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Risk of first and recurrent serious infection in sarcoidosis: a Swedish register-based cohort study

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Take-home message

Sarcoidosis is associated with an increased risk of serious infections, especially during the first two years after diagnosis. Patients in need of immunosuppressants around diagnosis are twice as likely to develop serious infections than those who do not.

ABSTRACT

Serious infections (SI) impair quality of life and increase costs. Our aim was to determine if sarcoidosis is associated with a higher rate of SI and whether this varies by age, sex, time since diagnosis, or treatment status around diagnosis.

We compared individuals with sarcoidosis (≥2 ICD codes in the Swedish National Patient Register 2003–2013; n=8737) and general population comparators matched 10:1 on age, sex, and residential location (n=86376). Patients diagnosed 2006–2013 who were dispensed ≥1 immunosuppressant ±3 months from diagnosis (Prescribed Drug Register) were identified. Cases and comparators were followed in the National Patient Register for hospitalisations for infection. Using Cox and flexible parametric models, we estimated adjusted hazard ratios and 95% confidence intervals (aHR;CI) for first and recurrent SIs (new SI >30 days after the previous).

We identified 895 first SIs in sarcoidosis and 3881 in comparators. The rate of SI was 1.8-fold increased in sarcoidosis compared to the general population (aHR 1.81 [95%CI 1.65, 1.98]). The aHR was higher in females than males and during the first two years of follow-up. Sarcoidosis cases treated with immunosuppressants around diagnosis had a threefold increased risk whereas non-treated patients had a 50% increased risk. The rate of SI recurrence was 2.8-fold higher in cases than in comparators.

SIs are more common in sarcoidosis than in the general population, particularly during the first few years after diagnosis. Patients who need immunosuppressant treatment around diagnosis are twice as likely to develop a serious infection than those who do not.

Keywords: sarcoidosis; serious infection; follow-up studies; corticosteroids; recurrent events

INTRODUCTION

Serious hospitalised infections (SI) are associated with impaired quality of life and high costs, particularly if they are recurrent [1–4]. They also contribute to the higher rate of premature death seen in sarcoidosis [4], but data on SI risks in sarcoidosis are limited. In other better-studied inflammatory diseases, SI risks are higher than in the general population and are often attributed to immunosuppressant treatment that is prescribed to almost all patients [5, 6]. However, risks from other inflammatory diseases cannot be readily extrapolated to sarcoidosis because about 60% of individuals with sarcoidosis do not need immunosuppressant treatment. Additionally, sarcoidosis resolves within less than five years from diagnosis in about half of patients [7].

In sarcoidosis, SI risks in comparison to the general population were investigated in only one study from the United States. In that study of 345 patients diagnosed between 1976 and 2013, a twofold increased rate of SI compared to the general population was reported [8]. The rate ratio for SI was even higher (2.4) in patients who received immunosuppressants during the course of their disease [8]. It is unclear if similar results can be obtained from contemporary and larger population-based sarcoidosis cohorts. Moreover, it remains uncertain which patients exhibit these perceived high risks for SI and whether they are at higher risk for developing recurrent SIs. This information could prove particularly useful to properly target patient groups who can benefit from preventive interventions.

To answer these unresolved questions, large and longitudinal data are required. We therefore used Swedish register data to investigate SI in sarcoidosis. Our aim was to estimate relative risks of first and recurrent SI associated with sarcoidosis and examine if these varied by age at diagnosis, sex, treatment status around diagnosis, or time since diagnosis.

METHODS

Study setting and data sources

In Sweden, the healthcare system is tax-funded and universally accessible to residents. Data generated by interaction with the healthcare system are captured in registers and can be linked using an individual's unique identification number. We created a large cohort of individuals with and without sarcoidosis by linking several nationwide and population-based registers. We collected information on hospitalisations and outpatient visits to specialist care from the National Patient Register (NPR; nationwide coverage since 1987 and 2001, respectively). Data quality is high [9], but results of histological or imaging examinations are not available in the NPR. Prescription medication dispensations were obtained from the Prescribed Drug Register (PDR), which were available starting July 2005.

Study population

Using inpatient and outpatient visit data in the NPR, we identified all individuals who had ≥2 visits listing an ICD code for sarcoidosis between Jan 1, 2003 and Dec 31, 2013. ICD codes are available in **Table S1** in the **Supplement**. Because most sarcoidosis cases are diagnosed in outpatient clinics [10], we allowed for two years of outpatient visit data to accumulate in the NPR so that we could capture newly diagnosed cases.

We further classified all individuals with sarcoidosis diagnosed starting Jan 1, 2006 into those treated or not for sarcoidosis around the time of diagnosis. Cases who were dispensed systemic corticosteroids, methotrexate, or azathioprine within three months before or after the first visit for sarcoidosis (PDR data) were allocated to the treated group (**Table S1**). We used treatment as an indicator of sarcoidosis severity around diagnosis [4, 7] and to study the role of treatment on the risk of SI.

At second visit for sarcoidosis, each case was matched on birth year, sex, and residential location to up to 10 general population comparators sampled from the Total Population Register who had no history of sarcoidosis at the time. To reduce sarcoidosis misclassification, we excluded cases and comparators younger than 18 or older than 85 years and those with a haematopoietic or lung malignancy recorded in the Cancer Register six months before or after the first visit for sarcoidosis or corresponding date for comparators (**Table S1**).

Ethical permission was provided by the Regional Ethics Review Board in Stockholm (2014/230-31).

Follow-up for first and recurrent serious infection

The outcome, serious infection, was defined as a hospitalisation in the NPR listing an ICD code for an infectious disease (**Table S1**). To minimize misclassification, infectious disease had to be the primary discharge diagnosis. We followed sarcoidosis cases and comparators from inclusion (second visit for sarcoidosis or corresponding date for comparators) to first admission for SI, death (Cause of Death Register), emigration (Total Population Register), or Dec 31, 2013, whichever occurred first. We identified the 10 most common diagnoses in cases and comparators and reported the frequency of serious opportunistic infections (i.e. aspergillosis, candidiasis, tuberculosis, other mycobacterial infections, and pneumocystosis).

In addition, we examined recurrent unrelated SIs by allowing for a SI to occur >30 days after the previous, irrespective of length of hospital stay. In both cases and comparators, occurrence of more than six SIs was infrequent. To ensure statistical model stability, we allowed for only up to six recurrent SIs per individual. To investigate the extent of differential loss to follow-up in the sarcoidosis and comparator groups, we identified deaths and deaths due to SI in the Cause of Death Register. For analyses of recurrent infections, follow-up started at inclusion and ended at the last SI (maximum six events per individual), death, emigration, or Dec 31, 2013, whichever came first.

Other variables

Confounding variables were evaluated at baseline using data obtained from various registers (see **Table S1** in the **Supplement** for details). Briefly, we collected information on birth date (to calculate age), sex, birth country (grouped into Nordic and non-Nordic), residential location (grouped into six healthcare regions), civil status (married or in registered partnership, or other), years of education (≤9, 10–12, ≥13 years, or missing) and salary earned the year before inclusion adjusted for 2014 inflation (www.statistikdatabasen.scb.se; 0–<100, 100–<300, 300–<600, ≥600 thousand Swedish krona, or missing).

In addition, we approximated general health status at inclusion by counting the total number of inpatient or outpatient visits in the NPR within two years before the first sarcoidosis visit or corresponding date for comparators (grouped into 0, 1–3, ≥4 visits). We also identified comorbidity associated with SI (autoimmune disease in study participants or first degree relatives [data from the Multi-Generation Register], primary immunodeficiency, stroke, diabetes, etc.) requiring ≥1 or ≥2 visits in the NPR or ≥2 dispensations in the PDR, as appropriate (**Table S1**). To better describe baseline SI risk, we also reported history of SI in the past year and dispensations of sarcoidosis treatments and antimicrobials (i.e. antibacterial, antimycobacterial, antifungal, or antiviral medications) within six months before inclusion (**Table S1**).

Statistical analysis

We estimated stabilized inverse probability of sarcoidosis weights that allowed us to obtain marginal adjusted estimates in subsequent analyses (see **Supplemental Methods** and **Table S2** for details). Using weighted Poisson regression models, we estimated adjusted rates and rate differences for SI and their corresponding 95% confidence intervals (CI). To compare sarcoidosis to the general population, we used Cox models with follow-up years as the time scale and the weights to estimate adjusted hazard ratios (aHR). Hazard ratios from unweighted models were also reported. Because

the risk of SI associated with sarcoidosis varied over time, therefore violating the Cox proportionality of hazards assumption, we used flexible parametric survival models [11] specified as described in the **Supplement**. We plotted aHRs and marginal cumulative probabilities (risks) for sarcoidosis overall and by treatment status around diagnosis (treated/untreated).

We further stratified our analyses by age at inclusion (18–44, 45–64, or 65–85 years), sex, history of autoimmune disease, and treatment status around diagnosis and examined modification of the aHRs by these factors using a likelihood ratio test. Because medication dispensation data became available mid-2005, analyses by treatment status were performed in a subset of the population (77% of all) that entered the cohort starting 2006.

We modelled recurrent SIs by adding a gamma frailty term to Cox and flexible parametric survival models to account for unobserved heterogeneity amongst individuals (see **Supplement** for model specification).

In sensitivity analyses, we used a stricter definition for SI requiring ≥1 dispensation of an antimicrobial ±15 days of the hospital admission for SI to check whether misclassification of SI could affect our results. In addition, assuming pneumonias were more likely in sarcoidosis due to repeated lung imaging, we excluded pneumonias from the definition of SI in both sarcoidosis and comparators. We also disregarded urinary tract infections to assess whether hospital-acquired infections could explain the association. Furthermore, to examine how a lower threshold for hospitalisation for SI in sarcoidosis could affect our findings, we required comparators to have a visit in the NPR within two years before inclusion. Last, to test our results in the presence of sarcoidosis misclassification, we excluded cases and comparators with a history of SI within a year before the first sarcoidosis visit or the corresponding date for comparators and investigated SI in sarcoidosis

cases diagnosed by pulmonologists at Karolinska University Hospital in Stockholm and registered in the local cohort.

Data were processed and analysed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.6.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We compared 8737 sarcoidosis cases to 86 376 matched general population comparators. Of cases diagnosed 2006–2013, 41% were treated with immunosuppressants around diagnosis. Cases and comparators were on average 50 years old (SD 14.7) and 45% were female (**Table 1**). At baseline, socioeconomic position was similar between the two groups, but history of morbidity, especially that of hypertension, diabetes, and autoimmune disease was more prevalent in sarcoidosis cases. Cases were also more likely to have a history of SI in the year before inclusion (4 vs. 1%) and to have been dispensed an immunosuppressive or antimicrobial treatment in the previous six months.

After a median 4.8 years (95% CI 4.8, 4.9; similar in cases and comparators), we observed 895 first SIs in sarcoidosis (rate 17.4/1000 person-years [95% CI 16.0, 18.9]) and 3881 SIs in comparators (rate 9.6/1000 person-years [95% CI 9.3, 9.9]; **Table 2**). In both groups, the most common SI was pneumonia (about 25%; **Table S3**) and opportunistic SIs were infrequent (**Table S4**). SI risks by follow-up years are depicted in **Figure 1** and risks at six months, five and ten years are summarized in **Figure S1**.

The aHR for SI comparing sarcoidosis to comparators was 1.81 (95% CI 1.65, 1.98). However, there was notable variation by years of follow-up; the aHR was highest (about threefold increased) around start of follow-up and decreased to about 1.4 within two years (**Figures 2** [aHRs] and **S2** [rates]). The aHR for first SI was similar across age groups, but it was higher in women compared to men (2.01 vs. 1.64, respectively; p=0.01) and in individuals treated compared to those not receiving immunosuppressive treatment around diagnosis (3.04 vs. 1.53, respectively; p<0.001; **Table 2**).

Recurrent SIs were twice as likely in sarcoidosis compared to the general population (within-individual aHR 2.79 [95% CI 2.51, 3.10]; **Table S7**) with variation of the aHR during follow-up (**Figure S3**).

In sensitivity analyses depicted in **Table 4**, the aHR did not change considerably when pneumonias or urinary tract infections were disregarded or when individuals with a history of SI in the past year were excluded. It increased slightly, however, when an antimicrobial medication dispensation was required around the time of admission for SI (aHR 2.23 [95% CI 1.96, 2.54]). The association weakened when we required comparators to have a NPR visit within two years before inclusion (aHR for overall sarcoidosis 1.23 [95% CI 1.12, 1.35]; treated and untreated sarcoidosis aHR 2.08 and 1.03, respectively). Last, we observed an aHR for SI of 1.49 in the sarcoidosis cohort at Karolinska (95% CI 1.02, 2.18).

DISCUSSION

In this large nationwide investigation, we found that sarcoidosis was associated with an overall 1.8-fold increased rate of first serious hospitalised infection (SI). SIs occurred at a higher rate during the first two years since sarcoidosis diagnosis compared to the rest of follow-up. In individuals treated with immunosuppressants around the time of sarcoidosis diagnosis, the risk of SI was double the risk of those who did not receive treatment. Compared to the general population, individuals with sarcoidosis were also more likely to develop multiple SIs.

Our main finding of an almost twofold increased rate of SI in sarcoidosis compared to the general population is in line with a report from the United States [8]. In that cohort of 345 primarily white American patients, investigators observed similar 10-year risks and rate ratios for SI to ours. We additionally found a slightly higher aHR for SI in females (2.0) than in males (1.6) but no differences by age at diagnosis.

Two key factors are likely to explain the higher risk for first and recurrent SI in sarcoidosis, especially the spike in SIs during the first two years after sarcoidosis diagnosis. During this time, patients are under frequent follow-up and about 40% receive immunosuppressants [10]. As indicated in sensitivity analyses and previous research [12], the peak in SI risk could be partly explained by the increased healthcare interaction or possibly a lower threshold of hospitalisation for infection. Our analyses, however, suggested that initiation of immunosuppressants, particularly that of systemic corticosteroids remains a major risk factor for SI in sarcoidosis.

In our study, individuals with sarcoidosis who were treated around diagnosis (almost all with corticosteroids) had a threefold increased rate of SI whereas those who were not had a 50% increased rate. Corticosteroids indisputably play some part in SI occurrence [8, 13, 14]. At the same time, we cannot rule out that sarcoid inflammation itself is responsible for some of the risk increase.

Indeed, patients with sarcoidosis who do not require treatment around diagnosis are at a notably higher risk for SI than general population comparators. In addition, the decline in the rate of SI in sarcoidosis coincides with disease remission, which in approximately 50% of patients is independent of treatment [7]. The pathophysiologic mechanisms that could elucidate these complex phenomena have yet to be adequately understood. Possibly, sarcoid inflammation triggers a state of anergy towards pathogens [15] that is presumably amplified by immunosuppressant agents.

The rate of SI is lower in sarcoidosis than in some autoimmune diseases that have been investigated using similar data. Rates ranging from 12 to 39 per 1000 person-years were reported in rheumatoid arthritis [16–18] and up to 100 per 1000 person-years in lupus [5, 19]. Relative to the general population, these rates vary from about twofold increased in rheumatoid arthritis [16–18] to up to 10-fold higher in lupus [19, 20]. In other respiratory diseases, the aHR for SI was lower in asthma than in sarcoidosis (aHR 1.5) [21], whereas in chronic obstructive pulmonary disease a much higher aHR of 5.0 was reported [22]. Because differences partly depend on distribution of factors that vary amongst diseases (e.g. age, sex, treatment, and study period), they should be interpreted with caution.

Individuals with sarcoidosis are more likely to be hospitalised for multiple SIs. True risks of SI recurrence are possibly higher than reported when one considers that premature death, which is more likely in sarcoidosis, prevents SIs from recurring. Because recurrence has a negative impact on quality of life and is an indicator of high mortality [1, 2, 4], future investigations are warranted to identify patients at risk for recurrence that could benefit from preventive interventions.

There are several limitations to our study, of which, misclassification of SI is the most prominent because SIs could not be validated using microbiological examination results. SI misclassification was more probable in sarcoidosis since one in four SI was a pneumonia, which may share a similar clinical

picture with the disease. To address this limitation, we used a strict definition requiring SI to be the primary discharge diagnosis, excluded all pneumonias, or required a dispensation of an antimicrobial in addition to the hospital admission. These changes in SI definition had little effect on our results.

Furthermore, we did not have information on lifestyle factors (e.g. smoking) or vaccination rates amongst sarcoidosis cases and comparators. Based on previously published bias simulations for smoking [4], we expect that the true sarcoidosis-SI association is somewhat stronger than then one we report here. Similarly, if individuals with sarcoidosis were more likely to be vaccinated, the observed findings may reflect an underestimation of the truth.

Due to the lack of detailed clinical information in the NPR, it is likely that there was some misclassification of sarcoidosis. However, preliminary validation data suggest that the accuracy of our definition is high (positive predictive value >90%; unpublished data), and as we have previously shown [4, 23], our results are robust to non-differential misclassification of sarcoidosis. In addition, we observed an association in the Karolinska sarcoidosis cohort despite small numbers and differences in SI predictors at baseline (e.g. age and treatment status; data not shown). We stratified our analyses by treatment status around diagnosis, but there were other comorbidities such as autoimmune diseases that were more prevalent in sarcoidosis than in the general population which may also modify the risk. In a post-hoc analysis, we found similar results stratifying by history of autoimmune disease (aHR for SI, 1.7 for history of autoimmune disease vs. 1.8 for no history). Last, in the absence of a severity index for sarcoidosis that is independent of treatment, we could not distinguish amongst SIs caused by treatment or sarcoid inflammation.

Nonetheless, by using longitudinal register data we were able to obtain a large and unselected sarcoidosis population, study recurrent SIs, and eliminate losses to follow-up. We expect our findings

to be generalizable to populations in which modifiers of SI risk such as healthcare standards, thresholds for hospitalisation, vaccination and treatment patterns are similar to Sweden's.

In summary, sarcoidosis is associated with a higher risk for serious infection compared to the general population, especially during the first two years after diagnosis. Individuals treated around the time of sarcoidosis diagnosis likely due to severe symptoms or impaired organ function are at noticeably higher risk for serious infection. Although we cannot withhold pharmacologic treatment in patients who need it, we should further examine which measures such as vaccinations, closer follow-up, or prescription of steroid-sparing medications could alleviate the excess risk of serious infection in these patients.

Author contributions (CRediT statement)

Marios Rossides: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. *Susanna Kullberg:* Writing – review & editing. *Anders Eklund:* Writing – review & editing. *Daniela Di Giuseppe:* Writing – review & editing. *Johan Grunewald:* Writing – review & editing. *Johan Askling:* Conceptualization, Writing – review & editing. *Elizabeth V. Arkema:* Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Conflict of interest

All authors report no conflict of interest.

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FIGURE LEGENDS

Figure 1. Risk of first serious infection in individuals with sarcoidosis (overall and stratified by treatment status around diagnosis) and their general population comparators. Treatment data were available for individuals with sarcoidosis entering the cohort starting 2006 hence follow-up for those was shorter than overall sarcoidosis and the general population comparators.

Figure 2. Adjusted hazard ratios for first serious infection by follow-up years comparing individuals with sarcoidosis to the general population.

TABLES

Table 1. Demographic and clinical characteristics at inclusion of individuals with sarcoidosis and their matched general population comparators.

	Sarcoidosis (n=8737)	**General population** (n=86 376)
Age in years, mean (SD)	49.8 (14.8)	49.8 (14.7)
Female, %	44.5	44.6
Born in non-Nordic country*, %	9.5	11.8
Attained education in years, %		
≤9	20.6	20.8
10–12	49.1	46.4
≥13	29.2	31.6
Missing	1.2	1.2
History of comorbidity, %		
Congestive heart disease	2.4	1.3
Atrial fibrillation	3.2	2.1
Acute myocardial infarction	2.1	1.8
Stroke	1.7	1.6
COPD	2.3	1.0
Asthma	4.6	2.4
Hypertension	21.4	15.9
Diabetes mellitus	7.5	4.2
Dyslipidaemia	10.8	8.2
Autoimmune disease	7.9	4.3
Primary immunodeficiency	0.4	0.1
Serious infection in the past year, %	3.9	0.8
≥1 medication dispensing in the past six months†, %	(n=6723)	(n=66 441)
Systemic corticosteroids	18.7	2.9
Other immunosuppressants‡	1.2	0.7
Hydroxychloroquine	0.1	0.1
Inhaled corticosteroids	7.3	1.9
NSAIDs	26.3	9.7
Antimicrobials§	32.6	13.2

SD = standard deviation; COPD = chronic obstructive pulmonary disease; NSAIDs = non-steroidal anti-inflammatory drugs.
Percentages may not sum to 100 owing to rounding.
*Nordic countries: Sweden, Denmark, Norway, Finland, and Iceland. Category excludes missing <0.5%.
†Ascertained in individuals who entered the cohort starting Jan 1, 2006 for whom medication dispensations could be obtained from the Prescribed Drug Register.
‡Other immunosuppressants include methotrexate, azathioprine, and leflunomide.
§Antimicrobials include antibacterial, antimycobacterial, antifungal, and antiviral medications.

Table 2. Rates, rate differences, and hazard ratios for first serious infection comparing sarcoidosis to the general population.

	Sarcoidosis (n=8737)		General population (n=86 376)				
First serious infection	**Events**	**Adjusted rate per 1000 person-years* (95% CI)**	**Events**	**Adjusted rate per 1000 person-years* (95% CI)**	**Adjusted rate difference per 1000 person-years* (95% CI)**	**Hazard ratio* (95% CI)**	**Adjusted hazard ratio* (95% CI)**
Overall	895	17.4 (16.0, 18.9)	3881	9.6 (9.3, 9.9)	7.8 (6.3, 9.2)	2.40 (2.23, 2.58)	1.81 (1.65, 1.98)
Age at inclusion†, years							
18–44	222	8.8 (7.4, 10.5)	937	5.1 (4.8, 5.4)	3.7 (2.2, 5.3)	2.39 (2.07, 2.77)	1.74 (1.44, 2.09)
45–64	327	16.1 (14.0, 18.5)	1334	8.5 (8.0, 8.9)	7.6 (5.4, 9.9)	2.58 (2.28, 2.91)	1.90 (1.64, 2.20)
65–85	346	58.3 (51.1, 66.4)	1610	27.0 (25.7, 28.3)	31.3 (23.5, 39.1)	2.45 (2.18, 2.75)	2.16 (1.88, 2.49)
Sex†							
Female	435	21.6 (19.2, 24.3)	1938	10.7 (10.3, 11.2)	10.9 (8.3, 13.5)	2.36 (2.13, 2.62)	2.01 (1.78, 2.28)
Male	460	14.3 (12.7, 16.1)	1943	8.7 (8.3, 9.1)	5.6 (3.8, 7.4)	2.45 (2.21, 2.71)	1.64 (1.45, 1.87)
Treatment status around diagnosis†,‡							
Treated	326	29.8 (25.9, 34.3)	948	9.8 (9.2, 10.4)	20.0 (15.8, 24.2)	3.70 (3.26, 4.19)	3.04 (2.61, 3.55)
Not treated	275	15.7 (13.5, 18.3)	1428	10.2 (9.7, 10.8)	5.5 (3.1, 7.9)	1.96 (1.72, 2.23)	1.53 (1.31, 1.80)

CI = confidence interval.

*Rates and rate differences were estimated using Poisson regression models weighted for inverse probability of sarcoidosis weights. Hazard ratios were estimated using Cox proportional hazards regression models with years of follow-up as the time scale in a cohort matched on age, sex, and residential location. Adjusted hazard ratios were estimated using inverse probability of sarcoidosis weights.

†P-value for effect measure modification from a likelihood ratio test for the adjusted models: age at inclusion (p=0.10); sex (p=0.01); treatment status around diagnosis (p<0.001).

‡Assessed in a subset of individuals who entered the cohort starting Jan 1, 2006 (treated analysis: sarcoidosis n=2762, general population n=27 325; not treated analysis: sarcoidosis n=3961, general population comparators n=39 116).

Table 3. Proportion of individuals and median time to recurrent serious infection and death, and hazard ratio for recurrent serious infection comparing individuals with sarcoidosis to the general population.

	Sarcoidosis (n=8737)		**General population** (n=86 376)	
Outcome/analysis	**n (%)**	**Median years to event (IQR)**	**n (%)**	**Median years to event (IQR)**
Serious infection				
0	7841 (89.7)	—	82 493 (95.5)	—
1	1224 (14.0)	1.9 (0.6, 4.1)	6158 (7.1)	2.9 (1.3, 5.2)
2	489 (5.6)	2.9 (1.3, 5.0)	1536 (1.8)	4.2 (2.3, 6.2)
3	248 (2.8)	3.8 (1.6, 5.5)	696 (0.8)	4.9 (2.7, 6.4)
4	150 (1.7)	4.4 (2.6, 5.7)	305 (0.4)	5.4 (3.2, 6.9)
5	84 (1.0)	5.4 (3.3, 6.8)	150 (0.2)	5.6 (2.9, 7.5)
6	105 (1.2)	6.2 (4.2, 7.4)	224 (0.3)	5.2 (3.6, 7.5)
Death				
Overall	539 (5.3)	2.7 (1.1, 5.4)	3010 (3.3)	3.6 (1.8, 5.8)
Due to serious infection*	109 (1.2)	—	499 (0.6)	—
Hazard ratio for recurrent serious infection† (95% CI)				
Crude	3.30 (2.99, 3.64)		1.00 [Referent]	
Adjusted	2.79 (2.51, 3.10)		1.00 [Referent]	

IQR = interquartile range; CI = confidence interval.

*Serious infection coded as underlying or contributing cause of death on the death certificate (data from the Cause of Death Register).

†Within-individual hazard ratio estimated from a Cox proportional hazards model with a gamma frailty term (per individual; a shared frailty model). Adjusted hazard ratio estimated using inverse probability of sarcoidosis weights.

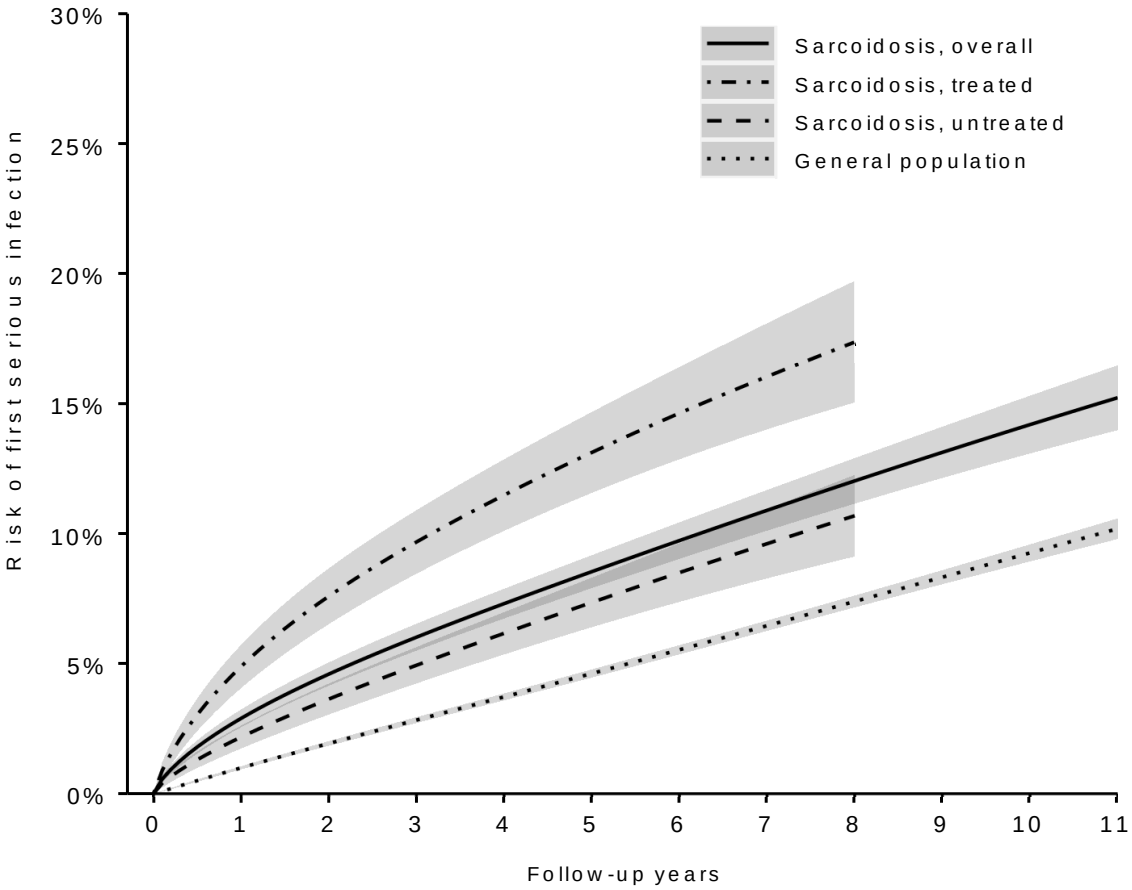
Table 4. Rates and hazard ratios for first serious infection comparing sarcoidosis to the general population in sensitivity analyses.

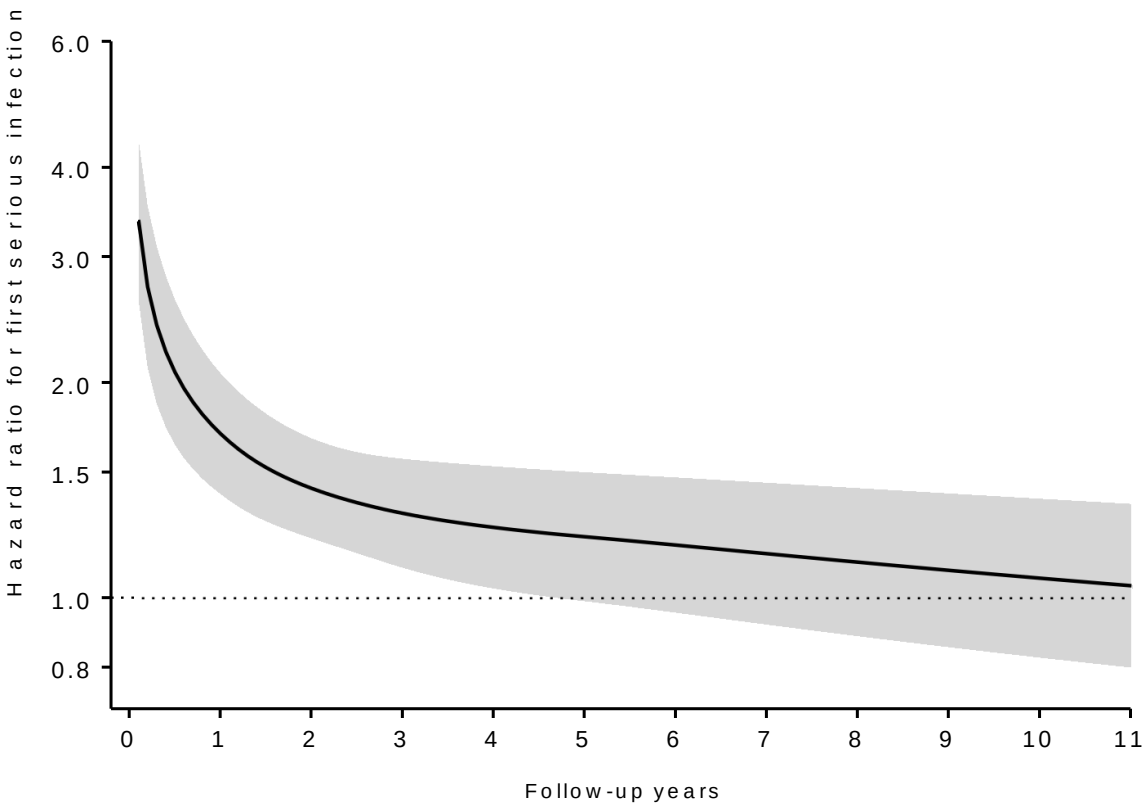
First serious infection	Individuals at risk	Events	Adjusted rate per 1000 person-years* (95% CI)	Hazard ratio* (95% CI)	Adjusted hazard ratio* (95% CI)
Hospitalisation and ≥1 dispensation of an antimicrobial ±15 days from hospital admission†					
Sarcoidosis	6723	427	14.7 (13.0, 16.6)	2.82 (2.53, 3.14)	2.23 (1.96, 2.54)
General population	66 441	1562	6.6 (6.3, 6.9)	1.00 [Referent]	1.00 [Referent]
Excluding pneumonias from serious infection definition					
Sarcoidosis	8737	694	13.1 (11.9, 14.4)	2.32 (2.14, 2.52)	1.72 (1.56, 1.90)
General population	86 376	3088	7.6 (7.3, 7.9)	1.00 [Referent]	1.00 [Referent]
Excluding urinary tract infections from serious infection definition					
Sarcoidosis	8737	866	16.8 (15.4, 18.3)	2.51 (2.33, 2.70)	1.89 (1.72, 2.07)
General population	86 376	3600	8.9 (8.6, 9.2)	1.00 [Referent]	1.00 [Referent]
Requiring comparators to have ≥1 healthcare visit in the NPR within two years before first visit for sarcoidosis or corresponding date in comparators					
Sarcoidosis, overall	8737	895	17.4 (16.0, 18.9)	1.59 (1.48, 1.72)	1.23 (1.12, 1.35)
General population	42 406	2704	14.2 (13.6, 14.7)	1.00 [Referent]	1.00 [Referent]
Sarcoidosis, treated†	2762	326	29.8 (25.9, 34.3)	2.45 (2.15, 2.80)	2.08 (1.77, 2.43)
General population†	13 852	696	14.4 (13.3, 15.5)	1.00 [Referent]	1.00 [Referent]
Sarcoidosis, not treated†	3961	275	15.7 (13.5, 18.3)	1.28 (1.12, 1.46)	1.03 (0.88, 1.22)
General population†	19 802	1054	15.2 (14.3, 16.2)	1.00 [Referent]	1.00 [Referent]
Excluding individuals with a serious infection within a year before first visit for sarcoidosis or corresponding date in comparators					
Sarcoidosis	8396	802	16.3 (15.0, 17.9)	2.30 (2.13, 2.49)	1.77 (1.61, 1.95)
General population	85 678	3716	9.2 (8.9, 9.5)	1.00 [Referent]	1.00 [Referent]
In Karolinska clinical cohort					
Sarcoidosis	693	47	11.1 (7.8, 15.9)	1.80 (1.32, 2.46)	1.49 (1.02, 2.18)
General population	6867	261	7.4 (6.6, 8.4)	1.00 [Referent]	1.00 [Referent]

CI = confidence interval; NPR = National Patient Register.

*Adjusted rates and adjusted hazard ratios were estimated using Poisson or Cox regression models weighted for inverse probability of sarcoidosis weights and years of follow-up as the time scale. Hazard ratios obtained from a cohort matched on age, sex, and residential location.

†Ascertained in individuals included starting Jan 1, 2006 for whom medication dispensations could be obtained from the Prescribed Drug Register.


30%
25%
20%
15%
10%
5%
0%
Risk of first serious infection
0
1
2
3
4
5
6
7
8
9
10
11
Follow-up years
Sarcoidosis, overall
Sarcoidosis, treated
Sarcoidosis, untreated
General population


Hazard ratio for first serious infection
6.0
4.0
3.0
2.0
1.5
1.0
0.8
0
1
2
3
4
5
6
7
8
9
10
11
Follow-up years

SUPPLEMENT

Risk of first and recurrent serious infection in sarcoidosis: a Swedish register-based cohort study

Marios Rossides, Susanna Kullberg, Anders Eklund, Johan Askling, Johan Grunewald, Elizabeth V. Arkema

Contents

SUPPLEMENTAL METHODS

Statistical analysis

Estimation of inverse probability of sarcoidosis weights

We estimated the probability of sarcoidosis (exposure) using a logistic regression model with the following covariates: age (continuous), sex, residential location, birth country, attained education, gross annual salary, civil status, calendar period, number of visits in the National Patient Register within two years before first sarcoidosis visit or corresponding date for comparators, and history of comorbidities including congestive heart disease, atrial fibrillation, hypertension, diabetes mellitus, dyslipidaemia, chronic obstructive pulmonary disease, asthma, acute myocardial infarction, stroke, autoimmune disease (in all analysis except for the stratification by history of autoimmune disease in the Discussion), primary immunodeficiency, and history of autoimmune disease or sarcoidosis in at least one first degree relative. We did not include history of serious infection in the year before inclusion in the model to avoid reverse causation bias as individuals with sarcoidosis were more likely to be in contact with healthcare at the time compared to their general population comparators. For more information, see [1, 2]. Variable definitions and encoding are available in **Table S1**. There were very few missing values (<1% in sarcoidosis and the general population) in a small number of covariates. Missing data were coded as a separate category.

Assuming consistency, positivity, and conditional exchangeability, stabilized inverse probability of exposure (sarcoidosis) weights for everyone in the dataset were then calculated using the formula $W_{st} = f(A)/f(A|L)$, where $f(A)$ denotes the proportion of exposed (with sarcoidosis) in our study population, and $f(A|L)$ the propensity score, i.e. the probability of exposure (sarcoidosis, yes/no) given confounders. To improve precision, we truncated (trimmed) the stabilized weights at the 1% of the extremes of their distribution [3]. That is, weights lower than the 1st percentile were set to the 1st-percentile weight and weights larger than the 99th percentile were set to the 99th percentile weight. We tested weight truncation in the range of 1% to 5% using our main analysis Cox model (with time to any serious infection as the outcome). We chose truncation at 1% after considering the variance-bias trade-off comparing deviation of the point estimate of the model with full and progressively truncated weights to that of the unadjusted (biased/unweighted model) [3].

We calculated standardized differences before and after applying the estimated stabilized and truncated inverse probability of sarcoidosis weights to check the balance of covariate distributions between exposed and unexposed (sarcoidosis vs. general population comparators) [4]. These are presented in **Table S2**. Standardized differences greater than 0.1 to 0.2 indicated covariate imbalance.

Cox proportional hazard models for first serious infection

We ran Cox proportional hazard models with time since diagnosis or matching (inclusion) as the time scale to estimate crude and adjusted hazard ratios and 95% confidence intervals comparing sarcoidosis (overall or either stratified by sarcoidosis treatment status around the time of diagnosis) to the general population comparators. To report marginal adjusted estimates, we incorporated

stabilized inverse-probability of sarcoidosis weights estimated as mentioned above. To account for the fact that some individuals may have been upweighted in adjusted (weighted) models even though weights were stabilized, we used robust (sandwich) standard errors were used to estimate 95% confidence intervals with better error coverage. The proportionality of hazards assumption was tested by inspecting Schoenfeld residuals plots for sarcoidosis (the only covariate in the models). As we *a priori* hypothesized, the proportionality assumption was violated, which lead to analyses performed with flexible parametric survival models described below.

Flexible parametric survival models for first serious infection

We used package *rstpm2* (version 1.5.1) [5] implemented in R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) to run flexible parametric survival models. Years since diagnosis or matching (for comparators) was used as the time scale in all models and the stabilized inverse-probability of sarcoidosis weights estimated as outlined above were integrated to the model. To identify the best model fit, we varied the degrees of freedom used in the natural cubic spline function to model the underlying (baseline) hazard function (on the log-cumulative hazard scale) and the time-varying effect of exposure (sarcoidosis or sarcoidosis, treated/not treated) from two to seven. A combination of model-derived hazard plots and the Akaike information criterion (AIC) was used in that order to choose the model with the best fit for the final analysis. Based on those, we used 4 degrees of freedom for modelling the baseline log-cumulative hazard and two degrees of freedom for modelling time-varying coefficients in all models.

Shared frailty models for recurrent serious infection

To model recurrent (up to six) serious infections and estimate adjusted within-individual hazard ratios and corresponding 95% confidence intervals comparing sarcoidosis to the general population, we ran a (random effects) shared frailty model using the package *survival* (version 3.1-8) in R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). In this model and in addition to stabilized inverse-probability of sarcoidosis weights estimated as explained above, a gamma frailty term was introduced to account for the dependence between recurrent events in individuals (correlation amongst survival times in individuals). We also ran a flexible parametric survival model using *rstpm2* as mentioned above but this time adding a gamma frailty term.

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3. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008; 168: 656–664.

4. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects

in observational studies. *Stat Med* 2015; 34: 3661–3679.

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SUPPLEMENTAL TABLES

Table S1. Description of variables used in the analyses including International Classification of Disease (ICD) and Anatomical Therapeutic Chemical (ATC) codes used to define diseases in the National Patient, Cancer, and Prescribed Drug registers, respectively. Dispensation data in the Prescribed Drug Register were available starting July 1, 2005.

Disease/Variable	Definition/Data source	Encoding	ICD and/or ATC codes*
Sarcoidosis	≥2 inpatient or outpatient visits in the NPR listing an ICD code for sarcoidosis.	Yes/no	*ICD-10:* D86 *ICD-8/9:* 135
Sarcoidosis treated around the time of diagnosis	≥1 dispensation of systemic corticosteroids, methotrexate, or azathioprine ±3 months from the first sarcoidosis visit.	Treated/untreated	*ATC:* H02AB01; H02AB02; H02AB04; H02AB06; H02AB07; L01BA01; L04AX03; L04AX01
Haematopoietic or lung malignancy around the time of sarcoidosis diagnosis	≥1 registration in the Swedish Cancer Register ±6 months from the first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-7:* 162–163; 200–205
Serious infection (primary outcome)	≥1 hospitalisation in the NPR listing an ICD code as the primary discharge diagnosis.	Yes/no	*ICD-10:* A00–B99; D73.3; E06.0; E32.1; G00–G07; H00.0; H44.0; H60.0; H60.1; H60.2; H60.3; H66; H67; H70; I30.1; I40.0; J00–J22; J32; J34.0; J36; J38.3; J39.0; J39.1; J44.0; J85; J86; K04.4; K04.6; K04.7; K10.2; K11.3; K12.2; K14.0; K57.0; K57.2; K57.4; K57.8; K61; K63.0; K65.0; K65.9; L00–L08; L30.3; M00; M01; M46.2; M46.3; M46.4; M60.0; M64.5; M65.0; M71.0; M71.1; M72.6; M86; N10–N12; N13.6; N15.1; N15.9; N30.0; N30.8; N34.0; N39.0; N41.2; N43.1; N45; N48.2; N61; N70–N74; N75.1; O23; O26.4; O41.1; O75.3; O85; O86; O88.3; O91; O98
Serious infection excluding urinary tract infections (secondary outcome)	≥1 hospitalisation in the NPR listing an ICD code as the primary discharge diagnosis, excluding ICD codes for urinary tract infection.	Yes/no	*ICD-10:* N30.0; N39.0 (used for exclusion)
Serious infection excluding pneumonia (secondary outcome)	≥1 hospitalisation in the NPR listing an ICD code as the primary discharge diagnosis, excluding ICD codes for pneumonia.	Yes/no	*ICD-10:* J12–J18 (used for exclusion)

Table S1. (Continued).

Disease/Variable	Definition/Data source	Encoding	ICD and/or ATC codes*
Congestive heart disease	≥1 visit listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* I42; I50 *ICD-9:* 425; 428 *ICD-8:* 425; 427,0; 427,1; 428,9
Atrial fibrillation	≥1 visit listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* I48 *ICD-9:* 427D *ICD-8:* 427,92
Acute myocardial infarction	≥1 visit listing an ICD code in the NPR's inpatient component before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* I21 *ICD-8/9:* 410
Stroke	≥1 visit listing an ICD code in the NPR's inpatient component before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* I60; I61; I63; I64 *ICD-9:* 430; 431; 433; 434; 436 *ICD-8:* 430–434; 436
Hypertension	≥1 visit listing an ICD code in the NPR or ≥2 dispensations in the PDR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* I10–I15 *ICD-9:* 400–405 *ICD-8:* 400–404 *ATC:* C02CA; C07; C08; C09
Diabetes mellitus	≥1 visit listing an ICD code in the NPR or ≥2 dispensations in the PDR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* E10–E11 *ICD-8/9:* 250 *ATC:* A10
Dyslipidaemia	≥1 visit listing an ICD code in the NPR or ≥2 dispensations in the PDR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* E78 *ICD-8/9:* 272 *ATC:* C10
Chronic obstructive pulmonary disease	≥1 visit listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* J41; J42; J43; J44.1; J44.8; J44.9 *ICD-9:* 491A; 491B; 491X; 492; 496 *ICD-8:* 491; 492
Asthma	≥1 visit listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* J45–J46 *ICD 8/9:* 493

Table S1. (Continued).

Disease/Variable	Definition/Data source	Encoding	ICD and/or ATC codes*
Autoimmune disease	≥2 visits listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* D51.0; D59.1; D68.6; D69.3; E05.0; E06.3; E10; E27.1; G35; G61.0; G70.0; K50; K51; K74.3; K90.0; L10; L12; L40; L63; M05–M09; M31.3; M31.5; M31.6; M32.1; M32.8; M32.9; M33; M34; M35.0; M35.1; M35.2; M45; [D86 in relatives] *ICD-9:* 136B; 242A; 245C; 255E; 281A; 283A; 287D; 340; 357A; 358A; 446E; 446F; 555; 556; 571G; 579A; 694E; 694F; 696; 704A; 710; 714; 720; [135 in relatives] *ICD-8:* 136,07; 242,00; 245,30; 255,10; 269,10; 281,0; 283,90; 287,10; 340; 357; 446,20; 446,30; 446,38; 563; 694; 696; 704,00; 712; 716; 733,00;734,0; 734,1; 734,9; [135 in relatives]
Autoimmune disease or sarcoidosis in ≥1 first degree relative	≥1 visit listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators in ≥1 first degree relative (biological mother, father, full sibling, or child) identified through the Multi-Generation Register.		
Primary immunodeficiency	≥1 visit listing an ICD code in the NPR before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ICD-10:* D80–D84 *ICD-9:* 279J; 279L; 279M; 279X
Systemic corticosteroids	≥1 dispensation in the PDR within six months first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ATC:* H02AB
Other immunosuppressants	≥1 dispensation in the PDR within six months before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ATC:* L01BA01; L04AX03; L04AX01; L04AA13
Hydroxychloroquine	≥1 dispensation in the PDR within six months before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ATC:* P01BA02
Non-steroidal anti-inflammatory drugs	≥1 dispensation in the PDR within six months before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ATC:* M01A

Table S1. (Continued).

Disease/Variable	Definition/Data source	Encoding	ICD and/or ATC codes*
Inhaled corticosteroids	≥1 dispensation in the PDR within six months before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ATC:* R03BA
Antimicrobials	≥1 dispensation in the PDR within six months before first sarcoidosis visit or corresponding date for comparators.	Yes/no	*ATC:* J01; J02; J04; J05
Age	Data from the TPR.	Continuous	—
Region of residence	Data from the TRP. As registered the year before inclusion. Stockholm [Stockholm and Gotland counties]; Uppsala-Örebro [Uppsala, Södermanland, Värmland, Örebro, Västmanland, Dalarna, and Gävleborg]; West [Västra Götaland and Halland]; South [Skåne, Kronoberg, and Blekinge]; Southeast [Östergötland, Jönköping, and Kalmar]; North [Västernorrland, Jämtland, Västerbotten, and Norrbotten].	Stockholm (including Gotland), Uppsala-Örebro, West, South, Southeast, North	—
Birth country	Data from the TRP. Nordic [Sweden, Denmark, Norway, Finland, and Iceland].	Nordic, non-Nordic, missing	—
Attained education	Data from LISA. Completed education during the year before inclusion.	≤9, 10–12, ≥13 years, missing	—
Gross annual salary	Data from LISA. Earned during the year before first sarcoidosis visit or corresponding date for comparators and adjusted to 2014 inflation rate.	0–<100, 100–<300, 300–<600, ≥600 thousand SEK, missing	—
Married or in registered partnership	Data from LISA. Registered civil status during the year before inclusion.	Yes/no	—
Healthcare visits in the past two years	Sum of all visits in the NPR during the past two years before first sarcoidosis visit or corresponding date for comparators.	0, 1–2, ≥3 visits	—

ICD = International Classification of Disease; ATC = Anatomical Therapeutic Chemical; NPR = National Patient Register; PDR = Prescribed Drug Register; TPR = Total Population Register; LISA = Longitudinal Integrated Database for Health Insurance and Labour Market Studies.

*All sub-codes in the classification system are included if the full ICD or ATC code is not explicitly mentioned. The Swedish ICD classification system's 10^{th} revision was in use starting 1997, the 9^{th} revision between 1987 and 1996 (and 1997 in some healthcare practices) and the 8^{th} revision between 1969 and 1986.

Table S2. Demographic and clinical characteristics of individuals with sarcoidosis (n=8737) and their matched general population comparators (n=86 376) at baseline and standardized differences calculated before and after inverse probability of sarcoidosis weighting (IPSW).

	Before inverse probability weighting			After inverse probability weighting		
	Sarcoidosis	General population	Standardized difference*	Sarcoidosis	General population	Standardized difference*
Age in years, mean (SD)	49.8 (14.8)	49.8 (14.7)	0.003	48.9 (13.8)	49.8 (14.7)	-0.063
Age groups in years, %			—			—
18–44	42.5	42.5		45.5	42.5	
45–64	39.5	39.7		38.5	39.6	
65–85	18.1	17.8		16.1	17.9	
Female, %	44.5	44.6	0.001	42.8	44.6	0.036
Region of residence, %			<0.001			0.049
Stockholm	20.4	20.5		20.6	20.5	
Uppsala-Örebro	22.1	22.1		23.0	22.1	
West	18.0	18.0		18.2	18.0	
South	16.8	16.8		15.7	16.8	
Southeast	11.6	11.6		11.5	11.6	
North	11.1	11.1		11.0	11.0	
Birth country†, %			0.064			0.064
Nordic	90.2	87.8		89.9	88.0	
Non-Nordic	9.5	11.8		9.7	11.6	
Missing	0.3	0.4		0.3	0.4	
Attained education in years, %			0.070			0.050
≤9	20.6	20.8		19.4	20.7	
10–12	49.1	46.4		47.9	46.7	
≥13	29.2	31.6		31.7	31.4	
Missing	1.2	1.2		1.0	1.2	

Table S2. (Continued).

	Before inverse probability weighting			After inverse probability weighting		
	Sarcoidosis	General population	Standardized difference	Sarcoidosis	General population	Standardized difference
Gross annual salary in 1000 SEK[‡], %			0.025			0.145
0–<100	40.2	39.3		37.8	39.4	
100–<300	30.3	30.0		31.1	30.0	
300–<600	26.0	27.3		27.6	27.2	
≥600	3.0	3.3		3.3	3.3	
Missing	0.5	<0.1		0.2	<0.1	
Married or in registered partnership, %	48.6	48.1	0.010	47.1	48.1	-0.020
Calendar period, %			<0.001			0.054
2003–2007	41.2	41.1		43.9	41.2	
2008–2013	58.8	58.9		56.1	58.8	
Health care visits in the past two years, %			0.875			0.101
0	16.9	50.9		42.6	47.8	
1–2	25.2	25.9		27.8	25.8	
≥3	57.9	23.2		29.6	26.4	
History of comorbidity, %						
Congestive heart disease	2.4	1.3	0.088	1.5	1.4	0.014
Atrial fibrillation	3.2	2.1	0.071	2.3	2.2	0.007
Acute myocardial infarction	2.1	1.8	0.025	1.8	1.8	0.000
Stroke	1.7	1.6	0.005	1.6	1.6	0.000
COPD	2.3	5.9	0.105	1.2	1.1	0.008
Asthma	4.6	2.4	0.119	2.8	2.6	0.013
Hypertension	21.4	15.9	0.142	16.4	16.4	-0.001
Diabetes mellitus	7.5	4.2	0.141	4.8	4.5	0.018
Dyslipidaemia	10.8	8.2	0.089	8.5	8.5	0.000
Autoimmune disease	7.9	4.3	0.152	5.2	4.6	0.029
Primary immunodeficiency	0.4	0.1	0.069	0.2	0.1	0.016

Table S2. (Continued).

	Before inverse probability weighting			After inverse probability weighting		
	Sarcoidosis	General population	Standardized difference	Sarcoidosis	General population	Standardized difference
Serious infection in the past year, %	3.9	0.8	—	2.3	0.9	—
≥1 first degree relative with autoimmune disease or sarcoidosis	1.1	0.5	0.069	0.7	0.5	0.026
≥1 medication dispensing in the past six months§, %						
Systemic corticosteroids	18.7	2.9	—	15.0	3.0	—
Other immunosuppressants	1.2	0.7	—	0.8	0.8	—
Hydroxychloroquine	0.1	0.1	—	0.1	0.1	—
Inhaled corticosteroids	7.3	1.9	—	7.5	2.0	—
NSAIDs	26.3	9.7	—	27.5	10.0	—
Antimicrobials**	32.6	13.2	—	30.2	13.7	—

SD = standard deviation; SEK = Swedish krona; COPD = chronic obstructive pulmonary disease; NSAIDs = non-steroidal anti-inflammatory drugs.
Percentages may not sum to 100 owing to rounding.
*Standardized difference >0.2 indicates covariate imbalance.
†Nordic countries include Sweden, Denmark, Norway, Finland, and Iceland.
‡Adjusted to 2014 inflation level. 1.00 SEK ≈ 0.10 USD, 0.09 EUR or 0.08 GBP.
§Ascertained in individuals who entered the cohort starting Jan 1, 2006 for whom medication dispensations could be obtained from the Prescribed Drug Register (sarcoidosis, n=6723; general population, n=66 441).
Other immunosuppressants include methotrexate, azathioprine, and leflunomide.
**Antimicrobials include antibacterial, antimycobacterial, antifungal, and antiviral medications.

Table S3. Ten most common first serious infections after start of follow-up in individuals with sarcoidosis and their general population comparators.

Order	Disease (Swedish ICD-10 code)	n	% of individuals	% of all serious infections
Sarcoidosis			(n=8737)	(n=895)
1	Pneumonia, organism unspecified (J18)	138	1.6	15.4
2	Bacterial pneumonia (J15)	93	1.1	10.4
3	Urinary tract infection (N39)	56	0.6	6.3
4	Sepsis (A41)	52	0.6	5.8
5	Pyelonephritis (N10)	47	0.5	5.3
6	Erysipelas (A46)	44	0.5	4.9
7	Gastroenteritis and colitis (A09)	35	0.4	3.9
8	Acute upper respiratory infection (J06)	27	0.3	3.0
9	Viral intestinal infection (A08)	24	0.3	2.7
10	Bacterial intestinal infection (A04)	23	0.3	2.6
	Other			39.7
General population			(n=86 376)	(n=3881)
1	Pneumonia, organism unspecified (J18)	546	0.6	14.1
2	Urinary tract infection (N39)	346	0.4	8.9
3	Bacterial pneumonia (J15)	344	0.4	8.9
4	Sepsis (A41)	235	0.3	6.1
5	Erysipelas (A46)	205	0.2	5.3
6	Pyelonephritis (N10)	188	0.2	4.8
7	Gastroenteritis and colitis (A09)	159	0.2	4.1
8	Acute bronchitis (J20)	101	0.1	2.6
9	Unspecified infectious disease (B99)	85	0.1	2.2
10	Bacterial intestinal infection (A04)	84	0.1	2.2
	Other			40.8

ICD = International Classification of Diseases.

Table S4. Opportunistic first serious infections after inclusion in individuals with sarcoidosis and their general population comparators. Exact numbers for less than five events are not reported to eliminate the risk of identifying study participants.

	Sarcoidosis			General population		
Disease (Swedish ICD-10 code)	**n**	**% of individuals**	**% of all serious infections**	**n**	**% of individuals**	**% of all serious infections**
		(n=8737)	(n=895)		(n=86 376)	(n=3881)
Aspergillosis (B44)	≤5	—	—	≤5	—	—
Candidiasis (B37)	≤5	—	—	15	0.0	0.4
Tuberculosis (A15–A19)	11	0.1	1.2	13	0.0	0.4
Other mycobacterial infection (A31)	≤5	—	—	0	—	—
Pneumocystosis (B59)	≤5	—	—	7	0.0	0.2

ICD = International Classification of Diseases.

SUPPLEMENTAL FIGURES

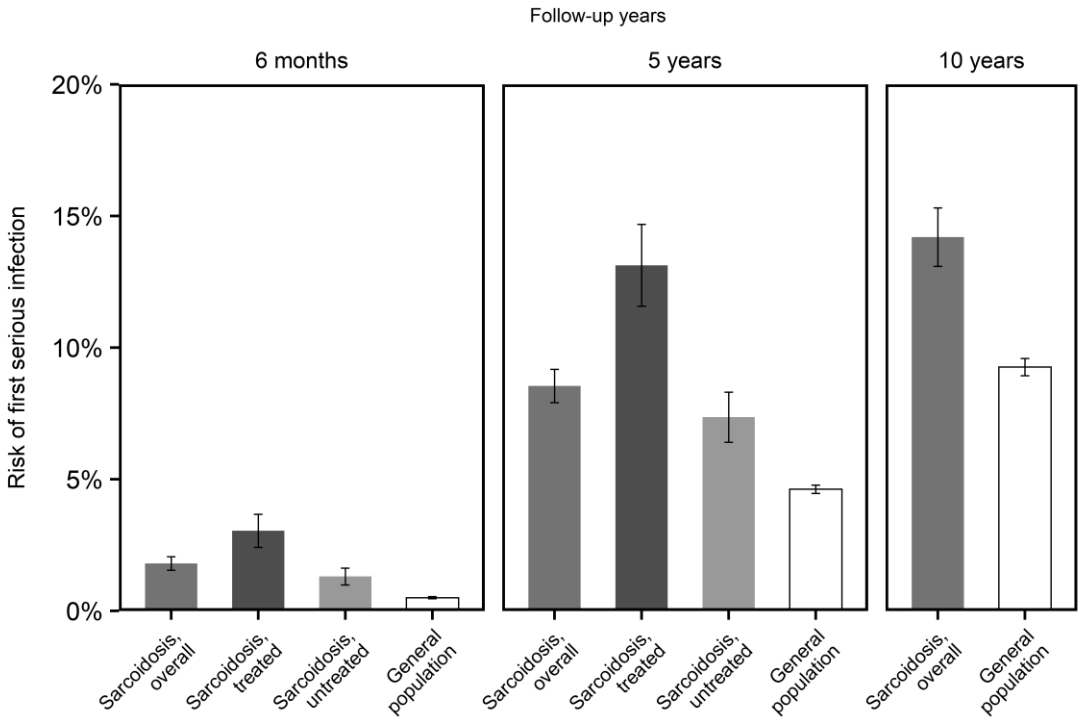

Figure S1. Risk of serious infection in sarcoidosis and the general population at six months, five, and ten years of follow-up. No risk estimates by treatment status could be obtained at 10 years because maximum follow-up in the treated and untreated groups was seven years.

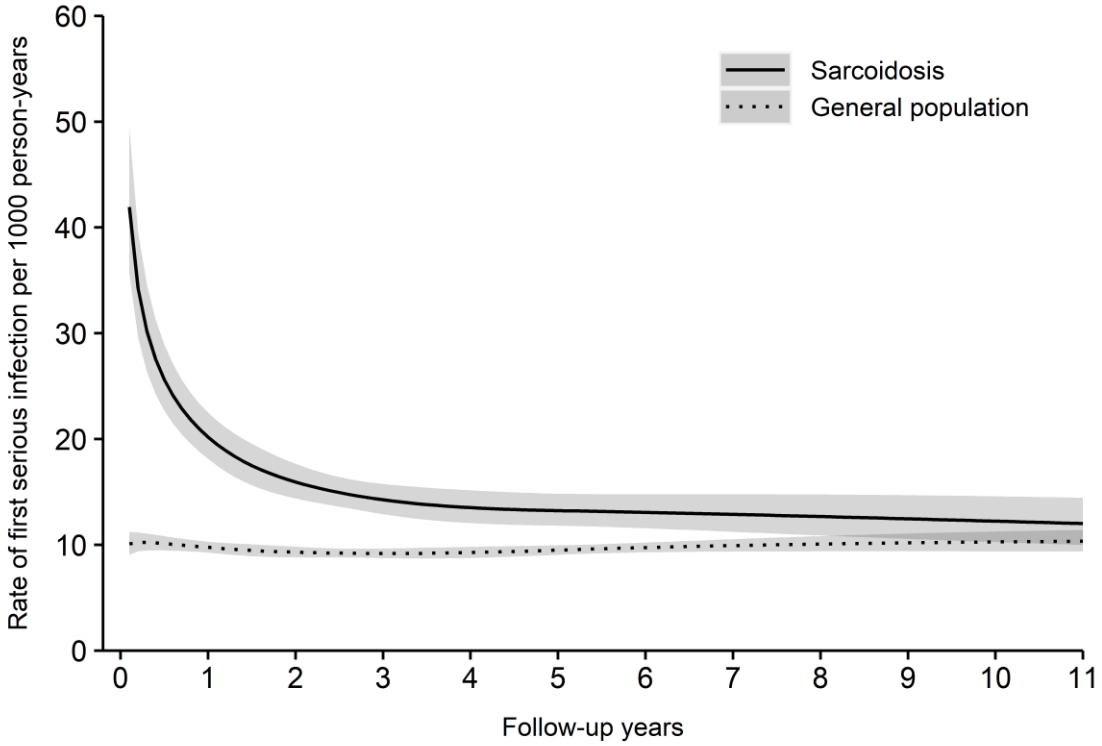

Figure S2. Adjusted rates of first serious infection in sarcoidosis and general population comparators by years of follow-up.

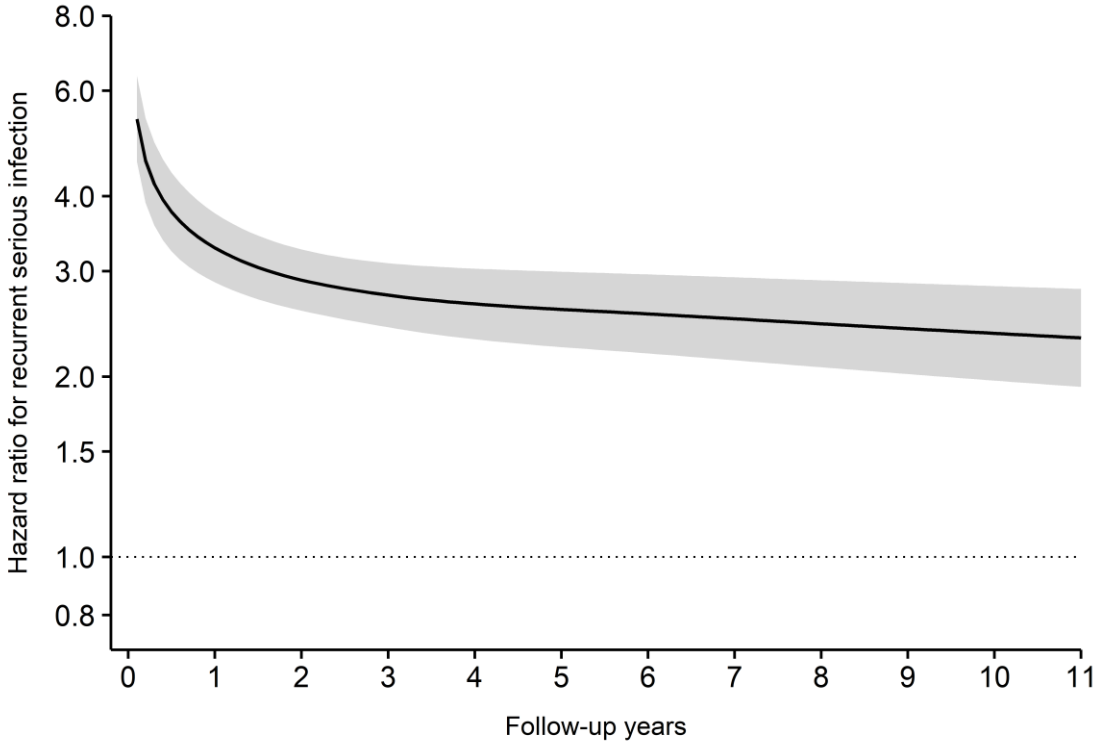

Figure S3. Adjusted within individual hazard ratios for recurrent serious infection by years of follow-up comparing sarcoidosis to the general population.