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Risk and predictors of heart failure in sarcoidosis in a population-based cohort study from Sweden

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ABSTRACT

Objectives Previous studies showed a strong association between sarcoidosis and heart failure (HF) but did not consider risk stratification or risk factors to identify useful aetiological insights. We estimated overall and stratified HRs and identified risk factors for HF in sarcoidosis.

Methods Sarcoidosis cases were identified from the Swedish National Patient Register (NPR; ≥2 International Classification of Diseases-coded visits, 2003–2013) and matched to general population comparators. They were followed for HF in the NPR. Treated were cases who were dispensed ≥1 immunosuppressant ±3 months from the first sarcoidosis visit (2006–2013). Using Cox models, we estimated HRs adjusted for demographics and comorbidity and identified independent risk factors of HF together with their attributable fractions (AFs).

Results During follow-up, 204 of 8574 sarcoidosis cases and 721 of 84 192 comparators were diagnosed with HF (rate 2.2 vs 0.7/1000 person-years, respectively). The HR associated with sarcoidosis was 2.43 (95% CI 2.06 to 2.86) and did not vary by age, sex or treatment status. It was higher during the first 2 years after diagnosis (HR 3.7 vs 1.9) and in individuals without a history of ischaemic heart disease (IHD; HR 2.7 vs 1.7). Diabetes, atrial fibrillation and other arrhythmias were the strongest independent clinical predictors of HF (HR 2.5 each, 2-year AF 20%, 16% and 12%, respectively).

Conclusions Although low, the HF rate was more than twofold increased in sarcoidosis compared with the general population, particularly right after diagnosis. IHD history cannot solely explain these risks, whereas ventricular arrhythmias indicating cardiac sarcoidosis appear to be a strong predictor of HF in sarcoidosis.

INTRODUCTION

Heart failure (HF) is a leading cause of impaired functional capacity, low quality of life and premature death in the general population.[1] In sarcoidosis, a systemic granulomatous disease of unknown aetiology, HF is a common cause of excess mortality.[2] Recently, studies showed that rates of HF are about twofold higher in sarcoidosis compared with the general population,[3–5] with more than sevenfold higher risks observed close to sarcoidosis diagnosis.[4] It remains unknown, however, which patients are at the highest risk of HF and may benefit most from preventive interventions.

Also limited is the knowledge on risk factors that contribute to HF risks in sarcoidosis. Diabetes mellitus, ischaemic heart disease (IHD) and other traditional risk factors for HF in the general population[1] are presumed to also play a role in sarcoidosis. Unique to sarcoidosis is that cardiac involvement may lead to HF.[6] Cardiac sarcoidosis overtly or covertly affects 5%–30% of patients and commonly manifests with ventricular arrhythmias (12-fold increased risk associated with sarcoidosis,[7] conduction anomalies, sudden cardiac arrest or death,[6 8–10] and rarely as atrial fibrillation).[11 12] Data on the relative contribution of traditional and sarcoidosis-specific risk factors to HF are scarce.[6] Because the underlying mechanisms leading to HF in sarcoidosis may vary greatly, it is critical to examine the factors that contribute the most to HF occurrence, which could aid early identification of at-risk patients who might be targeted with the appropriate preventive, diagnostic or therapeutic measures.

Our aim was therefore twofold: (a) to estimate HRs of HF associated with sarcoidosis, overall and by age, sex, sarcoidosis treatment status, time since sarcoidosis diagnosis and history of IHD; and (b) to identify which clinical risk factors confer the highest risk of HF in sarcoidosis.

METHODS

Study population

We conducted a cohort study using data from Swedish nationwide registers. The sarcoidosis cohort was comprised of individuals with ≥2 inpatient or outpatient International Classification of Diseases (ICD)-coded visits for sarcoidosis in the National Patient Register (NPR) between 2003 and 2013 (see online supplemental table S1 for ICD codes). The NPR, a valid resource for identifying sarcoidosis,[13] captures hospitalisations since 1964 (nationwide since 1987) and outpatient visits to secondary care since 2001. Individuals with any sarcoidosis visit before 2003 were excluded to focus on newly diagnosed disease.

At the second visit for sarcoidosis (index date), up to 10 general population comparators without any sarcoidosis visits in the NPR were randomly sampled from the Total Population Register and matched to each case on year of birth, sex and residential location. To reduce sarcoidosis misclassification, we restricted the study population to adults 18–85 years old at index date and to those without a haematopoietic or lung malignancy recorded in the Cancer Register ±6 months from the first visit for sarcoidosis or corresponding date for comparators. Records across registers were linked using a

participant's unique identification number which is allocated by authorities at birth or immigration.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Follow-up for HF

The study population was followed for HF, which was defined as an inpatient or outpatient visit in the NPR listing an ICD code for HF or cardiomyopathy as the primary discharge diagnosis (see online supplemental table S1 for codes). This definition for HF yielded positive predictive values of >80% in validation studies.[14] Follow-up started at index date and ended at the earliest of hospital admission or outpatient visit for HF, emigration (Total Population Register), death (Cause of Death Register) or 31 December 2013. Individuals with a history of HF at the start of follow-up were excluded from all analyses.

Other variables and predictors of HF

Demographic variables were evaluated at the start of follow-up using data obtained from the Total Population Register and the Longitudinal Integrated Database for Health Insurance and Labor Market Studies. They included age, sex, region of residence (grouped into six healthcare regions),[15] country of birth (Nordic, non-Nordic or missing), attained education (≤9, 10–12, ≥13 years or missing) and civil status (married or in registered partnership, or other).

Using nationwide data on filled prescriptions that first became available in the Prescribed Drug Register (PDR) in July 2005, we classified sarcoidosis cases who entered the cohort in 2006 or later as treated around diagnosis if they were dispensed ≥1 systemic corticosteroid, methotrexate or azathioprine ±3 months from the first sarcoidosis visit. We aimed to capture sarcoidosis cases with debilitating or progressing disease at diagnosis for whom treatment with immunosuppressants is recommended (see codes in online supplemental table S1).[2 15 16]

To account for differences in general health status, we counted NPR visits within 2 years before the first sarcoidosis visit or the corresponding date for comparators (0, 1–3, ≥4 visits). In addition, we evaluated several clinical confounders and/or potential predictors of HF using data on healthcare visits or medical procedures from the NPR and/or medication dispensations in the PDR, as appropriate (see online supplemental table S1). Comorbidities included hypertension, diabetes mellitus, dyslipidaemia, IHD including acute myocardial infarction (AMI), heart valve disease, atrial fibrillation, other arrhythmias (a composite variable made up of ventricular arrhythmias, conduction anomalies, cardiac arrest, implantation of a cardioverter-defibrillator, receipt of cardiac resynchronisation therapy or ≥2 dispensations of a class I/III antiarrhythmic medication), pulmonary hypertension, chronic obstructive pulmonary disease, chronic kidney disease, alcohol-related disorders and autoimmune disease. When used as confounders, comorbidities were evaluated 3 months before the first sarcoidosis visit or the corresponding date in comparators to avoid surveillance bias favouring the sarcoidosis group.[15] Last, we defined use of medications that could have altered the risk of HF at baseline as ≥1 dispensation in the PDR between 3 and 9 months before the first sarcoidosis visit or the corresponding date for comparators.

Statistical analysis

We estimated incidence rates and rate differences comparing sarcoidosis with the general population and their corresponding 95% CIs using Poisson regression models adjusted for age, sex and region of residence. We used Cox proportional hazards models with attained age as the time scale to estimate HRs of HF comparing sarcoidosis with the general population. Models were sequentially adjusted for: (1) age, sex and region of residence; (2) country of birth, education, civil status and calendar period; (3) hypertension, diabetes mellitus, dyslipidaemia, heart valve disease, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, alcohol-related disorders, autoimmune disease, and healthcare visits within 2 years before the first sarcoidosis visit or corresponding period for comparators. Unless otherwise stated, the missing-indicator method was used to account for missingness in country of birth and education.

We further investigated differences in HRs comparing sarcoidosis with the general population among groups defined by age at start of follow-up (18–44, 45–64, or 65–85 years), sex, sarcoidosis treatment status around diagnosis (treated vs untreated), time since start of follow-up (≤2 vs >2 years when sarcoid inflammation is expected to subside in about 50% of cases[17]), and by history of IHD/AMI, both causes of ischaemic HF. A two-tailed p value of <0.05 from a likelihood ratio test was considered indicative of significant differences among groups.

Restricting to the sarcoidosis cohort, we used a Cox model with years since sarcoidosis diagnosis as the time scale adjusted for age at sarcoidosis diagnosis, sex, region of residence, country of birth and education to examine whether predefined predictors evaluated at sarcoidosis diagnosis (second NPR visit) were independently associated with HF. To rank the clinical predictors according to their potential contribution of HF cases, we estimated the attributable fraction at 2 and 10 years after sarcoidosis diagnosis.[18]

We conducted several sensitivity analyses which are detailed in the online supplemental methods section.

We used SAS V.9.4 (SAS Institute) and R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) for data management and analyses.

RESULTS

We followed 8574 individuals with sarcoidosis and 84 192 matched general population compactors for HF. Mean age at start of follow-up was 49 years (SD 14 years) and 45% of participants were women (table 1). Hypertension, diabetes, dyslipidaemia, atrial fibrillation, chronic obstructive pulmonary, chronic kidney and autoimmune disease were more prevalent in sarcoidosis. Of individuals with sarcoidosis who entered the cohort in 2006 and onwards with available data in the PDR, 41% were dispensed an immunosuppressant treatment around the time of diagnosis. Sarcoidosis cases were more likely to have been dispensed medications used to treat comorbidities (eg, diuretics or β-blockers) than comparators (online supplemental table S2).

Association between sarcoidosis and HF

During a median follow-up of 4.8 years (IQR 2.3–7.6), 204 individuals with sarcoidosis and 721 general population comparators were diagnosed with HF. The incidence rate of HF was higher in sarcoidosis (2.2/1000 person-years (95% CI 1.9 to 2.6)) than in comparators (0.7/1000 person-years (95% CI 0.7 to 0.8); table 2). After adjusting for demographics and comorbidity, sarcoidosis was associated with a 2.4-fold higher risk of HF (HR 2.43 (95% CI 2.06 to 2.86); table 3). The proportional hazards

Table 1 Demographic and clinical characteristics at start of follow-up in individuals with sarcoidosis and their matched general population comparators

	Sarcoidosis	General population
Individuals	8574	84 192
Age, years	49.5 (14.6)	49.3 (14.5)
Female	3824 (44.6)	37 606 (44.7)
Region of residence		
Stockholm	1761 (20.5)	17 323 (20.6)
Uppsala-Örebro	1897 (22.1)	18 620 (22.1)
West	1543 (18.0)	15 206 (18.1)
South	1447 (16.9)	14 198 (16.9)
Southeast	977 (11.4)	9565 (11.4)
North	949 (11.1)	9280 (11.0)
Country of birth*		
Nordic	7731 (90.2)	73 841 (87.7)
Non-Nordic	816 (9.5)	10 015 (11.9)
Missing	27 (0.3)	336 (0.4)
Education, years		
≤9	1732 (20.2)	16 974 (20.2)
10–12	4202 (49.0)	39 216 (46.6)
≥13	2493 (29.1)	26 842 (31.9)
Missing	147 (1.7)	1160 (1.4)
Married or in registered partnership	4153 (48.4)	40 366 (47.9)
Calendar period		
2003–2007	3540 (41.3)	34 804 (41.3)
2008–2013	5034 (58.7)	49 388 (58.7)
Healthcare visits within 2 years before the first sarcoidosis visit, n		
0	1462 (17.1)	43 268 (51.4)
1–3	2180 (25.4)	21 799 (25.9)
≥4	4932 (57.5)	19 125 (22.7)
History of morbidity†		
Hypertension	1586 (18.5)	12 104 (14.4)
Diabetes mellitus	586 (6.8)	3176 (3.8)
Dyslipidaemia	827 (9.6)	6218 (7.4)
Ischaemic heart disease or acute myocardial infarction	339 (4.0)	2735 (3.2)
Atrial fibrillation	199 (2.3)	1361 (1.6)
Heart valve disease	69 (0.8)	470 (0.6)
Chronic obstructive pulmonary disease	145 (1.7)	681 (0.8)
Chronic kidney disease	115 (1.3)	297 (0.4)
Alcohol-related disorder	184 (2.1)	2134 (2.5)
Autoimmune disease	629 (7.3)	3428 (4.1)

Data are n, n (%), or mean (SD). Category percentages may not sum up to 100 owing to rounding.
*Nordic countries include Sweden, Denmark, Norway, Finland and Iceland.
†Evaluated in the period up to 3 months before the first sarcoidosis visit in the National Patient Register or the corresponding date for matched general population comparators.

assumption was visualised using Schoenfeld residuals plots and was found to hold in all analyses. The HR did not vary by age (p=0.77), sex (p=0.38) or treatment status around sarcoidosis diagnosis (p=0.29). It was, however, higher during the first 2 years compared with the rest of follow-up (fully adjusted HR 3.74 (95% CI 2.93 to 4.77) vs 1.86 (95% CI 1.50 to 2.31); p<0.001) and in individuals *without* compared with those with a history of IHD/AMI (HR 2.74 (95% CI 2.28 to 3.29) vs 1.70 (95% CI 1.19 to 2.44); p=0.02; table 3).

In sensitivity analyses, we found a similar HR to the main analysis when we disregarded HF diagnoses during the first 6 months to account for potential surveillance bias in sarcoidosis (overall HR 2.30 (95% CI 1.94 to 2.74); HR within 2 years from sarcoidosis diagnosis (3.50 (95% CI 2.64 to 4.63)) and a slightly attenuated HR (1.87 (95% CI 1.62 to 2.15)) when we included secondary diagnoses in the HF definition (online supplemental table S3).

Predictors of HF in sarcoidosis

As shown in table 4, individuals with sarcoidosis who developed HF were more likely to be older, have lower education and more comorbidity (eg, diabetes, IHD, etc) than those who did not develop HF. Arrhythmias were also more common at sarcoidosis diagnosis in those who were diagnosed with HF during follow-up. In a mutually adjusted Cox model including demographic and other clinical predictors, diabetes mellitus, atrial fibrillation, and other arrhythmias were each independently associated with a 2.5-fold increased risk of HF (table 4) and were each estimated to account for 20%, 16%, and 12% of HF cases at 2 years after sarcoidosis diagnosis, respectively (attributable fraction; figure 1). Although history of IHD was one of the most prevalent comorbidities in those who developed HF, it was associated with a 40% increased risk of HF diagnosis during follow-up (mutually adjusted HR 1.4 (95% CI 1.0 to 2.1); attributable fraction at 2 years 7%).

In separate analyses restricting to those diagnosed with sarcoidosis 2006–2013, sarcoidosis treatment status around diagnosis (treated/untreated) and cumulative defined daily doses (DDDs) of systemic corticosteroids within 6 months before sarcoidosis diagnosis did not independently predict HF (online supplemental tables S4 and S5). However, dispensation of >300 DDDs (high tertile; one DDD prednisolone=10 mg) of systemic corticosteroids within 6 months after sarcoidosis diagnosis was associated with a twofold increased risk of HF after 6 months compared with ≤150 DDDs (low tertile; online supplemental table S5). Time-varying analyses resulted in a somewhat higher HRs than those from the main analysis for other arrhythmias and IHD (3.1 (95% CI 2.2 to 4.3) and 1.9 (95% CI 1.4 to 2.6), respectively), whereas associations for other predictors did not change markedly (online supplemental table S6).

DISCUSSION

In this large study, sarcoidosis was associated with a 2.4-fold increased hazard of HF compared with the general population. The HR of HF was highest during the first 2 years after sarcoidosis diagnosis (HR 3.7) but did not vary by age, sex or sarcoidosis treatment status around diagnosis. A higher HR of HF associated with sarcoidosis was observed in individuals without a history of IHD compared with those diagnosed with IHD. Among patients with sarcoidosis, history of diabetes mellitus, atrial fibrillation and other arrhythmias or conduction anomalies at sarcoidosis diagnosis were the strongest independent contributors to HF diagnosis.

Although the overall rate of HF was low given the relatively young age of the sarcoidosis population (mean 50 years), they were markedly higher than those in the matched general population group, even after adjusting for several confounders. This observation was in line with previous investigations.[3–5] The highest rates of HF were observed in individuals ≥65 years old and in those with a history of IHD/AMI, but HF was also seen in younger patients with sarcoidosis and in those without a history of IHD. These findings together with an increased HR of HF

Table 2 Incidence rates and rate differences of heart failure (per 1000 person-years) comparing sarcoidosis with the general population, overall and by age at start of follow-up, sex, sarcoidosis treatment status around sarcoidosis diagnosis, time since sarcoidosis diagnosis, and history of ischaemic heart disease or acute myocardial infarction

	Sarcoidosis		General population		
	Events/ N at risk	Incidence rate* (95% CI)	Events/ N at risk	Incidence rate* (95% CI)	Rate difference* (95% CI)
Overall	204/8574	2.2 (1.9 to 2.6)	721/84 192	0.7 (0.7 to 0.8)	1.5 (1.1 to 1.8)
Age at start of follow-up, years					
18–44	18/3699	0.8 (0.5 to 1.3)	53/36 549	0.2 (0.2 to 0.3)	0.6 (0.2 to 1.0)
45–64	68/3394	3.3 (2.6 to 4.3)	225/33 578	1.1 (0.9 to 1.3)	2.2 (1.4 to 3.1)
65–85	118/1481	19.0 (15.8 to 22.9)	443/14 065	6.6 (5.9 to 7.3)	12.5 (8.9 to 16.0)
Sex					
Female	90/3824	1.8 (1.4 to 2.4)	329/37 606	0.6 (0.5 to 0.8)	1.2 (0.8 to 1.6)
Male	114/4750	2.4 (2.0 to 3.0)	392/46 586	0.8 (0.7 to 0.9)	1.6 (1.2 to 2.1)
Sarcoidosis treatment around diagnosis†					
Treated	62/2696	3.0 (2.2 to 4.1)	161/26 479	0.7 (0.6 to 0.9)	2.3 (1.4 to 3.1)
Untreated	79/3889	2.1 (1.6 to 2.8)	234/38 120	0.6 (0.5 to 0.8)	1.5 (1.0 to 2.0)
Time since sarcoidosis diagnosis, years					
≤2	98/8574	1.2 (0.9 to 1.5)	223/84 192	0.5 (0.4 to 0.6)	0.7 (0.4 to 0.9)
>2	106/6585	1.0 (0.8 to 1.3)	498/65 949	0.2 (0.2 to 0.3)	0.8 (0.5 to 1.0)
History of ischaemic heart disease or acute myocardial infarction					
Yes	37/339	26.9 (19.4 to 37.4)	186/2735	13.6 (11.5 to 16.1)	13.3 (4.4 to 22.2)
No	167/8235	2.1 (1.8 to 2.5)	535/81 457	0.6 (0.6 to 0.7)	1.5 (1.1 to 1.8)

*Rates and rate differences per 1000 person-years were estimated using Poisson regression models adjusted for age, sex (if applicable) and region of residence.
†Evaluated in individuals with start of follow-up from 2006 and onwards for whom medication dispensation data were available in the Prescribed Drug Register.

during the first 2 years since sarcoidosis diagnosis, a period of active inflammation in most individuals, suggested that HF and sarcoidosis may be linked by common pathogenetic mechanisms.

Interestingly and similar to a smaller investigation,[3] HRs of HF were not significantly different between sarcoidosis cases who did and did not receive immunosuppressant treatment around diagnosis. Contrary to what we previously observed for mortality and infection risks,[2 16] treatment status around diagnosis might not be useful for stratifying patients with sarcoidosis in terms of future HF risk. We should acknowledge,

Table 3 HRs of heart failure comparing sarcoidosis with the general population, overall and by age at start of follow-up, sex, sarcoidosis treatment status around sarcoidosis diagnosis, time since sarcoidosis diagnosis, and history of ischaemic heart disease or acute myocardial infarction

	HR* (95% CI)		
	Multivariable model 1	Multivariable model 2	Multivariable model 3
Overall	3.03 (2.59 to 3.53)	3.05 (2.61 to 3.57)	2.43 (2.06 to 2.86)
Age at start of follow-up, years			
18–44	3.34 (1.96 to 5.70)	3.29 (1.93 to 5.61)	2.79 (1.63 to 4.78)
45–64	3.09 (2.35 to 4.05)	3.14 (2.39 to 4.12)	2.53 (1.92 to 3.34)
65–85	2.95 (2.41 to 3.62)	2.98 (2.43 to 3.65)	2.32 (1.88 to 2.87)
Sex			
Female	2.92 (2.31 to 3.68)	2.95 (2.33 to 3.72)	2.25 (1.77 to 2.86)
Male	3.12 (2.53 to 3.84)	3.14 (2.55 to 3.87)	2.59 (2.08 to 3.21)
Sarcoidosis treatment around diagnosis†			
Treated	4.23 (3.15 to 5.66)	4.24 (3.17 to 5.69)	3.35 (2.48 to 4.53)
Untreated	3.43 (2.66 to 4.43)	3.43 (2.66 to 4.43)	2.71 (2.08 to 3.52)
Time since sarcoidosis diagnosis, years			
≤2	4.69 (3.70 to 5.95)	4.73 (3.73 to 6.00)	3.74 (2.93 to 4.77)
>2	2.30 (1.87 to 2.84)	2.32 (1.88 to 2.86)	1.86 (1.50 to 2.31)
History of ischaemic heart disease or acute myocardial infarction			
Yes	2.05 (1.44 to 2.92)	2.06 (1.45 to 2.94)	1.70 (1.19 to 2.44)
No	3.32 (2.79 to 3.96)	3.35 (2.82 to 3.99)	2.74 (2.28 to 3.29)

*HRs were estimated using Cox proportional hazards models with attained age as the time scale. The multivariable model 1 was adjusted for age at start of follow-up, sex and region of residence. The multivariable model 2 was further adjusted for country of birth, education, civil status and calendar period. The multivariable model 3 was further adjusted for healthcare visits within 2 years before inclusion, history of hypertension, diabetes mellitus, dyslipidaemia, heart valve disease, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, alcohol-related disorders and autoimmune disease. Differences in HRs from the multivariable model 3 among groups were tested using likelihood ratio tests: age at start of follow-up (p=0.77); sex (p=0.38); sarcoidosis treatment around diagnosis (p=0.29); time since sarcoidosis diagnosis (p<0.001); history of ischaemic heart disease or acute myocardial infarction (p=0.02).
†Evaluated in individuals with start of follow-up from 2006 and onwards for whom medication dispensation data were available in the Prescribed Drug Register.

Table 4 HRs of heart failure in sarcoidosis associated with covariates evaluated at start of follow-up (second visit for sarcoidosis in the National Patient Register)

	Heart failure		HR* (95% CI)		
	Yes (n=204)	No (n=8370)	Univariable	Multivariable model 1	Multivariable model 2
Age at sarcoidosis diagnosis†, years	67 (59, 76)	48 (37, 60)	2.4 (2.2 to 2.7)	—	1.9 (1.7 to 2.2)
Male	114 (56)	4636 (55)	1.0 (0.8 to 1.3)	—	1.5 (1.1 to 2.0)
Education‡, years				—	
≤9	98 (48)	1781 (21)	4.1 (2.8 to 6.1)		1.9 (1.3 to 2.9)
10–12	73 (36)	4129 (49)	1.3 (0.9 to 2.0)		1.3 (0.9 to 2.0)
≥13	33 (16)	2460 (29)	1.0 (reference)		1.0 (reference)
Hypertension	107 (52)	1789 (21)	5.7 (4.3 to 7.5)	2.2 (1.6 to 2.9)	1.2 (0.9 to 1.7)
Diabetes mellitus	58 (28)	609 (7)	6.2 (4.5 to 8.4)	3.2 (2.3 to 4.4)	2.5 (1.8 to 3.6)
Chronic kidney disease	20 (10)	173 (2)	6.2 (3.9 to 9.9)	1.9 (1.2 to 3.1)	1.4 (0.8 to 2.2)
Alcohol-related disease	10 (5)	186 (2)	2.9 (1.5 to 5.5)	2.4 (1.3 to 4.5)	2.0 (1.0 to 3.9)
Chronic obstructive pulmonary disease	11 (5)	225 (3)	2.4 (1.3 to 4.4)	1.1 (0.6 to 2.1)	1.1 (0.6 to 2.1)
Heart valve disease	16 (8)	73 (1)	11.1 (6.6 to 18.5)	3.8 (2.2 to 6.4)	1.8 (1.0 to 3.1)
Ischaemic heart disease or acute myocardial infarction	47 (23)	343 (4)	7.7 (5.6 to 10.7)	2.4 (1.7 to 3.4)	1.4 (1.0 to 2.1)
Atrial fibrillation	49 (24)	214 (3)	13.6 (9.9 to 18.8)	4.6 (3.2 to 6.5)	2.6 (1.8 to 3.9)
Other arrhythmia or heart block	39 (19)	277 (3)	8.1 (5.7 to 11.5)	4.2 (2.9 to 6.0)	2.5 (1.6 to 3.7)
Pulmonary hypertension	≤5 (2)	7 (<1)	Not estimable	Not estimable	Not estimable
Autoimmune disease	27 (13)	674 (8)	2.0 (1.3 to 3.0)	1.7 (1.1 to 2.5)	1.1 (0.7 to 1.7)

Data are n (%) or median (IQR).

*HRs were estimated from Cox proportional hazards models with years since sarcoidosis diagnosis as the time scale. The multivariable model 1 included age (continuous), sex, region of residence (six healthcare regions), country of birth (Nordic/non-Nordic) and education. The multivariable model 2 included the covariates age, sex, region of residence, country of birth, education and all comorbidities in the table except pulmonary hypertension due to small numbers.

†Effect per 10-year increase.

‡Category '≤9 years' includes <1% missing.

however, that a higher risk of death in the treated compared with the untreated[2] may have led to a slight underestimation of the true HR of HF in the first. In a separate analysis among treated patients with sarcoidosis, we found that a higher dose of systemic corticosteroids dispensed within 6 months after sarcoidosis diagnosis was associated with a higher hazard of HF thereafter. The role of immunosuppressant treatment, especially that of corticosteroids, should be investigated further with larger numbers while accounting for disease severity that is an indication for treatment.

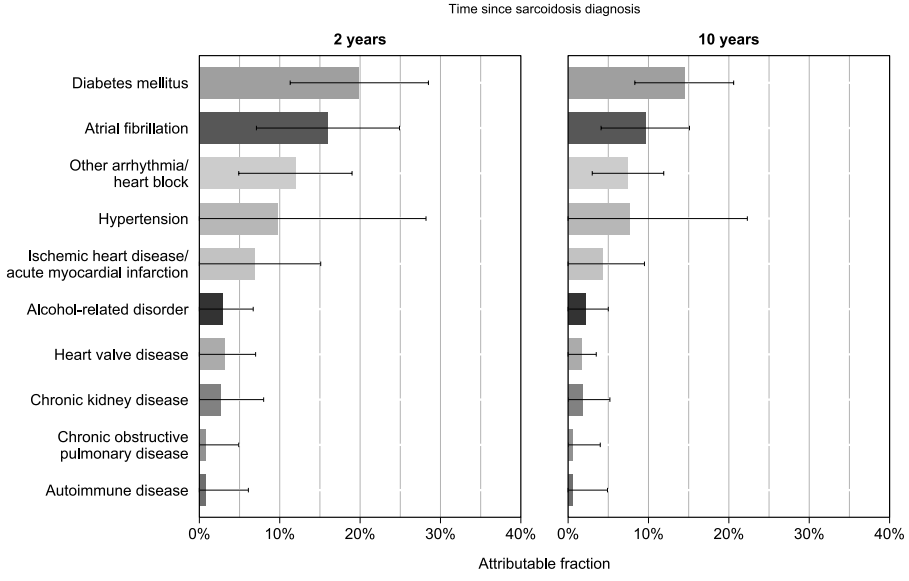

Figure 1 Fraction of heart failure cases at 2 and 10 years after sarcoidosis diagnosis attributed to risk factors evaluated at start of follow-up (second visit for sarcoidosis in the National Patient Register). Attributable fractions were estimated using a Cox model with years since sarcoidosis diagnosis as the time scale and the following time-fixed covariates: age (continuous), sex, region of residence (six healthcare regions), country of birth (Nordic/non-Nordic), education (in three categories) and comorbidities listed in the figure. Error bars indicate 95% CIs.

Among patients with sarcoidosis, sociodemographic factors such as older age, male sex and lower education were associated with a higher hazard of HF. Diabetes mellitus and atrial fibrillation, two traditional risk factors of HF,[19 20] were among the strongest predictors of HF diagnosis also in sarcoidosis. However, no association was observed between hypertension and HF likely due to the inclusion of other predictors of cardiovascular disease. Risks of diabetes and atrial fibrillation peak immediately after sarcoidosis diagnosis[4 21 22] and although it is disputed whether the latter is a manifestation of cardiac sarcoidosis,[11 12] their presence might lead to diagnosis of HF. A large proportion of future HF cases (>35%) could therefore be attributed to factors unrelated to sarcoid heart involvement.

In our study, 19% of patients with sarcoidosis who developed HF had a diagnosis of a ventricular arrhythmia, heart block or cardiac arrest; their prevalence increased to 30% during follow-up. Presumed to be a consequence of cardiac sarcoidosis,[6–8 23] a composite predictor including these severe arrhythmias was independently and equally predictive of increased HF in sarcoidosis as other traditional HF risk factors. Although one study showed congestive HF was more common in patients hospitalised for sarcoidosis with than those without an arrhythmia,[24] data on HF risk factors from other populations are scarce to compare our findings.

IHD and AMI, strong predictors of HF in the general population and other inflammatory diseases,[25–27] were less predictive of HF in sarcoidosis accounting for 7% of HF cases 2 years after sarcoidosis diagnosis. Even though HF rates in our study were notably higher in those with IHD compared with those without irrespective of sarcoidosis status, a higher HR of HF associated with sarcoidosis was observed in those without a history of IHD (2.7 vs 1.7). This observation supports the notion that cardiac sarcoidosis and not IHD alone drives the increased HR of HF. Indeed, unpublished findings showing similar risks of AMI between sarcoidosis and the general population are suggestive of a weaker role of IHD on HF in sarcoidosis.

Certain limitations of this study are worth considering. No data are available in the NPR to characterise the precise aetiology or severity of HF or define cardiac sarcoidosis. Moreover, because sarcoidosis and HF share symptoms and the diagnostic work-up for the first may reveal the latter, differential misclassification of HF was possible. However, our findings are unlikely to have been greatly affected by this bias as shown in a sensitivity analysis where we disregarded HF diagnoses during the first 6 months since sarcoidosis diagnosis, which yielded similar results to the main analysis. In addition, HF rates reported here may be somewhat underestimated as we have missed some HF cases treated solely in primary care data from which we did not have.[28]

Furthermore, we lacked data on obesity and smoking, two potential confounders of the association between sarcoidosis and HF. It is unlikely, however, that knowledge of these factors would have altered our conclusions by explaining away the strong association. That is because the magnitude of the positive association between obesity and sarcoidosis is the same to that of the inverse association between smoking and sarcoidosis.[29 30] Assuming also a similar effect on HF risk and in the absence of substantial interactions, we would expect a null net effect on the sarcoidosis–HF associations. Our findings are transportable to populations with similar prevalence and severity of cardiac sarcoidosis and other comorbidities predisposing to HF.

Overall, individuals with sarcoidosis are at a considerably higher risk of developing HF compared with the general population, especially during the first 2 years after sarcoidosis diagnosis. Traditional risk factors such as older age, diabetes mellitus and IHD are associated with an increased hazard of HF in sarcoidosis but are unlikely to explain all the observed risks in this population. Ventricular and other arrhythmias, which may be related to cardiac sarcoidosis, are one of the strongest independent predictors of HF and may be responsible for more than 10% of HF cases within 2 years after sarcoidosis diagnosis. Further studies are warranted to identify optimal measures that could help prevent HF in high-risk individuals with sarcoidosis.

Key messages

What is already known on this subject?

- Previous studies suggested that sarcoidosis is associated with notably high relative risks of heart failure. It remains unknown, however, whether risks are increased in specific patient groups or all patients, or if ischaemic heart disease, sarcoidosis-related complications or treatment are associated with heart failure in sarcoidosis.

What might this study add?

- This large cohort study of individuals with sarcoidosis and matched general population comparators showed that sarcoidosis is associated with a more than twofold increased risk of heart failure. Relative risks are equally high in women and men and in all ages but are higher during the first 2 years after diagnosis, and in individuals who do not have a history of ischaemic heart disease at the time of sarcoidosis diagnosis. A high proportion of heart failure cases after sarcoidosis may be attributed to diabetes mellitus, atrial fibrillation and sarcoidosis-related arrhythmias.

How might this impact on clinical practice?

- Awareness of the higher risks of heart failure in sarcoidosis compared with the general population and of the risk factors to tackle is needed among physicians who care for this patient group.

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Contributors MR—conceptualisation, data curation, formal analysis, methodology, software, visualisation, writing (original draft) and writing (review and editing). SK—conceptualisation and writing (review and editing). JG—conceptualisation and writing (review and editing). AE—conceptualisation and writing (review and editing). DDG—conceptualisation and writing (review and editing). JA—conceptualisation and writing (review and editing). EVA—conceptualisation, funding acquisition, resources, supervision and writing (review and editing).

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Competing interests MR reports non-promotional speaker fees from Teva, outside the submitted work.

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