare diseases, which have a low prevalence but a high associated mortality and disability, and which mainly affect young people in developed countries, burden of disease could be an important parameter to be taken into account as a health measure.

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REFERENCES

1. US Food and Drug Administration. The Orphan Drug Act. Washington, DC: US Food and Drug Administration; 1983. Available from: www.fda.gov/orphan/oda.htm (accessed August 3, 2007).
2. Ferri C, Valentini G, Cozzi F, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1012 Italian patients. Medicine 2002;81:139-53.
3. Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis 1998;57:682-6.
4. Jacobsen S, Halberg P, Ullman S. Mortality and causes of death of 344 Danish patients with systemic sclerosis (scleroderma). Br J Rheumatol 1998;37:750-5.
5. Simeon CP, Armadans L, Fonollosa V, et al. Mortality and prognostic factors in Spanish patients with systemic sclerosis. Rheumatology Oxford 2003;42:71-5.
6. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med 2005;118:2-10.
7. Nishioka K, Katayama I, Kondo H, et al. Epidemiological analysis of prognosis of 496 Japanese patients with progressive systemic sclerosis. Scleroderma Research Committee Japan. J Dermatol 1996;23:677-82.
8. Posada de la Paz M, Martínez López de Letona J, Masa Vázquez C, et al. Esclerosis sistémica progresiva. Un problema diagnóstico. Rev Clin Esp 1983;170:237-41.
9. Medsger TA Jr. Classification of systemic sclerosis. In: Jayson MIV, Black CM, editors. Systemic sclerosis: scleroderma. London: John Wiley; 1988:1-6.
10. Giordano M, Valentini G, Migliaresi S, et al. Different antibody patterns and different prognoses in patients with scleroderma with various extent of skin sclerosis. J Rheumatol 1986;13:911-6.
11. Chandran G, Smith M, Ahern MJ, et al. A study of scleroderma in South Australia: prevalence, subset characteristics and nailfold capillaroscopy. Aust NZ J Med 1995;25:688-94.
12. Alamanos Y, Tsifetaki N, Voulgari PV, et al. Epidemiology of systemic sclerosis in northwest Greece 1981 to 2002. Semin Arthritis Rheum 2005;34:714-20.
13. UK Scleroderma Study group. How can treatment of systemic sclerosis be improved? BMJ 1998;317:294-5.
14. Posada de la Paz M, Philen RM, Borda AI. Toxic oil syndrome: the perspective after 20 years. Epidemiol Rev 2001;23:231-47.
15. Valesini G, Litta A, Bonavita MS, et al. Geographical clustering of scleroderma in a rural area in the province of Rome. Clin Exp Rheumatol 1993;11:41-7.
16. Roberts-Thomson PJ, Jones M, Hakendorf P, et al. Scleroderma in South Australia: epidemiological observations of possible pathogenic significance. Intern Med J 2001;31:220-9.
17. Tan FK. Systemic sclerosis: the susceptible host (genetics and

environment). Rheum Dis Clin North Am 2003;29:211-37.
18. Arnesen T, Nord E. The value of DALY life: problems with ethics and validity of disability adjusted life years. BMJ 1999;319:1423-5.
19. Victorian Burden of Disease Study (2005). Mortality and Morbidity in 2001. Public Health Group. Melbourne: Victorian Government Department of Human Services; 2005. Available at: http://www.health.vic.gov.au/healthstatus/bod/bod_vic.htm (accessed August 3, 2007).
20. Murray CJL, Salomon JA, Mathers C. A critical examination of summary measures of population health. Bull World Health Organ 2000;78:981-94.
21. Schopper D, Pereira J, Torres A, et al. Estimating the burden of disease in one Swiss canton: what do disability adjusted life years (DALY) tell us? Int J Epidemiol 2000;29:871-7.
22. Skull SA, Butler JRG, Robinson P, Carnie J. Should programmes for community-level meningococcal vaccination be considered in Australia? An economic evaluation. Int J Epidemiol 2001;30:571-8.
23. Strong K, Mathers C, Epping-Jordan J, Beaglehole R. Preventing chronic disease: a priority for global health. Int J Epidemiol 2006;35:492-4.
24. Murray CJL, López AD, editors. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Global Burden of Disease and Injury. Harvard School of Public Health on behalf of WHO. Cambridge, MA: Harvard University Press; 1996.
25. Cifras de Población. Revisión del Padrón Municipal 2001. Madrid: Instituto Nacional de Estadística (INE). Available from: www.ine.es/inebase/index.html (accessed August 3, 2007).
26. Instituto Nacional de Estadística. Fichero de microdatos individuales de defunciones con causa de muerte. Año 2001. Madrid: Instituto Nacional de Estadística; 2001.
27. World Health Organization (WHO). International statistical classification of diseases and related health problems, 10th revision, ICD-10, vols. 1-3. Geneva: World Health Organization; 1992-1994.
28. Coale A, Guo G. Revised regional model life tables at very low levels of mortality. Popul Index 1989;55:613-43.
29. Silman A, Jannini S, Symmons D, et al. An epidemiological study of scleroderma in the West Midlands. Br J Rheumatol 1988;27:286-90.
30. Mayes MD. The establishment and utility of a population-based registry to understand the epidemiology of systemic sclerosis. Curr Rheumatol Rep 2000;2:512-6.
31. Allcock RJ, Forrest I, Corris PA, et al. A study of the prevalence of systemic sclerosis in northeast England. Rheumatology Oxford 2004;43:596-602.
32. Englert H, Small-McMahon J, Davis K, et al. Systemic sclerosis prevalence and mortality in Sydney 1974-88. Aust NZ J Med 1999;29:42-50.
33. Le Guern V, Mahr A, Mouthon L, et al. Prevalence of systemic sclerosis in a French multi-ethnic county. Rheumatology Oxford 2004;43:1129-37.
34. Medsger TA Jr. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. Rheum Dis Clin North Am 2003;29:255-73.
35. DisMod II. Software developed by J. Barendregt, Department of Public Health, Erasmus University, Rotterdam. In collaboration with the WHO. Available from: www.hsph.harvard.edu/Organizations/bdu/DisMod.html (accessed August 3, 2007).
36. Stouthard MEA, Essink-Bot ML, Bonsel GJ, et al. Disability weights for diseases in The Netherlands. Rotterdam: Department of Public Health, Erasmus University; 1997.
37. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. Health Policy Plan 2006;21:402-8. doi: 10.1093/heapol/czl018.
38. Khanna D, Ahmed M, Furst DE, et al. Health values of patients with systemic sclerosis. Arthritis Rheum 2007;57:86-93.
39. GesMor: Software developed by the International Health Department, Carlos III Institute of Public Health (Instituto de Salud Carlos III). Supported by the Mexican Health Foundation (FUNSALUD) and the Interamerican Bank for Development. Available from: http://www.funsalud.org.mx/red-jlb/gesmor.htm (accessed August 3, 2007).
40. Alvarez E, Génova R, Morant C, Freire JM. Estimación de la carga de enfermedad de España en el año 2000. Gac Sanit 2004;18 Supl 3:36.
41. Genova R, Alvarez E, Morant C. Carga de enfermedad y tendencias de morbilidad de la población española. In: Puyol R y Abellán A (coord). Envejecimiento y dependencia. Una mirada al panorama futuro de la población española. Madrid: Mundial Assistance; 2006:91-108.
42. Wilson L. Cost-of-illness of scleroderma: the case for rare diseases. Semin Arthritis Rheum 1997;27:73-84.
43. Smyth AE, MacGregor AJ, Mukerjee D, et al. A cross-sectional comparison of three self-reported functional indices in scleroderma. Rheumatology Oxford 2003;42:732-8.
44. Belotti Masserini A, Zeni S, Cossutta R, Soldi A, Fantini F. Analisi dei costi nella sclerosi sistemica. Studio retrospettivo in una casistica di 106 pazienti. [Cost-of-illness in systemic sclerosis: a retrospective study of an Italian cohort of 106 patients]. Reumatismo 2003;55:245-55.
45. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. N Engl J Med 1985;313:1263-9.
46. Silman AJ. Mortality from scleroderma in England and Wales 1968-1985. Ann Rheum Dis 1991;50:95-6.
47. Mayes MD. Epidemiology of systemic sclerosis and related diseases. Curr Opin Rheumatol 1997;9:557-61.
48. Mérida Fernández SM, Margolles Martins M. Enfermedades raras: La esclerosis sistémica (esclerodermia) en Asturias, 1996-2003. Gac Sanit 2005;19 Suppl 1:72.
49. Mayes MD. Scleroderma epidemiology. Rheum Dis Clin North Am 1996;22:751-64.
50. Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis Care Res 1991;4:27-31.
51. Danieli E, Airo P, Bettoni L, et al. Health-related quality of life measured by the Short Form 36 (SF-36) in systemic sclerosis: correlations with indexes of disease activity and severity, disability, and depressive symptoms. Clin Rheumatol 2005;24:48-54.
52. Matsuura E, Ohta A, Kanegae F, et al. Frequency and analysis of factors closely associated with the development of depressive symptoms in patients with scleroderma. J Rheumatol 2003;30:1782-7.
53. Cubo E, Álvarez E, Morant C, et al. Burden of disease related to Parkinson's disease in Spain in the year 2000. Mov Disord 2005;20:1481-7.
54. Pereira Candel J, Cañón Campos J, Álvarez Martín E, et al. La medida de la magnitud de los problemas de salud en el ámbito internacional: los estudios de carga de enfermedad. Rev Admin Sanitaria 2001;19:441-66.
55. World Health Organization. Global burden of disease estimates. GBD 2001 estimates by sub-region. Available at: http://www.who.int/healthinfo/bodestimates/en/index.html (accessed August 3, 2007).
56. Wurthwein R, Gbangou A, Sauerborn R, Schmidt CM. Measuring the local burden of disease. A study of years of life lost in sub-Saharan Africa. Int J Epidemiol 2001;30:501-8.
57. Ebrahim S, Lau E. Commentary: Sick populations and sick individuals. Int J Epidemiol 2001;30:433-4.