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Sarcoidosis-related mortality and the impact of corticosteroid treatment: A population-based cohort study

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SUMMARY AT A GLANCE

We evaluated mortality in a cohort of 9,795 sarcoidosis cases during an 18-year follow-up period (2001-2018). Mortality was significantly increased in sarcoidosis cases, compared with the background population. Corticosteroid treatment was associated with particularly high mortality rates.
ABSTRACT

Background and objective: The aims of this national cohort study were: 1) to evaluate mortality in patients with sarcoidosis, stratified by gender, age and SC treatment; and 2) to characterize comorbidities in this cohort.

Methods: Patients diagnosed with sarcoidosis from 2001-2015 were identified in the Danish National Patient Registry. Subgroup analyses were performed on cases treated/not treated with systemic corticosteroids within three years of the initial sarcoidosis diagnosis (as a proxy for disease severity). The Deyo-Charlson Comorbidity Index was used to evaluate pre-diagnostic comorbidity. Cases were matched 1:4 with controls from the general population.

Results: We identified 9,795 cases with sarcoidosis. Mean age was 46.5 ± 15.9 years and 55% were male. The adjusted hazard ratio (HR) for death was 1.48 (95% CI 1.31-1.68). Mortality was higher than for controls in all age groups and in both genders. HR for death for cases treated with systemic corticosteroids was 1.78 (95% CI 1.49-2.13) and, for cases receiving no treatment, 1.24 (95% CI 1.04-1.48). Sarcoidosis was the most commonly registered cause of death (13.3%).

Conclusion: Patients with sarcoidosis have an increased mortality, compared with matched controls. Mortality is particularly high in patients treated with systemic corticosteroids.
Short title: Sarcoidosis-related mortality

Keywords: Sarcoidosis, Mortality, Therapeutics, Comorbidity, corticosteroid treatment, population-based, cohort study
INTRODUCTION

Sarcoidosis is a multisystem disease with granulomatous inflammation that affects individuals of all ages, albeit with peak incidence in the third to fifth decades (1-3). Generally, sarcoidosis is considered a benign disease; full remission is seen in half of all patients within the first two years of diagnosis and the rate of remission improves over time. However, chronic and/or progressive sarcoidosis is also seen – most frequently due to irreversible pulmonary fibrosis or end-stage sarcoidosis complications, including impaired lung function and pulmonary hypertension (4, 5).

Because of the self-limiting course of sarcoidosis, the majority of patients do not need treatment. The indications for initiating systemic treatment are life-threatening or organ-threatening disease and, in rare cases, when life impairment, such as severe fatigue, is unacceptable (5). Treatment regimens vary widely between countries, regions and study populations (6-9). The main treatment is systemic corticosteroids (SC), whereas antimetabolites such as methotrexate (MTX) and azathioprine (AZA) are primarily used as corticosteroid-sparing treatment. Monoclonal anti-TNFα antibody (infliximab) can be indicated in rare treatment-refractory cases with progressive disease (5, 10, 11).

Previous studies have demonstrated an excess mortality and an increased economic health burden, even several years after initial sarcoidosis diagnosis (12, 13). As the vast majority of patients with sarcoidosis have a mild and self-limiting course, it has been suggested that excess mortality is primarily driven by subgroups of patients with more severe disease (12, 14, 15).

The aims of this national cohort study were: 1) to evaluate mortality in patients with sarcoidosis, stratified by gender, age and SC treatment; and 2) to characterize comorbidities in this cohort.

METHODS

Setting
In Denmark, all citizens have access to tax-funded universal health care. A unique ten-digit Civil Registration System (CPR) number is assigned to all Danish citizens upon birth or immigration, enabling precise, individual-level record linkage across all Danish registries (16).

Sarcoidosis
Patients diagnosed with sarcoidosis from 1 January 2001 – 31 December 2015 were identified in the Danish National Patient Registry (DNPR) and included as incident cases. Prevalent cases would bias the results and therefore a three-year washout period was applied (1998-2000), excluding patients diagnosed before the inclusion period. The DNPR has achieved complete nationwide coverage on all non-psychiatric admissions since 1978 and out-patient clinic contacts since 1995 (17). Registration includes diagnoses,
diagnostic procedures and administrative information. Primary and secondary diagnoses are classified according to the International Classification of Diseases and Related Health problems 10th Revision (ICD-10). ICD-10 D86 code was applied to identify patients with a primary or secondary diagnosis of pulmonary and/or extra-pulmonary sarcoidosis. Given the morphological and pathological similarities between sarcoidosis and cancer, which can lead to initial misdiagnosis of cancer as sarcoidosis, cases diagnosed with cancer (ICD-10 C00-C97) six months before and after the time of sarcoidosis diagnosis were excluded (Figure 1).

Mortality
Information on all-cause mortality was obtained from the Danish Civil Registration System (DCRS) from 2001-2018. The DCRS has recorded information on date of birth, gender, residency and daily electronic updates on vital status and migration since 1968 (16).

Covariates
Information on comorbidities (ICD-10 diagnostic codes) were obtained from the DNPR from 1998 - 2018. To evaluate the impact of baseline comorbidities on mortality, the Deyo-Charlson Comorbidity Index (DCCI) was computed (see Table S1 in the Supporting Information for ICD-10 codes and weighted scores) by including comorbidities in the three-year period before sarcoidosis was diagnosed (18-20). The DCCI has a positive predictive value (PPV) of 98% in the DNPR (21). The DCCI was presented in three categories according to the weighted scores (0, 1-2 and >2 points).
Information on causes of death was obtained from the Danish Register of Causes of Death (22).
The DNPR does not provide information on disease severity. As a proxy for disease severity, we identified cases in the Danish Register of Medicinal Product Statistics (DRMPS) who redeemed prescriptions on SC (ATC H02AB), MTX (ATC L01BA01/L04AX03) or AZA (ATC L04AX01) from three months prior to, until three years after, sarcoidosis diagnosis and denoted this group the treatment cohort. A similar approach was used by Rossides et al. (12). Cases who did not redeem a prescription was denoted the non-treatment cohort. The DRMPS consists of high quality data and includes data on all prescription drugs dispensed in Danish community pharmacies since 1995 (23). Biological treatment was rarely used for sarcoidosis in Denmark during the observation years and therefore not included.

Controls
Cases were individually matched on the date of the first sarcoidosis registration to a population-based comparison cohort without sarcoidosis randomly selected from the background population using the CPR. Cases and controls were matched 1:4 by gender, birth-year, civil status, and municipality and matching was successful in more than 99% of cases. Cases and controls were followed until death, migration or end of follow-up in 2018.

Statistical analysis
The survival probability after the index date (i.e. date of first sarcoidosis diagnosis) for cases and controls was estimated using the Kaplan-Meier method. Kaplan-Meier survival curves
are nonparametric and take censoring of data into account. Mortality rates for cases, as compared with controls, were estimated using Cox proportional hazard model. The DCCI three years prior to diagnosis was included in the Cox proportional hazard model as an explanatory variable. Estimates were given with 95% confidence intervals (CI) and a significance level of 0.05 was assumed. Statistical analysis was performed using SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA).

RESULTS

In total, data on 10,521 cases and 42,070 matched controls were extracted and 9,795 cases were included in the sarcoidosis cohort, after excluding 726 cases due to cancer. The mean age at diagnosis was 46.5 ±15.9 years; 46% of cases were between 30-49 years old at diagnosis and males were slightly overrepresented (55.2%) (Table 1). A DCCI of ≥1 three years prior to diagnosis was evident in 16.4% of cases and 8.6% of controls (Table 1). SC was initiated in 44% of cases and 6% received second-line treatment (Figure 1). Comorbidities three years before and after diagnosis were largely overrepresented in the sarcoidosis cohort, compared with controls (Figure 2).

The treatment cohort had a higher pre-diagnostic DCCI and more out-patient clinic visits three years after diagnosis (2.7 vs. 1.4 visits per patient-years) than the non-treatment cohort (Table S2 and S3 in the Supporting Information). For details on demographics and comorbidities in the subgroups, please refer to Table S2 and Table S4 in the Supporting Information.

Mortality

Demographic and survival data were complete for all cases and controls. Mortality rate was increased in the sarcoidosis cohort compared with the matched controls (HR 1.68; 95% CI 1.49-1.90) in the 18-year follow-up period, also when adjusting for comorbidity (HR 1.48; 95% CI 1.31-1.68) (Table 2). The average 5-, 10-, 18-year survival probabilities were, respectively, 0.94, 0.89 and 0.82 in the sarcoidosis cohort and 0.96, 0.92 and 0.86 in the comparison cohort (Figure 3). The absolute share of deaths was low in cases diagnosed with sarcoidosis at a young age (0-29 years = 16 deaths) and increased with age. HR for death was higher among cases than controls in all age groups. The gender-associated HR for death was higher than controls in both genders (males; HR 1.34; 95% CI 1.22-1.47 and females; HR 1.22; 95% CI 1.11-1.35) (Table 2). The treatment cohort had an adjusted HR of 1.78 (95% CI 1.49-2.13) and the non-treatment cohort an adjusted HR of 1.24 (95% CI 1.04-1.48).

In total, 1,198 cases died during follow-up and information on causes of death was available in 1,077 cases. The 20 most common causes of death in the sarcoidosis cohort and the distribution in the control group, the non-treatment cohort and the treatment cohort are shown in Figure 4. Diseases of the immune system including sarcoidosis were the most commonly registered causes of death (13.3%) in the sarcoidosis cohort with a higher share in the treatment cohort (17.7%) compared with the non-treatment cohort (8.3%). Death from chronic respiratory diseases was only slightly more prevalent in the sarcoidosis cohort than in
the control group with the highest share in the treatment cohort (5.5%). Death from interstitial pulmonary diseases was 3.7% in the sarcoidosis cohort with the highest share in the treatment cohort (5.1%) compared with the non-treatment cohort (2.2%) and no deaths in the control group.

Death caused by cancers are to be interpreted with caution when comparing cases and controls because 726 cases were excluded from the sarcoidosis cohort due to cancer and therefore not displayed in Figure 4.

DISCUSSION

This large cohort study confirms that all-cause mortality rates in patients with sarcoidosis are higher than in individuals without sarcoidosis. Furthermore, sarcoidosis was coded as the most common cause of death and survival was reduced during the 18-year follow-up, thus indicating an impact of sarcoidosis even several years after diagnosis. Our results also highlight an association between sarcoidosis and increased mortality at all ages. Although death was rare among young cases, the HR was highest among the younger cases because of the low mortality in the age-matched controls. Gender-associated mortality varies between studies (12, 13, 24). We found no strong association between gender and mortality, with only a slightly higher mortality in males than females.

The present findings on mortality rates are in line with several other studies on sarcoidosis (25, 26) and support the Rossides et al. study that found an increased all-cause mortality (HR 1.61; 95% CI 1.47-1.72), as compared with a matched control group and a reduced survival 10 years after diagnosis (12).

Systemic corticosteroid (SC) treatment is largely initiated in more severe cases of sarcoidosis and serves as a crude proxy for disease severity in the present study. The treatment cohort in our present study had more contacts with the out-patient clinics than had the non-treatment cohort after diagnosis (Table S2 in the Supporting Information), and mortality was high in the treatment cohort. Likewise, Rossides et al. found a more than twofold higher mortality than controls in cases receiving immunosuppressant three months pre/post diagnosis (12), thus supporting the hypothesis that subgroups of patients with more severe disease drive the excess mortality.

The most common cause of death in the sarcoidosis cohort in our study was sarcoidosis. Interestingly, subgroup analyses showed that cases treated with SC were more likely to die from sarcoidosis and respiratory diseases than the non-treated cases, whereas death from heart diseases did not differ much between the two cohorts. It is important to remember that the causes of death listed are not exhaustive. For instance, cases who die from a sarcoidosis-related complication, such as pulmonary fibrosis, several years after sarcoidosis was diagnosed, will most likely not be coded with sarcoidosis as the cause of death. Furthermore, our data did not withhold sub-diagnoses, such as neuro-sarcoidosis and cardiac sarcoidosis.
Nevertheless, our study indicates that sarcoidosis and respiratory complications are important contributors to death – particularly in cases treated with SC. No causality between SC and mortality can be made. However, our results confirm the need for future research to focus on further characterization of the subgroup of patients driving the excess mortality.

Comorbidities within all organ systems (ICD-10, chapters 1-14) prior to the sarcoidosis diagnosis were increased, compared with the control group (Figure 2). In particular, diagnoses related to eyes, skin, the respiratory system, rheumatologic diseases and the blood/immune-system were increased and indicate sarcoidosis-related contact with the hospital before the initial sarcoidosis diagnosis. Furthermore, unspecified contacts, such as contact with health services (chapter 21) and abnormal clinical and laboratory findings (chapter 18) were highly overrepresented in the sarcoidosis cohort prior to diagnosis, supporting the complex and sometimes prolonged course of diagnosis.

The literature on toxicity of corticosteroid treatment in patients with sarcoidosis is sparse. However, studies suggest that adverse effect from corticosteroid treatment contributes to the increased comorbidity burden and mortality in patients with sarcoidosis (27-29). The present study found a particularly high occurrence of endocrine/metabolic (OR 3.47 95% CI 3.14-3.82) and infectious diseases (OR 4.02 95% CI 3.49-4.63) after diagnosis in the treatment cohort (Table S4 in the Supporting Information), which might reflect the burden of steroid-associated adverse effects, such as diabetes and suppressed immune system. However, as SC therapy is by far most frequently initiated in patients with more severe sarcoidosis, the increase in infectious diseases is likely to be caused by a suppressed immune system. For that reason, SC serves as a proxy for severe sarcoidosis and not as a cause of other diseases, per se. Furthermore, it is important to use caution in any interpretation of the increase in comorbidities after diagnosis, given that ICD-10 codes are used only in the secondary healthcare sector. Pre-existing diseases handled by the general practitioner before the sarcoidosis diagnosis, such as mild diabetes or hypertension, will more often tend to be coded in the DNPR after sarcoidosis is diagnosed. Consequently, these diagnoses appear as new diseases in the DNPR, leading to an overestimation of the increase in comorbidities after sarcoidosis diagnosis.

The strengths of the present study are the large and nationwide study population, the 18-year study period and the complete follow-up. Importantly, most cases with sarcoidosis are diagnosed in hospital settings, including mild cases that are not followed in tertiary centres. Hence, we expect our data to be highly representative of the entire Danish sarcoidosis population and our findings to be generalizable to populations with a standard of medical care similar to that in Denmark.

Sarcoidosis is not validated in the DNPR, which could lead to misclassification and an overestimation of the share of cases with sarcoidosis. However, validation studies of the DNPR generally show a high PPV, particularly for diseases that are primarily followed in specialized departments, such as sarcoidosis (21, 30). We sought to reduce the risk of this
misclassification by excluding cases diagnosed with cancer around the time of diagnosis. Given that cancer diagnoses have a PPV in the DNPR (31), we expect misclassification of cancer to be minimal. Although we cannot rule out that some cases had, in fact, concurrent sarcoidosis and cancer, we expect it to represent a small proportion of the excluded cases. No adjustment was made for ethnicity. Over 90% of the Danish population were of Caucasian ethnicity during the study period; thus, we expect this potential bias to be minimal (32).

Cases with severe sarcoidosis, who died before a SC prescription was redeemed, are classified to the non-treatment cohort. This could lead to an overestimation of mortality in the non-treatment cohort, and an underestimation in the treatment cohort. However, as rapidly progressing sarcoidosis is rare, we expect this bias to be limited. The DRMPS provides information on all redeemed medication. However, we do not know the true indications for treatment, whether or not the collected medication was ingested, or whether SC was prescribed but not collected. Also, the study does not include SC dispensed at hospitals, which could tend to underestimate the extent of treatment in some patients.

In conclusion, patients with sarcoidosis have an increased mortality over an 18-year follow-up period, and mortality is particularly high in patients where SC treatment is initiated. Sarcoidosis is the most common cause of death in the sarcoidosis cohort, with sarcoidosis and chronic respiratory diseases more prevalent in the treatment cohort than in the non-treatment cohort. The absolute share of deaths is low in cases diagnosed with sarcoidosis at a young age. However, cases younger than 40 years of age have a particular high excess mortality rate, as compared with matched controls. Continued investigation into further characterizing the subgroup of patients with poor outcomes may provide important and helpful knowledge in early detection of patients with high sarcoidosis-related morbidity and mortality.
Acknowledgements
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Conflict of Interest
MGS received unrestricted grants from the University of Southern Denmark and the Region of Southern Denmark for the current work. OH, RI and AL did not declare any conflicts of interest.

Human Ethics Approval Statement
The study was approved by the Danish Data Protection Agency. The study involved only register-based data and research ethical approval was not required.

Data Availability Statement
Data are anonymized from the national databases and are not publicly available.

Authors’ contributions
MGS, AL and OH all contributed to the planning and design of the study. AL, MGS and RI had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. The statistical analysis was primarily performed by RI and MGS. The first draft of the manuscript was written by MGS, with input from AL and OH. All authors revised the manuscript and accepted the final version. All authors take responsibility for the integrity of the work as a whole, including the data and analysis.
References

Table 1: Baseline characteristics of the sarcoidosis cohort and matched controls

<table>
<thead>
<tr>
<th></th>
<th>Sarcoidosis cohort</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>9,795</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,406</td>
<td>55.2</td>
</tr>
<tr>
<td>Female</td>
<td>4,389</td>
<td>44.8</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>46.5 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Age groups (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-29</td>
<td>1,419</td>
<td>14.5</td>
</tr>
<tr>
<td>30-39</td>
<td>2,400</td>
<td>24.5</td>
</tr>
<tr>
<td>40-49</td>
<td>2,080</td>
<td>21.2</td>
</tr>
<tr>
<td>50-59</td>
<td>1,712</td>
<td>17.5</td>
</tr>
<tr>
<td>60-69</td>
<td>1,238</td>
<td>12.6</td>
</tr>
<tr>
<td>&gt;70</td>
<td>946</td>
<td>9.7</td>
</tr>
<tr>
<td>Civil status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone</td>
<td>3,086</td>
<td>31.5</td>
</tr>
<tr>
<td>Married</td>
<td>5,089</td>
<td>52.0</td>
</tr>
<tr>
<td>Cohabiting</td>
<td>1,620</td>
<td>16.5</td>
</tr>
<tr>
<td>DCCI, 3 years prior to diagnosis</td>
<td>8,190</td>
<td>83.6</td>
</tr>
<tr>
<td>0</td>
<td>1,321</td>
<td>13.5</td>
</tr>
<tr>
<td>1-2</td>
<td>284</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Data are presented as n, years (SD) or n (%). SD: standard deviation. DCCI: Deyo-Charlson Comorbidity Index.
### Table 2: Share of cases and matched controls in the sarcoidosis cohort and subgroups who died during follow-up and the corresponding hazard ratios of all-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Sarcoidosis cohort</th>
<th>Controls</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>Adjusted* HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths per person-year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subjects, n</strong></td>
<td>n = 9,795</td>
<td>n = 39,168</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1,198/92,170</td>
<td>3,460/378,112</td>
<td>1.68 (1.49;1.90)</td>
<td>&lt; 0.001</td>
<td>1.48 (1.31;1.68)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>652/50,128</td>
<td>1,761/205,901</td>
<td>1.52 (1.39;1.66)</td>
<td>&lt; 0.001</td>
<td>1.34 (1.22;1.47)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>546/42,042</td>
<td>1,699/172,210</td>
<td>1.31 (1.19;1.45)</td>
<td>&lt; 0.001</td>
<td>1.22 (1.11;1.35)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Age at inclusion (year)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-29</td>
<td>16/14,926</td>
<td>28/59,967</td>
<td>2.30 (1.24;4.24)</td>
<td>0.008</td>
<td>2.30 (1.24;4.25)</td>
<td>0.008</td>
</tr>
<tr>
<td>30-39</td>
<td>54/25,179</td>
<td>117/101,321</td>
<td>1.86 (1.35;2.56)</td>
<td>&lt; 0.001</td>
<td>1.84 (1.33;2.54)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>40-49</td>
<td>97/20,176</td>
<td>234/81,570</td>
<td>1.68 (1.32;2.12)</td>
<td>&lt; 0.001</td>
<td>1.40 (1.10;1.79)</td>
<td>0.007</td>
</tr>
<tr>
<td>50-59</td>
<td>201/15,929</td>
<td>550/65,605</td>
<td>1.51 (1.28;1.77)</td>
<td>&lt; 0.001</td>
<td>1.43 (1.22;1.68)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>60-69</td>
<td>308/10,469</td>
<td>817/44,031</td>
<td>1.60 (1.40;1.82)</td>
<td>&lt; 0.001</td>
<td>1.38 (1.21;1.57)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt;70</td>
<td>522/5,491</td>
<td>1,714/25,617</td>
<td>1.42 (1.28;1.56)</td>
<td>&lt; 0.001</td>
<td>1.29 (1.17;1.43)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-treatment cohort</td>
<td>566/52,239</td>
<td>1,903/211,476</td>
<td>1.37 (1.15;1.63)</td>
<td>&lt; 0.001</td>
<td>1.24 (1.04;1.48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Treatment cohort</td>
<td>632/92,170</td>
<td>1,557/166,635</td>
<td>2.12 (1.77;2.53)</td>
<td>&lt; 0.001</td>
<td>1.78 (1.49;2.13)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

HR: Hazard ratio for matched cases and controls; *adjusted for DCCI (Deyo-Charlson Comorbidity Index). HR was estimated using Cox proportional hazard model.
**Figure legends**

**Figure 1:** Selection of the sarcoidosis cohort and matched controls from the Danish National Patient Registry (DNPR). Furthermore, distribution of cases (n) in the non-treatment cohort and the treatment cohort. *594 cases in the treatment cohort also received second-line treatment (methotrexate or azathioprine).

**Figure 2:** Comorbidities in the sarcoidosis cohort and controls before (top) and after (bottom) sarcoidosis was diagnosed. Comorbidities are grouped according to the ICD-10 21 chapters of diseases.

**Figure 3:** Kaplan-Meier curves displaying the survival distribution during the 18-year follow-up period for: a) the sarcoidosis cohort, b) the non-treatment cohort, and c) the treatment cohort and the matched controls.

**Figure 4:** The 20 most common causes of death in the sarcoidosis cohort and the distribution in the non-treatment cohort and the treatment cohort.
*The corresponding ICD-10 codes: Sarcoidosis (D80-89), chronic respiratory diseases (J40-47), other heart diseases (I30-52), cerebrovascular diseases (I60-69), pulmonary cancer (C30-39), diabetes (E10-14), gastrointestinal cancer (C15-26), unknown causes (R95-99), interstitial pulmonary diseases (J80-84), haematological cancer (C81-96), mental disorders (F00-09), bacterial diseases (A30-49), influenza and pneumonia (J09-18), liver diseases (K70-77), accidents (V01-X59), arterial diseases (I70-79), ill-defined cancers (C76-80), intentional self-harm (X60-84) and gynaecologic cancer (C51-58).
Sarcoidosis-related mortality and the impact of corticosteroid treatment – A population-based cohort study

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Figure 1

Cases identified in the DNPR from 2001-2015 using the ICD-10 D86 code
n=10,521

Excluded because of cancer six months before or after sarcoidosis diagnosis
n = 726

Sarcoidosis cohort
n = 9,795

Controls
n = 39,168

Died during follow-up
n = 1,198

Died during follow-up
n = 3,460

Sarcoidosis cohort divided according to systemic corticosteroid treatment

| Non-treatment cohort | No collection of prescribed SC three months prior to and three years after diagnosis | n = 5,483 (56.0%) |
| Treatment cohort     | Collection of ≥1 prescription of SC between three months prior to and three year after diagnosis | n = 4,312* (44.0%) |
Figure 2

Share of comorbidities before diagnosis

ICD-10 chapters

Factors influencing health status
External causes of morbidity and mortality
External causes
Abnormal clinical and laboratory findings
Congenital malformations
Conditions originating in the perinatal period
Pregnancy, childbirth and the puerperium
Diseases of the genitourinary system
Musculoskeletal system and connective tissue
Diseases of the skin and subcutaneous tissue
Diseases of the digestive system
Diseases of the respiratory system
Diseases of the circulatory system
Diseases of the ear and mastoid process
Diseases of the eye and adnexa
Diseases of the nervous system
Endocrine, nutritional and metabolic diseases
Diseases of the blood and blood-forming organs
Neoplasms
Certain infectious and parasitic diseases

Share of comorbidities (%)

Case n = 9,795  Control n = 39,168
<table>
<thead>
<tr>
<th>ICD-10 chapters</th>
<th>Share of comorbidities (%)</th>
<th>Case n = 9 795</th>
<th>Control n = 39 168</th>
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<tr>
<td>Factors influencing health status</td>
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<td>External causes</td>
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<td>Conditions originating in the perinatal period</td>
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<td>Pregnancy, childbirth and the puerperium</td>
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<td>Diseases of the genitourinary system</td>
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<td>Diseases of the skin and subcutaneous tissue</td>
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<td>Mental and behavioural disorders</td>
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<td>Endocrine, nutritional and metabolic diseases</td>
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Share of comorbidities after diagnosis
Figure 3

Survival analysis for the Sarcoidosis cohort compared to controls. The hazard ratio (HR) is 1.48 (95% CI 1.31;1.68).
Non-treatment cohort

HR* = 1.24 (95% CI 1.04;1.48)
Hazard ratio (HR) for death adjusted for Deyo-Charlson Comorbidity Index

HR* = 1.78 (95%CI 1.49;2.13)

*Hazard ratio (HR) for death adjusted for Deyo-Charlson Comorbidity Index
Figure 4

The graph illustrates the percentage of total deaths within different cohorts and groups. The x-axis represents causes of death, and the y-axis shows the percentage of total deaths. The causes of death are categorized into various groups, including immune system, chronic respiratory diseases, ischaemic heart disease, cerebrovascular disease, pulmonary cancer, gastrointestinal cancer, diabetes, unknown causes, hematological cancer, mental disorders, bacterial diseases, influenza and pneumonia, liver diseases, accidents, arterial diseases, ill-defined cancers, intentional self-harm, and gynaecological cancer.

- **Sarcoidosis cohort** is represented by blue bars.
- **Controls** are shown in red bars.
- **Non-treatment cohort** is indicated by green bars.
- **Treatment cohort** is marked with purple bars.