

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

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

Contents

SUPPLEMENTAL METHODS	2
Sensitivity analyses.....	2
SUPPLEMENTAL TABLES	3
Supplemental Table S1	3
Supplemental Table S2	6
Supplemental Table S3	7
Supplemental Table S4	8
Supplemental Table S5	9
Supplemental Table S6	10

SUPPLEMENTAL METHODS

Sensitivity analyses

We conducted several sensitivity analyses. First, to test whether surveillance bias could explain higher risks of heart failure in sarcoidosis than in comparators, we disregarded heart failure diagnoses during the first six months since start of follow-up (second visit for sarcoidosis in the National Patient Register or corresponding date for comparators) in both groups. In addition, we changed our definition of heart failure to also include secondary discharge diagnoses (in addition to the primary) to test the robustness of the definition of heart failure used in our main analyses.

Second, to investigate the role of immunosuppressant treatment for sarcoidosis on the risk of heart failure, we repeated our analysis of heart failure predictors restricting to individuals diagnosed 2006 and onwards for whom data in the Prescribed Drug Register were available. As in the main analyses, we used a Cox model with time since sarcoidosis diagnosis (second visit for sarcoidosis in the National Patient Register) as the time scale and included treatment status around diagnosis in addition to demographic and clinical covariates.

Third, we examined the effect of systemic corticosteroids that patients were dispensed within six months before, and separately, six months after sarcoidosis diagnosis on the risk of heart failure. We used Cox models restricted to individuals who received at least one defined daily dose during the corresponding six-month period before or after sarcoidosis diagnosis to estimate hazard ratios of heart failure associated with dispensation of 50 defined daily doses of systemic corticosteroids, and separately, comparing high and middle to low tertiles of systemic corticosteroids DDDs. In the analysis of cumulative defined daily doses of systemic corticosteroids that were dispensed within six months before sarcoidosis diagnosis, time zero was the date of sarcoidosis diagnosis (second visit for sarcoidosis in the National Patient Register). In the analysis of cumulative defined daily doses within six months after sarcoidosis diagnosis, we started counting follow-up time six months after sarcoidosis diagnosis. Consequently, the latter analysis was restricted to individuals with sarcoidosis living in Sweden at start of follow-up who by that time had not developed heart failure. Due to small numbers, Cox models in both analyses were adjusted for age, sex, region of residence, country of birth (Nordic or non-Nordic including few missing), and education (≤ 9 years including few missing, 10–12, or ≥ 13 years).

Last, in a separate analysis including all individuals with sarcoidosis irrespective of the year of diagnosis, we repeated the mutually adjusted Cox model from in the main analysis this time allowing clinical predictors of heart failure to change value during follow-up (time-varying predictors).

SUPPLEMENTAL TABLES

Supplemental Table S1. International Classification of Diseases (ICD; 1964–2013), medical procedure codes (KVÅ; 1997–2013), and Anatomical Therapeutic Chemical (ATC) codes (July 2005–2013) used to define diseases in the National Patient Register and the Prescribed Drug Register.

Disease/Medication	Definition	ICD*, KVÅ, and/or ATC codes
Sarcoidosis	≥2 inpatient or outpatient visits in the National Patient Register	ICD-8/9: 135 ICD-10: D86
Hematopoietic or lung malignancy	≥1 diagnosis ±6 months from first sarcoidosis visit or corresponding date for comparators	ICD-7: 162; 163; 200–205
Sarcoidosis treatment status around diagnosis	≥1 dispensation ±3 months from first sarcoidosis visit	ATC: H02AB01/02/04/06/07; L01BA01; L04AX01/03
Heart failure	≥1 inpatient or outpatient visit where the ICD code for heart failure appears as the primary discharge diagnosis	ICD-8: 402,99; 425,08; 425,09; 427,00; 427,10; 428,99 ICD-9: 425A; 425B; 425E; 425X; 428 ICD-10: I42.0; I42.1; I42.8; I42.9; I43; I50
Hypertension	History of ≥1 visit or ≥2 dispensations evaluated at three months before the first sarcoidosis visit or corresponding date for comparators (or at start of follow-up when used as predictor)	ICD-8: 401–404 ICD-9: 401–405 ICD-10: I10–I15 ATC: C07; C08; C09
Diabetes mellitus	Same as hypertension	ICD-8/9: 250 ICD-10: E10; E11 ATC: A10
Dyslipidemia	Same as hypertension	ICD-8/9: 272 ICD-10: E78 ATC: C10
Stroke	History of ≥1 inpatient visit evaluated at three months before the first sarcoidosis visit or corresponding date for comparators	ICD-8: 430; 431; 432; 433; 434; 436 ICD-9: 430; 431; 433; 434; 436 ICD-10: I60; I61; I63; I64
Heart valve disease	History of ≥1 visit evaluated at three months before the first sarcoidosis visit or corresponding date for comparators (or at start of follow-up when used as predictor)	ICD-9: 424A–424D ICD-10: I34–I37 KVÅ: FMA; FMC; FMD; FMW; FK
Ischemic heart disease or acute myocardial infarction	Same as heart valve disease	ICD-8/9: 410–414 ICD-10: I20–I25
Atrial fibrillation	Same as heart valve disease	ICD-8: 427,92 ICD-9: 427D ICD-10: I48
Chronic obstructive pulmonary disease	Same as heart valve disease	ICD-8: 491; 492 ICD-9: 491A; 491B; 491X; 492; 496 ICD-10: J41–J43; J44.1; J44.8; J44.9

Supplemental Table S1. (Continued.)

Disease/Medication	Definition	ICD*, KVÅ, and/or ATC codes
Chronic kidney disease	Same as heart valve disease	ICD-8: 582–584 ICD-9: 585; 586 ICD-10: N18; N19; Z49.1 Z49.2 KVÅ: DR014; DR015; DR016; DR020; DR012; DR013; DR023; DR024; TJA33; TJA35; KAS00; KAS10; KAS20
Alcohol-related disorders	Same as heart valve disease	ICD-8: 303; 571,0; 577,1 ICD-9: 305A; 535D; 571A; 571B; 571C; 571D; 577B ICD-10: E24.4; F10; G31.2; G62.1; G72.1; K29.2; K70; K86.0; T51
Autoimmune disease	History of ≥ 2 visits evaluated at three months before the first sarcoidosis visit or corresponding date for comparators (or at start of follow-up when used as predictor)	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 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 ICD-10: D51.0; D59.1; D68.6; D69.3; E06.3; E05.0; E10; E27.1; G70.0; G35; G61.0; 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
Other arrhythmia or heart block	History of ≥ 1 visit or ≥ 2 dispensations evaluated at start of follow-up (and during follow-up depending on the analysis)	ICD-8: 426; 427,20–427,98 ICD-9: 416A; 416B; 426; 427 ICD-10: I27.0; I27.2; I44; I45–I47; I49; Z45.0; Z95.0 KVÅ: FPE; PPF; FPG ATC: C01B
Pulmonary hypertension	History of ≥ 1 visit evaluated at start of follow-up (and during follow-up depending on the analysis)	ICD-8: 426 ICD-9: 416A; 416B ICD-10: I27.0; I27.2
Systemic corticosteroids (defined daily doses analyses)	No. dispensed defined daily doses within six months before/after start of follow-up	ATC: H02AB01/02/04/06/07
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	≥ 1 dispensation within the period -6 to -3 months from the first sarcoidosis visit or corresponding date for comparators	ATC: C09
β -blockers		ATC: C07
Calcium channel blockers		ATC: C08
Aldosterone antagonists		ATC: C03DA
High-ceiling diuretics		ATC: C03C
Antidiabetics		ATC: A10
Lipid-lowering medications		ATC: C10

Supplemental Table S1. (Continued.)

Disease/Medication	Definition	ICD*, KVÅ, and/or ATC codes
Acetylsalicylic acid	≥1 dispensation within the period -6	ATC: B01AC06
Warfarin	to -3 months from the first	ATC: B01AA03
Nitroglycerin	sarcoidosis visit or corresponding	ATC: C01DA02/A14
Digoxin	date for comparators	ATC: C01AA05

ICD = International Classification of Diseases; ATC = Anatomical Therapeutic Chemical; KVÅ = Swedish classification of medical procedures (Klassifikation av vårdåtgärder).

*The Swedish ICD classification system's 10th revision was in use starting 1997, the 9th revision between 1987 and 1996 (and 1997 in some healthcare practices) and the 8th revision between 1969 and 1986.

Supplemental Table S2. History of dispensation of medications related to heart failure risk at baseline (≥ 1 dispensation in the Prescribed Drug Register within six to three months before the first sarcoidosis visit in the National Patient Register or corresponding period for matched general population comparators). Evaluated in individuals who entered the cohort from January 1, 2006 and onwards for whom data in the Prescribed Drug Register were available.

	Sarcoidosis	General population
Individuals	6585	64 599
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	689 (10.5)	5319 (8.2)
β -blocker	647 (9.8)	4790 (7.4)
Calcium channel blocker	365 (5.5)	2727 (4.2)
Aldosterone antagonist	43 (0.7)	281 (0.4)
High-ceiling diuretic	212 (3.2)	931 (1.4)
Antidiabetic including insulin	385 (5.8)	2062 (3.2)
Lipid-lowering medication	572 (8.7)	4121 (6.4)
Acetylsalicylic acid	417 (6.3)	3199 (5.0)
Warfarin	95 (1.4)	554 (0.9)
Nitroglycerin	85 (1.3)	640 (1.0)
Digoxin	18 (0.3)	116 (0.2)

Data are n or n (%).

Supplemental Table S3. Hazard ratios of heart failure comparing sarcoidosis to the general population from sensitivity analyses.

	Sarcoidosis	General population
Excluding diagnoses of heart failure during the first six months of follow-up		
Overall		
Events/N at risk	182/7994	663/78 360
Incidence rate* (95% CI)	2.2 (1.8, 2.6)	0.8 (0.7, 0.9)
Hazard ratio† (95% CI)	2.30 (1.94, 2.74)	1.00 [Reference]
≤2 years since sarcoidosis diagnosis		
Events/N at risk	72/7994	172/78 360
Hazard ratio† (95% CI)	3.50 (2.64, 4.63)	1.00 [Reference]
>2 years since sarcoidosis diagnosis		
Events/N at risk	110/6597	491/65 447
Hazard ratio† (95% CI)	1.90 (1.53, 2.35)	1.00 [Reference]
Heart failure from main and contributory diagnoses in the National Patient Register		
Events/N at risk	258/8465	1154/82 713
Incidence rate* (95% CI)	2.6 (2.3, 3.1)	1.2 (1.0, 1.3)
Hazard ratio† (95% CI)	1.87 (1.62, 2.15)	1.00 [Reference]

CI = confidence interval.

Data are n unless otherwise stated.

*Rates per 1000 person-years were estimated using Poisson regression models adjusted for age, sex, and region of residence.

†Hazard ratios were estimated using Cox proportional hazards models with attained age as the time scale and adjusted for age at start of follow-up, sex, region of residence, country of birth, education, civil status, calendar period, healthcare visits within two years before inclusion, history of hypertension, diabetes mellitus, dyslipidemia, heart valve disease, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, alcohol-related disorders, and autoimmune disease.

Supplemental Table S4. Hazard ratios of heart failure in individuals with sarcoidosis diagnosed 2006–2013 associated with covariates evaluated at start of follow-up (second visit for sarcoidosis in the National Patient Register).

	Heart failure		Hazard ratio* (95% CI)
	Yes (n=141)	No (n=6444)	
Median age at sarcoidosis diagnosis† (IQR), years	67 (58, 77)	48 (38, 61)	1.8 (1.6, 2.2)
Male	82 (58)	3557 (55)	1.7 (1.2, 2.4)
Education‡, years			
≤9	61 (43)	1357 (21)	1.8 (1.1, 3.0)
10–12	58 (41)	3207 (50)	1.4 (0.8, 2.3)
≥13	22 (16)	1880 (29)	1.0 [Reference]
Hypertension	86 (61)	1643 (25)	1.2 (0.8, 1.8)
Diabetes mellitus	46 (33)	519 (8)	2.4 (1.6, 3.6)
Chronic kidney disease	12 (9)	144 (2)	1.4 (0.7, 2.6)
Alcohol-related disease	7 (5)	167 (3)	1.6 (0.7, 3.5)
Chronic obstructive pulmonary disease	9 (6)	176 (3)	1.2 (0.6, 2.4)
Heart valve disease	10 (7)	68 (1)	1.5 (0.8, 3.0)
Ischemic heart disease or acute myocardial infarction	38 (27)	277 (4)	1.9 (1.2, 2.9)
Atrial fibrillation	32 (23)	183 (3)	2.2 (1.3, 3.6)
Other arrhythmia or heart block	28 (20)	242 (4)	2.2 (1.3, 3.5)
Pulmonary hypertension	≤5 (1)	7 (<1)	Not estimable
Autoimmune disease	24 (17)	554 (9)	1.5 (1.0, 2.5)
Sarcoidosis treatment around diagnosis	62 (44)	2634 (41)	1.2 (0.8, 1.7)

CI = confidence interval; IQR = interquartile range.

Data are n (%) or mean (standard deviation) unless otherwise stated. Category percentages may not sum up to 100 owing to rounding.

*Hazard ratios were estimated from a Cox proportional hazards model with years since sarcoidosis diagnosis as the time scale that included the covariates age (continuous), sex, region of residence (six healthcare regions), country of birth (Nordic/non-Nordic), education, sarcoidosis treatment around diagnosis (yes/no), and all comorbidities in the table except pulmonary hypertension due to small numbers.

†Effect per 10-year increase.

‡Category “≤9 years” includes <1% missing.

Supplemental Table S5. Hazard ratios of heart failure in individuals with sarcoidosis diagnosed 2006–2013 associated with dispensed defined daily doses of systemic corticosteroids within six months before or six months after sarcoidosis diagnosis (second visit for sarcoidosis in the National Patient Register).

	Heart failure		Hazard ratio* (95% CI)
	Yes	No	
Defined daily doses of systemic corticosteroids within six months before sarcoidosis diagnosis			
Individuals	49	2000	
Mean† (SD)	180 (136)	172 (138)	1.0 (0.9, 1.1)
Median (IQR)	150 (100, 250)	150 (75, 208)	
Low tertile (≤ 100)	21 (43)	926 (46)	1.0 [Reference]
Mid tertile (101– ≤ 200)	14 (29)	573 (29)	0.9 (0.4, 1.7)
High tertile (> 200)	14 (29)	501 (25)	1.1 (0.6, 2.2)
Defined daily doses of systemic corticosteroids within six months after sarcoidosis diagnosis			
Individuals	59	2255	
Mean† (SD)	306 (221)	257 (191)	1.1 (1.0, 1.1)
Median (IQR)	300 (146, 400)	200 (100, 373)	
Low tertile (≤ 150)	18 (31)	839 (37)	1.0 [Reference]
Mid tertile (151– ≤ 300)	15 (25)	772 (34)	0.8 (0.4, 1.6)
High tertile (> 300)	26 (44)	644 (29)	2.1 (1.1, 3.8)

CI = confidence interval; SD = standard deviation; IQR = interquartile range.

Data are n (%) unless otherwise stated. Category percentages may not sum up to 100 owing to rounding.

*Hazard ratios were estimated from Cox proportional hazards models with years since sarcoidosis diagnosis as the time scale and adjusted for age (continuous), sex, region of residence (six healthcare regions), country of birth (Nordic/non-Nordic including missing), and education (≤ 9 years including missing/10–12/ ≥ 13 years).

†Effect per 50 defined daily doses of systemic corticosteroids.

Supplemental Table S6. Hazard ratios of heart failure in individuals with sarcoidosis associated with covariates evaluated at start and during follow-up.

	Heart failure		Hazard ratio* (95% CI)
	Yes (n=204)	No (n=8370)	
Median age at sarcoidosis diagnosis† (IQR), years	67 (59, 76)	48 (37, 60)	1.6 (1.4, 1.8)
Male	114 (56)	4636 (55)	1.4 (1.0, 1.8)
Education‡, years			
≤9	98 (48)	1781 (21)	2.0 (1.3, 3.0)
10–12	73 (36)	4129 (49)	1.3 (0.9, 2.0)
≥13	33 (16)	2460 (29)	1.0 [Reference]
Hypertension	157 (77)	2971 (35)	1.8 (1.2, 2.6)
Diabetes mellitus	77 (38)	992 (12)	2.2 (1.6, 3.1)
Chronic kidney disease	31 (15)	324 (4)	1.5 (1.0, 2.3)
Alcohol-related disease	11 (5)	275 (3)	1.7 (0.9, 3.2)
Chronic obstructive pulmonary disease	22 (11)	387 (5)	1.6 (1.0, 2.6)
Heart valve disease	24 (12)	142 (2)	1.6 (1.0, 2.6)
Ischemic heart disease or acute myocardial infarction	70 (34)	540 (6)	1.9 (1.4, 2.6)
Atrial fibrillation	72 (35)	385 (5)	2.7 (1.9, 3.8)
Other arrhythmia or heart block	62 (30)	489 (6)	3.1 (2.2, 4.3)
Pulmonary hypertension	≤5 (2)	22 (<1)	Not estimable
Autoimmune disease	39 (19)	981 (12)	1.1 (0.8, 1.6)

CI = confidence interval; IQR = interquartile range.

Data are n (%) or mean (standard deviation) unless otherwise stated. Category percentages may not sum up to 100 owing to rounding.

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

†Effect per 10-year increase.

‡Category “≤9 years” includes <1% missing.