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Short communication

Risk of acute myocardial infarction in sarcoidosis: A population-based cohort study from Sweden

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ABSTRACT

Due to conflicting findings in previous studies, it remains unclear whether individuals with sarcoidosis are at a higher relative risk of acute myocardial infarction. In this cohort study, individuals with sarcoidosis and matched general population comparators were followed for acute myocardial infarction in Swedish nationwide registers. A small (20%) risk increase associated with sarcoidosis was identified, which did not markedly vary by age at diagnosis, sex, treatment status around diagnosis, and time since diagnosis. The highest relative risk (1.4) was observed in individuals who received immunosuppressant treatment around the time of sarcoidosis diagnosis. Future studies should examine the clinical characteristics of acute myocardial infarction in these patients and investigate whether early diagnostic or preventive interventions might be beneficial for these patients.

1. Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology that mostly affects adults in their 50's [1,2]. Sarcoid inflammation appears to dysregulate lipid metabolism and accelerate atherosclerosis [3,4]. Whether these or other pathways lead to higher risks for acute myocardial infarction (AMI) in sarcoidosis compared to the general population remains unclear due to conflicting results in recent epidemiologic investigations [5,6]. Moreover, it is unclear whether AMI risk is uniformly increased or varies by age, sex, treatment, or time since sarcoidosis diagnosis. Risk stratification allows for proper targeting of high-risk patients with diagnostic and/or therapeutic measures. Therefore, we conducted a cohort study using Swedish register data to estimate relative risks of AMI associated with sarcoidosis overall and stratified by age, sex, sarcoidosis treatment status around diagnosis, and time since diagnosis.

2. Methods

The study population is described in detail elsewhere [7,8]. Briefly, sarcoidosis cases were adults (18–85 years old) with ≥2 visits listing an International Classification of Diseases (ICD) code for sarcoidosis in the National Patient Register (NPR), the first of which appearing in 2003 or later to capture newly diagnosed disease (ICD-9/8 135; ICD-10 D86; positive predictive value 94% [9]). They were matched to general population comparators without sarcoidosis (10:1; Total Population Register) on age, sex, and residential location at the case's second visit (index date). From the Prescribed Drug Register (PDR; data available since July 2005), we obtained data on filled prescriptions of immunosuppressant medications to identify individuals with sarcoidosis with presumably extensive, progressive, or debilitating disease [1]. Thus, patients diagnosed in 2006 and onwards who were dispensed ≥1 systemic corticosteroid (Anatomical Therapeutic Chemical code H02AB01/02/04/06/07), methotrexate (L01BA01/L04AX03), or azathioprine (L04AX01) ±3 months from the first sarcoidosis visit were considered treated around sarcoidosis diagnosis. Records across registers were linked using an individual's unique identification number. Ethical permission was obtained from the Regional Ethics Review Board in Stockholm (2014/230-31).

The outcome in this study was non-fatal/fatal AMI, defined as a

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hospitalization in the NPR or a record in the Cause of Death Register listing an ICD code for AMI (ICD-8 411; ICD-9 410/412; ICD-10 I21/I22/I25.2; positive predictive value >95% [10]). Follow-up started at index date and ended at first of hospital admission for AMI, death, emigration (Total Population Register), or December 31, 2013. Those with history of AMI at index date were excluded from the analytical sample.

Rates of AMI were estimated using Poisson models adjusted for the matching variables age, sex, and region of residence. Using Cox models with attained age as the underlying time scale, we estimated hazard ratios (HR) of AMI comparing sarcoidosis to the general population. They were adjusted for the matching variables and further for birth country (Nordic/non-Nordic/missing), years of education (≤9/10–12/≥13/missing), civil status (married/other), calendar period (2003–2007/2008–2013), number of NPR visits within two years before the first sarcoidosis visit or corresponding period for comparators (0/1–3/≥4), family history of AMI or ischemic stroke (≥1 NPR visit or mention as cause of death [Cause of Death Register] in ≥1 biologic parent identified from the Multi-Generation Register; yes/no/no parents identified), and comorbidities defined using NPR and PDR data if applicable (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, heart valve disease, chronic obstructive pulmonary disease, alcohol-related disorder, chronic kidney disease, and autoimmune disease). We further performed subgroup analyses by age at start of follow-up (18–44/45–64/65–85 years), sex, sarcoidosis treatment status around diagnosis (treated/untreated), and years since diagnosis (≤2/>2). A two-sided *P*-value <0.05 from a likelihood ratio test indicated statistically significant differences in HRs among subgroups. Examining Schoenfeld residuals plots, we found the proportional hazards assumption to hold. Post-hoc analyses examining the role of sarcoidosis treatment are detailed in the Supplemental Material. We preformed all analyses with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

We followed 8508 individuals with sarcoidosis (age 49 ± 15 years; female 45%) and 82 571 matched general population comparators for a median of 4.7 years (interquartile range 2.3, 7.6). We found no notable differences in sociodemographic factors or family history of AMI or ischemic stroke, but hypertension, diabetes, and autoimmune disease were more prevalent in individuals with sarcoidosis than comparators and slightly more pronounced among treated than untreated patients (Table 1 and S1 in the Supplemental Material). As shown in Table 2, we identified 170 incident events of AMI in sarcoidosis (rate 2.0/1000 person-years) and 1240 in the general population (1.5/1000 person-years). After adjusting for demographics and comorbidities, we observed a small (20%) increased risk of AMI associated with sarcoidosis (HR 1.2 [95% confidence interval [CI] 1.0, 1.4]). There was slight variation of the HR in subgroups defined by age at start of follow-up, sex, sarcoidosis treatment status around diagnosis, or time since sarcoidosis diagnosis, albeit no statistically significant differences were found (*P*-value for HR modification >0.05 for all comparisons). The highest HR (1.4 [95% CI 1.0, 1.9]) was observed in individuals treated with an immunosuppressant medication around diagnosis. Post-hoc analyses showed a 50% higher risk of AMI in those treated also during follow-up, but no clear evidence of a dose-response relation between the amount of systemic corticosteroids patients were dispensed and AMI risk (Table S2). Sensitivity analyses in which we included unstable angina in the outcome definition or estimated relative risks during the first year since start of follow-up yielded similar results to the main analysis (data not shown).

4. Discussion

Emerging evidence from molecular studies suggests atherosclerotic inflammation is accelerated in sarcoidosis [3,4]. Using AMI as a hard

Table 1
Baseline demographic and clinical characteristics of individuals with sarcoidosis and their matched general population comparators.

	Sarcoidosis	General population
Individuals	8508	82 571
Age, years	49.3 (14.6)	48.9 (14.4)
Female	3805 (44.7)	37 171 (45.0)
Region of residence		
Stockholm	1758 (20.7)	17 194 (20.8)
Uppsala-Örebro	1881 (22.1)	18 232 (22.1)
West	1530 (18.0)	14 899 (18.0)
South	1425 (16.7)	13 804 (16.7)
Southeast	980 (11.5)	9460 (11.5)
North	934 (11.0)	8982 (10.9)
Country of birth[a]		
Nordic	7667 (90.1)	72 335 (87.6)
Non-Nordic	814 (9.6)	9903 (12.0)
Missing	27 (0.3)	333 (0.4)
Education, years		
≤9	1700 (20.0)	16 356 (19.8)
10–12	4174 (49.1)	38 538 (46.7)
≥13	2491 (29.3)	26 525 (32.1)
Missing	143 (1.7)	1152 (1.4)
Married or in registered partnership	4115 (48.4)	39 386 (47.7)
Calendar period		
2003–2007	3530 (41.5)	34 298 (41.5)
2008–2013	4978 (58.5)	48 273 (58.5)
Healthcare visits within two years before the first sarcoidosis visit, n		
0	1460 (17.2)	42 778 (51.8)
1–3	2178 (25.6)	21 374 (25.9)
≥4	4870 (57.2)	18 419 (22.3)
History of morbidity[b]		
Hypertension	1531 (18.0)	11 085 (13.4)
Diabetes mellitus	551 (6.5)	2909 (3.5)
Dyslipidemia	747 (8.8)	5229 (6.3)
Ischemic stroke	87 (1.0)	736 (0.9)
Ischemic heart disease	208 (2.4)	1436 (1.7)
Atrial fibrillation	217 (2.6)	1326 (1.6)
Heart valve disease	78 (0.9)	456 (0.6)
Chronic obstructive pulmonary disease	144 (1.7)	652 (0.8)
Chronic kidney disease	105 (1.2)	294 (0.4)
Alcohol-related disorder	182 (2.1)	2071 (2.5)
Autoimmune disease	611 (7.2)	3302 (4.0)
Family history of acute myocardial infarction or stroke (in ≥1 biologic parent)		
Yes	2666 (31.3)	24 425 (29.6)
No	4608 (54.2)	44 676 (54.1)
No parents identified	1234 (14.5)	13 470 (16.3)

Data are n, n (%), or mean (standard deviation).
[a] Nordic countries include Sweden, Denmark, Norway, Finland, and Iceland.
[b] Evaluated in the period up to three months before the first sarcoidosis visit in the National Patient Register or the corresponding date for matched general population comparators.

Table 2
Incidence rates per 1000 person-years and hazard ratios of acute myocardial infarction comparing sarcoidosis to the general population, overall and by age at start of follow-up, sex, sarcoidosis treatment status around diagnosis, and time since sarcoidosis diagnosis.

	Sarcoidosis		General population		Hazard ratio[b] (95% CI)	Adjusted hazard ratio[b] (95% CI)	*P* for hazard ratio modification[c]
	Events/N at risk	Incidence rate[a] (95% CI)	Events/N at risk	Incidence rate[a] (95% CI)			
Overall	170/8508	2.0 (1.7, 2.4)	1240/82 571	1.5 (1.3, 1.6)	1.4 (1.2, 1.6)	1.2 (1.0, 1.4)	
Age at start of follow-up, years							0.45
18–44	14/3707	0.4 (0.2, 0.7)	87/36 605	0.3 (0.2, 0.4)	1.6 (0.9, 2.8)	1.4 (0.8, 2.5)	
45–64	60/3366	3.0 (2.3, 3.9)	507/32 916	2.6 (2.3, 2.9)	1.2 (0.9, 1.5)	1.0 (0.8, 1.3)	
65–85	96/1435	15.2 (12.4, 18.6)	646/13 050	10.4 (9.5, 11.3)	1.5 (1.2, 1.8)	1.2 (1.0, 1.5)	
Sex							0.37
Female	72/3805	1.8 (1.4, 2.4)	483/37 171	1.2 (1.0, 1.4)	1.5 (1.2, 2.0)	1.3 (1.0, 1.6)	
Male	98/4703	2.1 (1.7, 2.6)	757/45 400	1.7 (1.5, 1.9)	1.3 (1.0, 1.6)	1.1 (0.9, 1.3)	
Sarcoidosis treatment around diagnosis[d]							0.40
Treated	51/2686	2.4 (1.7, 3.3)	299/26 037	1.4 (1.1, 1.6)	1.7 (1.3, 2.3)	1.4 (1.0, 1.9)	
Untreated	57/3845	1.8 (1.4, 2.5)	401/37 264	1.4 (1.2, 1.6)	1.3 (1.0, 1.8)	1.2 (0.9, 1.5)	
Time since sarcoidosis diagnosis, years							0.76
≤2	59/8508	0.5 (0.4, 0.7)	412/82 571	0.4 (0.3, 0.5)	1.4 (1.1, 1.9)	1.2 (0.9, 1.6)	
>2	111/6578	1.4 (1.2, 1.7)	828/64 782	1.1 (1.0, 1.2)	1.3 (1.1, 1.6)	1.1 (0.9, 1.4)	

CI = confidence interval.
[a] Incidence rates per 1000 person-years were estimated using Poisson regression models adjusted for age, sex (if applicable), and region of residence.
[b] Hazard ratios were estimated using Cox proportional hazards models with attained age as the underlying time scale and adjusted for the matching variables age, sex, and region of residence. Adjusted hazard ratios were estimated using Cox models further adjusted for country of birth, education, civil status, calendar period, number of visits in the National Patient Register within two years before the first sarcoidosis visit or corresponding period for comparators, family history of acute myocardial infarction or ischemic stroke, and history of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, heart valve disease, chronic obstructive pulmonary disease, alcohol-related dkisorder, chronic kidney disease, and autoimmune disease.
[c] Two-sided P-value from a likelihood ratio test for the adjusted hazard ratio Cox models.
[d] Evaluated in individuals with start of follow-up from 2006 and onwards for whom medication dispensation data were available in the Prescribed Drug Register.

outcome, we found little evidence that these molecular processes translate into an overall, clinically measurable risk in this large patient population from Sweden. Our HR for overall AMI is similar to the one reported in an earlier Swedish investigation restricted to patients hospitalized for sarcoidosis [11] (<9% of sarcoidosis cases in Sweden [12]). In addition, equal proportions of AMI-related death were previously reported in sarcoidosis and non-sarcoidosis comparators in our cohort [13]. However, a recent study from the UK reported lower overall rates of AMI in sarcoidosis compared to the general population (1.6 vs. 3.2/1000 person-years), while HRs associated with sarcoidosis were increased in males but not females (1.6 vs. 0.9) [6]. It is unclear which factors contributed to the differences between our and the UK study. Despite a small increased relative risk overall, we observed a slightly higher HR in patients who received immunosuppressant treatment around sarcoidosis diagnosis. Although this finding merits further investigation to understand whether sarcoid inflammation or treatment is responsible, it is in line with studies indicating that sarcoid granulomatous and atherosclerotic activity appear to correlate well [3].

This investigation has some limitations. We could not adjust for smoking status and obesity, two unmeasured confounders. As we previously showed, however, no notable change is expected in the HR because the opposing effect of these two factors tends to cancel out [7]. In addition, we could not disentangle between AMI risks due to corticosteroid treatment and sarcoid inflammation because we lacked a clinical or molecular severity index for sarcoidosis. A major strength of this study is the use of a large and population-based sample that allowed for subgroup analyses to be performed and improved generalizability.

To conclude, we found a slightly increased risk of AMI associated with sarcoidosis, which did not vary considerably by age at diagnosis, sex, treatment status around diagnosis or time since sarcoidosis diagnosis. However, a 40% higher risk associated with sarcoidosis was observed in a subgroup of patients who received immunosuppressant treatment around sarcoidosis diagnosis likely due to more severe disease. Future studies should investigate clinical characteristics of AMI in these patients and establish which measures are necessary to modify high risks.

Availability of data

The datasets used for the conduct of this study are covered by ethics and secrecy agreements and are not publicly available.

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Role of the funding source

The funder of this work had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CRediT authorship contribution statement

Marios Rossides: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Susanna Kullberg:** Conceptualization, Writing – review & editing. **Johan Grunewald:** Conceptualization, Writing – review & editing. **Anders Eklund:** Conceptualization, Writing – review & editing. **Daniela Di Giuseppe:** Conceptualization, Writing –

review & editing. **Johan Askling:** Conceptualization, Writing – review & editing. **Elizabeth V. Arkema:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Marios Rossides reports non-promotional speaker fees from Teva, outside the submitted work. Elizabeth V. Arkema reports a grant from the Swedish Heart-Lung Foundation (Hjärt-Lungfonden) during the conduct of this study. Susanna Kullberg, Johan Grunewald, Anders Eklund, Daniela Di Giuseppe, and Johan Askling report no competing interests.

Abbreviation list

AMI	acute myocardial infarction
CI	confidence interval
HR	hazard ratio
ICD	International Classification of Diseases
NPR	National Patient Register

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2021.106624.

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