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# Type 2 diabetes risk in sarcoidosis patients untreated and treated with corticosteroids

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**Title:** Type 2 diabetes risk in sarcoidosis patients untreated and treated with corticosteroids

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**Summary/take home massage:** Corticosteroid-treated sarcoidosis patients have a high risk of developing type 2 diabetes right after their sarcoidosis diagnosis.

## ABSTRACT

**Background:** The rate of type 2 diabetes mellitus (T2D) is increased in sarcoidosis patients but it is unknown if corticosteroid treatment plays a role. We investigated whether the T2D risk is higher in untreated and corticosteroid-treated sarcoidosis patients compared to the general population.

**Methods:** In this cohort study individuals with ≥2 ICD codes for sarcoidosis were identified from the Swedish National Patient Register (NPR; n=5,754). Corticosteroid dispensations ±3 months from first sarcoidosis diagnosis were identified from the Prescribed Drug Register (PDR). General population comparators without sarcoidosis were matched to cases 10:1 on age, sex and region of residence (n=61,297). Incident T2D was identified using ICD codes (NPR) and antidiabetic drug dispensations (PDR). Follow-up was from second sarcoidosis diagnosis/matching date until T2D, emigration, death or study end (Dec 2013). Cox regression models adjusted for age, sex, education, country of birth, healthcare regions and family history of diabetes estimated hazard ratios (HR 95%CI). We used flexible parametric models to examine the T2D risk over time.

**Results:** 40% of sarcoidosis patients were corticosteroid-treated at diagnosis. The T2D rate was 7.7/1000 person-years in untreated sarcoidosis, 12.7 in corticosteroid-treated sarcoidosis and 5.5 in comparators. The HR for T2D was 1.4 (95%CI 1.2-1.8) associated with untreated sarcoidosis and 2.3 (95%CI 2.0-3.0) associated with corticosteroid-treated sarcoidosis. The T2D risk was highest for corticosteroid-treated sarcoidosis in the first 2 years after diagnosis.

**Conclusion:** Sarcoidosis is associated with an increased risk of T2D especially in older, male, corticosteroid-treated patients at diagnosis. Screening for T2D for these patients is advisable.

## INTRODUCTION

Sarcoidosis is an inflammatory disease characterised by the occurrence of granulomas in any organ, most often in the lungs [1]. The natural course of the disease varies from natural resolution to severe progression sometimes causing organ dysfunction and failure [1]. The incidence of sarcoidosis in Sweden is among the highest in the world, with 11.5 incident cases per 100,000 person-years [2].

Patients with sarcoidosis suffer from excess mortality and increased risk of several comorbidities, such as infection and congestive heart failure [3-5]. Diabetes has also been shown to be more prevalent in sarcoidosis patients compared to age- and sex-matched controls [6, 7]. Type 2 diabetes mellitus (T2D) is characterised by a reduced blood glucose uptake caused by insulin resistance and impaired insulin secretion [8]. Risk factors for T2D include high body mass index, clinical inflammation, low physical activity, poor dietary habits and genetic factors [8]. T2D is associated with long-term health complications, leading to a high burden of disease worldwide [9]. If at-risk individuals are identified before overt hyperglycaemia develops, lifestyle modifications can be implemented to prevent T2D.

Two longitudinal follow-up studies found that sarcoidosis patients are at an increased risk of incident T2D, indicating that they may benefit from preventative measures [10, 11]. These studies reported conflicting findings about when the increased risk occurs, with one study reporting the highest increased risk within the first year after diagnosis [11] and the other reporting the highest increased risk 5 years after diagnosis [10]. Furthermore, neither study accounted for the effect of corticosteroid use. Corticosteroids are the first line treatment for sarcoidosis and are known to induce insulin resistance [12-15], which occurs soon after the initiation of a steroid treatment and diminishes after discontinuation [16, 17].

A comprehensive assessment of the risk of T2D associated with sarcoidosis considering also corticosteroid treatment is needed to inform guidelines for screening and follow-up of sarcoidosis patients. Our aim was to determine if sarcoidosis is associated with an increased risk of T2D and how this risk differs by corticosteroid treatment.

## METHODS

### Study population

We used Swedish register data to conduct a matched cohort study. Several nationwide population-based registers were linked using each individual's unique identification number. All individuals with ≥2 visits listing a sarcoidosis diagnosis (ICD-10 D86) in the National

Patient Register (NPR) between 2006 and 2013 were identified. We excluded those with any sarcoidosis-coded visits before 2006 to capture only incident sarcoidosis. The NPR includes data on all inpatient visits in Sweden since 1987 and outpatient visits since 2001. Dispensations of prescribed drugs were identified from the Prescribed Drug Register (PDR), which has data available starting in July 2005. The sarcoidosis patients were categorized into two groups: untreated sarcoidosis and corticosteroid-treated sarcoidosis at diagnosis. All sarcoidosis patients with a corticosteroid dispensation (ATC H02AB) +/- 3 months from their first sarcoidosis diagnosis were identified as corticosteroid-treated (see Table S1 for type of corticosteroid treatment). Sarcoidosis patients with a dispensation of a second line treatment for sarcoidosis (methotrexate, azathioprine, leflunomide, mycophenolate mofetil and hydroxychloroquine), within +/- 3 months around their sarcoidosis diagnosis were excluded (n=162) because they may have a contraindication for corticosteroid use which is associated with an increased risk of T2D. Hence, these group should be studied separately, which was not possible due to few observations in this group. A flow chart of the study population is shown in Figure 1. The date of inclusion into the cohort was date of second sarcoidosis diagnosis or date of corticosteroid dispensation, whichever came last.

Each individual with sarcoidosis was matched to 10 general population comparators without sarcoidosis on year of birth, sex, residence, and the time the matched sarcoidosis case was included in the study (index date). The study population was restricted to adults (≥18 years old) and Swedish residents at index date. Individuals with a previous history of diabetes (type 1 and type 2) before index date were excluded. Additionally, all individuals with a diagnosis of lymphosarcoma and other neoplasms of the lymphatic system (ICD-7 200-205) or a diagnosis of malignant neoplasms of trachea, bronchus or lung (ICD-7 162-163) within +/- 6 months of their first sarcoidosis diagnosis were excluded due to possible misclassification of true cancer as sarcoidosis.

**Type 2 Diabetes Mellitus**

Newly diagnosed T2D after sarcoidosis diagnosis was defined as ≥2 in- or outpatient visits listing an ICD code for T2D (ICD-10 E11) in the NPR during follow-up or with ≥2 dispensations of a blood glucose lowering drug excluding insulin (ATC A10B) in the PDR during follow-up. In Sweden, most T2D patients receive their T2D diagnosis in primary care settings, therefore these T2D drugs capture patients treated by primary care physicians [18].

**Covariates**

Information on family history of diabetes was obtained as a proxy for genetic risk for T2D by linking the NPR, PDR and the Multigeneration Registry. The Multigeneration Registry includes data on relatives of all Swedish born people since 1961. Individuals with at least one first degree relative who had ≥2 in- or outpatient care visits listing a T1D or T2D diagnosis or ≥2 dispensations of a T2D drug (ATC A10B) were classified as having a family history of diabetes.

Age in years, sex, and residence (categorized into health regions) of the study population were obtained from the Total Population Register. Education level was obtained from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies and categorized into ≤9 years, 10 to 12 years, ≥12 years and missing. Country of birth was categorized as Nordic, non-Nordic or missing.

**Follow-up time**

Follow up started for individuals with sarcoidosis at second ICD-coded sarcoidosis visit or corticosteroid dispensation, whichever came last and for the non-sarcoidosis comparators at their corresponding matched index date. End of follow up was first dispensation of a T2D drug, first T2D diagnosis, emigration, death, or the end of follow up (December 31, 2013), whichever came first.

**Statistical analysis**

Cox proportional hazard models were used to estimate crude and adjusted hazard ratios of T2D. Cox models were adjusted for age, sex, education, health region, country of birth, and family history of diabetes. There were missing data on education (1.2%) and country of birth (0.4%). An additional category *missing* was created for these variables and individuals with missing data were included in all analysis.

Flexible parametric survival models were used to study the change in the T2D rate across the time of follow-up [19, 20]. The degrees of freedom for the flexible parametric models were chosen based on the AIC and BIC criteria [19]. The best fit was obtained using 3 degrees of freedom for the baseline hazard function, 3 degrees of freedom for the time-dependant effect of corticosteroid-treated sarcoidosis and 2 degrees of freedom for the spline function of mean-centred age. The knot position for the splines were chosen based on quantiles of the log survival time as recommended by Roysten and Parmar [20]. Results from flexible parametric models were reported as hazard ratios and as absolute hazard rates for an average person in

the data set (i.e. age equal to the mean age in the study population, with 10-12 years of education, living in Stockholm, born in a Nordic country and no family history of diabetes).

We used probabilistic bias analyses to examine the robustness of our results in the presence of unmeasured confounding of high body mass index (BMI) on the association between sarcoidosis and T2D [21]. The assumptions for the analysis are described in Table S2.

Because some patients could have been prescribed corticosteroids for another disease other than sarcoidosis, we performed an additional sensitivity analysis excluding individuals with any history of a disease before index date which requires long-term corticosteroid treatment (see table S4 for excluded diseases and ICD codes).

Statistical analyses and data management were performed using the statistical software environment R [22]. Cox models were estimated using the survival package for R [23], FPMs were estimated using the rstpm2 package for R [24].

**RESULTS**

5,754 unique individuals with sarcoidosis and 61,297 general population comparators were included in the study population. We excluded 598 individuals (9.2%) from the sarcoidosis group and 3,285 (5.1%) from the general population who had a history of diabetes before start of follow up (Chi-squared test p-value<0.01). Among individuals with sarcoidosis, 40% received a corticosteroid treatment around the time of diagnosis (Table 1). Corticosteroid-treated sarcoidosis patients had a lower median age and had fewer years of education compared to comparators and untreated sarcoidosis patients (Table 1). We found differences in the geographical distribution of corticosteroid treated and untreated sarcoidosis patients across health regions in Sweden. The geographical distribution of sarcoidosis patients and comparators were similar due to matching (Table 1).

During a median of 3.49 years of follow-up, we identified 1,222 incident T2D cases in the general population comparators, 95 in the untreated sarcoidosis group and 104 in the corticosteroid-treated sarcoidosis group (Table 2). Most T2D cases were identified through dispensations for anti-diabetic medications in the PDR (86%). The T2D rate was higher in both the corticosteroid-treated sarcoidosis group (12.7 per 1000 person-years) and the untreated sarcoidosis group (7.7 per 1000 person-years) compared to the general population comparators (5.5 per 1000 person-years; Table 3). The risk of T2D was 44% higher in untreated sarcoidosis patients compared to the general population (adjusted HR=1.44, 95%CI 1.17-1.77). The T2D risk was over two times higher among corticosteroid-treated sarcoidosis

patients compared to the general population (adjusted HR=2.44, 95% CI 2.00-2.99; Table 3). Results were similar after excluding 410 sarcoidosis patients and 1901 comparators who were diagnosed with a disease that requires a long-term corticosteroid treatment prior to their sarcoidosis diagnosis (Table S4).

The hazard ratio of T2D associated with untreated sarcoidosis was relatively stable over follow up (Figure 2). In contrast, there was an 8-fold increased T2D risk in corticosteroid-treated sarcoidosis compared to the general population during the first month of follow-up (HR=8.55; 95%CI 5.24-13.96) which decreased after 2 years of follow up to a 2-fold increased T2D risk. The HRs associated with corticosteroid-treated and untreated sarcoidosis were similar 2 years after sarcoidosis diagnosis.

Stratified by sex, the T2D rate was highest in males who received corticosteroid treatment at sarcoidosis diagnosis (15.0 per 1000 person-years; Table 3). The hazard ratios of T2D associated with untreated and corticosteroid-treated sarcoidosis were higher for males compared to females (untreated sarcoidosis: HR=1.52 in males vs. HR=1.37 in females, corticosteroid-treated sarcoidosis HR=3.22 in males vs. HR=1.95 in females). The proportion of sarcoidosis patients receiving a diagnosis with T2D increased with age at diagnosis as expected (Figure 3), and older corticosteroid-treated sarcoidosis patients had the highest cumulative incidence of T2D. For example, among 65-year-old female and male corticosteroid-treated sarcoidosis patients with otherwise average covariates, 10.0% (95%CI 7.3%-13.7%) and 15.3% (95%CI 11.2%-20.9%) were diagnosed with T2D over the course of the study, in total 8 years, respectively.

The probabilistic bias analysis accounting for the unmeasured confounding effect of high BMI yielded lower estimates than in the main analysis but there was still an increased risk for T2D associated with corticosteroid-treated sarcoidosis (untreated sarcoidosis HR=1.22, 95%CI 0.97-1.48; corticosteroid-treated sarcoidosis HR=2.07, 95%CI 1.66-2.51; Table S5 in supplement).

## DISCUSSION

In this large population-based cohort study, sarcoidosis was associated with an increased risk for T2D which was highest in corticosteroid-treated sarcoidosis patients. The relative risk associated with untreated sarcoidosis was stable over time since diagnosis. However, the T2D relative risk associated with corticosteroid-treated sarcoidosis was increased directly after diagnosis. At approximately 2 years after sarcoidosis diagnosis it decreased to the same level

as in the untreated group. The T2D rates were highest for male and older sarcoidosis patients compared to female and younger sarcoidosis patients.

Our observation of an increased T2D risk in sarcoidosis patients is in line with previous published studies from Sweden and the United States [10, 11], which found a 50-200% increased risk. However, neither study addressed differences in risk associated with treatment, which is an important modifier of the association.

The increased T2D risk in corticosteroid-treated sarcoidosis patients observed in our study soon after their sarcoidosis diagnosis might be a combined effect of the corticosteroid treatment [12-14, 16], a higher sarcoidosis severity and/or a higher screening level. Previous studies show that corticosteroid treatment has a direct effect both on the beta cell function, leading to impaired insulins secretion, and on the liver and muscle leading to insulin resistance and increased risk of T2D [12, 13, 17]. Initial need for treatment at sarcoidosis diagnosis is associated with poor sarcoidosis prognosis, as it indicates a higher disease severity [1, 3]. Treatment itself, however, might be harmful and may play a role in comorbidity development [25-27]. Additionally, treatment with corticosteroids might lead to a higher screening rate among these sarcoidosis patients, although the Swedish guidelines for sarcoidosis care do not suggest a routine T2D screening before and during corticosteroid-treatment of sarcoidosis patients [28]. The T2D incidence rate decreased in the corticosteroid-treated group after two years, which likely indicates that susceptible patients were diagnosed early after sarcoidosis diagnosis and a less susceptible population remained after two years.

Interestingly, we also observed an increased risk of T2D in the sarcoidosis group who did not receive corticosteroid treatment at diagnosis. This could partly be explained by the unmeasured confounding of high BMI, which is a risk factor for both T2D and sarcoidosis [29-31]. Even before diagnosis, patients with sarcoidosis had a higher prevalence of diabetes indicating a predisposition to develop T2D. Inflammation processes are known to be involved in the T2D pathogenesis, which might lead to an increased T2D risk in patients with chronic inflammatory diseases like sarcoidosis [32].

This study has several strengths with regard to methods and data sources. This is the first study to investigate the association between sarcoidosis and T2D with regard to corticosteroid use, an important factor associated with T2D. The large study population allowed for enough power to estimate associations stratified by patient characteristics. Due to the use of population-based register data, there was little loss to follow up and it is unlikely to be

differential between exposure and outcome groups. The use of flexible parametric models allowed us to investigate the hazard ratio of T2D associated with sarcoidosis across the follow-up time. Our findings may be generalisable to other populations with similar patterns of T2D risk modifiers, such as lifestyle habits.

Besides the above-mentioned strengths, our study also faces limitations. The reported estimates may be affected by unmeasured confounding through high BMI and smoking behaviour, since these data are not available from the registries used in this study. High BMI is a known risk factor for both sarcoidosis and T2D and is therefore a positive confounder of the association between sarcoidosis and T2D [29-31, 33]. In a probabilistic bias analysis, we showed that the increased T2D rate in corticosteroid-treated sarcoidosis patients cannot be explained by the confounding effect of high BMI. In contrast to high BMI, smoking is thought to be a negative confounder of the association between sarcoidosis [31, 34, 35] thus leading to an underestimation of the reported association between sarcoidosis and T2D. We are likely missing cases of T2D which were diagnosed in primary care and did not receive treatment. Between 2006 and 2013, 25% of diabetes patients in primary care did not receive any drug treatment [18]. If sarcoidosis patients are more likely than the general population to receive a T2D diagnosis in outpatient care or receive treatment, this may have led to an overestimation of the association between sarcoidosis and T2D. We only assessed the corticosteroid treatment status around the time of sarcoidosis diagnosis, which is when patients are most likely to receive treatment [36]. Two-thirds of treated patients were still on a corticosteroid treatment 6 months after their diagnosis. Our results should only be used to assess T2D risk in newly diagnosed sarcoidosis patients. Future studies should investigate the time-varying effect of corticosteroid treatment during follow-up and incorporate measures of disease severity, as these are highly intertwined.

In conclusion, sarcoidosis patients are at an increased risk of T2D, which is highest for corticosteroid-treated sarcoidosis patients within the first two years after their sarcoidosis diagnosis. Further, the T2D risk was higher for male and older sarcoidosis patients compared to female and younger sarcoidosis patients. The elevated T2D rate in corticosteroid-treated sarcoidosis patients indicates that screening for T2D in this patient group is advisable at disease onset.

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## TABLES

**Table 1** Study population characteristics of the general population comparators, untreated sarcoidosis patients and corticosteroid-treated sarcoidosis patients.

| | **General population comparators** | | **Sarcoidosis untreated** | | **Sarcoidosis corticosteroid-treated** | |
|---|---|---|---|---|---|---|
| | **No.** | **(%)** | **No.** | **(%)** | **No.** | **(%)** |
| Overall | 61 297 | | 3 448 | | 2 306 | |
| Survival time, years, median (IQR) | 3.5 | (1.7; 5.5) | 3.3 | (1.7; 5.4) | 3.5 | (1.5; 5.5) |
| Age, median (IQR) | 48.3 | (38.3; 61) | 48.4 | (38.4; 61) | 47.2 | (37.2; 60.4) |
| Sex | | | | | | |
| *Females* | 27 470 | (44.8) | 1 571 | (45.6) | 954 | (41.4) |
| *Males* | 33 827 | (55.2) | 1 877 | (54.4) | 1 352 | (58.6) |
| Family history of diabetes | 15 284 | (24.9) | 946 | (27.4) | 649 | (28.1) |
| Education | | | | | | |
| *≤ 9 years* | 12 069 | (19.7) | 633 | (18.4) | 478 | (20.7) |
| *10 to 12 years* | 28 297 | (46.2) | 1 669 | (48.4) | 1 192 | (51.7) |
| *≥ 12 years* | 20 185 | (32.9) | 1 098 | (31.8) | 620 | (26.9) |
| *Missing* | 746 | (1.2) | 48 | (1.4) | 16 | (0.7) |
| Health region | | | | | | |
| *Stockholm* | 12 586 | (20.5) | 839 | (24.3) | 349 | (15.1) |
| *Uppsala-Örebro* | 13 331 | (21.7) | 717 | (20.8) | 532 | (23.1) |
| *West* | 10 985 | (17.9) | 607 | (17.6) | 430 | (18.6) |
| *South* | 10 433 | (17) | 526 | (15.3) | 452 | (19.6) |
| *Southeast* | 7 114 | (11.6) | 337 | (9.8) | 322 | (14) |
| *North* | 6 848 | (11.2) | 422 | (12.2) | 221 | (9.6) |
| Country of birth | | | | | | |
| *Outside Nordics* | 7 568 | (12.3) | 366 | (10.6) | 204 | (8.8) |
| *Inside Nordics* | 53 483 | (87.3) | 3 066 | (88.9) | 2 097 | (90.9) |
| *Missing* | 246 | (0.4) | 16 | (0.5) | 5 | (0.2) |

IQR: Interquartile range.

**Table 2** Characteristics of the T2D cases among the general population comparators, untreated sarcoidosis patients and corticosteroid-treated sarcoidosis patients.

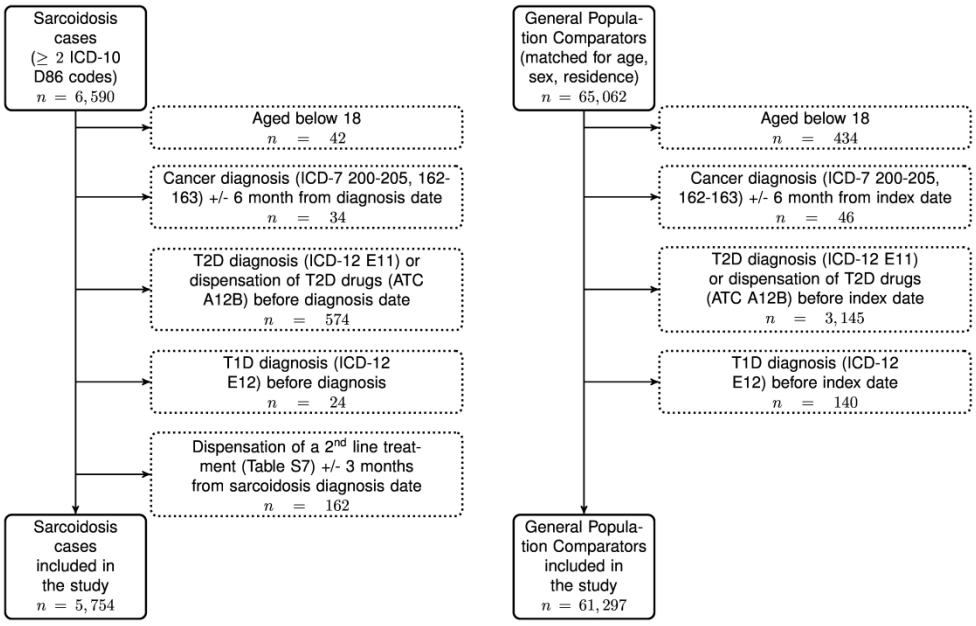
| | **General population comparators** | | **Sarcoidosis untreated** | | **Sarcoidosis corticosteroid-treated** | |
|---|---|---|---|---|---|---|
| | **No.** | **(%)** | **No.** | **(%)** | **No.** | **(%)** |
| Overall | 1222 | | 95 | | 104 | |
| Median age at T2D diagnosis, years (IQR) | 61.1 | (52.2; 69.2) | 62.4 | (52.3; 69.4) | 56.6 | (45.3; 64.4) |
| Male | 731 | (59.8) | 53 | (55.8) | 54 | (51.9) |
| Family history of diabetes | 506 | (41.4) | 32 | (33.7) | 48 | (46.2) |
| Register were T2D was first identified† | | | | | | |
| *Inpatient Register* | 79 | (6.5) | 12 | (12.6) | 11 | (10.6) |
| *Outpatient Register* | 72 | (5.9) | 9 | (9.5) | 17 | (16.3) |
| *Prescribed Drug Register* | 1071 | (87.6) | 74 | (77.9) | 76 | (73.1) |

IQR: Interquartile range.
†: Shows in which registries the T2D cases first reached criteria to be included as cases in this study.

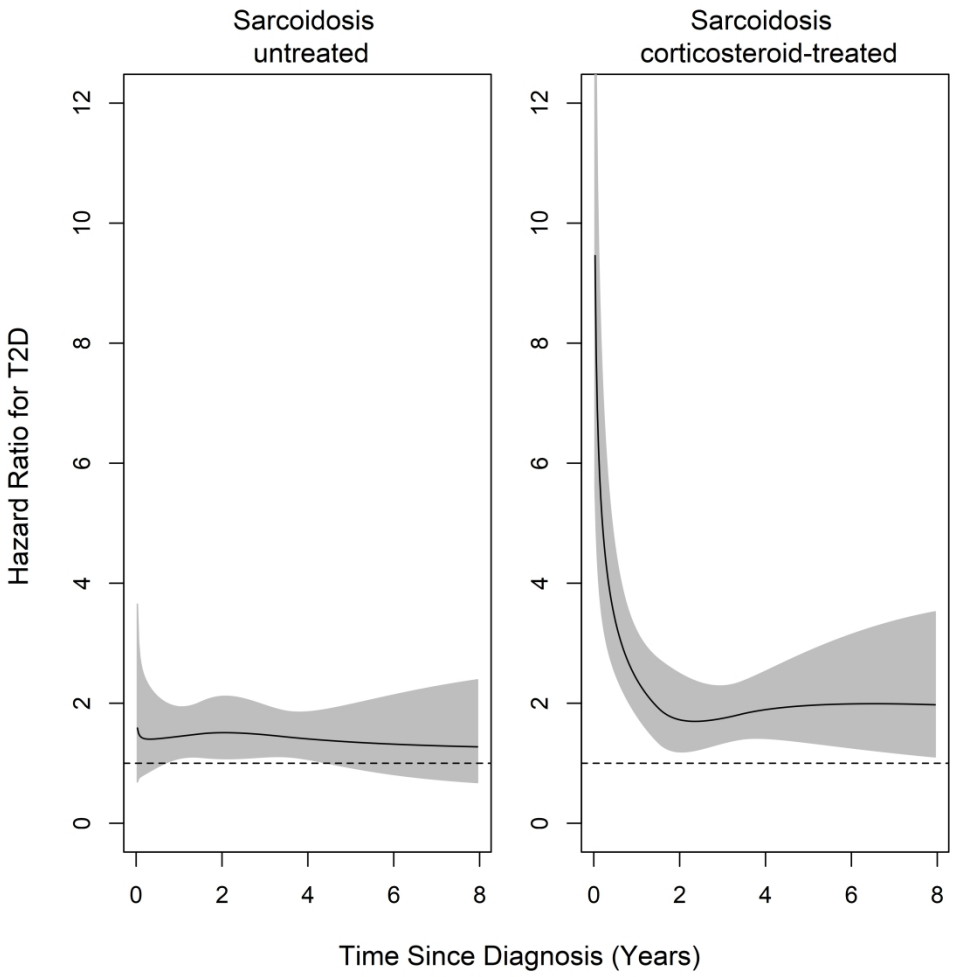
**Table 3** Crude incidence rates, hazard ratios (HR) and adjusted hazard ratios for T2D comparing matched general population comparators, untreated sarcoidosis patient and sarcoidosis patient treated with corticosteroids overall and stratified by sex.

| | No. Events | Survival time, yrs. | Incidence Rate† | Hazard Ratio 95%CI | | Adjusted HR‡ 95% CI | |
|---|---|---|---|---|---|---|---|
| **Overall** | | | | | | | |
| Gen. pop. comparators | 1 222 | 222 798 | 5.5 | 1 | (Reference) | 1 | (Reference) |
| Sarcoidosis untreated | 95 | 12 278 | 7.7 | 1.41 | (1.14-1.74) | 1.44 | (1.17-1.77) |
| Sarcoidosis corticosteroid-treated | 104 | 8 213 | 12.7 | 2.31 | (1.89-2.82) | 2.44 | (2.00-2.99) |
| **Males** | | | | | | | |
| Gen. pop. comparators | 491 | 100 525 | 4.9 | 1 | (Reference) | 1 | (Reference) |
| Sarcoidosis untreated | 42 | 5 591 | 7.5 | 1.54 | (1.12-2.10) | 1.52 | (1.11-2.08) |
| Sarcoidosis corticosteroid-treated | 50 | 3 335 | 15.0 | 3.08 | (2.30-4.12) | 3.22 | (2.40-4.31) |
| **Females** | | | | | | | |
| Gen. pop. comparators | 731 | 122 274 | 6.0 | 1 | (Reference) | 1 | (Reference) |
| Sarcoidosis untreated | 53 | 6 687 | 7.9 | 1.32 | (1.00-1.75) | 1.37 | (1.03-1.81) |
| Sarcoidosis corticosteroid-treated | 54 | 4 878 | 11.1 | 1.85 | (1.40-2.44) | 1.95 | (1.48-2.57) |

HR are presented as point estimate with 95% confidence intervals.
†: Incident rate per 1,000 person-years.
‡: Model is adjusted for mean centered age, education, family history of diabetes, birth country and county of residence.




Flow chart of the study population starting with incident sarcoidosis patients with ≥ 2 inpatient or outpatient visits listing a sarcoidosis diagnosis living in Sweden between 2006 and 2013, and their comparators.




Hazard ratio for type 2 diabetes comparing untreated sarcoidosis patients and sarcoidosis patients receivinga corticosteroid treatment with general population comparators without sarcoidosis. Hazard ratios wereobtained from the flexible parametric models and are adjusted for age, sex, education, region of residence,family history of diabetes and born in a Nordic country.

**SUPPLEMENT**

**Table S1** Number and percentage of sarcoidosis patients dispensed specific corticosteroids as first corticosteroid treatment.

| Agent name | ATC Code | No. | (%) |
|---|---|---|---|
| Betamethasone | H02AB01 | 179 | (7.8) |
| Dexamethasone | H02AB02 | 1 | (0) |
| Fluocortolone | H02AB03 | 0 | (0) |
| Methylprednisolone | H02AB04 | 33 | (1.4) |
| Paramethasone | H02AB05 | 0 | (0) |
| Prednisolone | H02AB06 | 2039 | (88.4) |
| Prednisone | H02AB07 | 37 | (1.6) |
| Triamcinolone | H02AB08 | 2 | (0.1) |
| Hydrocortisone | H02AB09 | 15 | (0.7) |
| Cortisone | H02AB10 | 0 | (0) |
| Prednylidene | H02AB11 | 0 | (0) |
| Rimexolone | H02AB12 | 0 | (0) |
| Deflazacort | H02AB13 | 0 | (0) |
| Cloprednol | H02AB14 | 0 | (0) |
| Meprednisone | H02AB15 | 0 | (0) |
| Cortivazol | H02AB17 | 0 | (0) |

**Table S2** Assumptions for the probabilistic sensitivity analysis of the unmeasured confounding effect of BMI on the association of between sarcoidosis and T2D.

| | Estimate | 95% CI | | SD | Distribution | Source |
|---|---|---|---|---|---|---|
| **Prevalence of overweight** | | | | | | |
| Sweden | 0.36 | 0.35 | 0.37 | 0.005 | Normal | [29] |
| Sarcoidosis patients | 0.37 | 0.32 | 0.42 | 0.023 | Normal | [30] |
| **Prevalence of obesity** | | | | | | |
| Sweden | 0.14 | 0.13 | 0.15 | 0.005 | Normal | [29] |
| Sarcoidosis patients | 0.21 | 0.17 | 0.25 | 0.020 | Normal | [30] |
| **RR of T2D by BMI** | | | | | | |
| 18.5 < BMI < 25 | 1 | | | | | |
| 25 < BMI < 30 | 2.92 | 2.42 | 3.71 | 0.403 | Normal | [27] |
| 30 < BMI | 7.24 | 6.38 | 8.23 | 0.505 | Normal | [27] |
| **RR of T2D in sarcoidosis** | | | | | | |
| General population comparators | 1 | | | | | |
| Sarcoidosis untreated | 1.44 | 1.17 | 1.77 | 0.168 | Normal | [Table 3] |
| Sarcoidosis corticosteroid-treated | 2.44 | 2.00 | 2.99 | 0.281 | Normal | [Table 3] |

SD: standard deviation, RR: Rate Ratio.

**Table S3** Diseases and ICD codes considered for the exclusion of sarcoidosis patients with disease that require a long-term corticosteroid treatment other than sarcoidosis.

| Disease | ICD-10 codes | ICD-9 codes | ICD-8 codes |
|---|---|---|---|
| Inflammatory bowel disease | K50, K51 | 555, 556 | 563.00, 563.10, 569.02 |
| Ankylosing spondylitis | M45 | 720A | 712.40, 726.99 |
| Juvenile arthritis | M08-M09 | 714D | 712.00 |
| Systemic lupus erythematosus | M32.1, M32.8-M32.9 | 710A | 734.10 |
| Arthropathic psoriasis | L40.5, M07.0, M07.1, M07.3 | 696A, 713D | 696.00 |
| Psoriasis | L40 | 696 | 696 |
| Rheumatoid arthritis | M05-M05.9, M06.0, M06.2, M06.3, M06.8, M06.9, M12.3 | 714A-714C, 714W, 719D | 712.10, 712.20, 712.38, 712.39 |
| Spinal enthesopathy | M46.0, M46.1, M46.8, M46.9 | 720C, 720W, 720X | 713.13, 726.99 |
| Sjögren's syndrome | M35.0 | 710C | 734.90 |
| Myositis | M60.8, M60.9, M33.0-M33.2, G72.4 | 710C, 710D, 710E | 734.90, 732.00-732.90 |
| Drug-induced interstitial lung disorder | J70.2-J70.4 | 508W-508X | |
| Hypersensitivity pneumonitis | J67 | 495 | |
| Idiopathic thrombocytopenic purpura | D69.3 | 287C | |
| Interstitial pulmonary fibrosis | J84.1 | 515 | |
| Systemic sclerosis | M34 | 710B | |
| Vasculopathies | M31 | 446-447 | 446-447 |

**Table S4** Crude incidence rates (IR), hazard rate ratios (HR) and adjusted hazard rate ratios (HRadj) for T2D comparing matched general population comparators, untreated sarcoidosis patient and sarcoidosis patient treated with corticosteroids (CS) overall and stratified by sex after exclusion of patients with a history of disease that requires long-term corticosteroid treatment.

| | No. Events | Survival time, yrs. | Incidence Rate† | Hazard Ratio 95%CI | | Adjusted HR‡ 95% CI | |
|---|---|---|---|---|---|---|---|
| **Overall** | | | | | | | |
| Gen. pop. comparators | 1181 | 216557 | 5.5 | 1 | (Reference) | 1 | (Reference) |
| Sarcoidosis untreated | 90 | 11754 | 7.7 | 1.4 | (1.13-1.74) | 1.43 | (1.15-1.77) |
| Sarcoidosis corticosteroid-treated | 93 | 7488 | 12.4 | 2.28 | (1.85-2.82) | 2.46 | (1.99-3.04) |
| **Males** | | | | | | | |
| Gen. pop. comparators | 469 | 96916 | 4.8 | 1 | (Reference) | 1 | (Reference) |
| Sarcoidosis untreated | 38 | 5267 | 7.2 | 1.49 | (1.07-2.07) | 1.46 | (1.05-2.04) |
| Sarcoidosis corticosteroid-treated | 42 | 2933 | 14.3 | 2.97 | (2.16-4.07) | 3.15 | (2.30-4.33) |
| **Females** | | | | | | | |
| Gen. pop. comparators | 712 | 119641 | 6.0 | 1 | (Reference) | 1 | (Reference) |
| Sarcoidosis untreated | 52 | 6487 | 8.0 | 1.34 | (1.01-1.78) | 1.39 | (1.05-1.84) |
| Sarcoidosis corticosteroid-treated | 51 | 4555 | 11.2 | 1.88 | (1.41-2.50) | 2.01 | (1.51-2.68) |

HR are presented as point estimate with 95% confidence intervals.
†: Incident rate per 1,000 person-years.
‡: Model is adjusted for mean centered age, education, family history of diabetes, birth country and county of residence.

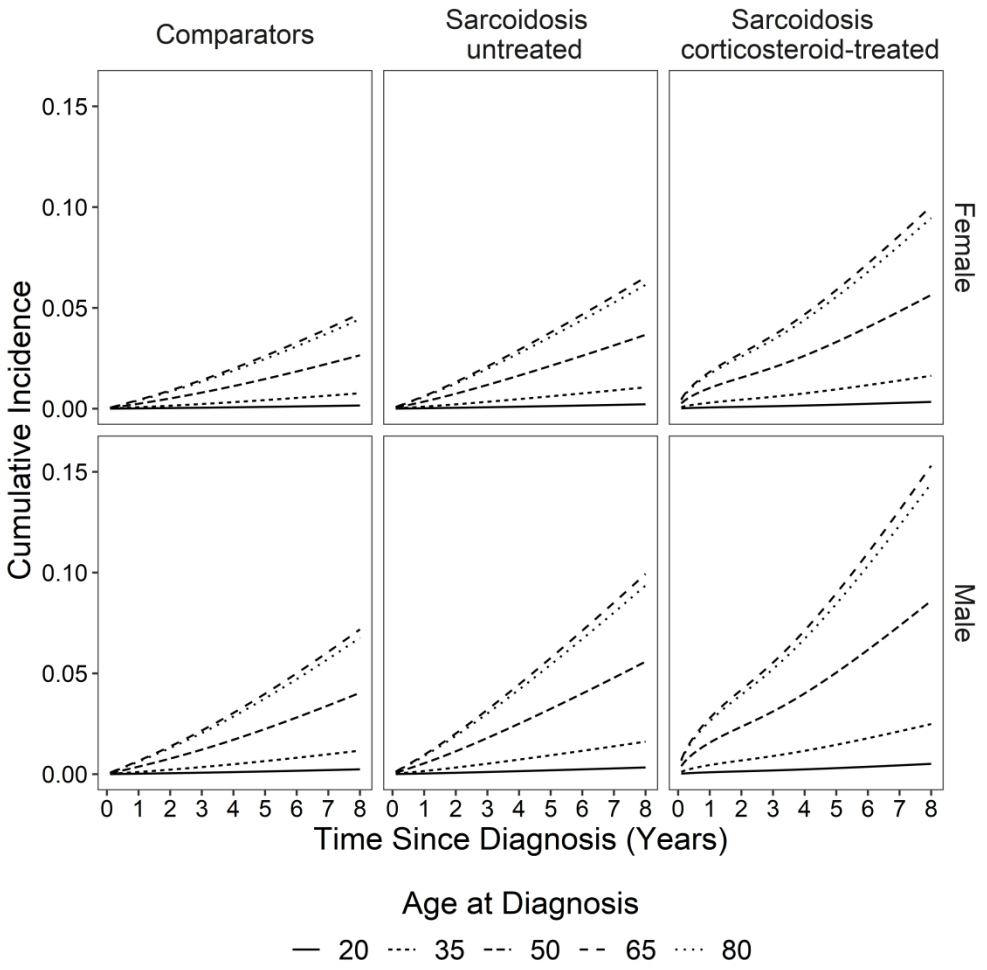
**Table S5** Results from the probabilistic sensitivity analysis of the unmeasured confounding effect of BMI on the association between sarcoidosis and T2D.

| | **Exposure groups** | | | |
|---|---|---|---|---|
| | **Sarcoidosis untreated** | | **Sarcoidosis corticosteroid-treated** | |
| RR not adj. for BMI | 1.44 | (1.17-1.77) | 2.44 | (2.00-2.99) |
| RR adj. for BMI | 1.22 | (0.97-1.48) | 2.07 | (1.66-2.51) |

The hazard rate ratios not adjusted for BMI are obtained from the cox model presented in Table 3. The rate ratios (RR) obtained from the sensitivity analysis are presented as median hazard rate ratio and 5th and 95th quantile of the bootstrapped (n = 10,000) hazard rate ratios adjusted for the effect of BMI.

**Table S6** ATC codes used to identify patients dispensing second line treatment drugs for sarcoidosis.

| Agent name | ATC code |
|---|---|
| Methotrexate | L01BA01, L04AX03 |
| Azathioprine | L04AX01 |
| Leflunomide | L04AA13 |
| Mycophenolate mofetil | L04AA06 |
| Hydroxychloroquine | P01BA02 |




Cumulative incidence of T2D comparing general population comparators with untreated sarcoidosis patientsand sarcoidosis patients receiving a corticosteroid treatment. The cumulative incidences were obtained foran average person in the data set using the flexible parametric survival model.