



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

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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 with the general population.

Methods: In this cohort study, individuals with two or more International Statistical Classification of Diseases and Related Health Problems (ICD) codes for sarcoidosis were identified from the Swedish National Patient Register (NPR) (n=5754). Corticosteroid dispensations within 3 months before or after the first sarcoidosis diagnosis were identified from the Swedish Prescribed Drug Register (PDR). General population comparators without sarcoidosis were matched to cases 10:1 on age, sex and region of residence (n=61297). Incident T2D was identified using ICD codes (NPR) and antidiabetic drug dispensations (PDR). Follow-up was from the second sarcoidosis diagnosis/matching date until T2D, emigration, death or study end (December 2013). Cox regression models adjusted for age, sex, education, country of birth, healthcare regions and family history of diabetes were used to estimate hazard ratios (HRs). We used flexible parametric models to examine the T2D risk over time.

Results: 40% of sarcoidosis patients were treated with corticosteroid at diagnosis. The T2D rate was 7.7 per 1000 person-years in untreated sarcoidosis, 12.7 per 1000 person-years in corticosteroid-treated sarcoidosis and 5.5 per 1000 person-years 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.

Conclusions: 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.



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Corticosteroid-treated sarcoidosis patients have a high risk of developing type 2 diabetes within 2 years after their sarcoidosis diagnosis. The risk is higher for male and older patients compared with female and younger patients. <https://bit.ly/3l6mkXM>

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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 with 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 (BMI), 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 also considering 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 two or more visits listing a sarcoidosis diagnosis (International Statistical Classification of Diseases and Related Health Problems (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 categorised into two groups: untreated sarcoidosis and corticosteroid-treated sarcoidosis at diagnosis. All sarcoidosis patients with a corticosteroid dispensation (Anatomical Therapeutic Chemical (ATC) H02AB) within 3 months before or after their first sarcoidosis diagnosis were identified as corticosteroid-treated sarcoidosis (see supplementary 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 before or after 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, this group should be studied separately, which was not possible due to few observations in this group. A flowchart of the study population is shown in figure 1. The date of inclusion into the cohort was the date of second sarcoidosis diagnosis or the 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 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 the index date. Individuals with a previous history of diabetes (type 1 and type 2) before the 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 the trachea, bronchus or lung (ICD-7 162–163) within 6 months before or after 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 two or more inpatient or outpatient visits listing an ICD code for T2D (ICD-10 E11) in the NPR during follow-up or two or more dispensations of a blood glucose lowering drug excluding insulin (ATC A10B) in the PDR during follow-up. In Sweden,

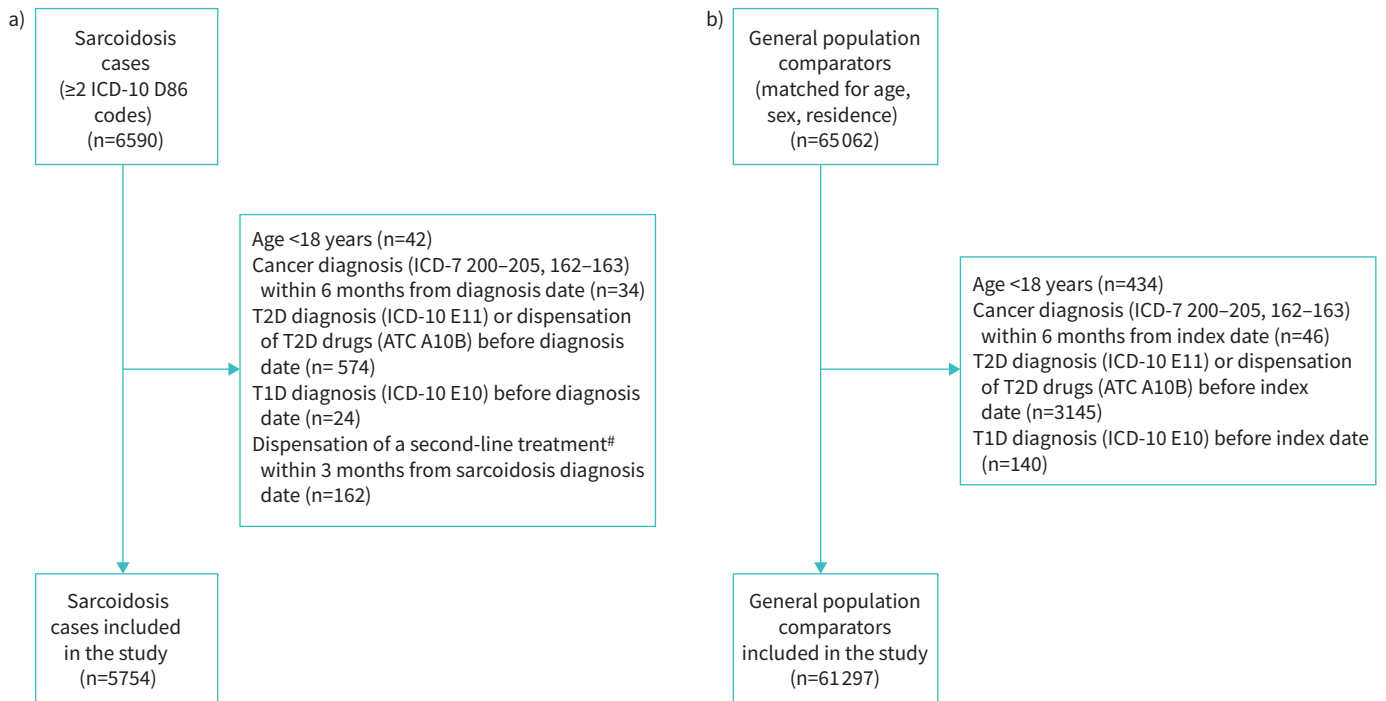


FIGURE 1 Flowchart of a) the study population starting with incident sarcoidosis patients with two or more inpatient or outpatient visits listing a sarcoidosis diagnosis living in Sweden between 2006 and 2013, and b) their comparators. ICD: International Statistical Classification of Diseases and Related Health Problems; T2D: type 2 diabetes mellitus; ATC: Anatomical Therapeutic Chemical; T1D: type 1 diabetes mellitus. #: see supplementary table S6.

most T2D patients receive their T2D diagnosis in primary care settings, therefore we used T2D drug dispensations to 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 Register. The Multigeneration Register includes data on relatives of all people born in Sweden since 1961. Individuals with at least one first-degree relative who had two or more inpatient or outpatient care visits listing a diabetes (type 1 or type 2) diagnosis or two or more dispensations of a T2D drug (ATC A10B) were classified as having a family history of diabetes.

Age in years, sex and residence (categorised 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 categorised into ≤9, 10–12 or ≥13 years, or missing. Country of birth was categorised as Nordic or non-Nordic, or missing.

Follow-up time

Follow-up started for individuals with sarcoidosis at the 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 the first dispensation of a T2D drug, first T2D diagnosis, emigration, death or end of follow-up (31 December 2013), whichever came first.

Statistical analysis

Cox proportional hazard models were used to estimate crude and adjusted hazard ratios (HRs) 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 “missing” category 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 T2D rate across the time of follow-up [19, 20]. The degrees of freedom for the flexible parametric models were chosen based on the Akaike Information Criterion and Bayesian Information Criterion [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 was chosen based on quantiles of the log survival time as recommended by ROYSTEN and PARMAR [20]. Results from the flexible parametric model were reported as hazard ratios and as absolute hazard rates for an average person in the dataset (*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 BMI on the association between sarcoidosis and T2D [21]. The assumptions for the analysis are described in supplementary 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 the index date that required long-term corticosteroid treatment (see supplementary table S3 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] and flexible parametric models were estimated using the rstpm2 package for R [24].

Results

5754 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 3285 (5.1%) from the general population who had a history of diabetes before the start of follow-up (Chi-squared test, $p < 0.01$). 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 with 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 was similar due to matching (table 1).

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

	General population comparators	Untreated sarcoidosis	Corticosteroid-treated sarcoidosis
Subjects	61 297	3448	2306
Survival time years	3.5 (1.7–5.5)	3.3 (1.7–5.4)	3.5 (1.5–5.5)
Age years	48.3 (38.3–61.0)	48.4 (38.4–61.0)	47.2 (37.2–60.4)
Sex			
Female	27 470 (44.8)	1571 (45.6)	954 (41.4)
Male	33 827 (55.2)	1877 (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)
10–12 years	28 297 (46.2)	1669 (48.4)	1 192 (51.7)
≥13 years	20 185 (32.9)	1098 (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 (17.0)	526 (15.3)	452 (19.6)
Southeast	7 114 (11.6)	337 (9.8)	322 (14.0)
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)	3066 (88.9)	2097 (90.9)
Missing	246 (0.4)	16 (0.5)	5 (0.2)

Data are presented as n, median (interquartile range) or n (%).

During a median of 3.49 years of follow-up, we identified 1222 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 of antidiabetic 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 with the general population comparators (5.5 per 1000 person-years) (table 3). The risk of T2D was 44% higher in untreated sarcoidosis patients compared with 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 with 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 required a long-term corticosteroid treatment prior to their sarcoidosis diagnosis (supplementary table S4).

The hazard ratio of T2D associated with untreated sarcoidosis was relatively stable over follow-up (figure 2a). In contrast, there was an 8-fold increased T2D risk in corticosteroid-treated sarcoidosis compared with 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 (figure 2b). The hazard ratios 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 with females (untreated sarcoidosis HR 1.52 in males *versus* HR 1.37 in females; corticosteroid-treated sarcoidosis HR 3.22 in males *versus* 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%), respectively, were diagnosed with T2D over the course of the study, in total 8 years.

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) (supplementary table S5).

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 hazard ratio associated with untreated sarcoidosis was stable over time since diagnosis. However, the T2D hazard ratio associated with corticosteroid-treated sarcoidosis was increased directly after diagnosis. At ~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 with female and younger sarcoidosis patients.

TABLE 2 Characteristics of the type 2 diabetes mellitus (T2D) cases among the general population comparators, untreated sarcoidosis patients and corticosteroid-treated sarcoidosis patients

	General population comparators	Untreated sarcoidosis	Corticosteroid-treated sarcoidosis
Subjects	1222	95	104
Age at T2D diagnosis years	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 where 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]

Data are presented as n, median [interquartile range] or n [%]. [#]: shows in which registers the T2D cases first reached criteria to be included as cases in this study.

TABLE 3 Crude incidence rates, hazard ratios and adjusted hazard ratios for type 2 diabetes mellitus comparing matched general population comparators, untreated sarcoidosis patients and corticosteroid-treated sarcoidosis patients overall and stratified by sex

	Events n	Survival years	Incidence rate [#]	HR (95% CI)	Adjusted HR [¶] (95% CI)
Overall					
General population comparators	1222	222 798	5.5	1 (reference)	1 (reference)
Untreated sarcoidosis	95	12 278	7.7	1.41 (1.14–1.74)	1.44 (1.17–1.77)
Corticosteroid-treated sarcoidosis	104	8 213	12.7	2.31 (1.89–2.82)	2.44 (2.00–2.99)
Males					
General population comparators	491	100 525	4.9	1 (reference)	1 (reference)
Untreated sarcoidosis	42	5 591	7.5	1.54 (1.12–2.10)	1.52 (1.11–2.08)
Corticosteroid-treated sarcoidosis	50	3 335	15.0	3.08 (2.30–4.12)	3.22 (2.40–4.31)
Females					
General population comparators	731	122 274	6.0	1 (reference)	1 (reference)
Untreated sarcoidosis	53	6 687	7.9	1.32 (1.00–1.75)	1.37 (1.03–1.81)
Corticosteroid-treated sarcoidosis	54	4 878	11.1	1.85 (1.40–2.44)	1.95 (1.48–2.57)

[#]: per 1000 person-years; [¶]: model adjusted for mean-centred age, education, family history of diabetes, birth country and county of residence.

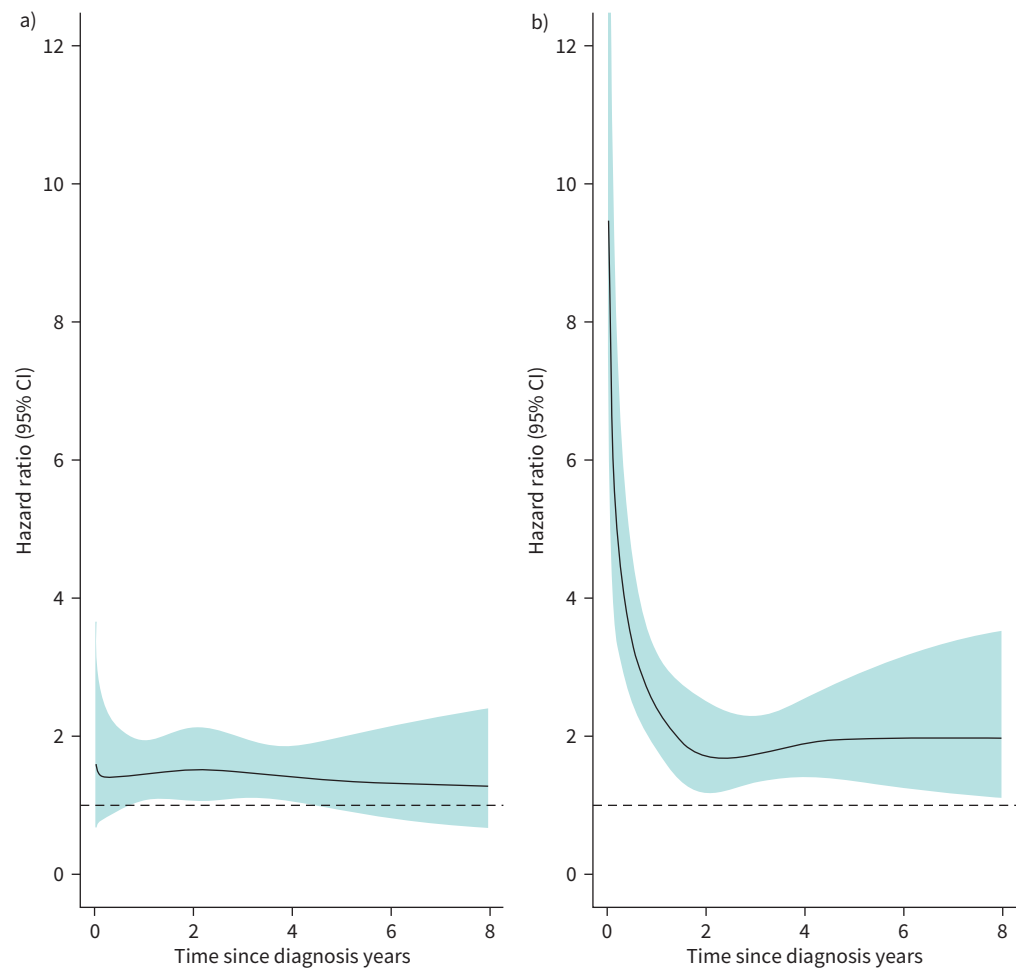


FIGURE 2 Hazard ratio for type 2 diabetes mellitus comparing a) untreated sarcoidosis patients and b) corticosteroid-treated sarcoidosis patients with general population comparators without sarcoidosis. Hazard ratios were obtained from the flexible parametric models, and are adjusted for age, sex, education, region of residence, family history of diabetes and born in a Nordic country.

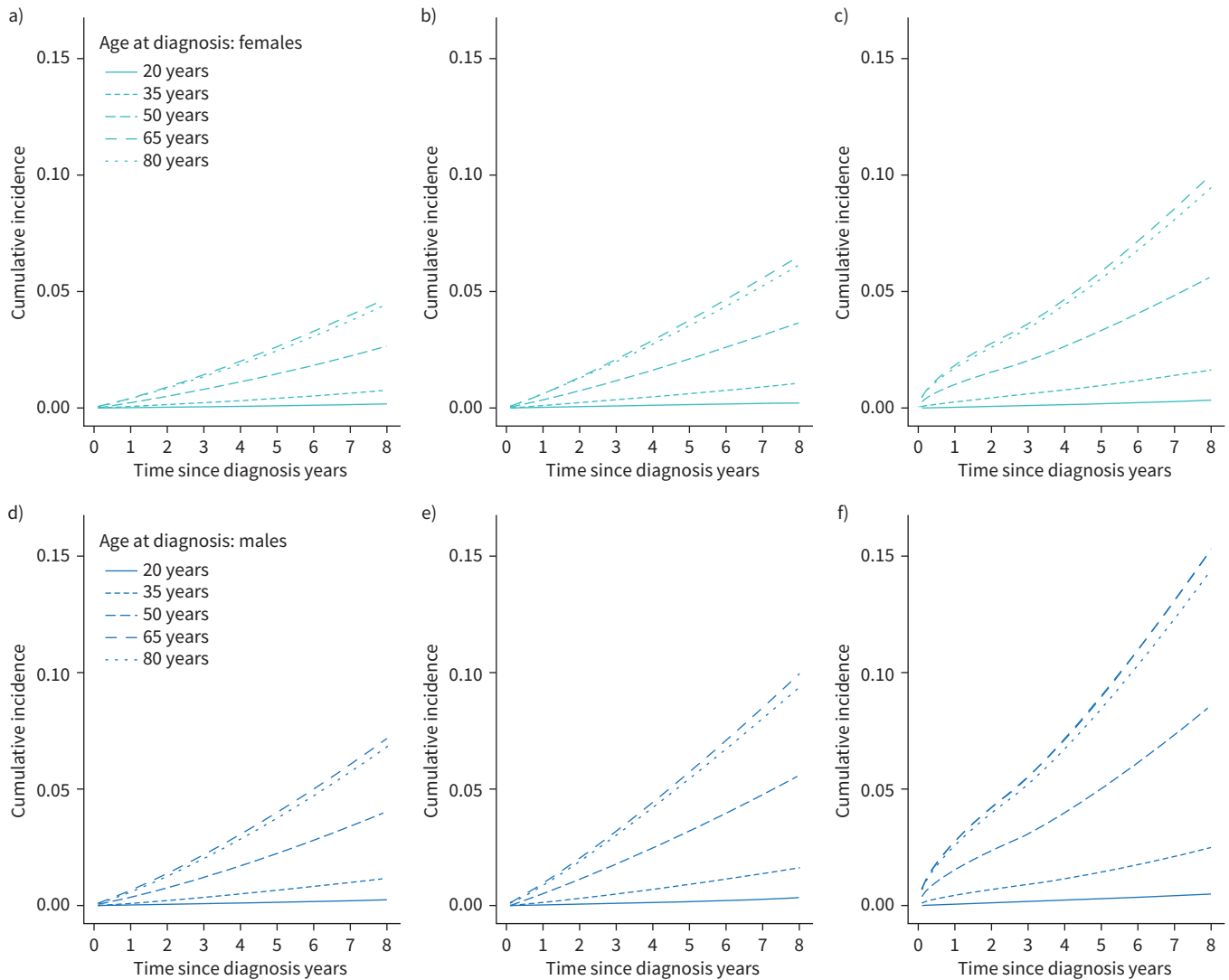


FIGURE 3 Cumulative incidence of type 2 diabetes mellitus comparing a, d) general population comparators with b, e) untreated sarcoidosis patients and c, f) corticosteroid-treated sarcoidosis patients in a–c) females and d–f) males. The cumulative incidences were obtained for an average person in the dataset using the flexible parametric survival model.

Our observation of an increased T2D risk in sarcoidosis patients is in line with previous published studies from Sweden and the USA that found a 50–200% increased risk [10, 11]. 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 β -cell function, leading to impaired insulin secretion, and on 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 routine T2D screening before and during corticosteroid treatment of sarcoidosis patients [28]. The T2D incidence rate decreased in the corticosteroid-treated group after 2 years, which likely indicates that susceptible patients were diagnosed early after sarcoidosis diagnosis and a less susceptible population remained after 2 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 T2D pathogenesis, which might lead to an increased T2D risk in patients with chronic inflammatory diseases such as 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.

Our study also has some limitations. The reported estimates may be affected by unmeasured confounding through high BMI and smoking behaviour, since these data are not available from the registers 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 2 years after their sarcoidosis diagnosis. Furthermore, the T2D risk was higher for male and older sarcoidosis patients compared with 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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Author contributions: J.P. Entrop: conceptualisation, formal analysis, visualisation, interpretation of data and writing (original draft, review and editing). S. Kullberg, J. Grunewald, A. Eklund and K. Brismar: interpretation of data and writing (review and editing). E.V. Arkema: conceptualisation, funding acquisition, supervision, interpretation of data and writing (review and editing).

Conflict of interest: None declared.

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