

Using Multiple Cause-of-Death Analysis to Estimate Systemic Autoimmune Disease Mortality Burden in Low- and Middle-Income Countries

Halbert Hernández-Negrín MD, Yeniver Roque-Dapresa MD, Onan Martínez-Morales MD, Anabel Mederos-Portal MD

ABSTRACT

Autoimmune diseases are not always recognized as urgent health issues, despite a worldwide prevalence of 4%–5%. Most estimates come from high-income countries, as low- and middle-income countries face more issues of under-reporting. Despite this and the lack of recognition under current reporting practices, the role these diseases play in mortality must be acknowledged. In particular, considering multiple causes of death as opposed to a single cause of death results in a 1.5–4.2-fold increase in deaths classified as relating to autoimmune diseases, evidence of their share in overall mortality burden, a factor important for patient care and healthcare policy decision making.

However, formulating such policies and programs for timely, appropriate diagnoses and care is stymied in low- and middle-income countries by the shortage of methodologically sound studies on mor-

tality from systemic autoimmune diseases. This limitation exacerbates inequalities and health gaps among patients in different countries and localities.

Multiple cause-of-death methodology has been validated for research on other diseases and demonstrates the mortality burden of these illnesses in countries where traditional methodological approaches, primarily based on prospective cohort studies, are not feasible. Studying mortality from systemic autoimmune diseases by analyzing multiple causes of death with data from national mortality registries is a low-cost alternative to traditional mortality analysis. The objective of this paper is to demonstrate and defend the usefulness of this approach to estimate mortality burden.

KEYWORDS Autoimmune diseases, mortality, cause of death, Cuba

INTRODUCTION

It is estimated that autoimmune disease prevalence is 4%–5% in high-income countries, and predicted to increase worldwide.[1] In the United States and the United Kingdom, autoimmune diseases are among the 10 main causes of death in women <65 years of age, and are expected to affect 15–20 million people in the coming decades.[2,3]

Within the group of autoimmune diseases are systemic autoimmune diseases (SAD). SAD (as opposed to organ-specific autoimmune diseases) involve pathological processes in which the immune system organizes a response against the host body, causing chronic inflammation and damage to various organs.[1] The most clinically and epidemiologically relevant SAD are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), dermatomyositis/polymyositis (DM/PM), and Sjögren's syndrome (SjS), although incidence and prevalence rates vary between countries and regions.[1,4–8]

It is difficult to estimate the burden of SAD disease and mortality in low- and middle-income countries, because they lack services specialized in diagnosing, treating and monitoring SAD patients. Therefore, injuries caused by these diseases often remain undiscovered until an autopsy is performed.[9] RA is the most researched disease; in 2010 it had a global prevalence of 0.24%

IMPORTANCE

This paper discusses multiple cause-of-death analysis and recommends its use in assessing systemic autoimmune disease mortality in countries where it is difficult to diagnose and monitor autoimmune disease patients using expensive cohort studies, due to resource limitations.

(95% CI: 0.23%–0.25%) responsible for 4.8 million disability-adjusted life years (DALYs) (95% CI: 3.7–6.1). In 2010, the Global Burden of Diseases study ranked it number 42 among diseases that contributed the most disability of all 291 conditions in the study, just below malaria and just above iodine deficiency.[4] Other SADs were not included as independent entities in the study.

In 2016, SLE global incidence was estimated at 0.3–31.5 per 100,000 person-years, with a prevalence of 3.2–515.5 per 100,000 population. These variations are related to multiple factors, including genetic and geographic differences and methods used in case identification.[5] SSc has an incidence of 0.4–4.3 per 100,000 person-years and a prevalence of 8.8–44.3 per 100,000.[6] DM/PM incidence is 0.11–1.93 per 100,000 person-years, with a prevalence of 2.4–33.8 per 100,000 population.[7] For SjS, the incidence is 6.92 per 100,000 person-years, with a prevalence of 60.82 per 100,000 population.[8] One open-population study performed in Cuba reported an SLE prevalence of 63.3 per 100,000 population and an RA prevalence of 1236 per 100,000 population.[10]

While SAD signs, symptoms and disease progression can be mild, many patients experience severe forms that are refractory to current treatments, and are associated with higher mortality rates than those of the general population, contributing to premature mortality.[11,12]

Mortality is considered the primary and most universal health indicator. Yet, SAD mortality is a topic that has been 'abandoned' by the scientific community; this, despite the fact that RA mortality rates are comparable to those of HIV/AIDS and cardiovascular diseases according to standardized mortality ratios (SMR): 1.47 versus 1.30 and 1.26 respectively.[11,13] SMRs for SLE, SSc, and DM/PM are similar to or greater than those of type 2 diabetes mellitus (SMR: 2.4–4.8 vs. 2.6).[11,14] There are many reasons why SAD mortality receives little attention, but chief among them are:

many patients were unaware of their SAD at time of death as it was never diagnosed; fewer resources are dedicated to researching SAD mortality than to studying deaths from cardiovascular or neoplastic diseases; it is uncommon to find longitudinal databases monitoring SAD patients over 5–20 years; and death certificates do not typically include all rheumatic diseases.[11,15]

In order to recognize the extent of SAD as an important global health problem, and for health systems to design and implement policies that improve medical care quality and healthcare coverage of SAD patients, more data is needed than is currently available.[16] In particular, SAD mortality must be estimated to inform decision makers developing health strategies and facilitate comparisons among health programs in different places.[15–17]

Mortality studies based on the causes of death listed on death certificates are not common in international literature, and those that exist generally only take into account the underlying cause of death.[12,18] Studying the underlying cause of death provides important information, but underestimates the implication of chronic conditions, which undoubtedly are among the many influencing factors in the death. This is especially the case for SAD, which are generally present in patients with multiple comorbidities.[18,19]

Since the mid-20th century, mortality studies that analyze multiple causes of death in chronic disease patients have been considered important for gaining new insights into disease prevention.[19,20] In the last decade, there have been studies that use this methodology in SAD mortality.[18,20–26] However SAD mortality studies in developing countries are scarce, and have not had the impact necessary to impart the importance of SADs as an urgent health issue or to implement health policies designed to reduce mortality.[9,27,28] There are few mortality studies in Cuba that use multiple-cause-of-death analysis, but none of them are related to SADs.[29–31]

In this paper, we discuss the relevance and utility of using multiple-cause-of-death analysis for estimating SAD mortality in Cuba and developing countries with reliable data sources in an effort to encourage healthcare programs and policies to acknowledge the impact of SADs.

DEVELOPMENT

SAD in policy and practice In formulating health policies and programs, decisions must be evidence-based, requiring reliable and timely information to assess the magnitude of the diseases within populations and impacts of the programs designed to eliminate or control them, and to establish research priorities accordingly. Mortality registries are the standardized sources of information most commonly used for these purposes.[16,32]

In high-income countries like the United States and Sweden, cardiovascular diseases are the leading cause of death, followed by cancer. However, deaths from diseases deemed ‘rare’ are often ignored. Among these diseases are SADs, which are substantial contributors to premature death.[17] In Cuba, cardiovascular diseases have also been the leading cause of death for several years, but reports from the National Medical Records and Health Statistics Bureau in 2008–2010 placed “systemic connective tissue disorders” among the top 10 causes of death for women aged

15–34 years,[33] and the total deaths attributed to these diseases in 2009–2019 were 1419 for both sexes (84% female).[34] The age group in which those deaths were clustered reinforces the importance of properly diagnosing and treating SADs and of addressing them in health system policies.

A few years ago, SAD were not considered ‘fatal,’ and it was thought that they did not increase short-term mortality, but evidence indicates that mortality may be up to four times higher in SAD patients than in the general population (SMR from 1.44–4.8).[11,12,14,18] One of the reasons low SAD mortality rates are reported in comparison to other diseases is underestimation, since SAD deaths are not reported on death certificates, or at least, not as underlying causes of death—the disease or injury that began the chain of pathological events that directly led to death.[15,16,18,22,35]

Thus, even though these diseases may represent an important burden on individual and population health, they are not recognized as such by many countries when drafting health policies, or determining priorities for research and education.[15,16,22] In response to these deficiencies, WHO promoted 2000–2010 as the ‘Bone and Joint Decade’ in an effort to raise awareness about SADs and decrease their impact on health.[16,36]

Some countries and regions have adopted health policies addressing SADs, but they are few and far between. In response to WHO’s call, the Presidency of the Council of the European Union held a conference in October 2010 on rheumatic and musculoskeletal diseases, where it was recommended that SAD be prioritized in crafting health policy agendas, and that funding for research in EU member countries be increased accordingly. Spain was one of the first countries to design a Comprehensive National Strategy for Rheumatic and Musculoskeletal Diseases.[36] which was supplemented with other regional strategies including the Andalusian Plan for Rheumatic and Musculoskeletal Diseases. It also proposed improving healthcare, increasing SAD awareness and available information, and promoting research and professional training.[36,37]

Several countries have developed SAD-specific policies: for example the National Lupus Public Health Agenda in the United States, which, with 6 priorities, 15 strategies, and 63 recommendations, has achieved both better understanding and management of SLE.[38]

In 2015, the US National Institutes of Health recognized SLE as one of the leading causes of death in young women and increased funding for research into this disease to US\$90 million annually. However, despite SLE having an SMR comparable to diabetes mellitus and HIV/AIDS, funding designated for research on diabetes (US\$1.01 billion) and HIV/AIDS(US\$3.17 billion) remains considerably higher.[22]

Countries that already have SAD-specific policies in place relied on information on disease burden, mortality, social determinants of health, the diseases’ temporal and geographic trends, and the use of services related to SAD. That data was supplemented with qualitative studies using evaluations of patients and professionals related to their experiences in patient care.[37,38] In low- and middle-income countries, it is more difficult to obtain this information due to the high cost and organizational and infrastructural dif-

difficulties associated with cohort studies and research that provide reliable data on disease burden and mortality, as these countries do not always have services and specialists dedicated to caring for SAD patients.[9,31]

Health authorities in developing countries are hard pressed to fund studies facilitating policy design and implementation for SADs, when forced to dedicate scarce resources to the double burden of diseases that no longer affect high-income countries: communicable diseases plus pressing chronic non-communicable diseases such as diabetes, hypertension, cardiovascular disease, cancer and rheumatic disease.[31,39]

The lack of health policies aimed at improving care for SAD patients in developing countries is evident in the results of a study that analyzed global trends in SAD-related deaths, 2001–2014. In this study, SLE age-standardized mortality rate (ASMR) in Latin America was five times higher than in Europe, and during the 2003–2014 period, there was a significantly increasing trend in SLE ASMRs in Latin America and Asia, while Europe, North America, and Oceania, saw a decreasing trend and ASMRs in Africa remained stable.[1] Hernández Negrín discussed increasing SLE mortality in Latin America and its inverse correlation to country wealth by compiling information from five studies on the topic that obtained their data from mortality registries based on standard WHO death certificates.[27]

Even though health policy deficiencies in recognizing and treating SAD have an important role in SAD severity and high mortality rates, regionalized unfavorable health statistics are due to multiplicity of factors including poverty, malnutrition, low education levels, lack of treatment adherence, adverse perception and non-adaptive behaviors regarding the disease, low clinical suspicion, lack of access to specialized treatments and services, geographic isolation, lack of social support systems, inadequate public policies, and low gross domestic product.[5,9,30,31]

In Cuba, universal health coverage and access provides equitable medical care and epidemiological services to the Cuban population.[40] Yet, despite the existence of rheumatology services designed to diagnose and treat SAD and a Rheumatology Institute conducting research in the field, these diseases are not included in objectives aimed at reducing premature death from select non-communicable chronic diseases (diseases of the arteries and arterioles, cerebrovascular disease, ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and asthma).[41] Specific public policies for SAD patients are therefore required.

Those policies must be oriented toward improving health professionals' training pertaining to SADs, increasing human resources for diagnosing and treating SAD patients and researching these diseases, developing health models focused on SAD, establishing standardized national guidelines for SAD clinical management, the systematic collection of clinical and epidemiological data to better understand SAD, raising public awareness, creating support groups for SAD patients and their families, improving access to immunological diagnostic testing, and empowering patients to actively participate in disease management.[9,37,38]

SAD mortality study limitations Medical care for SAD patients is tricky due to diverse (but not uncommon) clinical presentation, and because conventional immunological diagnostic methods can

provide similar results for several SADs. Clinical studies arising during the course of SAD treatment are occasionally biased and designed inappropriately, and data quality is not optimal.[15] thus contributing little knowledge related to SAD mortality trends within populations, causes of death, or factors influencing prognoses.[1]

Many SAD studies are based on retrospective analyses of clinical histories of hospitalized or prospectively-monitored patients in specialized clinics or patients referred to specialists in hospitals. A select population is seen in these institutions, composed of the most serious cases and cases receiving the most comprehensive medical care, so information that they provide has selection biases that makes it difficult to extrapolate results to other sites, even within in the same country.[12,15]

Many published mortality studies are monocentric, where the cause of death is determined by reviewing clinical histories and autopsy reports, or by contacting the physician who cared for the patient in their final moments. Others use statistics from medical services, disability pensions from institutions and hospital statistics, which are not representative of the general population and are, therefore, often biased.[12,15]

SAD mortality studies conducted in Cuba are the result of case series that summarize the experience of a single doctor or institution (generally at secondary- or tertiary-care levels), with small samples, focused on a single disease. One of their limitations is that they do not capture mortality from SAD over time, nor do they reflect the true burden of these diseases within the general population. Studies that evaluate a single entity are useful in estimating its relevance as a health problem but tend to overestimate the importance of the specific condition on which they are focused. [12,15,42]

SAD mortality using multiple causes-of-death analysis The growing availability of data generated during medical care and monitoring of SAD incidence and clinical progression have transformed the outlook of health research. There was a time that health data collected through routine procedures was considered to be of no investigative interest. But these sources of information (including specific disease registries, primary care databases, administrative databases, archives, cancer registries, mandatory disease-reporting registries and mortality registries) open up opportunities for innovative, efficient, and cost-effective research to aid decisions made in clinical practice; to plan health services, programming and policies; and to improve patient care and healthcare efficiency in various settings and geographic regions worldwide.[43]

Mortality registries have been used as data sources to research mortality in SAD patients, [12,18,20–26] but there are few studies based on these registries despite the fact that they allow for closer examination of population mortality rates, and for inclusion of a greater number of patients over a longer period, which reduces selection bias and sample size problems. They are also more representative of the population than traditional cohort studies conducted among patients who receive specialized care. [15] Moreover, such prospective cohort studies are common for rheumatological research but require close patient monitoring and are expensive, which means that they are not always a viable alternative to research SAD in low-income environments. [9,15,31]

Despite Cuba's high-quality mortality statistics,[33] only one study was conducted in Cuba on the mortality registry that included SAD among the immunopathological conditions considered,[44] which opens up an opportunity for research into a topic that has been understudied in the country.

Death is the result of complex pathological interactions, so the declared underlying cause of death may not entirely reflect causal processes. This aspect is important in SAD patients who often have combinations of diseases with physio-pathological implications and prognoses that are not entirely clear.[12,19] One methodological alternative to resolve this problem is to use multiple cause-of-death analysis. This term identifies an approach to mortality that considers all causes of death reported on the death certificate with no distinction between underlying and circumstantial causes.[18,19,28]

Analyzing multiple causes of death is a powerful epidemiological tool facilitating a more comprehensive understanding of the morbidity process.[18] Often the underlying cause of death is difficult to predict or is diagnosed after the fact. Conversely, the causes or complications derived from underlying causes may be predicted and even expected, which may help in monitoring or even prevention.[19,27]

While multiple cause-of-death analysis has been used since the first half of the 20th century, the last decade has seen an increase in epidemiological research that uses it as a strategy to address death from various health problems such as: opioid use,[45] obesity,[46] cardiovascular diseases,[47] aortic aneurysm dissection,[48] diabetes mellitus,[32] pulmonary embolism,[49] sepsis[50] and hemophilia.[51]

In countries with medium- or high-quality mortality registries representative of the population, these should be used as a source of SAD data, thus reducing patient selection bias and allowing for comparisons between countries as well as study of disease behavior over long periods at a relatively low cost. This potential is revealed in studies carried out in six countries, which show that deaths related to SAD that were identified using

multiple-cause-of-death analysis increased 1.5 to 4.2 times compared to those identified using only the underlying cause (Table 1).

When the underlying cause of death is attributed to SAD, associated causes vary depending on the type of disease. In the case of RA, the most frequently associated causes are cardiovascular diseases, infectious diseases and respiratory diseases.[52] In SLE patients, the leading associated causes of death were renal, cardiovascular and infectious,[21] while in SSc patients these causes were infectious, followed by respiratory, cardiovascular and renal.[26] The causes of death most frequently associated with PM/DM were respiratory diseases, infectious diseases and cancer.[20]

Use of data from death certificates is limited by its failure to permit estimation of indicators of importance such as incidence rates and SMR or for life table analysis. The role of SAD disease progression and organ damage cannot be determined. However, perhaps the most important limitation is related to death certificate validity, as a significant percentage of SADs are not declared as either underlying causes or contributing causes of death.[12,15,17]

Despite these limitations, SAD patient mortality profiles could help raise awareness of the need to allocate more material and human resources to manage these diseases, more focused studies on the topic, and more data-driven attention to comparisons between countries and study trends.

CONCLUSIONS


In many countries, SAD is not recognized as an important health issue because the burden of mortality is unknown or has not been properly assessed. This fact makes formulation of policies and programs to monitor SAD difficult, and creates inequalities and health gaps. Studying SAD mortality by analyzing multiple causes of death with data from national mortality registries is a low-cost alternative that offers evidence on mortality burdens in countries where it is not feasible to apply traditional methodological approaches based on prospective cohort studies. 

Table 1: SAD mortality studies using multiple causes of death

Reference	Country	Study period	SAD	Number of deaths identified		Ratio Multiple causes of death/ Underlying cause *
				Underlying cause	Multiple causes of death	
Falasinu T, et al.[53]	USA	2014	SLE	1,180	2,036	1.7
Mitratza M, et al.[42]	Netherlands	2013–2017	SLE	100	251	2.5
Mitratza M, et al.[42]	Netherlands	2013–2017	SSc	268	403	1.5
Mitratza M, et al.[42]	Netherlands	2013–2017	DM/PM	100	212	2.1
Mitratza M, et al.[42]	Netherlands	2013–2017	SjS	48	204	4.2
Poubel Vieira et al.[26]	Brazil	2006–2015	SSc	223	374	1.7
Avouac J, et al.[52]	France	2000–2011	RA	4,597	13,208	2.9
Elhai M, et al.[23]	France	2000–2014	SSc	1,608	2,719	1.7
Thomas G, et al.[25]	France	2000–2009	SLE	637	1,593	2.5
Kiadaliri A et al.[18]	Switzerland	1998–2014	RA	369	1,512	4.1
Pinheiro F, et al.[24]	Brazil	1996–2010	RA	1,095	3,955	3.6
Sato EI, et al.[54]	Brazil	1987–2007	SLE	3,133	4,815	1.5
Santo AH, et al.[20]	Brazil	1985–2007	DM/PM	350	634	1.8

DM/PM: Dermatomyositis/polymyositis; RA: Rheumatoid arthritis; SAD: Systemic Autoimmune Disease; SjS: Sjögren's syndrome; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis

*The ratio between number of cases identified using multiple causes of death and the number of cases identified using the underlying cause of death indicates how many times the number of deaths somehow related to SADs study increased when using the multiple-causes-of-death method.

REFERENCES

1. Scherlinger M, Mertz P, Sagez F, Meyer A, Felten R, Chatelus E, et al. Worldwide trends in all-cause mortality of auto-immune systemic diseases between 2001 and 2014. *Autoimmun Rev* [Internet]. 2020 Jun [cited 2020 Jul 7];19(6):102531. Available at: <http://dx.doi.org/10.1016/j.autrev.2020.102531>
2. Roberts MH, Erdei E. Comparative United States autoimmune disease rates for 2010-2016 by sex, geographic region, and race. *Autoimmun Rev* [Internet]. 2020 Jan [cited 2020 Jul 7];19(1):102423. Available at: <http://dx.doi.org/10.1016/j.autrev.2019.102423>
3. Thomas SL, Griffiths C, Smeeth L, Rooney C, Hall AJ. Burden of mortality associated with autoimmune diseases among females in the United Kingdom. *Am J Public Health*. 2010 Nov;100(11):2279–87.
4. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* [Internet]. 2014 Jul [cited 2020 Jun 2];73(7):1316–22. Available at: <http://dx.doi.org/10.1136/annrheumdis-2013-204627>
5. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol* [Internet]. 2016 Oct [cited 2020 Jun 2];12(10):605–20. Available at: <http://dx.doi.org/10.1038/nrrheum.2016.137>
6. Royle JG, Lanyon PC, Grainge MJ, Abhishek A, Pearce FA. The incidence, prevalence, and survival of systemic sclerosis in the UK Clinical Practice Research Datalink. *Clin Rheumatol* [Internet]. 2018 Aug [cited 2020 Jul 7];37(8):2103–11. Available at: <http://dx.doi.org/10.1007/s10067-018-4182-3>
7. Meyer A, Meyer N, Schaeffer M, Gottenberg J-E, Geny B, Sibilia J. Incidence and prevalence of inflammatory myopathies: a systematic review. *Rheumatology*. 2015 Jan [cited 2020 Jul 7];54(1):50–63. Available at: <http://dx.doi.org/10.1093/rheumatology/keu289>
8. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjogren's syndrome: a systematic review and metaanalysis. *Ann Rheum Dis* [Internet]. 2015 Nov [cited 2020 Jul 7];74(11):1983–9. Available at: <http://dx.doi.org/10.1136/annrheumdis-2014-205375>
9. Dey D, Sciascia S, Pons-Estel GJ, Ding H, Shen N. Health disparities in rheumatic diseases. Understanding global challenges in Africa, Europe, Latin America, and Asia and proposing strategies for improvement. *Rheum Dis Clin N Am* [Internet]. 2021 [cited 2021 Feb 20];47(1):119–32. Available at: [https://www.rheumatic.theclinics.com/article/S0889-857X\(20\)30121-6/pdf](https://www.rheumatic.theclinics.com/article/S0889-857X(20)30121-6/pdf)
10. Reyes-Llerena GA, Guibert-Toledano M, Penedo-Coello A, Pérez-Rodríguez A, Baez-Dueñas RM, Charnicharo-Vidal R, et al. Community-based study to estimate prevalence and burden of illness of rheumatic diseases in Cuba: a COPCORD study. *J Clin Rheumatol* [Internet]. 2009 Mar [cited 2020 Jun 2];15(2):51–5. Available at: <http://dx.doi.org/10.1097/RHU.0b013e31819b61cb>
11. Pincus T, Gibson KA, Block JA. Premature mortality: a neglected outcome in rheumatic diseases? *Arthritis Care Res (Hoboken)* [Internet]. 2015 Aug [cited 2020 Jun 2];67(8):1043–6. Available at: <http://dx.doi.org/10.1002/acr.22554>
12. Abu-Shakra M, Novack V. Mortality and multiple causes of death in systemic lupus erythematosus - Role of the death certificate. *J Rheumatol* [Internet]. 2012 Mar [cited 2020 Feb 5];39(3):458–60. Available at: <http://dx.doi.org/10.3899/jrheum.111556>
13. van Kruijsdijk RC, van der Graaf Y, Koffijberg H, de Borst GJ, Nathoe HM, Jaap Kappelle L, et al. Cause-specific mortality and years of life lost in patients with different manifestations of vascular disease. *Eur J Prev Cardiol* [Internet]. 2016 Jan [cited 2020 Jul 7];23(2):160–9. Available at: <http://dx.doi.org/10.1177/2047487314566698>
14. Toledano E, Candelas G, Rosales Z, Martínez Prada C, León L, Abásolo L, et al. A meta-analysis of mortality in rheumatic diseases. *Reumatol Clin* [Internet]. 2012 Nov–Dec [cited 2020 Jul 7];8(6):334–41. Available at: <http://dx.doi.org/10.1016/j.reuma.2012.05.006>
15. Cardiel MH, Ambriz Murillo Y. Epidemiología de las enfermedades inflamatorias reumatológicas. In: Alba Fériz R, Muñoz Louis R, Espinoza LR, Khamashta M, Matucci-Cerinic M, Sanmartí R, editors. *Enfermedades Inflamatorias Reumatológicas*. Bogotá: Producciones Científicas Ltda; 2016. Spanish.
16. Woolf AD, Vos T, March L. How to measure the impact of musculoskeletal conditions. *Best Pract Res Clin Rheumatol* [Internet]. 2010 [cited 2020 Jun 2];24(6):723–32. Available at: <http://dx.doi.org/10.1016/j.berh.2010.11.002>
17. Falasinnu T, Rossides M, Chaichian Y, Simard JF. Do death certificates underestimate the burden of rare diseases? The example of systemic lupus erythematosus mortality, Sweden, 2001-2013. *Public Health Rep* [Internet]. 2018 [cited 2020 Jun 2];133(4):481–8. Available at: <http://dx.doi.org/10.1177/0033354918777253>
18. Kiadaliri AA, Turkiewicz A, Englund M. Mortality from musculoskeletal disorders including rheumatoid arthritis in southern Sweden: A multiple-cause-of-death analysis, 1998–2014. *J Rheumatol* [Internet]. 2017 May [cited 2020 Jun 2];44(5):571–9. Available at: <http://dx.doi.org/10.3899/jrheum.161219>
19. Egidí V, Salvatore MA, Rivellini G, D'Angelo S. A network approach to studying cause-of-death interrelations. *Demogr Res* [Internet]. 2018 Jan 26 [cited 2020 Jul 7];38(Art. 16):373–400. Available at: <http://dx.doi.org/10.4054/DemRes.2018.38.16>
20. Santo AH, Souza JMP, Pinheiro CE, Souza DC, Sato EI. Trends in dermatomyositis- and polymyositis related mortality in the state of São Paulo, Brazil, 1985-2007: multiple cause-of-death analysis. *BMC Public Health* [Internet]. 2010 Oct 11 [cited 2020 Jul 15];10:597. Available at: <http://dx.doi.org/10.1186/1471-2458-10-597>
21. Sato EI, Souza DC, Santo AH. [Mortality profile related to systemic lupus erythematosus: a multiple cause-of-death analysis]. *J Rheumatol* [Internet]. 2012 [cited 2020 Jul 15];39(3):496–503. Available at: <https://www.jrheum.org/content/39/3/496.long>
22. Yen EY, Singh RR. Brief report: Lupus-an unrecognized leading cause of death in young females: a population-based study using nationwide death certificates, 2000-2015. *Arthritis Rheumatol* [Internet]. 2018 Aug [cited 2020 Jul 15];70(8):1251–5. Available at: <http://dx.doi.org/10.1002/art.40512>
23. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* [Internet]. 2017 Nov [cited 2020 Jul 17];76(11):1897–905. Available at: <http://dx.doi.org/10.1136/annrheumdis-2017-211448>
24. Pinheiro FAG, Souza DCC, Sato EI. A study of multiple causes of death in rheumatoid arthritis. *J Rheumatol* [Internet]. 2015 Dec [cited 2020 Jul 15];42(12):2221–8. Available at: <http://dx.doi.org/10.3899/jrheum.150166>
25. Thomas G, Mancini J, Jourde-Chiche N, Sarlon G, Amoura Z, Harlé JR, et al. Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. *Arthritis Rheumatol* [Internet]. 2014 Sep [cited 2020 Jul 15];66(9):2503–11. Available at: <http://dx.doi.org/10.1002/art.38731>
26. Poubel Vieira de Rezende R, Altenburg Gismondi R, Cesar Maleh H, de Miranda Coelho E, Sartori Vieira C, Garcia Rosa M, et al. Distinct mortality profile in systemic sclerosis: a death certificate study in Rio de Janeiro, Brazil (2006–2015) using a multiple causes of death analysis. *Clin Rheumatol* [Internet]. 2019 Jan [cited 2020 Jul 15];38(1):189–94. Available at: <http://dx.doi.org/10.1007/s10067-017-3951-8>
27. Hernández-Negrín H, Padilla-Cueto D, Martínez Morales O. Tendencia creciente en la mortalidad por lupus eritematoso sistémico en América Latina como expresión de las desigualdades sociales en salud. [Increasing trend in mortality from systemic lupus erythematosus in Latin America as an expression of social disparities in health]. *Reumatol Clin* [Internet]. 2020 Aug 10 [cited 2020 Jul 7]. Available at: <http://dx.doi.org/10.1016/j.reuma.2020.07.004>. Spanish, English.
28. Tazi Mezalek Z, Bono W. Challenges for lupus management in emerging countries. *Presse Med*. 2014 Jun [cited 2020 Jul 15];43(6 Pt 2):e209–e20. Available at: <http://dx.doi.org/10.1016/j.lpm.2014.04.002>
29. Mesa Machado AC, Tejeiro Fernández A. Causas múltiples de muerte. *Rev Cub Hig Epidemiol* [Internet]. 1998 Aug [cited 2020 Jun 1];36(2):116–26. Available at: http://scielo.sld.cu/scielo.php?script=sci_abstract&pid=S1561-30031998000200004&lng=es&nrm=iso. Spanish.
30. Seuc AH, Fernández L, Mirabal-Sosa M, González CA. Cuban application of two methods for analyzing multiple causes of death. *MEDICC Rev*. 2018 Jul;20(3):30–5.
31. Fernández González L, Seuc Jo AH, Rodríguez García CA. Método de mortalidad ponderado según múltiples causas de muerte. *Rev Finlay* [Internet]. 2019 Oct [cited 2020 May 29];9(3):197–209. Available at: <http://www.revfinlay.sld.cu/index.php/finlay/article/view/701>. Spanish.
32. Mathers CD, Ma Fat D, Inoue M, Rao C, López AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Org*. 2005 Mar;83(3):171–7.
33. National Health Statistics and Medical Records Division (CU). 10 primeras causas de muerte por grupos de edad y sexo en el adulto mayor. Cuba 2008 [Internet]. Havana: Ministry of Public Health (CU); 2009 Aug [cited 2020 Dec 10]. 4 p. Available at: http://www.sld.cu/galerias/pdf/sitios/dne/adulto_mayor_10_1ras_causas_2008.pdf. Spanish.
34. INFOMED [Internet]. Havana: Ministry of Public Health (CU); c1999–2021. Anuario Estadístico de Salud del Ministerio de Salud Pública; [cited 2020 Dec 10]. Available at: <http://www.bvscuba.sld.cu/2017/11/20/anuario-estadistico-de-salud-de-cuba/>. Spanish.
35. World Health Organization. International Classification of Diseases and related health problems, 10th revision: Volume II. Geneva: World Health Organization; 1993.
36. Estrategia en enfermedades reumáticas y musculoesqueléticas del Sistema Nacional de Salud. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013. Spanish.
37. Pérez Venegas JJ, Lama Herrera CM, Sanz Amores R, Martínez Concepción E, Abad Ramírez R, Aguiar García F, et al. Plan Andaluz de Enfermedades Reumáticas y Musculoesqueléticas. Sevilla: Junta de Andalucía, Consejería de Salud; 2018. p. 79. Spanish.

38. National Association of Chronic Disease Directors; Center for Disease Control and Prevention; Lupus Foundation of America. National Public Health Agenda for Lupus. A Blueprint for Action. Atlanta: Center for Disease Control and Prevention; 2015. 31 p.
39. Cardiel MH. Presente y futuro de las enfermedades reumáticas en Iberoamérica. ¿Estamos preparados para hacerles frente? *Reumatol Clin* [Internet]. 2011 Sep–Oct [cited 2020 Jul 15];7(5):279–80. Available at: <http://dx.doi.org/10.1016/j.reuma.2010.12.009>. Spanish.
40. Morales Ojeda R, Mas Bermejo P, Castell-Florit Serrate P, Arocha Mariño C, Valdivia Onega NC, Druyet Castillo D, et al. Transformaciones en el sistema de salud en Cuba y estrategias actuales para su consolidación y sostenibilidad. *Rev Panam Salud Publica* [Internet]. 2018 Apr [cited 2020 Dec 10];42:e25. Available at: <http://dx.doi.org/10.26633/RPSP.2018.25>. Spanish, English.
41. Corratgé Delgado H. Objetivos de Trabajo y Criterios de Medidas para 2020. Ministerio de Salud Pública. INFODIR [Internet]. 2020 [cited 2020 Jun 1];31. Available at: <http://revinfor.sld.cu/index.php/infodir/article/view/757>. Spanish.
42. Mitratza M, Klijs B, Hak AE, Kardaun JWPF, Kunst AE. Systemic autoimmune disease as a cause of death: mortality burden and comorbidities. *Rheumatology (Oxford)* [Internet]. 2021 Mar 2 [cited 2020 Dec 10];60(3):1321–30. Available at: <http://dx.doi.org/10.1093/rheumatology/keaa537>
43. Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med* [Internet]. 2015 Oct 6 [cited 2020 Dec 10];12(10):e1001885. Available at: <http://dx.doi.org/10.1371/journal.pmed.1001885>
44. Venero Fernández SJ, Bonet Gorbea MH, Lage Dávila A, Macías Agraaham C, Suárez Medina M. Mortalidad por inmunopatologías en Cuba, 1989–2003. Havana: National Hygiene, Epidemiology and Microbiology Institute (CU); 2008 Jan. Spanish.
45. Gomes T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. The burden of opioid-related mortality in the United States. *JAMA Netw Open* [Internet]. 2018 Jun 1 [cited 2020 Dec 10];1(2):e180217. Available at: <http://dx.doi.org/10.1001/jamanetworkopen.2018.0217>
46. Barbieri M, Désesquelles A, Egidi V, Demuru E, Frova L, Mesle F, et al. Obesity-related mortality in France, Italy, and the United States: a comparison using multiple cause-of-death analysis. *Int J Public Health* [Internet]. 2017 May 11 [cited 2020 Dec 13];62(6):623–9. Available at: <http://dx.doi.org/10.1007/s00038-017-0978-1>
47. Adair T, Lopez AD. The role of overweight and obesity in adverse cardiovascular disease mortality trends: an analysis of multiple cause of death data from Australia and the USA. *BMC Med* [Internet]. 2020 Aug 4 [cited 2020 Dec 13];18(1):199. Available at: <http://dx.doi.org/10.1186/s12916-020-01666-y>
48. Santo AH, Puech-Leão P, Krutman M. Trends in aortic aneurysm- and dissection-related mortality in the state of São Paulo, Brazil, 1985–2009: multiple-cause-of-death analysis. *BMC Public Health* [Internet]. 2012 Oct 10 [cited 2020 Dec 13];12:859. Available at: <http://dx.doi.org/10.1186/14712458-12-859>
49. Barco S, Valerio C, Ageno W, Cohen AT, Goldhaber SZ, Hunt BJ, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000–18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. *Lancet Respir Med* [Internet]. 2020 Jan 1 [cited 2020 Dec 10];9(1):33–42. Available at: [http://dx.doi.org/10.1016/S2213-2600\(20\)30417-3](http://dx.doi.org/10.1016/S2213-2600(20)30417-3)
50. Pechholdová M. Sepsis-related mortality in the Czech Republic: multiple causes of death analysis. *Epidemiol Mikrobiol Imunol*. 2017 Summer;66(2):73–9.
51. Santo AH. Causes of death and mortality trends related to hemophilia in Brazil, 1999 to 2016. *Hematol Transfus Cell Ther* [Internet]. 2020 Jun 4 [cited 2020 Dec 13];S2531-1379(20)30056-0. Available at: <http://dx.doi.org/10.1016/j.htct.2020.02.003>
52. Avouac J, Amrouche F, Meune C, Rey G, Kahan A, Allanore Y. Mortality profile of patients with rheumatoid arthritis in France and its change in 10 years. *Semin Arthritis Rheum* [Internet]. 2017 Apr [cited 2020 Dec 13];46(5):537–43. Available at: <http://dx.doi.org/10.1016/j.semarthrit.2016.10.007>
53. Falasinnu T, Chaichian Y, Simard JF. Impact of sex on systemic lupus erythematosus-related causes of premature mortality in the United States. *J Womens Health (Larchmt)* [Internet]. 2017 Nov [cited 2020 Dec 13];26(11):1214–21. Available at: <http://dx.doi.org/10.1089/jwh.2017.6334>
54. Souza DCC, Santo AH, Sato EI. Trends in systemic lupus erythematosus mortality rates in the state of São Paulo, Brazil from 1985 to 2004. *Clin Exp Rheumatol*. 2010 Jul–Aug;28(4):519–24.

THE AUTHORS

Halbert Hernández-Negrín (Corresponding author: halberthn@gmail.com), internist at the Mario Muñoz University Polyclinic in Ranchuelo, Cuba. Instructor and adjunct researcher, Medical University of Villa Clara, Santa Clara, Cuba. <https://orcid.org/0000-0002-9992-9148>

Yeniver Roque-Dapresa, physician with dual specialties in family medicine and internal medicine. Chief of Internal Medicine, Arnaldo Milián Castro University Hospital, Medical University of Villa Clara, Santa Clara, Cuba. <https://orcid.org/0000-0001-7451-8038>

Onan Martínez-Morales, internist. Institución Prestadora de Servicios de Salud "Asistir Salud", Bogotá, Colombia. <https://orcid.org/0000-0002-5761-093X>

Anabel Mederos-Portal, anesthesiologist, Arnaldo Milián Castro University Hospital, Medical University of Villa Clara, Santa Clara, Cuba. <https://orcid.org/0000-0002-2968-0287>

Submitted: June 2, 2020
Approved for publication: April 16, 2021
Disclosures: None
