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Risk of depression and anxiety in 7.302 patients with sarcoidosis: A nationwide cohort study

Melina Gade Sikjμr[1,2,3], Ole Hilberg[1,3], Ingeborg Farver-Vestergaard[1,3], Rikke Ibsen[4], Anders Løkke[1,3]
[1]Department of Medicine, Lillebaelt Hospital, Vejle, Denmark; [2]Department of Pulmonary Diseases, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Regional Health Research, University of Southern Denmark, Odense, Denmark; [4]i2minds, Aarhus, Denmark

Abstract. *Background and aim:* The aim was to investigate the association between sarcoidosis and anxiety and/or depression (A/D) in patients with sarcoidosis and comparators matched on age, gender, residency, and cohabitation status. *Methods:* Patients with newly diagnosed sarcoidosis between 2001 and 2015 were identified in the Danish National Patient Register. Cases were matched 1:4 with non-sarcoidosis comparators. We estimated the cumulative incidence of A/D using the Cumulative Incidence Function and the subdistribution hazard ratio (sHR) for A/D using the Fine-Gray subdistribution hazard model. Estimates were adjusted for socio-economic status and Deyo-Charlson Comorbidity Index. *Results:* We identified 7.302 cases and 26.145 matched comparators. The cumulative incidence of A/D after five years was 6.0% (95%CI 5.5-6.4) for cases and 4.2% (95%CI 4.0-4.4) for matched comparators. The cumulative incidence was higher among cases for both males and females and in all age-groups compared with the matched comparators. The adjusted-sHR for A/D was 1.38 (95%CI 1.24-1.53). The adjusted-sHR for A/D was 1.51 (95%CI 1.30-1.75) for male cases and 1.25 (95%CI 1.08-1.45) for female cases compared with the matched comparators. The adjusted-sHR for A/D was higher for cases in all age-groups compared with the matched comparators, although not statistically significant among cases aged 30-39 years (a-sHR 1.15; 95%CI 0.92-1.44). *Conclusions*: Sarcoidosis cases had a higher risk of A/D compared with matched comparators during 18 years of follow-up. The risk of developing A/D was greater for male and female cases and within all age-groups compared with the matched comparators.

Key words: sarcoidosis, depression, anxiety, comorbidity, antidepressive agents

Background

Sarcoidosis is an inflammatory disease characterised by the formation of non-necrotizing granulomas. Spontaneous remission of sarcoidosis occurs in 50% of patients within the first two years of diagnosis, whereas advanced progressive sarcoidosis is seen in approximately 5% of patients (1-3). Persistent disabling symptoms such as arthralgia, general weakness, muscle weakness, and exercise limitation, are common complaints among patients with sarcoidosis and may not be directly related to any specific organ involvement (3-5). Moreover, studies evaluating patient reported outcomes have found that fatigue and symptoms of depression and anxiety are some of the most common reported symptoms among patients with sarcoidosis (6). The reported prevalence of concomitant depression is 20-66% and concomitant anxiety is 13-46% (7-14). Symptoms of depression and anxiety have been found to be negatively associated with fatigue (15-17). Psychiatric comorbidity is associated with a worse prognosis in other chronic respiratory diseases, but the prognosis in patients with sarcoidosis and psychiatric comorbidity is sparsely

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Correspondence:
Melina Gade Sikjμr, MD, Ph.D
Department of Medicine, Lillebaelt Hospital,
Beriderbakken 4, 7100 Vejle
Phone: +45 79409055
E-mail: melina.gade.sikjaer@rsyd.dk
ORCID: 0000-0002-5061-5367

investigated (18). One study found an association between psychological comorbidity in sarcoidosis and an increased risk of a worse clinical outcome (9). However, the majority of studies that investigate the association between sarcoidosis and psychiatric comorbidity use a cross-sectional study design, thus providing no information on causality (7, 10, 12). We hypothesise that patients with no history of anxiety and/or depression (A/D) at the time of diagnosis have a higher risk of developing A/D after sarcoidosis is diagnosed, compared with matched comparators. The aim of our study was to evaluate the association between sarcoidosis and A/D in patients with sarcoidosis compared with comparators matched on age, gender, residency, and cohabitation status.

Methods

Setting and data sources

This cohort study was conducted in Denmark, where all citizens have access to tax-funded universal healthcare including free access to general practitioners, hospital care, and partial reimbursement of prescribed medication. The Danish Civil Registration System (DCRS) holds information on age, gender, vital status, migration, and cohabitation (19). A unique ten-digit Civil Registration System (CPR) number is assigned in the DCRS to all Danish citizens upon birth or immigration, enabling individual-level record linkage across all Danish registries (19, 20).

The Danish National Patient Registry (DNPR) is an administrative registry that has achieved complete nationwide coverage of all non-psychiatric admissions since 1978 and out-patient clinic, emergency department contacts, and hospital psychiatric contacts since 1995 (21). Registration is mandatory and must be submitted by the handling doctor. Registration includes diagnoses, administrative information and diagnostic procedures. The DNPR does not hold information on symptoms, smoking history and disease severity. Diagnoses in the DNPR are classified according to the International Classification of Diseases and Related Health problems 10th Revision (ICD-10) (21). Statistics Denmark collect information on highest achieved educational level (22). Danish Register of Medicinal Product Statistics (DRMPS) consists of high-quality data on all prescription drugs dispensed in Danish community pharmacies since 1995 (23).

Study population

Patients aged ≥ 18 years with a first-time diagnosis of sarcoidosis were identified in the DNPR from 1 January 2001 to 31 December 2015 (Figure 1).

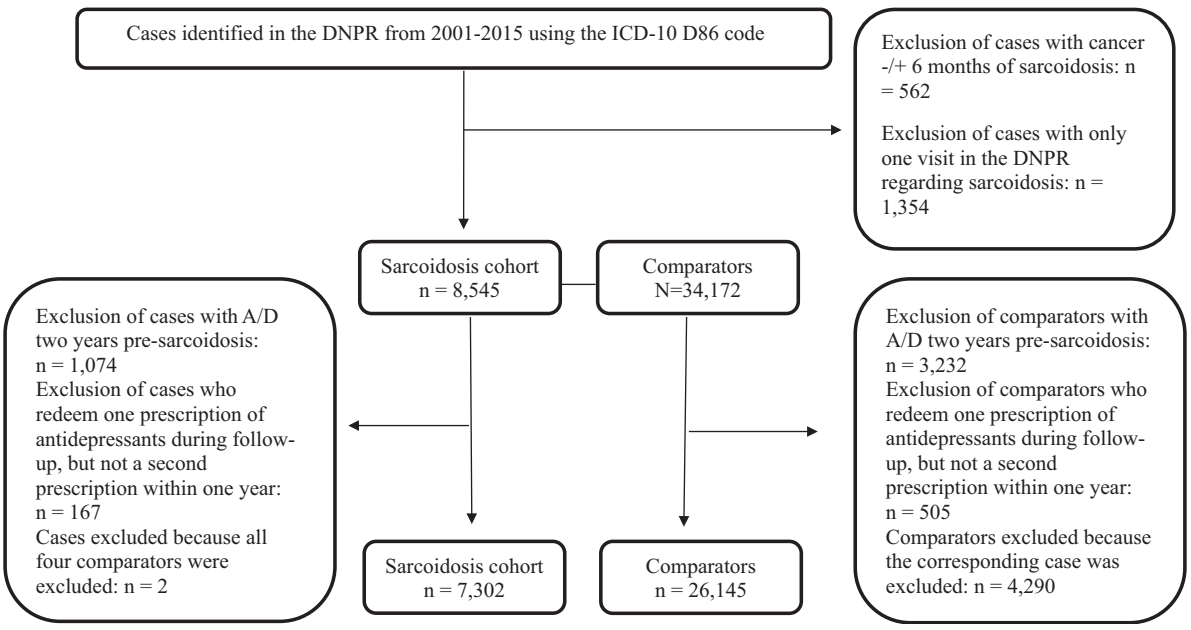

Figure 1. Selection of the sarcoidosis cohort and matched comparators from the Danish National Patient Registry (DNPR).

To ensure cases were included on the date of their first-time diagnosis of sarcoidosis, a three-year wash-out period was applied, to exclude patients with a sarcoidosis diagnosis from 1998-2000.

Sarcoidosis is not validated in the DNPR, which could lead to misclassification of cases. To reduce the risk of misclassification we restricted cases to individuals with > 1 contact regarding sarcoidosis within the first year of diagnosis. We also excluded cases diagnosed with cancer (ICD-10 C00-C97) within six months before or after the time of sarcoidosis diagnosis to minimise the risk of misclassifying cases with cancer or sarcoid-like reactions as sarcoidosis (Figure 1). Cancer diagnoses have a high positive predictive value (PPV) in the DNPR (21).

Cases were individually matched 1:4 on age, gender, residency, and cohabitation status with comparators. The DCRS was used to randomly select comparators from the background population. Comparators entered the study on the date of sarcoidosis diagnosis of the matched case (Figure 1). A two-year wash-out period was chosen to exclude cases and comparators with A/D at the time of inclusion. Therefore, cases and matched comparators who redeemed ≥ 1 prescription of antidepressants (Anatomical Therapeutic Chemical (ATC) N06 - excluding Duloxetin, N06AX21 20 and 40 mg (used for incontinence), and Bupropion, N06AX12 (used for smoking cessation) or who had a diagnosis of depression (ICD-10 codes F32, F33, F34) or anxiety (ICD-10 codes F40 and F41) in the DNPR within two years before sarcoidosis was diagnosed were excluded. Hence, the final study population comprised incident sarcoidosis cases and matched comparators with no A/D at the time of diagnosis.

Outcome

A/D was defined as more than one redeemed prescription of antidepressants within one year or an ICD-10 diagnosis in the DNPR of anxiety or depression during follow-up. The majority of patients with anxiety and depression are managed by their general practitioner (GP) and therefore not included in the DNPR. Redeemed prescriptions of antidepressants were therefore used to capture these patients. The Danish guidelines for treating A/D in general practice recommend anti-depressants as first-line treatment (24, 25). As the indication for prescribed antidepressants is not available in the DRMPS we defined the outcome as A/D. Because guidelines recommend a treatment duration for depression and anxiety of at least 6-12 months, we restricted the outcome to at least two redeemed prescriptions of antidepressants within one year. This ensured, that the outcome (A/D) enclosed cases where the indication of A/D was sustained by the GP for a longer period. The date of the first redeemed prescription was defined as the date of A/D. Benzodiazepines were not included in the definition of A/D because of the broad indications for prescribing benzodiazepines. Also, guidelines for treating anxiety recommend benzodiazepines for acute treatment of anxiety symptoms, but not as first-line treatment for anxiety disorders.

Covariates

Baseline characteristics of cases and comparators were obtained from the DCRS. SES was defined as the highest achieved educational level. Data on redeemed prescriptions of systemic corticosteroids (SCs) (ATC H02AB) before A/D was collected from the DRMPS. The effect of baseline comorbidities on the risk of A/D was assessed by the Deyo-Charlson Comorbidity Index (DCCI) (26). Information on comorbidities three years prior to diagnosis was collected from the DNPR. The DCCI has a 98% PPV in the DNPR (27).

Statistics

Cases and matched comparators were followed until A/D, death, migration, or end of follow-up in 2018, whichever came first. Baseline characteristics were presented as proportion, except age, which was summarised as a mean with standard deviation (SD). Differences in SES and DCCI between cases and matched comparators were estimated using the Chi2 test. The cumulative incidence of A/D was estimated starting on the day of inclusion using a Cumulative Incidence Function (CIF), which takes death into account as a competing risk. Cumulative incidence curves were plotted to describe the incidence of A/D over time. We used the Fine-Gray subdistribution hazard regression model (28) to estimate the association between sarcoidosis and A/D. The subdistribution hazard ratio (sHR) for A/D was adjusted for DCCI and SES. DCCI was treated as a categorical variable of three groups: 0, 1-2, and >2 points. We

performed a sensitivity analysis estimating the sHR for A/D where cases and comparators who only redeemed one prescription of antidepressants within one year were included in the cohorts. The cumulative incidence and sHR were stratified by age-group (18-29, 30-39, 40-49, 50-59 and ≥60 years) and gender. We used 95% confidence intervals (95% CI) and a significance level of 0.05. Statistical software: SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA).

Results

Table 1 displays baseline characteristics for cases and matched comparators. We identified 7,302 cases and 26,145 matched comparators with no A/D two years before inclusion. The mean age at diagnosis was 45 (±14.8) years, and 57% of cases were men. Cases had lower educational attainment level than the matched comparators. Baseline DCCI ≥ 1 was seen in 13.4% of cases and 7.0% of matched comparators.

In total, 502 (6.9%) cases and 1.274 (4.9%) developed A/D during follow-up (Table 2 and Table S1). The majority of cases (80.5%) and comparators (81.2%) were identified based on redeemed prescriptions of antidepressants (Table 2).

The cumulative incidence of A/D after five years was 6.0% (95% CI 5.5-6.4) for cases and 4.2% (95% CI 4.0-4.4) for the matched comparators (Table 3).

Table 1. Baseline characteristic of cases and matched comparators.

	Sarcoidosis case cohort		**Comparator cohort**		**P-value***
Total, n	7,302		26,145		
Gender, n (%)					
Male	4,281	58.6	15,684	60.0	
Age, years (SD)					
Total	45.3	14.8	45.0	14.7	
Male	44.5	13.8	44.3	13.7	
Female	46.5	16.1	46.0	16.0	
Regions, n (%)					
Capital region	1,837	25.2	6,669	25.5	
Region Zealand	976	13.4	3,486	13.3	
Central region	1,769	24.2	6,275	24.0	
Northern region	869	11.9	3,135	12.0	
Southern region	1,851	25.3	6,580	25.2	
Cohabitation, n (%)					
Living alone	2,091	28.6	7,138	27.3	
Cohabiting/married	5,211	71.3	19,007	72.6	
Educational level, n (%)					
Primary school	1,994	27.3	6,384	24.4	< 0.0001
Secondary school	455	6.2	1,920	7.3	
Vocational education	2,883	39.5	9,987	38.2	
Short higher education	379	5.2	1,331	5.1	
Bachelor degree	934	12.8	3,696	14.1	
Master degree/PhD	482	6.6	1,936	7.4	
Unknown	175	2.4	891	3.4	
DCCI, n (%)					
0	6,325	86.6	24,326	93.0	< 0.0001
1-2	823	11.3	1,570	6.0	
≥ 3	154	2.1	249	1.0	

Abbreviations: DCCI: Deyo-Charlson Comorbidity index; SD: standard deviation. * Chi2 test.

Table 2. Source of A/D diagnosis among cases and matched comparators who developed A/D during follow-up.

	Sarcoidosis case who developed A/D	Comparators who developed A/D	P-value*
Total, n	502	1,274	
Source of diagnosis, n (%)			
Redeemed prescriptions of antidepressants**	404 (80.5)	1,034 (81.2)	
Depression (ICD-10 F32-34)	66 (13.1)	136 (10.7)	0,1772
Anxiety (ICD-10 F40-41)	32 (6.4)	104 (8.2)	

Abbreviation A/D: Anxiety and/or depression. * Chi2 test ** ≥ two redeemed prescriptions of antidepressants within one year.

Table 3. The cumulative incidence of A/D five years and 18 years after sarcoidosis diagnosis in all cases and matched comparators and by gender and by age-group.

		Cumulative incidence of A/D (%) (95%CI)	
		5 years	18 years
Overall, (n)			
	Cases (7,302)	6.0 (5.5-6.4)	6.8 (6.4-7.3)
	Comparators (26,145)	4.2 (4.0-4.4)	4.6 (4.6-5.1)
Gender, (n)			
Female	Cases (3,021)	7.1 (6.2-8.0)	8.2 (7.4-9.2)
	Comparators (10,461)	5.6 (5.1-6.0)	6.4 (6.0-6.9)
Male	Cases (4,281)	5.0 (4.5-5.5)	5.8 (5.2-6.5)
	Comparators (15,684)	3.3 (3.1-3.6)	3.8 (3.5-4.1)
Age-group, (n)			
18-29 years	Cases (1,071)	5.1 (4.3-6.0)	6.0 (5.0-7.1)
	Comparators (3,954)	3.6 (3.3-4.0)	4.1 (3.7-4.6)
30-39 years	Cases (1,954)	5.5 (4.9-6.1)	6.4 (5.8-7.0)
	Comparators (7,098)	3.9 (3.6-4.2)	4.5 (4.2-4.8)
40-49 years	Cases (1,606)	5.8 (5.3-6.4)	6.8 (6.3-7.3)
	Comparators (5,769)	4.2 (4.5-4.5)	4.8 (4.6-5.1)
50-59 years	Cases (1,254)	6.2 (5.6-6.9)	7.3 (6.6-8.0)
	Comparators (4,423)	4.6 (4.3-4.8)	5.2 (4.9-5.5)
≥60 years	Cases (1,417)	6.6 (5.7-7.7)	7.8 (6.7-9.0)
	Comparators (4,901)	5.0 (4.5-5.4)	5.7 (5.2-6.2)

Abbreviation A/D: Anxiety and/or depression, CI: confidence Interval, n: number.

The difference in the cumulative incidence of A/D remained stable from five to 18 years after diagnosis (Figure 2A). The cumulative incidence after 18 years for female cases was 8.2% (95% CI 7.4-9.2) and 5.8% (95% CI 3.4-6.5) for male cases (Figure 2B and Table 3). The cumulative incidence decreased consecutively with descending age-group (Figure 2C). The cumulative incidence was higher in male cases, female cases, and all age-groups in the case cohort compared with the matched comparators (Figure 2B, Figure 2C, and Table 3). At least one prescription of SCs was redeemed before A/D in 45.4% of cases and 7.1% of comparators (Table S2).

Table 4 displays the sHR for developing A/D during follow-up for cases compared with the matched comparators. The adjusted sHR (a-sHR) for A/D was 1.38 (95%CI 1.24-1.53). No change in the a-sHR was seen when the outcome also included cases and comparators, who only redeemed one prescription of antidepressants (Table S3). The a-sHR

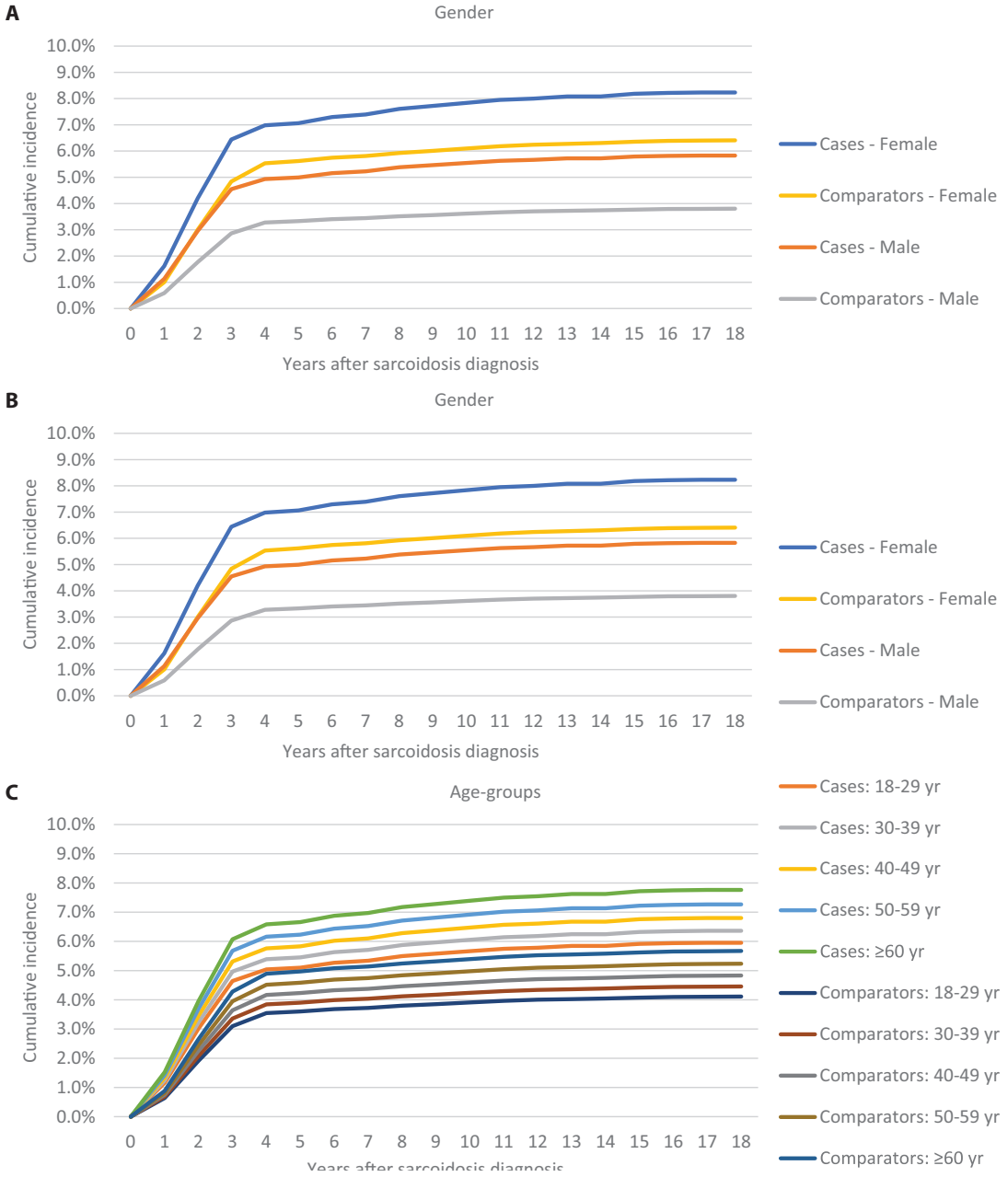

Figure 2. The cumulative incidence for A/D for cases and controls: A) all cases and controls, B) by gender and C) by age-group. yr = years.

for A/D for male cases compared with matched comparators was 1.51 (95%CI 1.30-1.75). The sHR for female cases compared with matched comparators was 1.25 (95%CI 1.08-1.45). The a-sHR for A/D was significantly increased in all age-groups, although not statistically significant among cases aged 30-39 years.

Discussion

The risk of A/D after sarcoidosis was diagnosed in 7,302 patients was higher compared with 26,145 matched comparators; also, after adjusting for SES and DCCI. The cumulative incidence for A/D was higher in cases compared with the matched

Table 4. Number of cases and matched comparators who developed A/D during follow-up and the corresponding sHRs for A/D.

	(A/D)/sarcoidosis cases	(A/D)/Comparators	sHR (95%CI)	a-sHR (95%CI)
	N=7,302	N=26,145		
Overall	502/7,302	1,274/26,145	1.43 (1.29-1.58)	1.38 (1.24-1.53)
Gender				
female	251/3,021	675/10,461	1.30 (1.13-1.50)	1.25 (1.08-1.45)
male	251/4,281	599/15,684	1.56 (1.34-1.80)	1.51 (1.30-1.75)
Age				
18-29	87/1,071	177/3,954	1.84 (1.43-2.38)	1.75 (1.35-2.28)
30-39	104/1,954	325/7,098	1.17 (0.94-1.46)	1.15 (0.92-1.44)
40-49	95/1,606	252/5,769	1.36 (1.08-1.72)	1.30 (1.03-1.67)
50-59	95/1,254	212/4,423	1.61 (1.26-2.05)	1.58 (1.24-2.01)
≥ 60	121/1,417	308/4,901	1.38 (1.12-1.71)	1.30 (1.06-1.20)

Abbreviations: A/D: anxiety and/or depression, CI: confidence Interval, sHRs: subdistribution hazard ratios, a-sHR: subdistribution hazard ratio for A/D adjusted for socioeconomic status and Deyo-Charlson Comorbidity Index.

comparators in both genders and in all age-groups. Sarcoidosis cases had an increased a-sHR for A/D compared with the matched comparators when stratified by gender and within all age-groups.

To our knowledge, this is the first study to investigate the incidence of A/D in patients with sarcoidosis in a longitudinal follow-up study. Hence, our results are difficult to directly compare to the existing literature, but our findings are in line with previous reports of high prevalence of A/D in patients with sarcoidosis (7-12, 14, 15, 17, 29-32). Three of these studies used a comparison cohort. Hinz et al. (11) evaluated a large sample of prevalent cases (N = 1.197) and controls (N=4.410) and Yeager et al. (31) found higher prevalence of depression and anxiety in cases compared with background population controls. Yeager et al. (31) found a prevalence of 46% of depression in sarcoidosis patients compared with 27% in a matched population-based control group. Conversely, in a small sample of patients with stage I and II sarcoidosis (N=33) Holas et al. (10) found a similar prevalence of anxiety and depression in cases and controls (N=32). In the present study, the absolute number of sarcoidosis cases with A/D was low (6.9%) compared with prevalence's found in other studies. Firstly, it is important to distinguish between the primary outcome in the present study (treatment with antidepressants or a clinical diagnosis) and the most common outcome in the existing literature. Most studies evaluate depressive symptoms or symptoms of anxiety through patient-reported questionnaires, and not a clinical diagnosis as such (7-12, 14, 15, 17, 29, 30) which will expectantly yield higher numbers of A/D than in our study. Also, we excluded cases with A/D at the time of diagnosis to ensure that only true incident A/D was investigated. This will lower the total number of patients with A/D compared with studies evaluating prevalent A/D among patients with sarcoidosis.

Cross-sectional studies are unable to evaluate the directionality of the association between sarcoidosis and psychiatric comorbidity. The novelty of our cohort study, is the finding of an increased risk of new A/D after sarcoidosis is diagnosed. Yet, unravelling the causality of why patients with sarcoidosis have increased rates of A/D is complicated. In our study, 54.6% of cases were treated with SCs before A/D compared to 7.1% of the comparators. SCs are known to affect mood and may therefore contribute to the increased risk of A/D. Our study was not designed to evaluate the impact of SCs on the risk of developing A/D in sarcoidosis as we do not know the dose and duration of treatment. Nor do we know if symptoms of A/D preceded systemic corticosteroid (SC) treatment, if SC treatment worsened pre-existing mood symptoms or if SC treatment triggered the debut of new A/D.

The mechanism behind increased A/D in patients with sarcoidosis is unknown. A higher incidence of depression and anxiety disorders in patients with immune-mediated inflammatory diseases compared with the general population is seen (33). Some

studies suggest that the relationship between fatigue and depression and fatigue and anxiety is bidirectional (16). For instance, sarcoidosis-related dyspnea may induce or worsen symptoms of anxiety and lead to reduced physical activity. Along with possible disabling symptoms directly caused by sarcoidosis-related involvement, this leads to deconditioning, adding to the dyspnea. Symptoms of anxiety and reduced physical activity can lead to social isolation, which can induce or worsen depression. Fatigue may contribute to the vicious circle by also reducing physical activity. However, studies have found that the degree of fatigue is not correlated to the severity of sarcoidosis (34, 35). In fact, fatigue often persists even when there are no signs of active sarcoidosis suggesting that fatigue is more likely a consequence of living with a chronic disease. The prevalence of A/D is increased in other chronic diseases as well and the consequence of living with a chronic disease is most likely also the key driver leading to A/D in sarcoidosis rather than inflammatory activity (36). We were not able to adjust for symptom burden (including fatigue) and severity of sarcoidosis and therefore not able to evaluate the impact of these on A/D development. Interestingly, we found that more cases (N = 1,074; 12.6%) than the matched comparators (N = 3,232; 9.5%) had a history of A/D at diagnosis indicating a possible impact of the pre-diagnostic inflammation in these patients. Another explanation may be the psychological burden of the diagnostic period which is often prolonged due to the heterogeneous presentations of sarcoidosis until the sarcoidosis diagnosis is finally established. Studies have found, that patients often have several contacts to the health care system months to years before the final diagnosis (37). Hence, more research into the specific mechanisms by which A/D develops in sarcoidosis is needed.

Age and gender

The literature on the effect of age and gender on the risk of developing A/D in patients with sarcoidosis is limited. One cross-sectional study (11) found a higher prevalence of depression and anxiety for both male and female sarcoidosis cases and among the youngest cases compared with matched comparators (11).

The prevalence of depression, anxiety, and prescribed antidepressants in the general population are higher in women than in men and in the elderly compared with the younger population (38-42). Our study showed similar results with a higher cumulative incidence of A/D for female compared with male cases and for elderly compared with younger cases. However, when comparing cases with their matched comparators, we found an increased a-sHR for A/D in cases compared with the matched comparators in both genders and in all age-groups although not statistically significant for cases aged 30-39 years. Hence, our results underline the importance of taking the effects of age and gender from the background population into account when investigating the age- and gender-associated risk of A/D in patients with sarcoidosis. The increased a-sHR for A/D for male and young cases compared with the matched comparators indicates a different risk profile for developing A/D than comparable non-sarcoid individuals in the general population. Weather this risk profile reflects unknown sarcoidosis-related risk factors or a different health-care seeking behaviour (leading to more opportunities for A/D being diagnosed) is unclear. Future research should focus on these two subgroups when investigating the association between sarcoidosis and A/D.

Strengths and limitations

The strengths of the study include the large, nationwide sample size and the 18-year study period. The population-based study design, a tax-funded, uniformly organised healthcare system, and virtually full case-by-case follow-up all contribute to reduced selection bias. We accounted for important potential confounders by matching for age, gender, cohabitation status, and municipality and adjusting for comorbidities and SES.

Some limitations of the study are to be addressed. Antidepressants are prescribed for indications other than A/D (42), but we expect the distribution to be similar between cases and controls. We do not know the share of cases and comparators receiving psychotherapy as mono-therapy, hence the results are limited to patients receiving medical treatment or a clinical diagnosis. A/D was defined as more than one redeemed prescription of antidepressants within one year to increase the likelihood of the A/D diagnosis. This may lead to an underestimation of A/D for both cases and comparators.

Conclusion

We found an increased risk of developing A/D in patients with sarcoidosis with no present history of A/D at the time of sarcoidosis diagnosis compared with matched comparators. The difference in the risk of A/D between cases and the matched comparators increased during the first five years, after which it remained stable.

In accordance with earlier studies, our results highlight that screening sarcoidosis cases for depressive symptoms and anxiety is important – also among male and young cases.

Our findings add to the evidence base, by indicating that the risk of developing A/D *after* sarcoidosis is diagnosed is higher than in the non-sarcoidosis population. Whether or not sarcoidosis or sarcoidosis related symptoms *directly* causes A/D remains unclear.

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Conflict of Interest: All authors declare no conflict of interest for the current work.

Ethical Approval: The study was approved by the Danish Data Protection Agency. The study only involved register-based data and ethical approval was not required.

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Appendix

Supplementary files

Table S1. Share of cases and matched comparators who were censored, died or developed A/D during follow-up.

	Sarcoidosis case population	**Comparison cohort**
Total, n	7,302	26,145
End state, n (%)		
Depression and/or anxiety	502 (6.9)	1,274 (4.9)
Dead	563 (7.7)	1,461 (5.6)
Censored	6,237 (85.4)	23,410 (89.5)

Table S2. Number of redeemed prescriptions of SCs among cases and matched comparators who developed A/D during follow-up.

	Sarcoidosis case N = 7,302	**Comparators N = 26,145**
A/D during follow-up, n (%)	502 (6.9)	1,274 (4.9)
Redeemed prescriptions of SCs before A/D, n (%)		
Redeemed 0 prescriptions	274 (54.6)	1,183 (92.9)
Redeemed 1-2 prescription	96 (19.1)	67 (5.3)
Redeemed ≥ 3 prescription	132 (26.3)	24 (1.9)

Abbreviation A/D: Anxiety and/or depression, SC: systemic corticosteroids.

Table S3. Number of cases and matched comparators who developed A/D during follow-up and the corresponding a-sHRs for A/D when *not* excluding cases and matched comparators who redeemed only one prescription of antidepressants within one year. Two definitions of the outcome of A/D is tested: A) A/D = one or more redeemed prescriptions of antidepressants within one year or an ICD-10 diagnosis in the DNPR of anxiety or depression and B) A/D = more than one redeemed prescription of antidepressants within one year or an ICD-10 diagnosis in the DNPR of anxiety or depression.

		Sarcoidosis cases	**Comparators**	**a-sHR (95%CI)**
	Total	N=7,470*	N=27,160**	
A	≥1 redeemed prescription within one year included as an outcome of A/D	N=670	N=1,746	1.37 (1.25-1.51)
B	One redeemed prescription within one year NOT included as an outcome of A/D	N=503	N=1,312	1.35 (1.21-1.51)

Abbreviations: A/D: anxiety and/or depression, CI: confidence Interval, a-sHR: subdistribution hazard ratio for A/D adjusted for socioeconomic status and Deyo-Charlson Comorbidity Index. *A total of 168 cases, who were excluded from the original case cohort, are included in the sensitivity analyses. Of these, 167 cases redeemed only one prescription of antidepressants within one year during follow-up. One case, who was originally excluded because all four matched comparators were excluded, was also included in the sensitivity case cohort. ** A total of 1,015 matched comparators, who were excluded from the original comparator cohort, are included in the sensitivity analyses. Of these, 502 comparators redeemed only one prescription of antidepressants within one year during follow-up and 613 comparators, who were originally excluded because the matched cases were excluded, were also included in the sensitivity comparator cohort.