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Increased Risk of Multimorbidity Among Patients With Sarcoidosis: A Population-Based Cohort Study 1976 – 2013

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Abstract

Objective—To evaluate the risk and pattern of multimorbidity in patients with sarcoidosis.

Methods—A cohort of Olmsted County, Minnesota residents first diagnosed with sarcoidosis between January 1, 1976 and December 31, 2013 was identified through the medical record-linkage system of the Rochester Epidemiology Project. Diagnosis was verified based on individual medical record review. A cohort of sex and age-matched comparators without sarcoidosis was assembled from the same population. Data on 18 chronic conditions recommended by the United States Department of Health and Human Services for both cases and comparators were retrieved and compared.

Results—The prevalence of multimorbidity (i.e., the presence of 2 or more chronic conditions) was similar between the 2 groups (111/345 cases and 110/345 comparator, $P=.99$). After index date, 156 cases and 142 comparators developed multimorbidity, corresponding to HR of 1.60 (95% CI, 1.27 – 2.01; $P<.001$). The cumulative incidence of the presence of 3, 4 and 5 chronic conditions was also consistently significantly higher among cases than comparators. Analysis by specific type of chronic condition revealed a significantly higher cumulative incidence of coronary artery disease, congestive heart failure, arrhythmia, stroke/transient ischemic attack, arthritis, depression, diabetes and major osteoporotic fracture.

Conclusion—In this population, patients with sarcoidosis had a significantly higher risk of developing multimorbidity compared with sex and age-matched subjects without sarcoidosis.

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Keywords

Sarcoidosis; Clinical epidemiology; Comorbidity; Multimorbidity

Introduction

Multimorbidity is defined as the co-existence of 2 or more chronic medical conditions in the same individual¹. The concept of multimorbidity is slightly different from the concept of comorbidity. In the traditional comorbidity model, an index disease is defined and is generally considered as the most important entity and studies on comorbidity generally focus on the co-occurrence of any additional disease entities and their effect on treatment/prognosis of the index disease. On the other hand, the concept of multimorbidity is more patient-centric with all morbidities regarded as of equal importance. Studies on multimorbidity usually put more emphasis on function and well-being of patients as a result of all morbidities^{1, 2}.

Comorbidity has long been a focus of epidemiologic studies of immune-mediated diseases. The incidence of several comorbidities, particularly cardiovascular diseases, is increased in different immune-mediated diseases such as rheumatoid arthritis, systemic lupus erythematosus, vasculitis and psoriasis³⁻⁸. More recently, attention has also turned to multimorbidity in patients with immune-mediated diseases, especially rheumatoid arthritis^{2, 9}. There is more limited understanding of the extent and influence of multimorbidity among patients with other diseases, including sarcoidosis. The current study used a previously identified population-based cohort of patients with sarcoidosis to describe the occurrence of multimorbidity compared with persons without sarcoidosis randomly selected from the same underlying population.

Methods

This study used a previously identified cohort of 345 cases of incident sarcoidosis diagnosed between January 1, 1976 and December 31, 2013, which was identified through the resources of the Rochester Epidemiology Project (REP)¹⁰. The REP is a unique medical record-linkage system that provides complete access to inpatient and outpatient medical records of all residents of Olmsted County, Minnesota for over six decades from all local healthcare providers, which include the Mayo Clinic, the Olmsted Medical Center and its affiliated hospitals, local nursing homes and the few private practitioners. The history and utility of the REP for epidemiologic investigations have been described in detail elsewhere¹¹.

This cohort of patients with sarcoidosis was initially identified from diagnostic codes related to sarcoidosis and non-caseating granuloma and was confirmed by individual medical record review, which required physician diagnosis of sarcoidosis supported by the presence non-caseating granuloma on biopsy, radiographic evidence of intrathoracic sarcoidosis and compatible clinical manifestations, after exclusion of other granulomatous diseases such as tuberculosis and fungal infection. The only exception for the histopathological requirement was stage I pulmonary sarcoidosis that required only the evidence of symmetric bilateral

hilar adenopathy on imaging study. Isolated extra-thoracic sarcoidosis of a specific organ without intra-thoracic sarcoidosis was included (except for isolated cutaneous disease) if there was no better alternative diagnosis for the presence of non-caseating granuloma.¹² Isolated cutaneous disease was not included as it could be mimicked by several conditions, including cutaneous foreign body reaction, resulting in over-ascertainment of cases in the face of diagnostic uncertainty. Patients diagnosed with sarcoidosis prior to residency in Olmsted County (i.e., prevalent cases) were excluded.

A cohort of sex and age (within 3 years)-matched comparators without sarcoidosis at the time of the patient's sarcoidosis diagnosis was randomly selected from the same underlying population at 1:1 ratio. Data on 20 chronic conditions recommended by the United States Department of Health and Human Services (DHHS)¹³ for both cases and comparators were retrieved electronically from the diagnostic codes in the REP medical record-linkage system. However, 2 chronic conditions recommended by DHHS (i.e., human immunodeficiency virus infections and autism spectrum disorders) were excluded from the analysis due to their rarity in this population. Diagnosis of the remaining 18 chronic conditions was made based on the presence of these diagnostic codes within a category at least twice (and separated by at least 30 days) except for selected conditions which were collected by manual medical record review. These included physician diagnoses of congestive heart failure (CHF), coronary artery disease (CAD), stroke, transient ischemic attack (TIA), osteoporotic fracture and/or hepatitis occurring at any time, either before or after index date, as well as hypertension, hyperlipidemia and diabetes mellitus diagnosed before index date^{14, 15}. Similarly, diagnosis of cancer was confirmed with the Mayo Clinic Cancer Registry, which continuously collects data on every type of malignancy except for non-melanoma skin cancer¹⁶. Data on use of glucocorticoids, disease modifying anti-rheumatic agents (DMARDs) and biologic agents after sarcoidosis diagnosis were collected among cases.

Approval for this study was obtained from the Mayo Clinic and the Olmsted Medical Center institutional review boards (Mayo Clinic IRB 14-008651, Olmsted Medical Center IRB 012-OMC-15). The need for informed consent was waived.

Statistical analysis

Descriptive statistics (percentages, mean, etc.) were used to summarize the characteristics of cases and comparators, as well as the prevalence of each chronic condition at incidence/index date. Comparisons between the cohorts were performed using Chi-square, Fisher's exact and rank sum tests. The cumulative incidence of the each chronic condition adjusted for the competing risk of death was estimated¹⁷. These methods are similar to the Kaplan-Meier method with censoring of patients who are still alive at last follow-up. However, patients who die before experiencing a chronic condition are appropriately accounted for to avoid overestimation of the rate of occurrence of the chronic condition, which can occur if such subjects are simply censored at death. For each chronic condition, patients whose diagnosis was prior to the diagnosis of sarcoidosis, or for subjects in the comparison cohort, prior to the index date, were excluded from the analysis of cumulative incidence. The date of occurrence of each of the combinations of multiple chronic conditions was the earliest date of occurrence of the specified number of individual conditions. For the accumulation of

chronic conditions, Aalen-Johansen (a multistate generalization of cumulative incidence) methods were used to estimate the cumulative occurrence of multiple chronic conditions over time. Chronic conditions that were diagnosed prior to the index date were included in the analyses of the probability of experiencing 2, 3, 4 or 5+ chronic conditions presented in figure 1.

Cox proportional hazards models were used to compare the rate of development of each chronic condition and the accumulation of multiple chronic conditions between patients with sarcoidosis and non-sarcoidosis comparators. Comparisons between cohorts of chronic conditions in the first years after incidence/index date were performed by truncating follow-up at 5 years. Comparisons between cohorts of chronic conditions after the first years of follow-up were performed among those with at least 5 years of follow-up by beginning follow-up at 5 years. The 5 year cut-point was chosen *a priori* as the highest disease activity and most of the medication use occurs during the first 5 years after diagnosis of sarcoidosis. The proportional hazards assumption was checked and no evidence of violation was found. A p-value of less than .05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The sarcoidosis cohort consisted of 345 patients first diagnosed with sarcoidosis between 1976 and 2013 (mean age 45.6 years, 50% female, 90% Caucasian and 5% African-American). The comparator cohort included 345 age and sex matched persons from the same population (mean age 45.4 years, 50% female, 95% Caucasian and 1% African-American). Baseline characteristics of the subjects in this study are described in table 1. There was a notable difference in baseline characteristics between the 2 groups, specifically obesity and smoking status. The median length of follow-up was 12.9 years for cases and 15.6 years for comparators. Among cases, oral glucocorticoids were the most commonly prescribed drug (113 cases) followed by hydroxychloroquine (13 cases), methotrexate (11 cases), other DMARDs (5 cases), tumor-necrosis factor (TNF) inhibitor (5 cases) and other biologic agents (4 cases). A total of 76 patients were exposed to glucocorticoids at a dose equivalent to 10 mg/day of prednisone for more than 90 days. Oral glucocorticoids were commonly discontinued within 5 years after the diagnosis with 81% of users who started during the first 5 years discontinuing by 5 years after sarcoidosis diagnosis. A total of 228 patients did not receive glucocorticoids or any other immunosuppressive agents.

Prevalence and incidence of individual comorbidity

The prevalence of individual comorbidities at index date was not significantly different between the 2 groups, except for the significantly higher prevalence of arrhythmia among patients with sarcoidosis. In contrast, a significantly higher cumulative incidence at 10 years among patients with sarcoidosis was observed for several comorbidities including CHF, CAD, arrhythmia, stroke/TIA, arthritis, depression, diabetes and major osteoporotic fracture. Further adjustment for baseline variables (smoking status and obesity) yielded a similar result. The prevalence of each comorbidity at index date, the cumulative incidence at 10

years and the hazards ratio (HR) of each comorbidity comparing cases with sarcoidosis and comparators without sarcoidosis are given in table 2.

Prevalence and incidence of multimorbidity

The prevalence of multimorbidity (i.e., the presence of 2 or more chronic conditions) was similar between the 2 groups (111/345 cases and 110/345 comparator, $p=.99$). The mean number of comorbidities at incidence/index date was 1.2 in both groups. After index date, 156 cases and 142 comparators developed multimorbidity, corresponding to a HR of 1.60 (95% CI, 1.27 – 2.01; $P<.001$). The cumulative incidence of the presence of 3, 4 and 5 chronic conditions was also consistently significantly higher among cases. Further adjustment for baseline smoking status and obesity yielded a similar result although statistical significance was not achieved for the presence of 3 and 4 chronic conditions (table 2). The cumulative probability of the presence of 2, 3, 4 and 5 chronic conditions over time (inclusive of the probability at index date) for cases and comparators is demonstrated in figure 1.

Analysis by time from index date

Analysis by time from index date was conducted using 5 years of follow up after the index date as the cut-off point. The HRs comparing cases with sarcoidosis to comparators without sarcoidosis of almost all comorbidities (except for diabetes mellitus) were numerically higher for the events that occurred within the first 5 years than after 5 years. Similarly, analysis of multimorbidity revealed a higher HR for multimorbidity that occurred within the first 5 years (HR 2.44; 95% CI, 1.58 – 3.78) than after 5 years (HR 1.34; 95% CI, 1.01 – 1.77) as demonstrated in table 3.

Combination of comorbidities

The most common combinations of conditions were hypertension-hyperlipidemia, hyperlipidemia-arthritis and hypertension-arthritis for both patients with sarcoidosis and comparators without sarcoidosis. There is no significant difference in frequency of the co-occurrence of any combinations of conditions between cases and comparators (figure 2).

Sensitivity analysis

A sensitivity analysis including only the 184 cases and 184 comparators with incidence/index date on or after January 1, 1995 was performed as the diagnostic codes in the REP medical record-linkage system were coded only yearly prior to 1994, which may have led to under-recognition or a delay in capture of comorbidities with onset prior to 1994. The cumulative incidence of some of the comorbidities was higher in both groups (data not shown). The relative risk comparisons between the groups were similar to the complete analysis although the statistical power was limited by the smaller sample size (supplementary data 1).

Discussion

Multimorbidity has important clinical implications for patient well-being and survivorship, and is associated with increased mortality¹⁸. It also has a substantial impact on healthcare

utilization and health economics. For instance, the per capita Medicare expenditures was increased by approximately 10 fold among beneficiaries with multimorbidity compared with beneficiaries without multimorbidity, and 95% of Medicare expenditure was utilized by those with multimorbidity, although they represented only 65% of Medicare beneficiaries¹⁹.

The current study was conducted to better describe the characteristics of multimorbidity among patients with sarcoidosis. A significantly increased risk of multimorbidity was found after the diagnosis of sarcoidosis. The risk appeared to be particularly high within the first 5 years after the diagnosis, suggesting an acceleration in the occurrence of comorbid conditions after occurrence of sarcoidosis. The pattern of co-occurrence of comorbidities was similar between the 2 groups.

There are several possible explanations for the observed increased multimorbidity risk. First, patients with sarcoidosis have increased inflammatory burden and chronic inflammation is linked to increased risk of several atherosclerotic cardiovascular comorbidities including CAD, CHF, arrhythmia and stroke^{3-6, 20-22}. While not specifically studied in sarcoidosis, several inflammatory cytokines, such as interleukin-1 and tumor necrosis factor, has been show to accelerate the atherogenic process through a number of mechanisms including vascular adhesion molecule-1, leukocyte and matrix metalloproteinase activation^{23, 24}. Chronic inflammation has also been linked to insulin resistance²⁵, driving several metabolic comorbidities, including diabetes mellitus, hyperlipidemia and hypertension²⁶. Analysis by time from the diagnosis of sarcoidosis demonstrated that the risk for these comorbid conditions was higher within the first 5 years after the diagnosis which may further support increased inflammatory burden during this period as an explanation for these comorbidities, as patients with sarcoidosis often achieve remission/radiologic improvement within the first few years.^{27, 28}

Second, the increased incidence of comorbidity and multimorbidity could be a complication of glucocorticoids, the most commonly used medications for treatment of sarcoidosis^{29, 30}. Several comorbidities analyzed in this study, including diabetes mellitus, hypertension, depression and osteoporotic fracture, are well-established complications of glucocorticoids³¹. In addition, recent studies have suggested an association between use of glucocorticoids and increased risk of cardiovascular disease (CAD, stroke and CHF)^{32, 33}. Analysis by time from the diagnosis of sarcoidosis may further support this explanation as the risk was higher within the first 5 years after the diagnosis which was the time that the majority of exposure to glucocorticoids occurred. Still, it is unlikely that use of glucocorticoids was the primary reason for increased multimorbidity as only about one-third of patients in this cohort were exposed to glucocorticoids (and less than one-fourth were exposed to high dose glucocorticoids for more than 90 days).

Third, the increased risk for development of one of these comorbidities could be a result of shared predisposing factors for both sarcoidosis and comorbidities. Obesity is a well-recognized risk factor for almost all comorbidities included in this study, particularly cardiovascular disease, diabetes mellitus, hyperlipidemia and hypertension³⁴. Interestingly, obesity has been found to be a risk factor for sarcoidosis in a large cohort study of African-

American females³⁵ and a higher prevalence of obesity of patients with sarcoidosis than comparators was observed in this cohort³⁶.

Fourth, the apparent increased incidence of multimorbidity could be a result of surveillance bias, as patients with sarcoidosis may have more medical examinations and laboratory investigations due to their sarcoidosis. Nonetheless, analysis by time from sarcoidosis diagnosis continued to show a significantly elevated risk of multimorbidity after 5 years of diagnosis, which may suggest that surveillance bias did not play a substantial role.

The major strength of this study is its population-based methodology with verification of sarcoidosis and selected comorbidities by individual medical record review. Thus, the accuracy of the diagnosis was high and the risk of misclassification was minimized. Moreover, the comprehensive resources of REP facilitated a virtually complete identification of all clinically recognized cases of sarcoidosis in the community and minimized the likelihood of selection bias of only more severe cases, a common concern of studies using referral-based cohorts. The duration of follow-up in this study was long (median length of follow-up of at least 13 years for both cases and comparators) which allowed analysis of trend and accumulation of comorbidities over time.

The study has some limitations that are inherent to its retrospective nature as medical information were obtained and recorded at the discretion of the physicians who saw the patients without a specific protocol. Therefore, some pertinent information may not be available. Some of the studied comorbidities such as asthma were code based and not verified by individual medical record review, which may lower the accuracy of the diagnosis. Identification of the exact time point of onset of the comorbidities could be imprecise, especially prior to 1994 when diagnoses were coded only once a year. Comorbidities are reported additively in this and other studies of multimorbidity, and no attempt was made to weight the relative influence of each comorbidity. Last, since the epidemiology and clinical phenotypes of sarcoidosis vary across different ethnic groups^{37, 38}, generalizability of the observations from this study may be limited, as the population of Olmsted County, Minnesota is predominately of Northern European ancestry. Moreover, there is a higher proportion of workers in health care industry who may have a different patterns of utilization of healthcare resources.

Conclusion

This first ever population-based assessment of multimorbidity in patients with sarcoidosis revealed that these patients have a significantly higher risk of developing multimorbidity compared with sex and age-matched subjects without sarcoidosis. Patients with sarcoidosis are at higher risk for several individual comorbidities related to the disease and its treatment, including some cardiovascular diseases, arthritis, depression and diabetes mellitus. These findings reflect the increased healthcare burden of sarcoidosis and are a reference point for patient management and healthcare policy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

HR	Hazard ratio
CI	confidence interval
MN	Minnesota
REP	Rochester Epidemiology Project
DHHS	Department of Health and Human Services
DMARDs	disease modifying anti-rheumatic agents
CHF	congestive heart failure
CAD	coronary artery disease
TIA	transient ischemic attack

References

1. van den Akker M, Buntix F, Knottnerus JA. Comorbidity or multimorbidity. What's in a name? A review of literature. *Eur J Gen Pract.* 1996; 2(2):65–70.
2. Radner H. Multimorbidity in rheumatic disease. *Wien Klin Wochenschr.* 2016; 128(21–22):786–790. [PubMed: 27738754]
3. Radner H, Lesperance T, Accortt NA, Solomon DH. Incidence and prevalence of cardiovascular risk factors among patients with rheumatoid arthritis, psoriasis, or psoriatic arthritis. *Arthritis Care Res.* (Hoboken). 2016 Dec 20. [Epub ahead of print].
4. Zoller B, Li X, Sunquist J, Sunquist K. Risk of subsequent coronary heart disease in patients hospitalized for immune-mediated diseases: A nationwide follow-up study from Sweden. *PLoS One.* 2012; 7(3):e33442. [PubMed: 22438933]
5. Ungprasert P, Suksaranjit P, Spanuchart I, Leeaphorn N, Permpalung N. Risk of coronary artery disease in patients with idiopathic inflammatory myopathies: A systematic review and meta-analysis of observational studies. *Semin Arthritis Rheum.* 2014; 44(1):63–77. [PubMed: 24684974]
6. Goldberg RJ, Urowitz MB, Ibañez D, Nikpour M, Gladman DD. Risk factor for development of coronary artery disease in women with systemic lupus erythematosus. *J Rheumatol.* 2009; 36(11):2454–2461. [PubMed: 19833754]
7. Tselios K, Sheane BJ, Gladman DD, Urowitz MB. Optimal monitoring for coronary heart disease risk in patients with systemic lupus erythematosus: A systematic review. *J Rheumatol.* 2016; 43(1):54–65. [PubMed: 26568591]
8. Mansouri B, Kivelevitch D, Natarajan B, et al. Comparison of coronary artery calcium scores between patients with psoriasis and type 2 diabetes. *JAMA Dermatol.* 2016; 152:1244–1253. [PubMed: 27556410]
9. Radner H, Yoshida K, Frits M, et al. The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. *Rheumatology (Oxford).* 2015; 54(11):2076–2084. [PubMed: 26163688]

10. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of sarcoidosis 1946–2013: A population-based study. *Mayo Clin Proc.* 2016; 91(2):183–8. [PubMed: 26727158]
11. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd. History of the Rochester Epidemiology Project: Half a century of medical records linkage in a U.S. population. *Mayo Clin Proc.* 2012; 87(12):1202–1213. [PubMed: 23199802]
12. Costabel U, Hunninghake GW. ATS/ ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *Eur Respir J.* 1999; 14(4):735–747. [PubMed: 10573213]
13. Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis.* 2013; 10:E66. [PubMed: 23618546]
14. Ungprasert P, Crowson CS, Matteson EL. Risk of cardiovascular disease among patients with sarcoidosis: A population-based retrospective cohort study, 1976 – 2013. *Eur Respir J.* 2017; 49(2) pii: 1601290.
15. Ungprasert P, Crowson CS, Matteson EL. Risk of fragility fracture among patients with sarcoidosis: A population-based study 1976 – 2013. *Osteoporos Int.* 2017; 28(6):1875–1879. [PubMed: 28210775]
16. Ungprasert P, Crowson CS, Matteson EL. Risk of malignancy among patients with sarcoidosis: A population-based study. *Arthritis Care Res (Hoboken).* 2017; 69(1):46–50. [PubMed: 27214645]
17. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999; 18(6):695–706. [PubMed: 10204198]
18. Nunes BP, Flores TR, Mielke GI, Thume E, Facchini LA. Morbidity and mortality in older adults: A systematic review and meta-analysis. *Arch Gerontol Geriatr.* 2016; 57:130–138.
19. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Int Med.* 2002; 162(20):2269–2276. [PubMed: 12418941]
20. Libby P. Inflammation in atherosclerosis. *Nature.* 2012; 420:868–874.
21. Montecucco F, Mach F. Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. *Rheumatology (Oxford).* 2009; 48:11–22. [PubMed: 18927189]
22. Ungprasert P, Srivali N, Kittanamongkolchai W. Psoriasis and risk of incidental atrial fibrillation: A systematic review and meta-analysis. *Indian J Dermatol Venereol Leprol.* 2016; 82(5):489–497. [PubMed: 27451924]
23. Cybulsky MI, Iiyama K, Li H, et al. A major role for VCAM-1, but not ICAM-1, in early atherosclerosis. *J Clin Invest.* 2001; 107(10):1255–1262. [PubMed: 11375415]
24. Rajavashisth TB, Liao JK, Galis ZS, et al. Inflammatory cytokines and oxidized low density lipoproteins increase endothelial cell expression of membrane type 1-matrix metalloproteinase. *J Biol Chem.* 1999; 274(17):11924–11929. [PubMed: 10207013]
25. Zand H, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. *Diabetes Metab Syndr.* 2017 Mar 10. [Epub ahead of print].
26. Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. *J Clin Hypertens (Greenwich).* 2011; 13(4): 238–243. [PubMed: 21466618]
27. Judson MA, Baughman RP, Thompson BW, et al. Two year prognosis of sarcoidosis: the ACCESS experience. *Sarcoidosis Vasc Diffuse Lung Dis.* 2003; 20(3):204–211. [PubMed: 14620163]
28. Nagai S, Handa T, Ito Y, Ohta K, Tamaya M, Izumi T. Outcome of sarcoidosis. *Clin Chest Med.* 2008; 29(3):565–574. [PubMed: 18539245]
29. Korsten P, Mirsaedi M, Sweiss NJ. Nonsteroidal therapy for sarcoidosis. *Curr Opin Pulm Med.* 2013; 19(5):516–523. [PubMed: 23884295]
30. Al-Kofahi K, Korsten P, Ascoli C, et al. Management of extrapulmonary sarcoidosis: challenges and solutions. *Ther Clin Risk Manag.* 2016; 12:1623–1634. [PubMed: 27853374]

31. Cain DW, Ciadlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol.* 2017; 17(4): 233–47. [PubMed: 28192415]
32. Souverein PC, Berard A, Van Staa TP, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart.* 2004; 90(8):859–865. [PubMed: 15253953]
33. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med.* 2004; 141(10):764–70. [PubMed: 15545676]
34. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med.* 2017; 376(3):254–266. [PubMed: 28099824]
35. Cozier YC, Coogan PF, Govender P, Berman JS, Palmer JR, Rosenberg L. Obesity and weight gain in relation to incidence of sarcoidosis in US black women. *Chest.* 2015; 147(4):1086–1093. [PubMed: 25411869]
36. Ungprasert P, Crowson CS, Matteson EL. Smoking, obesity and risk of sarcoidosis: a population-based nested case-control study. *Respir Med.* 2016; 120:87–90. [PubMed: 27817820]
37. Judson MA, Boan AF, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis.* 2012; 29(2):119–27. [PubMed: 23461074]
38. Mirsaedi M, Machado RF, Schraufnagel D, Sweiss NJ, Baughman RP. Racial difference in sarcoidosis mortality in the United States. *Chest.* 2015; 147(2):438–49. [PubMed: 25188873]

Figure 1. Probability of developing 2,3,4, 5+ comorbidities (inclusive of the probability at index date) according to years since sarcoidosis incidence/ index date for patients with sarcoidosis (S) and comparators (C). Probability at year 0 is the probability at index date (or prevalence at index date).

Figure 2.

Heat map of the co-occurrence of chronic conditions among patients with sarcoidosis (upper right triangle) and comparators (lower left triangle). The shading from light to dark indicates increasing absolute frequency of each combination. There is no significant difference in frequency of the co-occurrence of any combinations of conditions between cases and comparators.

Table 1

Characteristics of patients with sarcoidosis and comparators without sarcoidosis at baseline

	Cases (N = 345)	Comparators (N = 345)	P value
Mean age at diagnosis/index date in years (SD)	45.6 (13.6)	45.4 (13.7)	.87
Female	50%	50%	0.99
<u>Race</u>			<.001
Caucasian	90%	95%	
African-American	5%	1%	
Asian	2%	0%	
Native American	1%	0%	
Other	2%	4%	
<u>Smoking status at diagnosis/index date</u>			<.001
Never	60%	42%	
Ex-smoker	21%	22%	
Current smoker	19%	36%	
Obesity	42%	25%	<.001

Abbreviations: SD, standard deviation

Table 2

Prevalence at index date and cumulative incidence rate of developing additional comorbidities and multimorbidity in 345 patients with sarcoidosis in 1976–2013 compared to 345 subjects without sarcoidosis

Comorbidity	Prior to non-Sarcoidosis index/sarcoidosis incidence date, no. *	p-value comparing prior events	Number of events after incidence/index in non-sarcoidosis / Sarcoidosis	Cumulative incidence at 10 years for non-sarcoidosis subjects (95% CI), %	Cumulative Incidence at 10 years for sarcoidosis patients (95% CI), %	Hazard ratio (95% CI) adjusted for age, sex and calendar year	Hazard ratio (95% CI) adjusted for age, sex, calendar year, smoking and obesity
<u>Individual comorbidity</u>							
Hypertension	75 / 75	.99	91 / 98	14.4 (9.7, 18.9)	19.3 (13.9, 24.4)	1.19 (0.89, 1.58)	1.09 (0.74, 1.60)
Congestive heart failure	6 / 7	.99	24 / 45	1.8 (0.2, 3.4)	7.6 (4.5, 10.7)	2.06 (1.25, 3.38)	2.52 (1.36, 4.66)
Coronary artery disease	8 / 7	.99	38 / 54	5.3 (2.6, 7.9)	8.3 (5.0, 11.4)	1.55 (1.02, 2.35)	1.51 (0.90, 2.52)
Arrhythmia	17 / 33	.03	75 / 97	10.1 (6.5, 13.6)	13.7 (9.4, 17.8)	1.44 (1.06, 1.95)	1.42 (0.97, 2.08)
Hyperlipidemia	57 / 49	.46	121 / 138	23.8 (18.2, 29.0)	28.0 (22.2, 33.4)	1.23 (0.96, 1.58)	1.17 (0.86, 1.61)
Cerebrovascular (stroke or transient ischemic attack)	6 / 2	.29	17 / 36	0.7 (0.0, 1.6)	5.9 (3.1, 8.6)	2.36 (1.32, 4.20)	2.90 (1.36, 6.18)
Arthritis (rheumatoid arthritis or osteoarthritis)	44 / 49	.67	106 / 121	19.8 (14.7, 24.5)	29.3 (23.3, 34.9)	1.44 (1.11, 1.88)	1.32 (0.94, 1.84)
Asthma	26 / 34	.34	26 / 38	4.4 (1.9, 6.8)	7.3 (4.0, 10.4)	1.66 (1.00, 2.73)	1.74 (0.89, 3.41)
Cancer	7 / 6	.99	29 / 17	3.9 (1.6, 6.2)	1.8 (0.2, 3.3)	0.60 (0.33, 1.09)	0.59 (0.26, 1.37)
Chronic kidney disease	6 / 11	.33	36 / 50	5.1 (2.4, 7.6)	8.1 (4.8, 11.4)	1.47 (0.95, 2.26)	1.43 (0.83, 2.47)
Chronic obstructive pulmonary disease	53 / 54	.99	56 / 60	9.9 (6.1, 13.6)	15.3 (10.5, 19.7)	1.22 (0.84, 1.75)	1.38 (0.84, 2.28)
Dementia/Alzheimer's disease	3 / 2	.99	17 / 14	1.0 (0.0, 2.0)	0.9 (0.0, 2.0)	0.88 (0.43, 1.79)	0.76 (0.22, 2.63)
Depression	53 / 54	.99	50 / 66	9.3 (5.7, 12.8)	13.8 (9.4, 18.0)	1.52 (1.05, 2.20)	1.70 (1.04, 2.77)
Diabetes mellitus	26 / 31	.58	73 / 99	10.5 (6.8, 14.0)	17.5 (12.6, 22.2)	1.53 (1.13, 2.07)	1.40 (0.96, 2.05)
Hepatitis	3 / 3	.99	0 / 3	--	--	--	--
Major osteoporotic fracture	0 / 1	.99	18 / 33	2.4 (0.6, 4.1)	5.3 (2.6, 7.9)	2.12 (1.19, 3.78)	2.06 (0.97, 4.37)
Schizophrenia	3 / 2	.99	10 / 13	1.8 (0.2, 3.3)	1.8 (0.2, 3.3)	1.36 (0.59, 3.09)	1.94 (0.53, 7.07)
Substance abuse disorder	21 / 12	.15	22 / 16	3.3 (1.1, 5.5)	3.2 (1.1, 5.3)	0.82 (0.43, 1.56)	1.20 (0.41, 3.46)
<u>Multimorbidity</u>							
2 chronic conditions	110 / 111	.99	142 / 156	31.7 (25.1, 37.8)	45.5 (38.1, 52.0)	1.60 (1.27, 2.01)	1.63 (1.19, 2.23)

Comorbidity	Prior to non-Sarcoidosis index/ incidence date, no. *	p-value comparing prior events	Number of events after incidence/index in non-Sarcoidosis	Cumulative incidence at 10 years for non-Sarcoidosis subjects (95% CI), %	Cumulative Incidence at 10 years for sarcoidosis patients (95% CI), %	Hazard ratio (95% CI) adjusted for age, sex and calendar year	Hazard ratio (95% CI) adjusted for age, sex, calendar year, smoking and obesity
3 chronic conditions	55 / 64	.42	145 / 165	25.3 (19.7, 30.5)	35.4 (29.0, 41.3)	1.35 (1.07, 1.69)	1.28 (0.95, 1.72)
4 chronic conditions	30 / 38	.37	124 / 152	22.0 (16.8, 26.8)	27.8 (22.2, 33.1)	1.42 (1.12, 1.80)	1.34 (0.98, 1.84)
5 chronic conditions	16 / 21	.50	94 / 126	11.6 (7.7, 15.3)	21.1 (16.0, 25.8)	1.53 (1.17, 2.00)	1.46 (1.04, 2.06)

* Patients diagnosed with a chronic condition prior to the index date were excluded from its analysis. For the analyses of multiple chronic conditions, those who were diagnosed with the specified number of chronic conditions prior to index date were excluded from the analyses, but those with fewer chronic conditions were included as they were still at risk of developing the specified number of comorbidities during follow-up.

Abbreviations : CI, confidence interval

Table 3

Relative risk of comorbidities and multimorbidity in 345 patients with Sarcoidosis in 1976–2013 compared to 345 subjects without Sarcoidosis according to time after incidence/index date

	First 5 years only	After 5 years only
Comorbidity	Hazard ratio (95% CI) *	Hazard ratio (95% CI) *
Hypertension	1.92 (1.04, 3.53)	1.02 (0.73, 1.42)
Congestive heart failure	18.33 (2.43, 138.53)	1.37 (0.79, 2.37)
Coronary artery disease	2.33 (0.96, 5.66)	1.38 (0.86, 2.23)
Arrhythmia	1.89 (0.92, 3.86)	1.34 (0.96, 1.88)
Hyperlipidemia	1.90 (1.18, 3.06)	1.06 (0.79, 1.42)
Cerebrovascular (stroke or transient ischemic attack)	10.06 (1.29, 78.67)	1.87 (1.00, 3.50)
Arthritis (rheumatoid arthritis or osteoarthritis)	2.36 (1.38, 4.03)	1.23 (0.91, 1.67)
Asthma	2.18 (0.82, 5.82)	1.50 (0.84, 2.69)
Cancer	0.78 (0.21, 2.92)	0.55 (0.28, 1.09)
Chronic kidney disease	2.08 (0.78, 5.54)	1.33 (0.82, 2.17)
Chronic obstructive pulmonary disease	2.03 (0.98, 4.21)	1.01 (0.65, 1.55)
Dementia/Alzheimer's disease	1.50 (0.25, 8.97)	0.77 (0.35, 1.69)
Depression	2.00 (1.04, 3.85)	1.36 (0.87, 2.13)
Diabetes	1.02 (0.54, 1.91)	1.75 (1.24, 2.48)
Hepatitis	--	--
Major osteoporotic fracture	3.15 (0.85, 11.66)	1.85 (0.96, 3.57)
Schizophrenia	2.15 (0.39, 11.76)	1.19 (0.46, 3.10)
Substance abuse disorder	1.55 (0.44, 5.49)	0.63 (0.29, 1.38)
2 chronic conditions	2.44 (1.58, 3.78)	1.34 (1.01, 1.77)
3 chronic conditions	1.59 (1.03, 2.45)	1.28 (0.98, 1.67)
4 chronic conditions	1.92 (1.21, 3.04)	1.26 (0.95, 1.67)
5 chronic conditions	3.40 (1.77, 6.55)	1.24 (0.92, 1.68)

* adjusted for age, sex and calendar year of sarcoidosis/index date

Abbreviation: CI, confidence interval