Department of Global Public Health

Master Programme in Public Health Sciences
Public Health Epidemiology

Degree Project, 30 credits

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The association between sarcoidosis and type 2 diabetes mellitus stratified by corticosteroid treatment at sarcoidosis diagnosis: a registry-based matched cohort study

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Department of Global Public Health

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Background: Recent studies showed an increased risk of type 2 diabetes mellitus (T2D) in sarcoidosis patients. However, the association between corticosteroid (CS) treatment and the T2D rate in sarcoidosis patients is unknown.

Aim: To determine if the risk of type 2 diabetes mellitus is associated with untreated and CS-treated sarcoidosis.

Setting: Sweden (2006 till 2013).

Methods: In this matched cohort study exposed individuals with sarcoidosis were identified using diagnosis codes from the National Patient registry. A general population comparator without sarcoidosis was matched on age, sex and region of residence by a 1:10 ratio. The outcome T2D was identified using T2D diagnoses and T2D drug dispensation form the National Patient and Prescribed Drug Registry. Follow-up started from receiving CS treatment or index date until T2D, death, emigration, or end of follow-up (Dec 31, 2013). Cox and flexible parametric models adjusted for age, sex, education, family history of diabetes and health region estimated hazard ratios (HR).

Results: A total of 7,844 individuals with sarcoidosis (2,754 CS-treated) and 84,560 comparators were included. The T2D incidence rate was 8.44/1000 person-years in untreated sarcoidosis, 12.68 in CS-treated sarcoidosis and 5.74 in comparators. The adjusted HR was 1.52 ($CI_{95\%}$: 1.29-1.79) for untreated sarcoidosis and 2.41 ($CI_{95\%}$: 2.01-2.90) for CS-treated sarcoidosis. The result of the flexible parametric models showed the T2D rate was highest for CS-treated sarcoidosis patients within the first 2 years after sarcoidosis diagnosis.

Conclusion: Sarcoidosis is associated with an increased T2D rate, which is highest for CS-treated sarcoidosis patients at diagnosis.

Keywords: Diabetes Mellitus, Type 2; Sarcoidosis; Corticosteroids; Sweden

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List of Abbreviations

BMI	Body mass index
CS	Corticosteroids
DM	Diabetes mellitus
FPM	Flexible parametric survival models
GDPR	General Data Protection Regulation
IHME	Institute for Health Metrics and Evaluation
LISA	Swedish longitudinal integrated database for health insurance and labour market studies
NPR	Swedish National Patient Registry
PDR	Prescribed drug registry
T1D	Type one diabetes mellitus
T2D	Type two diabetes mellitus
TPR	Swedish Total Population Registry
US	United States of America
YLD	Year lived with disability

1. Background

1.1. Sarcoidosis

Sarcoidosis is a disease with inflammatory components that is characterised by the occurrence of granulomas in any organ, albeit it mostly affects the lungs [1]. In general little is known about the aetiology of sarcoidosis, however, some studies implicate an involvement of genetic [2–4] and environmental factors [4] as the disease prevalence varies across regions and populations [5]. The natural course of the disease varies from natural resolution to more severe progression, which may require acute medical interventions such as lung, heart or liver transplantations [1]. The proportion of females and males among sarcoidosis patients varies between countries [1]. In Sweden sarcoidosis patients are more likely to be male (55%) than female (45%) [6]. The average age at sarcoidosis diagnoses is 50.2 years in Sweden [6]. However, there are substantial differences in the age at sarcoidosis diagnosis by sex [6]. A study from Sweden showed that males are diagnosed 10 years earlier in life compared to females [6].

The first line treatment for sarcoidosis are corticosteroids (CS). In Sweden approximately 40% of sarcoidosis patients receive a CS-treatment around the time of their sarcoidosis diagnosis [7]. Corticosteroids are used for the treatment of the inflammatory component of sarcoidosis due to their anti-inflammatory effect [1]. Commonly they are used for the treatment of patients with severer symptoms which might indicate a more sever progression of the disease [1,8]. Besides corticosteroids other second line treatments can be used for the treatment of sarcoidosis, in case of complications with the corticosteroid treatment [1]. In Sweden these treatments are used in > 5% of the sarcoidosis patients around the time of their sarcoidosis diagnosis [7].

Sweden is among the countries that are most affected by sarcoidosis with regard to disease incidence [1]. A study from 2016 estimated a sarcoidosis incidence of 11.5 per 100,000 person-years in Sweden [6]. Additionally, the mortality risk was 61 % ($CI_{95\%}$:1.47, 1.76) higher among sarcoidosis patients compared to the general population in Sweden [8]. The Institute for Health Metrics and Evaluation (IHME) estimated that 78.74 ($CI_{95\%}$: 57.81, 94.49) disability adjusted life years per 100,000 inhabitants were lost in Sweden in 2017 due to pulmonary sarcoidosis and interstitial lung diseases [9]. Thus, persons affected by sarcoidosis face a substantial health burden.

1.2. Diabetes

One disease that may contribute to this health burden of sarcoidosis patients is diabetes mellitus (DM) [10,11]. DM is characterised by an impaired blood glucose uptake, which leads to an exceeded blood glucose level [12]. The reason for this impaired blood glucose uptake varies across different types of DM. In type 1 diabetes (T1D) the impaired blood glucose uptake is caused by a decreased insulin production and segregation [13]. Conversely, in the most common type of DM, type 2 diabetes mellitus (T2D), the blood glucose uptake is impaired by an insulin resistance of various cell types for instance muscle, liver and hepatic cells [12].

T2D is known to be strongly associated with lifestyle risk factors such as physical activity, dietary habits and stress [14] and leads to a high health burden worldwide and in Sweden [15,16]. According to the global burden of disease study, DM is among the top ten leading causes of death for both females and males worldwide in 2017 [15]. In Sweden, T2D led to 5.35 % ($CI_{95\%}$: 4.50 %, 6.24 %) of all years lived with disability (YLDs) in 2017 [16], which makes T2D the third leading cause of YLDs in Sweden in 2017 [17]. Furthermore, a study from 2015 predicted a 50 % increase in diabetes prevalence over the next few decades, with 10 % of the population predicted to have the disease in 2050 [18]. Hence, T2D may become an even more important public health issue in Sweden in the future.

1.3. Sarcoidosis and type 2 diabetes

Inflammatory disease are among various other factors hypothesised to increase the T2D risk [14,19]. The framework *Schematic representation of risk factors for T2D with convincing or highly suggestive evidence*, visualises a variety of factors involved in the genesis of diabetes [14]. Besides lifestyle, dietary and psychological factors, also the individual's medical history influences the risk of T2D [14]. One biological process that is hypothesized to play an important role in the onset of T2D is inflammation [19]. Hence, sarcoidosis may lead to an increased T2D risk due to its inflammatory component [1,19]. Nevertheless, whether a sarcoidosis patient develops diabetes depends on the interplay between the different risk factors mentioned above, as indicated by the framework [14].

Thus far, there have only been two studies, that investigated this association of diabetes and sarcoidosis and both suggest an increased risk of diabetes for sarcoidosis patients [10,11]. One of these studies on the association between sarcoidosis and T2D did not specifically focus on the T2D risk among sarcoidosis patients but estimated the pooled overall DM risk instead [11].

The DM risk was estimated to be increased by 53 % ($CI_{95\%}$: 1.13-2.07) in sarcoidosis patients compared to general population comparators [11]. Notwithstanding, T1D is usually diagnosed in younger ages [20] whereas sarcoidosis is most common in older ages [1]. Hence, it might be unlikely that T1D is a cause of sarcoidosis. Thus, it might be more precise to focus on the T2D risk in sarcoidosis patients which was done in another study from Sweden [10]. The authors of this study focused on the association between T2D and a variety of autoimmune diseases [10]. In their study they reported a 2.11 ($CI_{95\%}$: 1.95, 2.28) times higher T2D risk among sarcoidosis patients compared to the general population in Sweden [10].

However, none of the above-mentioned studies accounted for the effect of corticosteroid use on the association between sarcoidosis and T2D. Corticosteroids are known to be associated with an increased T2D risk due to a steroid induced insulin resistance [21–24]. This insulin resistance occurs soon after the initiation of a steroid treatment and diminishes after discontinuation [25,26]. Hence corticosteroids may modify the association between sarcoidosis and T2D and contribute to the observed increased T2D risk in sarcoidosis patients [21,24,27]. Thus, there might be a substantial difference in the T2D risk among untreated sarcoidosis patients and sarcoidosis patients receiving a corticosteroid treatment.

1.4. Knowledge gap

So far, we do not know how corticosteroid use affects the T2D risk in sarcoidosis patients. Hence, the overall evidence on T2D risk in sarcoidosis patients is limited [10,11]. However, stronger evidence is needed on the association between sarcoidosis and T2D which may be integrated into guidelines for sarcoidosis patients and improve care of sarcoidosis patients.

2. Aim and research questions

This study aims to determine if the risk of type 2 diabetes mellitus is associated with untreated and CS-treated sarcoidosis.

Therefore, the research questions for this study are as follows:

1. Is there an increased rate of T2D among untreated sarcoidosis patients and sarcoidosis patients treated with corticosteroids compared to individuals without sarcoidosis?
2. How does the rate of T2D associated with sarcoidosis change over time stratified by corticosteroid use?

3. How does the rate of T2D associated with sarcoidosis vary by age and sex stratified by corticosteroid use?

3. Methods

3.1. Study design

To investigate the research questions a matched open cohort study design has been used [28]. In this matched open cohort study exposed individuals were randomly matched to unexposed individuals from the general population on an individual level. The matching was conducted in a density-based fashion by time of occurrence with regard to possible confounding factors such as year of birth, sex and county of residence [28]. In contrast to a closed cohort study an open cohort study allows participants to enter the study population during the time of follow up. This increases the sample size and the generalisability of the findings [28]. In a matched cohort study individuals are matched based on their exposure status whereas in a case-control study they are matched based on their outcome status [28]. Aim of the matching is a more homogeneous distribution of possible confounding factors between the exposure groups, in case of a matched cohort study, or the outcome groups, in case of a case-control study [28]. This leads to a higher efficiency of the statistical analysis, since the matching on confounding variables accounts partially or completely for confounding effects, depending on the combination of study design and question [28]. A schematic illustration of the study design is shown in Figure 5 in the appendix.

There are several reasons why this study design has been chosen. *First*, a cohort study design allows to study the temporal relationship between exposure and outcome which is in accordance with the study aim of this thesis [28]. *Second*, sarcoidosis patients are known to differ from the general population with regard to age, sex and regional distribution within Sweden, as discussed in Section 1.1. Hence, matching of exposed and unexposed individuals by these factors increases the efficiency of the statistical analysis. However, in this study the matching was conducted between sarcoidosis and non-sarcoidosis individuals. Hence, the matching does not account for differences between untreated and CS-treated sarcoidosis patients and non-sarcoidosis individuals with regard to confounding factors. Therefore, an additional adjustment for confounding factors is still necessary in the statistical analysis. *Third*, due to the use of registry data the matching could be conducted at low costs [28].

3.2. Materials

Swedish registries provide a well-known and good data source for epidemiological research [29]. The Swedish National Patient Registry (NPR) includes data on all inpatients visits in Sweden from 1987 onwards [30]. Since 2001 the NPR also includes all outpatient visits in Sweden [30]. The NPR is augmented by the Swedish Prescribed Drug Registry, which covers all drug dispensations in Sweden since July 2005 [31]. Besides these medical registries Swedish registries also include data on demographics and socio-economic characteristics of their residents. The Swedish Total Population Registry (TPR) includes information on immigration to and emigration from Sweden, death, birth and other demographic variables [29]. Additionally, the Swedish longitudinal integrated database for health insurance and labour market studies (LISA) provides yearly updated data on socio-economic characteristics such as income, education, country of birth and employment of Swedish residents aged ≥ 16 years since 1990 [32]. Furthermore, the Swedish Multigeneration Registry includes data on relatives of Swedish born people since 1961 [33]. The coverage of the NPR, the PDR, the TPR, the LISA and the multi generation registry is nearly complete except for lower coverage around the time of registry initiation [29–33]. Information from these registries can be combined using the individual's unique personal ID number [29].

For this study data on sarcoidosis, T2D and other covariates were obtained by linking multiple Swedish registries. Data on sarcoidosis, T2D, family history of T2D and demographic characteristics were obtained by linking the NPR to the PDR, the Swedish Multigeneration Registry, the LISA and the TPR. Sarcoidosis patients were identified as all individuals with ≥ 2 in- or outpatient visit listing a sarcoidosis diagnosis (ICD-10 D86) in the NPR between 2005 and 2013. The positive predictive value of sarcoidosis diagnoses in the NPR is estimated with 93% (unpublished data), which indicates a low proportion of misclassification among sarcoidosis patients. All sarcoidosis patients with a dispensation of a second line treatment for sarcoidosis, within +/- 3 months around their sarcoidosis diagnosis were excluded. This allowed for a clear comparison between untreated and CS-treated sarcoidosis patients. Drugs considered as second line treatment were methotrexate (ATC L01BA01), azathioprine (ATC L04AA13), leflunomide (ATC L04AX01/3), mycophenolate (ATC L04AA06) and hydroxychloroquine (ATC P01BA02) [7]. Further all sarcoidosis patients were matched to 10 sarcoidosis free general population comparators on year of birth, sex, and county of residence. The matching ratio of 1:10 was chosen to ensure a sufficient power of the study design to detect differences

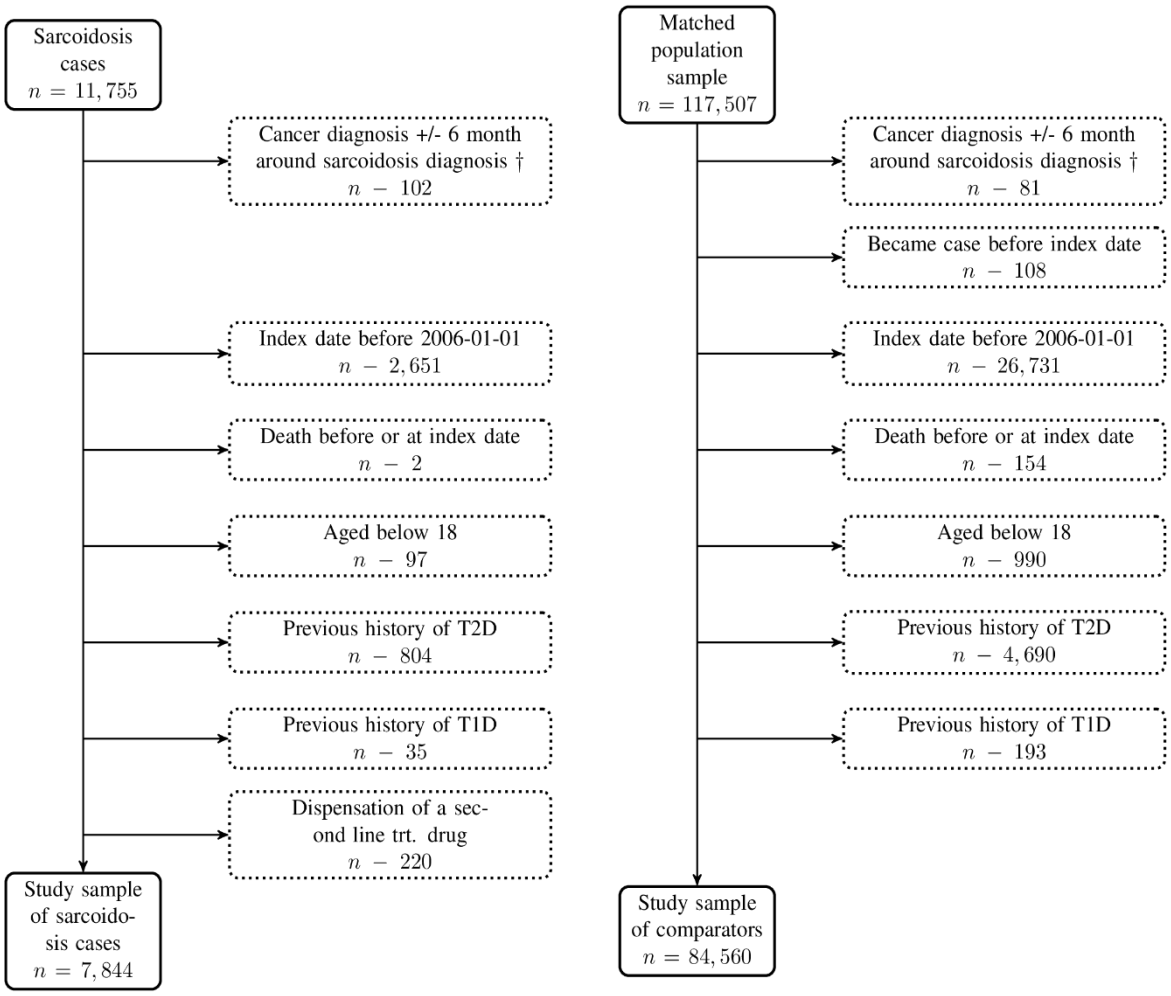

Figure 1: Flow chart of study samples of comparators and sarcoidosis patients. †: Types of cancers considered for the exclusion criteria were lymphosarcoma and other neoplasms of the lymphatic system (ICD-7 200-205) and malignant neoplasms of trachea, bronchus or lung (ICD-7 162-163).

between the exposure groups. Comparators and sarcoidosis patients were required to be aged ≥ 18 years and to live in Sweden at the time of sarcoidosis diagnosis or index date. All individuals with a previous history of DM before index date were excluded as shown in Figure 1. 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 around their sarcoidosis diagnosis were excluded due to possible misclassification of true cancer cases as sarcoidosis cases [34].

3.3. Variables

The outcome newly diagnosed T2D after sarcoidosis diagnosis was defined as adults with ≥ 2 in- or outpatient visits listing an ICD code for T2D (ICD-10 E11) in the NPR during follow-up

or with ≥ 2 dispensation of a T2D drug included in the ATC A10B group in the PDR during follow-up [34,35]. Most Swedish T2D patients receive their T2D diagnosis in primary care settings [36]. Therefore, information on dispensations of T2D drug were used as a proxy for these T2D diagnoses in primary care. Patients with T1D were assumed to receive an insulin treatment in contrast to T2D patients, which either get a metformin or a metformin plus insulin treatment. Hence, to distinguish between T1D and T2D patients, the ATC group A10B [35], that includes blood glucose lowering drugs excluding insulin, was used as a proxy for T2D.

The exposure newly diagnosed sarcoidosis was defined as described in Section 3.2. To acknowledge the association between corticosteroids and T2D, the exposure was further split into 3 exposure levels: no sarcoidosis, untreated sarcoidosis, and CS-treated sarcoidosis. All sarcoidosis patients with a dispensation of corticosteroids (ATC H02AB) within +/-3 months around their first sarcoidosis diagnosis were identified as CS-treated.

The participant's family history of DM was obtained as a proxy for genetic T2D risk factors by linking the NPR, PDR and the multigeneration registry. Participants with at least one first degree relative, that had ≥ 2 in- or outpatient care visits listing a T1D or T2D diagnosis or ≥ 2 dispensation of a T2D drug (ATC A10B) were classified as having a family history of DM [34,35].

Information on demographic characteristics of the patients were obtained from the TPR and the LISA. County of residence was summarised into health regions (Figure 6 in the appendix). Education was summarised into ≤ 9 full years of education, 10 to 12 full years of education, ≥ 12 full years of education and missing. Country of birth was categorised as born inside or outside of a Nordic country or missing. The Nordic countries include Sweden, Norway, Denmark, Iceland, and Finland. Age in years and sex was obtained from the TPR.

3.4. Follow-up time

Beginning of follow-up was at index date for the comparators and at the maximum of index data and corticosteroid dispensation for sarcoidosis patients in all models. End points of follow up were first dispensation of a T2D drug, first in- or outpatient diagnosis of T2D, first emigration, death or the end date of follow up which was December 31, 2013.

3.5. Statistical Analysis

To answer the first research question Cox proportional hazard models were used to estimate crude and adjusted hazard rate ratios of T2D associated with CS-treated sarcoidosis and

untreated sarcoidosis compared to no sarcoidosis [37]. The adjusted Cox model accounts for the confounding effect of age, sex, education, living in different health region, born in- or outside a Nordic country and family history of DM as shown in Figure 7 in the appendix. Furthermore, a probabilistic sensitivity analysis was conducted to account for the unmeasured confounding effect of the body mass index (BMI) on the association between sarcoidosis and T2D [38]. The assumptions for the analysis are described in Table 4 in the appendix.

To answer the second and third research question flexible parametric survival models (FPM) adjusted for age, sex, education, living in different health region, born in- or outside a Nordic country and family history of DM were used [39,40]. The degrees of freedom for the FPM were chosen based on the AIC and BIC criteria [39]. The knot position for the splines were chosen based on quantiles of the log survival time as recommended by Royston and Parmar [40]. First, different degrees of freedom for the baseline hazard were tested for a proportional hazard model adjusted for age, sex, education, health region, born in- or outside a Nordic country and family history of DM. The test results are presented in Table 6 in the appendix. Based on these results 3 degrees of freedom were chosen for the baseline hazard function. Afterwards the adjusted Cox model was tested for time-depending effects of untreated and CS-treated sarcoidosis on the risk of T2D. The Schoenfeld residuals presented in Figure 8 in the appendix indicate a time-depending effect for CS-treated sarcoidosis on the risk of T2D [41]. Therefore, different degrees of freedom for the time-depending effect of CS-treated sarcoidosis on the risk of T2D were tested for the FPM with 3 degrees of freedom for the baseline hazard function. The test results are presented in Table 7 in the appendix. Based on these results 3 degrees of freedom were chosen for the time-depending effect of CS-treated sarcoidosis on the risk of T2D. A spline function of mean cantered age was further added to the model, to allow the effect of age to change across follow-up time. Different degrees of freedom for this spline function were tested using the AIC and BIC criteria. The test results are presented in Table 8 in the appendix. Based on these results 2 degrees of freedom were chosen for the spline function of mean centred age. Results from the FPM were reported as hazard rate ratios and as absolute hazard rates for an average person in the data set. An average person was assumed to have an age equal to the mean age in the study population, 9 to 12 years of education, live in the health region of Stockholm, being born inside a Nordic country and no family history of DM.

There were missing data on education (1.3 %) and country of birth (0.4 %) in some of the included individuals. An additional category *missing* was created for these variables and all individuals with missing data were included in all analysis.

All statistical analysis was performed using the statistical software package *R* [42]. Data management were performed using the *tidyverse* package for R [43]. Furthermore, Cox models were estimated using the *survival* package for R [44]. Lastly, FPMs were estimated using the *rstpm2* package for R [45].

4. Ethical considerations

The value of this study may be considered as high, since no knowledge on association between sarcoidosis and T2D stratified by corticosteroid treatment is available yet. This study has the potential to shed light on this association and add knowledge which can be used to improve the care of sarcoidosis patients.

The use of registry data holds risks for the participant's data privacy. However, measures were taken to minimise these risks. Due to the use of the NPR, PDR and the multi-generation registry, data on the health status and drug use of the participants and the participant's relatives will be available. To secure the participant's data privacy all data will be pseudonymised, meaning that individuals cannot be identified without access to the matching key. To the best of the author's knowledge the key has been deleted to secure the pseudonymisation. However, certain combinations of data points may still allow to identify certain participants. Hence, all researchers involved in the research process are introduced to guidelines for secure handling and storing of registry data according to the General Data Protection Regulation (GDPR). Based on these measurements it may be unlikely that the participants are exposed to any harm connected to their participation in this study.

In conclusion, the value of this study balances the participant's risk of data privacy out. On the one hand, participants face a risk regarding their data privacy. On the other hand, this study may contribute a reasonable value for sarcoidosis patients and society in turn. This study received ethical clearance from the Regional Ethics Review Board in Stockholm (DNR: 2014/230-31).

5. Results

5.1. Description of the study population

7,844 sarcoidosis patients and 84,560 general population comparators were included in the analysis after exclusion as shown in Figure 1. Among these 7,844 eligible individuals with sarcoidosis, 5,090 received no treatment around the time of their sarcoidosis diagnosis and 2,754 sarcoidosis patients received a CS-treatment as shown in Table 1. Due to the matching of sarcoidosis patients and comparators, the demographical characteristics were homogenously distributed among comparators and untreated sarcoidosis patients. However, CS-treated sarcoidosis patients had a slightly lower median age and attended less years of education compared to comparators and untreated sarcoidosis patients. Additionally, there were differences in the regional distribution across the three exposure groups (Table 1). These indicated that sarcoidosis patients in Stockholm were less likely to be treated with corticosteroids compared to other health regions. Both, untreated and CS-treated sarcoidosis patients were more likely to have a family history of DM compared to the comparators (Table 1).

5.2. Description of T2D patients

In total, 2,048 cases of T2D were observed during follow up (Table 2). 1,774 of them were among the comparators, 153 among untreated sarcoidosis patients and 121 among CS-treated sarcoidosis patients. CS-treated sarcoidosis patients were around 5 years younger at the time of their T2D diagnosis than individuals in the comparison group. Additionally, the proportion of individuals with a family history of T2D was higher among T2D patients in the CS-treated sarcoidosis group compared to the comparator group. Conversely the T2D patients in the untreated sarcoidosis group had a lower proportion of individuals with a family history of T2D compared to the comparison group. As shown in Table 2 most T2D patients were identified through the PDR instead of the NPR.

5.3. T2D rate in sarcoidosis patients

The T2D rate was higher in both the CS-treated sarcoidosis group (12.68 per 1000 person-years) and the untreated sarcoidosis group (8.44 per 1000 person-years) compared to the general population comparators (5.74 per 1000 person-years), as can be seen in Table 3. There was a 52% increase in the T2D rate associated with untreated sarcoidosis (adjusted $\mathrm{HR} = 1.52, \mathrm{CI}_{95\%}$: 1.29, 1.79). In CS-treated sarcoidosis patient the T2D rate was

Table 1: Characteristics of the study population at baseline by exposure groups.

	General population comparators		Sarcoidosis untreated		Sarcoidosis CS-treated	
n	84,560		5,090		2,754	
Age	50	(39; 63)	50	(39; 62)	48	(37; 62)
Male, %	54		53		58	
Survival time, years	4	(2; 6)	3	(1; 6)	3	(1; 5)
Family history of diabetes, %	25		27		28	
Education, %						
≤ 9 years	21		20		21	
10 to 12 years	46		47		51	
≥ 12 years	32		31		27	
Missing	1		2		1	
Health region, %						
Stockholm	20		23		15	
Uppsala-Örebro	21		21		23	
West	18		18		19	
South	17		15		20	
Southeast	12		11		14	
North	11		12		10	
Country of birth, %						
Inside Nordics	87		89		91	
Outside Nordics	12		11		9	
Missing	0		0		0	

All estimates are presented as median with 25th and 75th quantile, if not stated differently.

over two times higher compared to the comparator group (adjusted $\mathrm{HR} = 2.41, \mathrm{CI}_{95\%}$: 2.01-2.90).

Stratified by sex, the crude T2D rate in untreated sarcoidosis was higher for females then for males (Table 3). Conversely, the crude T2D rate in CS-treated sarcoidosis patients was higher for males then for females. The rates of T2D in male and female untreated sarcoidosis patients were similar, albeit the T2D rate in males was slightly increased compared to females. With an almost threefold increase (adjusted $\mathrm{HR} = 2.88$, $\mathrm{CI}_{95\%}$: 2.18-3.79) T2D rate compared to the comparator group, the highest hazard ratio for T2D was associated with male CS-treated sarcoidosis patients.

Table 2: Characteristics of T2D patients by exposure groups.

	General population comparators		Sarcoidosis untreated		Sarcoidosis CS-treated	
n	1774		153		121	
Age at diagnosis	62	(53; 70)	63	(53; 70)	57	(46; 66)
Male, %	59		56		55	
Survival time, years	2	(1; 4)	3	(1; 4)	2	(0; 4)
Family history of diabetes, %	41		35		47	
Education, %						
≤ 9 years	34		35		31	
10 to 12 years	45		40		51	
≥ 12 years	20		23		16	
Missing	1		3		2	
Health region, %						
Stockholm	17		19		11	
Uppsala-Örebro	23		25		26	
West	17		15		19	
South	17		20		21	
Southeast	14		10		12	
North	12		10		12	
Country of birth, %						
Inside Nordics	84		87		84	
Outside Nordics	15		12		16	
Missing	1		1		0	
Register were T2D was first identified†, %						
Inpatient Registry	7		10		11	
Outpatient Registry	6		8		16	
Prescribed Drug Registry	87		82		74	

All estimates are presented as median with 25th and 75th quantile, if not stated differently.
†: Shows in which registries the T2D patients first reached criteria.

The probabilistic sensitivity analysis for the unmeasured confounding effect of BMI on the reported estimates for the hazard ratio of T2D yielded lower estimates then in the main analysis (Table 5). However, the results still suggested a significant increased T2D rate in both exposure groups compared to the comparators.

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

	Overall			Males			Females		
	Gen. pop. comparators	Sarcoidosis untreated	Sarcoidosis CS-treated	Gen. pop. Comparators	Sarcoidosis untreated	Sarcoidosis CS-treated	Gen. pop. Comparators	Sarcoidosis untreated	Sarcoidosis CS-treated
No. events	1,774	153	121	729	68	54	1,045	85	67
Survival time, yrs.	309,034	18,124	9,541	143,928	8,611	3,942	165,105	9,513	5,599
Incidence Rate†	5.74	8.44	12.68	5.07	7.90	13.70	6.33	8.94	11.97
Hazard Ratio	1	1.47	2.22	1	1.56	2.73	1	1.41	1.90
95% CI		(1.25-1.73)	(1.85-2.67)		(1.21-2.00)	(2.07-3.59)		(1.13-1.76)	(1.48-2.43)
Adjusted HR‡	1	1.52	2.41	1	1.60	2.88	1	1.47	2.10
95% CI		(1.29-1.79)	(2.01-2.90)		(1.25-2.05)	(2.18-3.80)		(1.18-1.83)	(1.64-2.68)

HR are presented as point estimate with 95 %-Confidence intervals.

†: Incidence rate per 1,000 person-years.

‡: Model is adjusted for mean centred age, education, family history of DM, birth country and county of residence.

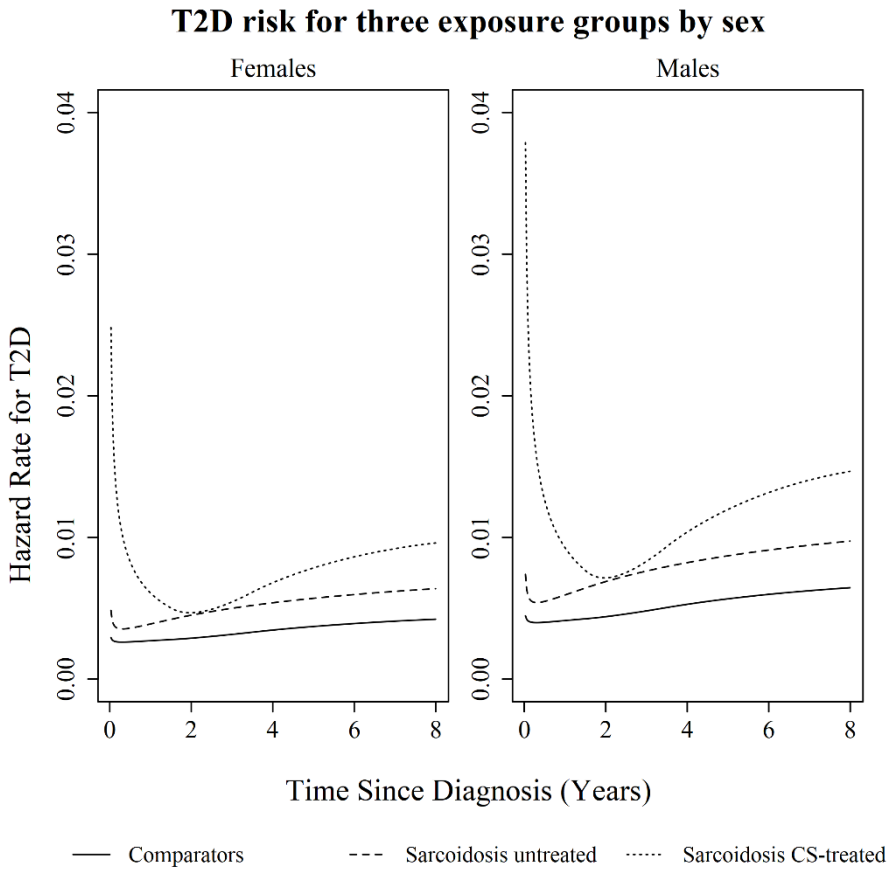

Figure 2: Hazard rate for T2D comparing untreated sarcoidosis patients and sarcoidosis patients treated with corticosteroids (CS) with matched general population comparators. The hazard rates were obtained for an average person in the data set using the FPM described in section 3.4.

5.4. T2D rate across time since sarcoidosis diagnosis

The rate of T2D changed differently in the three exposure groups across the time of follow up (Figure 2). For comparators and untreated sarcoidosis patients the T2D rate was relatively stable across the time of follow up, whereas the T2D rate for CS-treated sarcoidosis patients was highly increased within the first 2 years after sarcoidosis diagnosis. The same trend can be seen on a relative scale as presented in Figure 3. The T2D hazard ratio associated with untreated sarcoidosis compared to the comparison group was relatively stable along the time of follow up beside a small decrease at the beginning of follow up. Conversely, there was a 8-fold increased T2D rate associated with CS-treated sarcoidosis at the time of sarcoidosis diagnosis compared to the comparator group. After 2 years of follow up this hazard ratio stabilised at an approximate 2-fold increased rate for T2D. Furthermore, Figure 3 showed similar hazard ratios for T2D in both exposure groups 2 years after sarcoidosis diagnosis compared to the comparator group.

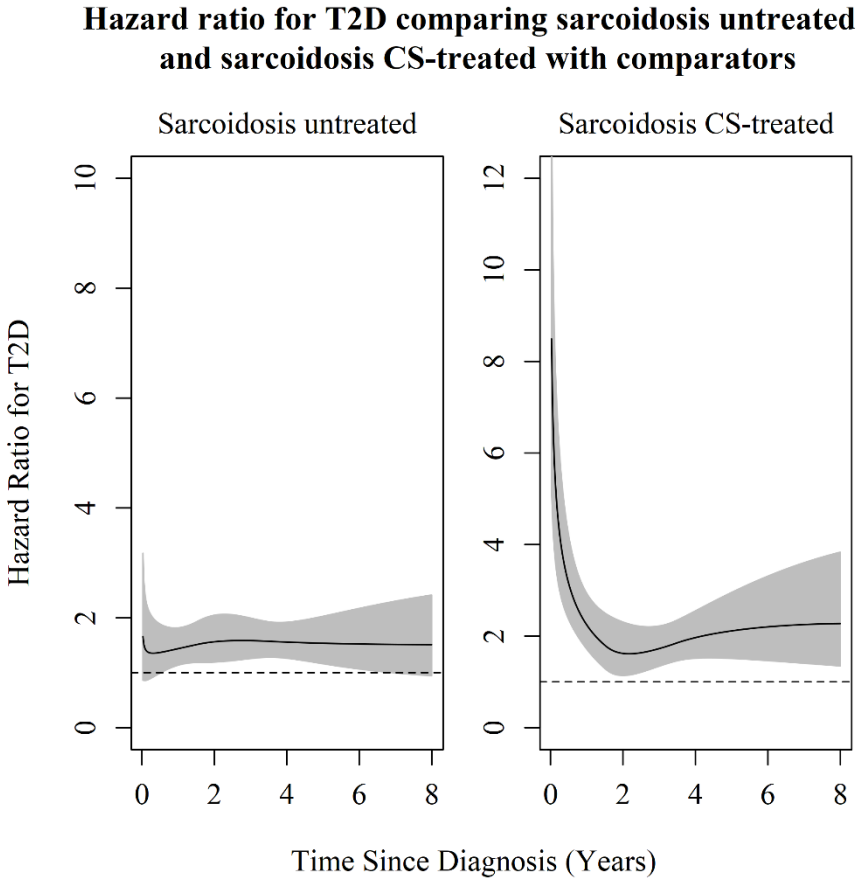

Figure 3: Hazard rate ratio for T2D across the time since sarcoidosis diagnoses, comparing untreated sarcoidosis patients and sarcoidosis patients receiving a corticosteroid (CS) treatment with the comparison group. The presented hazard rate ratios were obtained from the FPM described in section 3.4 and are adjusted for age, sex, education, region of residence, family history of DM and born inside a Nordic country.

5.5. T2D rate across age

The rate of T2D across the different exposure groups increased with higher age at beginning of follow up as shown in Figure 4. The rate of T2D increased across age until around 70 years in all three exposure groups. Around this age the rate peaked in all three exposure groups and decreased afterwards. Furthermore, also the differences in the T2D rates between the exposure groups increased with higher ages. For instance, the T2D rate was similar in all groups until the age of 40 and increases differently across the exposure groups by age. However, the magnitude of the differences in the T2D rates between the exposure groups by age varied across the time since sarcoidosis diagnosis as can be seen by comparing Figure 4 with Figure 9 in the appendix. These differences were due to the change in the hazard ratio of T2D between the exposure groups across time since sarcoidosis diagnosis. The overall trend of an increasing T2D rate along age at diagnosis however was stable across the time since diagnosis.

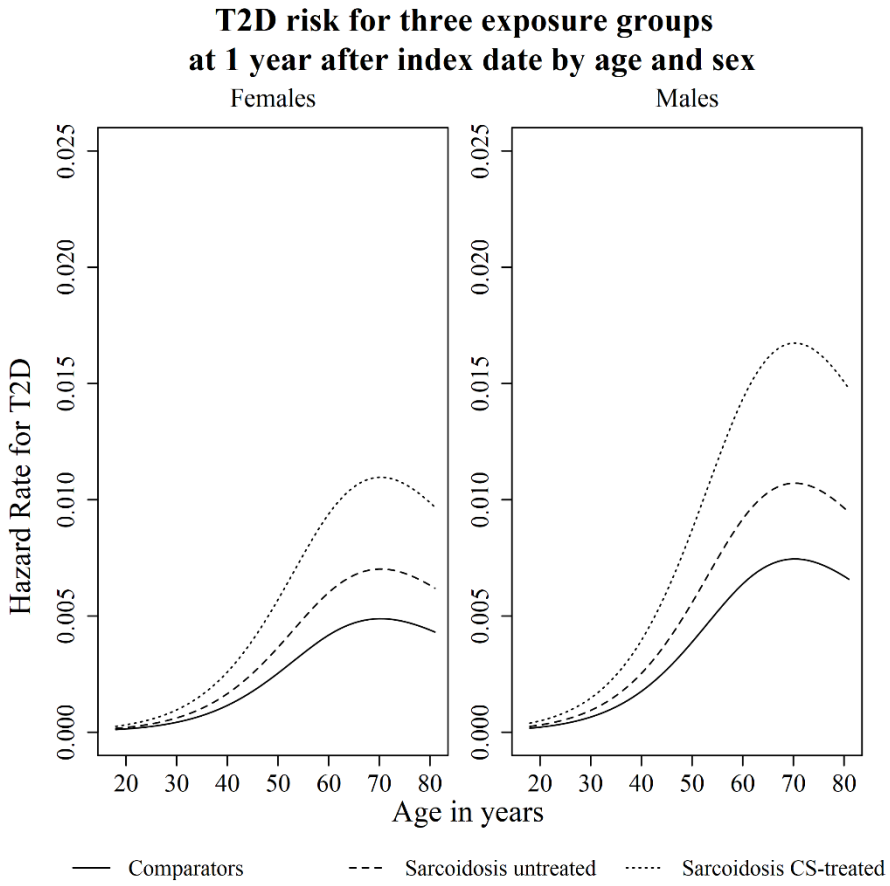

Figure 4: Hazard rate for T2D comparing untreated sarcoidosis patients and sarcoidosis patients treated with corticosteroids (CS) with matched general population comparators by age at diagnosis one year after sarcoidosis diagnosis. The hazard rates were obtained for an average person in the data set using the FPM described in section 3.4.

6. Discussion

This is the first study to determine the association between sarcoidosis and T2D with regard to corticosteroid use. Sarcoidosis was associated with an increased rate of T2D both if untreated and if treated with corticosteroids around the time of sarcoidosis diagnosis. The rate of T2D was found to be highest in CS-treated sarcoidosis patients. Further analyses showed that the hazard ratio of T2D in untreated sarcoidosis patients compared to the general population is stable across the time since sarcoidosis diagnosis. However, for CS-treated sarcoidosis patients the T2D rate was highest at the beginning of follow up. At approximately 2 years after sarcoidosis diagnosis it decreased to the same level as in the untreated group. In addition, the T2D rate was found to be higher for male and older sarcoidosis patients compared to female and younger sarcoidosis patients.

6.1. Comparison with previous knowledge

Our observation of an increased T2D rate in untreated sarcoidosis patients is in line with previous published studies [10,11]. A study from the United States of America (US) reported a 53 % increased DM risk in sarcoidosis patients compared to non-sarcoidosis comparators [11]. This relative risk estimate is similar to the reported estimate for untreated sarcoidosis patients in our study, although in the study from the US the authors did not differentiate between those sarcoidosis patients that receive a corticosteroid treatment and those who do not receive a corticosteroid treatment. Hence, the estimate reported in the study from the US was expected to be higher than the estimate for untreated sarcoidosis patients reported in our study. One reason why the rates were similar instead might be the lower DM incidence in the Swedish population compared to the population in the US, which gave rise to the comparison group in the study from the US [18,46].

Another study from Sweden, which used similar data as used in our study, found a 2-fold increased T2D rate in sarcoidosis patients compared to the general population [10]. This estimate lies between our estimates for untreated and CS-treated sarcoidosis patients. This might be expected since the authors of the previous study estimated the pooled T2D rate combining all sarcoidosis patients with no regard to treatment. Moreover, the authors reported an U-shape for the hazard ratio of T2D across time since diagnosis with the highest hazard ratio within one year after diagnosis, a lower hazard ratio in 2 to 5 years and an again increasing hazard ratio after more than 6 years after diagnosis [10]. This increase in the T2D rate 6 years after diagnosis is different from the results reported in our study. However, the hazard ratio estimates for the time six years after sarcoidosis diagnosis were only based on inpatient T2D diagnoses [10]. Hence, these results may be prone to differential outcome misclassification due to a higher inpatient health care utilisation of sarcoidosis patients compared to the general population. Thus, the reported results may be an overestimation of the true relative T2D rate in sarcoidosis patients 6 years after sarcoidosis diagnosis compared to the general population [10].

The increased T2D rate in CS-treated sarcoidosis patients soon after their sarcoidosis diagnosis might be a combined effect of the corticosteroids treatment [21–23,25], a higher sarcoidosis severity [8] and a higher screening rate. Previous evidence shows that corticosteroid treatment has a direct effect on the beta cell function, that leads to an immediate insulin resistance and onset of T2D [21,22,26]. This short temporality between corticosteroid treatment and insulin resistance may be one explanation for the steep increased T2D rate right after sarcoidosis

diagnosis in CS-treated sarcoidosis patients around the time of their diagnosis. Furthermore, a previous study from Sweden showed that those sarcoidosis patients with a corticosteroid treatment around the time of their sarcoidosis diagnosis experience a higher mortality than untreated sarcoidosis patients [8]. This implies, that corticosteroid treatment around the time of sarcoidosis diagnosis indicate a higher disease severity [8]. This higher disease severity might be another reason for the increased T2D rate. Additionally, the knowledge about the effect of corticosteroids on the beta cell function might lead to a higher screening rate among these sarcoidosis patients, albeit the Swedish guideline for sarcoidosis care does not suggest a T2D screening for sarcoidosis patients receiving a corticosteroid treatment [47]. This screening effect might partially explain the increase T2D rate in sarcoidosis patients treated with corticosteroids within the first months after their sarcoidosis diagnosis.

6.2. Strengths

This study has several strengths with regard to the used methods and data sources. The study population of sarcoidosis patients used in this study is among the largest worldwide allowing for enough power to detect differences between sarcoidosis patients and the general population [48]. Furthermore, due to the use of registry data loss to follow up is seldom and may be unlikely to be differential between exposure and outcome groups.

Our matched cohort study design allowed us to study the association and temporal relationship between sarcoidosis and T2D [28]. Hence, our estimates are less likely to be affected by reversed causation compared to a cross-sectional study design [28]. However, we were not able to control for the corticosteroid treatment as in a randomised control trial [28]. Thus, a randomised control trial study design would be favourable in order to study the causal effect of corticosteroid treatment in sarcoidosis patients on T2D.

Moreover, the use of FPM allowed to estimate the change in the hazard ratio of T2D in sarcoidosis patients compared to the general population across the time of follow-up. Hence, proportional hazards between the exposure groups did not need to be assumed. Due to this method substantial changes in the T2D rate among CS-treated sarcoidosis patients across the time since their sarcoidosis diagnosis could be revealed.

Most importantly, the hazard ratio of T2D could be estimated stratified by corticosteroid use using the PDR, which allowed to detected differences in the T2D rate between untreated and CS-treated sarcoidosis patients.

6.3. Limitations

Besides the above-mentioned strength, our study also faces limitations. *First*, the reported estimates may be affected by unmeasured confounding through BMI and smoking behaviour, since no data on these variables could be obtained from the registries used in this study. BMI is a known risk factor for both sarcoidosis and T2D and is therefore a positive confounder of the association between sarcoidosis and T2D [49,50]. Thus, the confounding effect of BMI has the potential to strongly influence the estimates for hazard ratio of T2D reported in this study towards an overestimation of the true association. Hence, to scrutinise the unmeasured confounding effect of BMI on the reported estimates a probabilistic bias analysis was conducted. It showed that the increased T2D rate in both untreated and CS-treated sarcoidosis patients cannot be explained by the confounding effect of BMI. However, conversely to BMI, smoking is likely to be a negative confounder of the association between sarcoidosis and T2D, since smoking is a known risk factor for T2D [51] and at the same time is a protective factor for sarcoidosis [49]. Thus, an adjustment for this effect would not change the direction of the estimated association between sarcoidosis and T2D. Instead the negative confounding effect of smoking would lead to an underestimation of the reported association between sarcoidosis and T2D.

Second, a differential misclassification of the outcome T2D may affect our results because no information on T2D diagnoses in primary care could be included in this study. Sarcoidosis patients may be more likely to get a T2D outside of primary care compared to the general population, since sarcoidosis patients are usually managed in hospitals or specialised clinics. Therefore, they may have easier access to care in hospitals or specialised clinics. To reduce this differential misclassification bias dispensation of T2D drugs in the PDR was used as a proxy for T2D diagnosis in primary care. However, based on this approach T2D patients diagnosed in primary care that do not receive a T2D drug treatment are not captured in this study. This might lead to an overestimation of the association between sarcoidosis and T2D.

Third, a non-differential misclassification of sarcoidosis may be introduced by the use of registry data. Sarcoidosis is in its presentation similar to other diseases, which makes the diagnosis of sarcoidosis difficult [1]. To decrease the misclassification of sarcoidosis, two sarcoidosis diagnosis were used as case definition for sarcoidosis, which is in line with previous studies from Sweden [8,48].

Fourth, a misclassification of untreated and CS-treated sarcoidosis patients may be introduced by assessing the exposure status only around the time of sarcoidosis diagnosis, since CS-treatment might be a time varying covariate. The proportion of sarcoidosis patients receiving a CS-treatment is highest around the time of sarcoidosis diagnosis and is decreasing with time since sarcoidosis diagnosis [7]. The same trend is observed for the dose of dispensed corticosteroids [7]. However, these trends suggest that most sarcoidosis patients that need a CS-treatment receive this around the time of their sarcoidosis diagnosis. Hence, a misclassification of the indication for a CS-treatment is unlikely. This difference in the T2D rate between sarcoidosis patients with and without an indication for a CS-treatment is the focus of this study. Time varying effects of the CS-treatment are unlikely to affect this classification.

6.4. External validity

The increased T2D rate in untreated and CS-treated sarcoidosis patients may be generalisable to other populations. It may be unlikely that the direction of the observed association varies across different study populations based on the assumption that the biological association between sarcoidosis, corticosteroids and T2D is the same across different populations. However, the strength of the association may differ across various population due to differences in the general risk of T2D across countries [12]. Transferring the results for instance to the population in the US, one would assume to see a weaker association due to a higher risk of T2D in the US population compared to the Swedish population [18,46].

6.5. Implications for public health and research

The findings of this study may improve the care of sarcoidosis patients in Sweden by implementing a screening for T2D in sarcoidosis patients. The estimated increased rate of T2D in sarcoidosis patients can be used as a rational for integrating an obligatory screening for T2D into the Swedish guidelines for sarcoidosis care. This might reduce the health impact of T2D in sarcoidosis patients through early detection of T2D. Based on the results of this study screening might be most important for CS-treated sarcoidosis patients and for patients aged above 40 at the time of their sarcoidosis diagnosis. Hence, the findings of this study can be used to advise health care professionals involved in sarcoidosis care, improve care for sarcoidosis patients in Sweden and thus add value to society.

For research, this study may be the basis for further studies scrutinising the role of corticosteroids in the occurrence of T2D in sarcoidosis patients. Augmenting the finding of this

study, it could be of value to include information on the doses and type of corticosteroids in further studies on the risk of T2D in sarcoidosis patients. Moreover, it would be interesting to disentangle the association of sarcoidosis and corticosteroids on T2D among CS-treated sarcoidosis patients. Likewise, the effect of discontinuing the corticosteroid treatment could be a topic for further research.

7. Conclusions

In conclusion, this study showed that sarcoidosis is associated with a higher rate of T2D compared to individuals without sarcoidosis. Further, the T2D rate in sarcoidosis patients was found to differ stratified by corticosteroid treatment. CS-treated sarcoidosis patients were found to have the highest hazard ratio of T2D compared to the general population. Furthermore, the hazard ratio of T2D for CS-treated sarcoidosis patients was highest within the first 2 years after sarcoidosis diagnosis. Additionally, the T2D rate was found to be higher for male and older sarcoidosis patients. Based on these results screening for T2D in sarcoidosis patients and especially among CS-treated sarcoidosis patients might be advisable.

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References

1. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. Nat Rev Dis Prim. 2019 Jul;5(1).

2. Rossides M, Grunewald J, Eklund A, Kullberg S, Di Giuseppe D, Askling J, et al. Familial aggregation and heritability of sarcoidosis: a Swedish nested case-control study. Eur Respir J. 2018;52(2).

3. Terwiel M, van Moorsel CHM. Clinical epidemiology of familial sarcoidosis: A systematic literature review. Respir Med. 2019;149:36–41.

4. Moller DR, Rybicki BA, Hamzeh NY, Montgomery CG, Chen ES, Drake W, et al. Genetic, immunologic, and environmental basis of sarcoidosis. Ann Am Thorac Soc. 2017 Dec 1;14:S429–36.

5. Sharma OP. Sarcoidosis Around the World. Clin Chest Med. 2008 Sep;29(3):357–63.

6. Arkema EVE, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016 Jul;48(6):1690–9.

7. Rossides M, Kullberg S, Eklund A, Grunewald J, Arkema E V. Sarcoidosis diagnosis and treatment in Sweden: A register-based assessment of variations by region and calendar period. Respir Med. 2020 Jan 1;161:105846.

8. Rossides M, Kullberg S, Askling J, Eklund A, Grunewald J, Arkema EV. Sarcoidosis mortality in Sweden: a population-based cohort study. Eur Respir J. 2018 Feb;51(2):1701815.

9. Institute for Health Metrics and Evaluation (IHME). GBD Compare: Sarcoidosis DALYs worldwide [Internet]. Seattle, WA: IHME, University of Washington; 2017. Available from: http://ihmeuw.org/50hp

10. Hemminki K, Liu X, Försti A, Sundquist J, Sundquist K, Ji J. Subsequent Type 2 Diabetes in Patients with Autoimmune Disease. Sci Rep. 2015 Sep;5(1).

11. Ungprasert P, Matteson EL, Crowson CS. Increased Risk of Multimorbidity in Patients With Sarcoidosis: A Population-Based Cohort Study 1976 to 2013. Mayo Clin Proc. 2017;92(12):1791–9.

12. Defronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nat Rev Dis Prim. 2015;1(1).

13. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, et al. Type 1 diabetes mellitus. Nat Rev Dis Prim. 2017 Mar 30;3.

14. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PLoS One. 2018 Mar 1;13(3):e0194127.

15. Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Stu. Lancet. 2018

Nov;392(10159):1859–922.

16. Institute for Health Metrics and Evaluation (IHME). GBD Compare: YLDs Sweden [Internet]. Seattle, WA: IHME, University of Washington; 2017. Available from: http://ihmeuw.org/4tys

17. Institute for Health Metrics and Evaluation (IHME). GBD Compare: Leading causes of YLDs in Sweden [Internet]. Seattle, WA: IHME, University of Washington; 2017. Available from: http://ihmeuw.org/50hq

18. Andersson T, Ahlbom A, Carlsson S. Diabetes Prevalence in Sweden at Present and Projections for Year 2050. PLoS One. 2015 Nov;10(11):e0143084.

19. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 2011 Feb 14;11(2):98–107.

20. Rawshani A, Landin-Olsson M, Svensson AM, Nyström L, Arnqvist HJ, Bolinder J, et al. The incidence of diabetes among 0-34 year olds in Sweden: New data and better methods. Diabetologia. 2014;57(7):1375–81.

21. Hwang JL, Weiss RE. Steroid-induced diabetes: A clinical and molecular approach to understanding and treatment. Diabetes Metab Res Rev. 2014 Feb;30(2):96–102.

22. Wallace MD, Metzger NL. Optimizing the Treatment of Steroid-Induced Hyperglycemia. Ann Pharmacother. 2018 Jan;52(1):86–90.

23. Esguerra JLS, Ofori JK, Nagao M, Shuto Y, Karagiannopoulos A, Fadista J, et al. Glucocorticoid induces human beta cell dysfunction by involving riborepressor GAS5 LincRNA. Mol Metab. 2020 Feb 1;32:160–7.

24. Clore JN, Thurby-Hay L. Glucocorticoid-iduced hyperglycemia. Endocr Pract. 2009;15(5):469–74.

25. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract. 2013 Mar;99(3):277–80.

26. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H. Glococorticoids and the Risk for Initiation of Hypoglycemic Therapy. Arch Intern Med. 1994;154(1):97–101.

27. Gulliford MC, Charlton J, Latinovic R. Risk of diabetes associated with prescribed glucocorticoids in a large population. Diabetes Care. 2006 Dec;29(12):2728–9.

28. Rothman KJ, Lash TL, Greenland S. Modern Epidemiology. 3rd Editio. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

29. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016 Feb 1;31(2):125–36.

30. Socialstyrelsen. The National Patient Register [Internet]. [cited 2020 Mar 6]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/

31. Wettermark B, Hammar N, MichaelFored C, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months.

Pharmacoepidemiol Drug Saf. 2007 Jul 1;16(7):726–35.

32. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019 Mar 30;34(4):423–37.

33. Statistics Sweden. Flergenerationsregistret 2016 [Internet]. 2017 [cited 2020 Mar 6]. Available from: https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/individregister/flergenerationsregistret/

34. ICD-10. International Statistical Classification of Diseases and Related Health Problems [Internet]. World Health Organization (WHO); 2016. Available from: https://www.who.int/classifications/icd/icdonlineversions/en/

35. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index [Internet]. World Health Organization (WHO); 2018. Available from: https://www.whocc.no/atc_ddd_index/

36. Gudbjörnsdottir, Soffia Svensson A-M, Eliasson B, Eeg-Olofsson K, Björck S, Linder E, Samuelsson P, et al. Årsrapport 2018 [Internet]. 2018. Available from: https://www.ndr.nu/pdfs/Arsrapport_NDR_2018.pdf

37. Hosmer DW, Lemeshow S, May S. Applied Survival Analysis. Wiley-Blackwell; 2008.

38. Lash TL, Fox MP, Fink AK. Applying Quantitative Bias Analysis to Epidemiologic Data. New York, NY: Springer New York; 2009.

39. Royston P, Lambert PC. Flexible Parametric Survival Analysis Using Stata. Stata Press; 2011.

40. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002 Aug 15;21(15):2175–97.

41. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. Biometrika. 1994 Aug;81(3):515.

42. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2019 [cited 2018 Feb 26]. Available from: https://www.r-project.org/

43. Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the Tidyverse. J Open Source Softw. 2019 Nov 21;4(43):1686.

44. Therneau TM. A package for survival Analysis in S [Internet]. 2015. Available from: https://cran.r-project.org/package=survival

45. Clements M, Liu X-R, Lambert PC, Jakobsen LH, Gasparini A, Smyth G, et al. rstpm2: Smooth Survival Models, Including Generalized Survival Models [Internet]. 2019. Available from: https://cran.r-project.org/web/packages/rstpm2/index.html

46. Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report, 2020 [Internet]. 2020. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

47. Svensk Lungmedicinsk Förening. Vårdprogram för Sarkoidos [Internet]. 2018.

Available from: http://slmf.se/wp-content/uploads/2018/08/VP_sarkoidos_web_180117_0.pdf

48. Arkema E, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016;48(6):1690–9.

49. Ungprasert P, Crowson CS, Matteson EL. Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study. Respir Med. 2016 Nov 1;120:87–90.

50. Abdullah A, Peeters A, de Courten M, Stoelwinder J. The magnitude of association between overweight and obesity and the risk of diabetes: A meta-analysis of prospective cohort studies. Diabetes Res Clin Pract. 2010 Sep;89(3):309–19.

51. Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: A systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2015 Dec 1;3(12):958–67.

52. Statistiska centralbyrån. Undersökningar av levnadsförhållanden (ULF/SILC) 2018 [Internet]. 2018. Available from: https://www.scb.se/contentassets/9608d268fa9c40178e30131f03776b76/halsa-2018.xlsx

53. Cremers JP, Drent M, Elfferich MD, Nelemans PJ, Wijnen PA, Witteman BJ, et al. Body composition profiling in a Dutch sarcoidosis population. Sarcoidosis Vasc Diffus Lung Dis. 2013;30(4):289–99.

Appendices

a. Tables

Table 4: Assumptions for the probabilistic sensitivity analysis of the unmeasured confounding effect of BMI on the association between sarcoidosis and T2D.

	Estimate	95% CI		SD	Distribution	Source
Prevalence of overweight						
Sweden	0.36	0.35	0.37	0.005102135	Normal	[52]
Sarcoidosis patients	0.37	0.32	0.42	0.023474749	Normal	[53]
Prevalence of obesity						
Sweden	0.14	0.13	0.15	0.005102135	Normal	[52]
Sarcoidosis patients	0.21	0.17	0.25	0.019804004	Normal	[53]
RR of T2D by BMI						
18.5 < BMI < 25	1					
25 < BMI < 30	2.92	2.42	3.71	0.403068631	Normal	[51]
30 < BMI	7.24	6.38	8.23	0.505111322	Normal	[51]
RR of T2D in sarcoidosis						
General population comparators	1					
Sarcoidosis untreated	1.52	1.29	1.79	0.137757633	Normal	Table 3
Sarcoidosis CS-treated	2.41	2.01	2.90	0.250004594	Normal	Table 3

SD: standard deviation, RR: Relative risk.

Table 5: 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 CS-treated	
RR not adj. for BMI	1.52	(1.29; 1.79)	2.41	(2.01; 2.90)
RR adj. for BMI	1.27	(1.06; 1.49)	2.09	(1.70; 2.50)

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

Table 6: AIC and BIC for the FPM with different degrees of freedom for the baseline hazard function.

DF	AIC	BIC
1	-658.42	-498.04
2	-684.39	*-514.58*
3	-686.26	-507.02
4	-687.19	-498.51
5	-688.20	-490.08
6	-687.95	-480.41
7	*-688.30*	-471.32
8	-687.94	-461.53
9	-686.96	-451.11
10	-685.83	-440.55

3300 was added to all numbers to improve readability.

Table 7: AIC and BIC for the FPM with 3 degrees of freedom for the baseline hazard function and different degrees of freedom for the time-depending effect of sarcoidosis treated with corticosteroids.

DF	AIC	BIC
1	-703.85	*-515.18*
2	-701.87	-503.76
3	*-703.89*	-496.35
4	-702.36	-485.38
5	-700.76	-474.34
6	-698.55	-462.71
7	-697.12	-451.84
8	-698.42	-443.71
9	-694.75	-430.60
10	-695.51	-421.92

3300 was added to all numbers to improve readability.

Table 8: AIC and BIC for the FPM with 3 degrees of freedom for the baseline hazard function, 3 degrees of freedom for the time-depending effect of sarcoidosis treated with corticosteroids and different degrees of freedom for the spline function of mean cantered age.

DF	AIC	BIC
1	-703.89	-496.35
2	*-994.27*	*-777.29*
3	-992.29	-765.88
4	-990.44	-754.59
5	-988.74	-743.46
6	-986.86	-732.15
7	-984.92	-720.77
8	-983.44	-709.86
9	-982.29	-699.28
10	-981.60	-689.14

3300 was added to all numbers to improve readability.

b. Figures

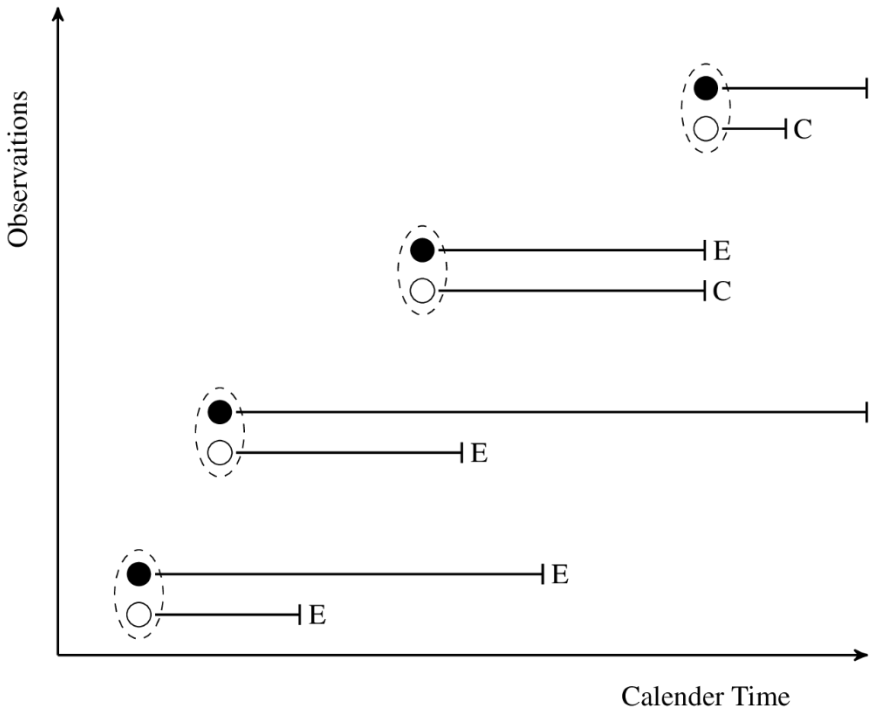

Figure 5: Schematic illustration of the individual density matched open cohort study design. The figure illustrates some combination of exposed and comparators. For the illustration one comparator were matched to each exposed, whereas in the actual used design 10 comparators were matched to one exposed. E: Event, C: Censored, Dashed ellipses: Matching of exposed and comparators.

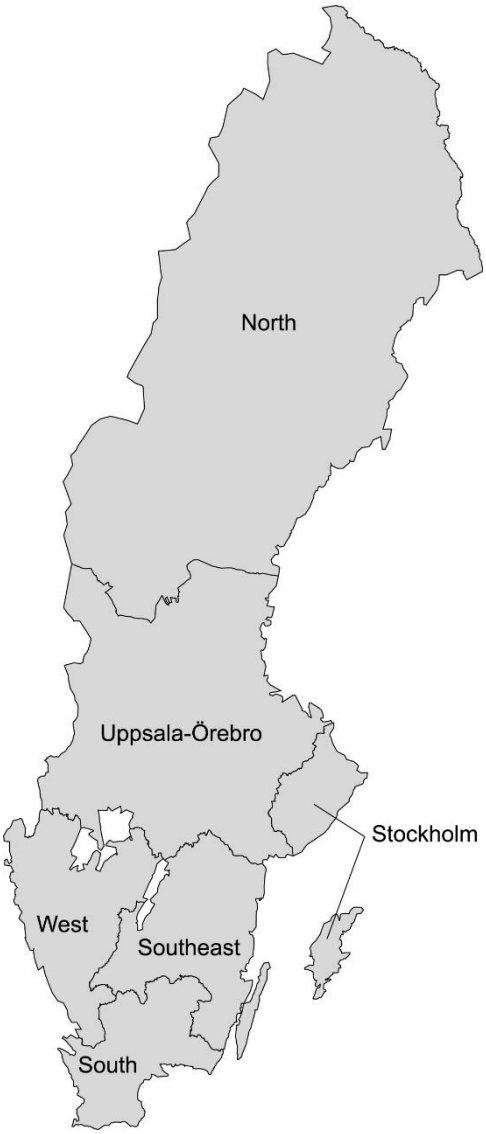

Figure 6: Map of Swedish health care regions (Stockholm [Stockholm and Gotland counties], Uppsala-Örebro [Uppsala, Södermanland, Värmland, Örebro, Västmanland, Dalarna, and Gävleborg], West [Västra Götland and Halland], South [Skåne, Kronoberg, and Blekinge], Southeast [Östergötland, Jönköping, and Kalmar], and North [Västernorrland, Jämtland, Västerbotten, and Norrbotten]) [7]. The figure and caption was replicated with the permission of the authors Rossides, Kullberg, Eklung et al [7].

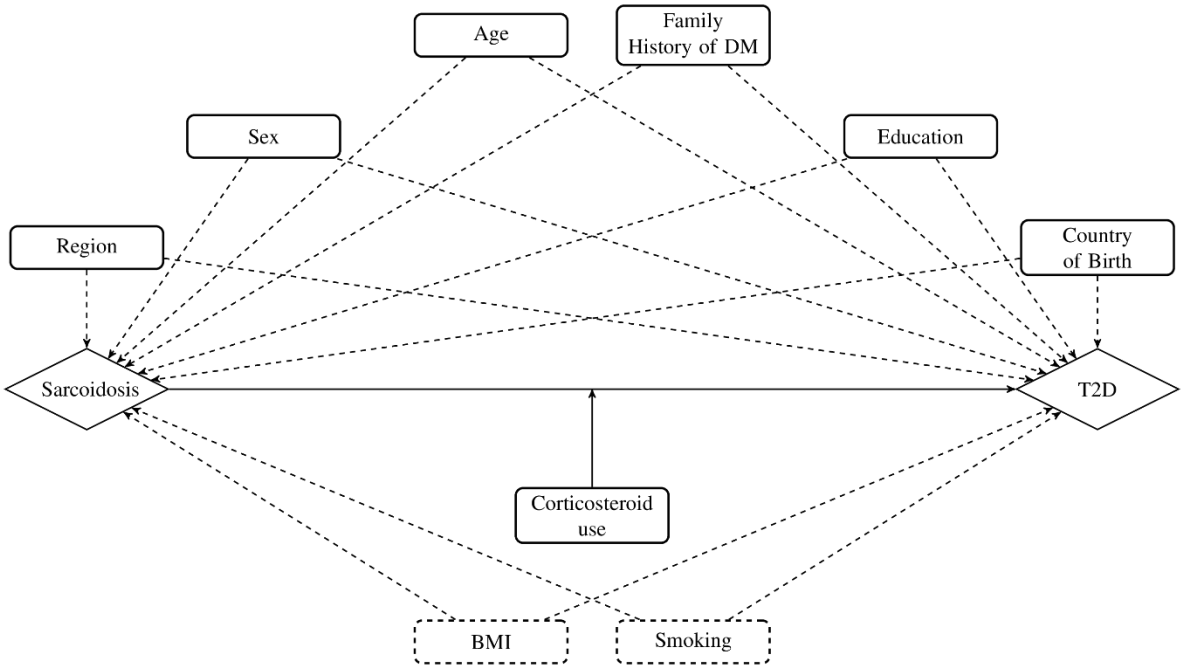

Figure 7: Directed acyclic graph of the association between sarcoidosis and T2D. Dashed boxes: unmeasured confounders.

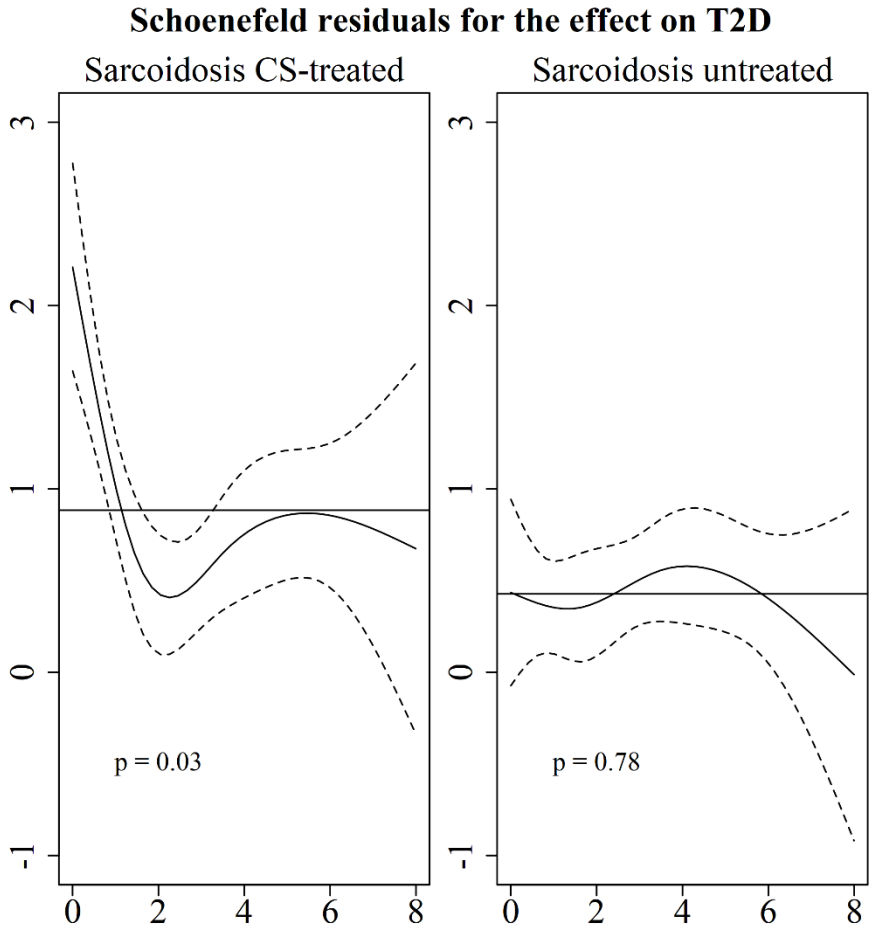

Figure 8: Schoenefeld residuals for the effect of untreated and CS-treated sarcoidosis on T2D based on the adjusted Cox survival model. The horizontal line indicates the beta coefficient for sarcoidosis in the cox model. The p-values are reported for the test of linearity of the residuals across survival time.

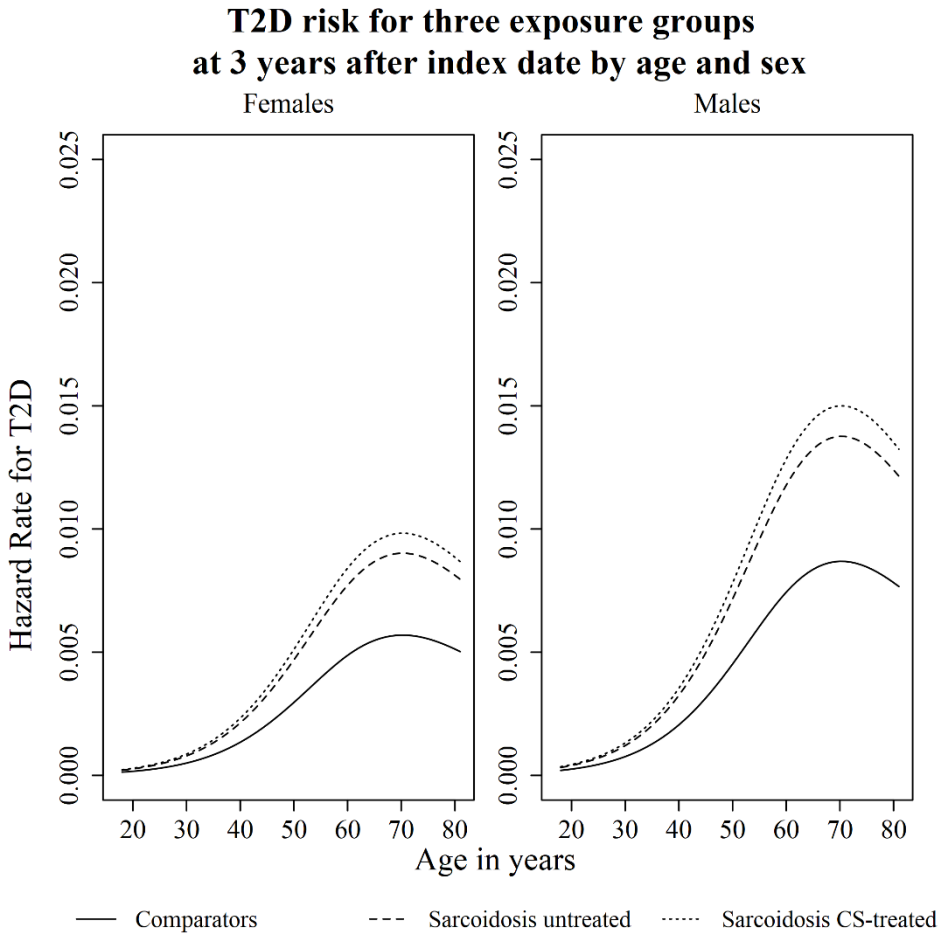

Figure 9: Hazard rate for T2D comparing untreated sarcoidosis patients and sarcoidosis patients treated with corticosteroids (CS) with matched general population comparators by age at diagnosis three years after sarcoidosis diagnosis. The hazard rates were obtained for an average person in the data set using the FPM described in section 3.4.