Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden

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ABSTRACT Our objective was to estimate the contemporary incidence and prevalence of sarcoidosis using Swedish population-based register data.

Adults with any sarcoidosis-coded visit were identified from the National Patient Register (hospitalisations 1964–2013 and outpatient care 2001–2013). Demographic and medication dispensing data were retrieved from national registers. We estimated the prevalence of sarcoidosis in 2013 overall and by county of residence. The incidence of sarcoidosis during 2003–2012 was estimated by sex, age, education level and year of diagnosis. Case definitions were varied to test their robustness.

More than 16 000 individuals had a history of sarcoidosis in 2013. When defined as two or more sarcoidosis-coded visits, the prevalence was 160 per 100 000. Using different definitions, the prevalence ranged from 152 (requiring a specialist visit) to 215 per 100 000 (only one visit required). The highest prevalence was observed in northern less densely populated counties. The incidence was 11.5 per 100 000 per year and varied by −10% to +30% depending on case definition. The incidence peaked in males aged 30–50 years and in females aged 50–60 years, but did not differ by education level and was stable over time.

This study represents the largest epidemiological investigation of sarcoidosis using population-based individual-level data. Age at diagnosis in men was 10 years younger than in women and geographical variation was observed.

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Sarcoidosis occurrence varied by region, age and sex; age at onset was 10 years younger in males than in females http://ow.ly/mKyN300E4Kp

This article has supplementary material available from erj.ersjournals.com
Received: March 06 2016 | Accepted after revision: May 15 2016

Support statement: This work was funded by Svenska Läkaresällskapet (Swedish Society of Medicine), Hjärt-Lungfonden (Swedish Heart–Lung Foundation), Vetenskapsrådet (Swedish Research Council), the Swedish Foundation for Strategic Research, Stockholm County Council, the Swedish Association for Chest Physicians, the Center for Inflammatory Diseases and Karolinska Institutet. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com
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Introduction

Sarcoidosis is a chronic, multiorgan inflammatory disorder which primarily affects the lungs and lymphatic system. Despite advancements since sarcoidosis was first described more than 100 years ago, much remains unknown about what causes the disease. Variations over time, place, age, sex and other characteristics may provide important information on how and why sarcoidosis occurs and reveal insights into its aetiology.

Reported prevalence estimates vary substantially over different geographical regions and ethnic groups, with the highest sarcoidosis prevalence reported in the Nordic countries and in African-Americans [1, 2]. Higher rates of sarcoidosis in certain areas could indicate a shared contagion, environmental exposure or genetic predisposition. Not only does the occurrence of sarcoidosis vary by region, but there also appear to be differences in the age and sex distribution of individuals with sarcoidosis. Some studies report that sarcoidosis is more common in women compared with men [3–5], while others have found no gender difference [6–9]. Studies from Europe and the USA report a peak age at onset between 20 and 50 years, and observe a younger age at onset in men compared with women [3, 6, 10–13]. Interestingly, two studies from Asia report that the peak incidence occurs at the same age in men and women [14, 15], which could indicate variation in the presentation of sarcoidosis across populations. Variations could, however, be due to the way that sarcoidosis has been identified and defined in these studies [16].

In studies from the mid-1900s, the prevalence of sarcoidosis was estimated based on mass radiographic screenings, detecting many asymptomatic cases [17]. An investigation of the occurrence of disease that requires clinical care would provide a more meaningful picture of the burden of sarcoidosis on the population. Reports from the last decade have used insurance billing data, medical records from specialist care, nationwide registers and epidemiological cohort studies to estimate the incidence and prevalence of sarcoidosis (table 1). Few of these studies were population-based and most were relatively small.

High-quality and comprehensive nationwide register data allow for assessments of disease occurrence in the entire population of Sweden. Sweden is the largest of the Scandinavian countries, with 9.6 million inhabitants in 2013 and covering 500 000 km² between latitudes 55° and 69° north. Our objective was to use Swedish register data to estimate the contemporary incidence and prevalence of clinically identified sarcoidosis by age, sex, education level and geographic region.

Methods

In Sweden, healthcare is universally accessible and tax funded. Sweden’s nationwide registers provide information on almost the entire population’s inpatient and outpatient care. Each individual’s unique personal identification number ("personnummer") can be used to link data across several registers.

Individuals with sarcoidosis

Individuals 18 years or older with any visit listing an International Classification of Disease (ICD) code for sarcoidosis (ICD-8 135, ICD-9 135 or ICD-10 D86) as a main or contributory diagnosis were identified from the National Patient Register (NPR) during 1964–2013. This register includes both inpatient hospitalisations since 1964 (nationwide since 1987) and nonprimary outpatient visits in secondary care since 2001. The coverage of the inpatient component of the NPR is almost 100% and the outpatient component coverage has been estimated to be 87%, with more missing data from private versus public caregivers [18]. From the NPR, we obtained the date and clinic or department where the sarcoidosis-coded visit was recorded.

Additional covariates

Birth date, county of residence, and dates of immigration and emigration were retrieved from the Total Population Register. Highest education level achieved was obtained from the Swedish Education Register and categorised into three groups: <9 years (less than high school education), 9–12 years (high school education), and >12 years (more than high school education). The Cause of Death Register provided date of death and the Prescribed Drug Register provided data on medication dispensed at all Swedish pharmacies from July 2005 through December 2013. Dispensing dates of immunomodulating and immunosuppressant drugs, hydroxychloroquine, and glucocorticoids were retrieved using Anatomical Therapeutic Chemical classification codes (referred to as sarcoidosis-related medication, see online supplementary table E1 for a detailed list).

Definitions of prevalent sarcoidosis

The primary definition for prevalent sarcoidosis was defined as anyone 18 years or older registered as living in Sweden with a history of at least two visits listing an ICD code for sarcoidosis as of December 31, 2013. To assess the robustness of this estimate when using more liberal or stricter definitions, we 1) required only one sarcoidosis-coded visit and 2) required at least two sarcoidosis-coded visits with at
<table>
<thead>
<tr>
<th>Study and year</th>
<th>Country, sex and race</th>
<th>Time period</th>
<th>Incidence</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
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<td>Byg et al., 2003 [10]</td>
<td>Denmark, men and women, race not reported</td>
<td>1980–1994</td>
<td>5536</td>
<td>7.2</td>
<td>Register-based and nationwide, hospitalisations only</td>
</tr>
<tr>
<td>Cozier et al., 2011 [34]</td>
<td>USA, women, African-Americans</td>
<td>1995–2007</td>
<td>435</td>
<td>71</td>
<td>Black Women’s Health Study, self-reported sarcoidosis with medical record review</td>
</tr>
<tr>
<td>Crain et al., 2009 [35]</td>
<td>USA, men and women, race not reported</td>
<td>2004–2005</td>
<td></td>
<td>459</td>
<td>Insurance billing data from five major health insurers in Vermont</td>
</tr>
<tr>
<td>Deubelbeiss et al., 2010 [11]</td>
<td>Switzerland, men and women, race not reported</td>
<td>2002–2005</td>
<td>2925</td>
<td>7</td>
<td>Register-based and nationwide, hospitalisations, biopsies, outpatient visits for a subset</td>
</tr>
<tr>
<td>Dumas et al., 2016 [36]</td>
<td>USA, women, multiracial</td>
<td>1989–2011</td>
<td>261</td>
<td>Overall: 11; black: 43; white: 11</td>
<td>Nurses’ Health Study, self-reported sarcoidosis</td>
</tr>
<tr>
<td>Erdal et al., 2012 [5]</td>
<td>USA, men and women, multiracial</td>
<td>1995–2010</td>
<td></td>
<td>3758</td>
<td>Electronic medical records from Ohio State University Medical Center</td>
</tr>
<tr>
<td>Gorham et al., 2004 [37]</td>
<td>USA, men, multiracial</td>
<td>1975–2001</td>
<td>674</td>
<td>Black: 24.9; white: 3.5</td>
<td>Navy personnel, hospitalisations only</td>
</tr>
<tr>
<td>Gribbin et al., 2006 [8]</td>
<td>UK, men and women, race not reported</td>
<td>1991–2003</td>
<td>1019</td>
<td>5.0</td>
<td>The Health Improvement Network, diagnoses from 255 primary care general practices</td>
</tr>
<tr>
<td>Kim, 2001 [14]</td>
<td>Korea, men and women, race not reported</td>
<td>1992–1999</td>
<td>309</td>
<td>0.13</td>
<td>Nationwide survey for biopsy-proven sarcoidosis, hospitalised cases only</td>
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<tr>
<td>Kowalska et al., 2014 [13]</td>
<td>Poland, men and women, race not reported</td>
<td>2006–2010</td>
<td>1217</td>
<td>5.1–7.3</td>
<td>Register-based, data from the National Health fund in Katowice, Silesia</td>
</tr>
<tr>
<td>Rybicki et al., 1997 [4]</td>
<td>USA, men and women, multiracial</td>
<td>1990–1994</td>
<td>259</td>
<td>Black: 35.5; white: 10.9</td>
<td>Insurance billing data in Michigan, confirmed by chart review</td>
</tr>
<tr>
<td>Thomeer et al., 2001 [9]</td>
<td>Belgium, men and women, race not reported</td>
<td>1992–1999</td>
<td>69</td>
<td>0.26</td>
<td>Respiratory medicine centres (n=20) registered cases by respiratory specialists</td>
</tr>
<tr>
<td>Arkema et al., 2016 (present study)</td>
<td>Sweden, men and women, race not reported</td>
<td>2003–2013</td>
<td>10787</td>
<td>10.4–14.8</td>
<td>Register-based and nationwide, hospitalisations and outpatient visits</td>
</tr>
</tbody>
</table>

Data are presented as n, unless otherwise stated.
least one from a department of internal medicine, dermatology, respiratory medicine, rheumatology or neurology. We additionally assessed the prevalence of treated sarcoidosis, acknowledging that not all cases need such treatment, which required at least two sarcoidosis-coded visits and any history of a sarcoidosis-related medication (see above) during 2005–2013. Furthermore, we defined a subgroup of individuals who were seen for care for sarcoidosis in 2013 by requiring at least one visit listing a diagnosis code for sarcoidosis between January 1 and December 31, 2013.

**Definitions of incident sarcoidosis**
Incident sarcoidosis was assessed between January 1, 2003 and December 31, 2012. As data were available through the end of 2013, this allows for a second visit for sarcoidosis within 1 year of the first visit. This time span also provides a washout period of \( \geq 16 \) years with regard to hospitalisations (since the inpatient register became nationwide) and \( \geq 2 \) years with regard to outpatient visits. The primary definition of incident sarcoidosis required at least two sarcoidosis-coded visits from 2003 to 2013. We varied the definition to assess its robustness by examining incidence defined as 1) at least one sarcoidosis-coded visit, 2) at least two sarcoidosis-coded visits, at least one of which in a department of internal medicine, dermatology, respiratory medicine, rheumatology or neurology, or 3) at least two sarcoidosis-coded visits within 1 year. We also estimated how many individuals had at least two sarcoidosis-coded visits plus any sarcoidosis-related medication dispensing within 6 months of first diagnosis to determine how many newly diagnosed individuals were treated with medication.

**Statistical analysis**
The Swedish population alive and living in Sweden on December 31, 2013 aged 18 or older was obtained from national census data (Statistics Sweden: [www.scb.se](http://www.scb.se)) and used as the denominator for prevalence calculations \((n=7692386)\). The adult Swedish population for each year was used as the denominator to determine annual incidence rates. Each estimate was calculated using the different definitions listed above to determine how they changed with increasingly strict criteria. For each sarcoidosis definition, we calculated the percentage male and mean age at diagnosis as well as the incidence and prevalence by age group and sex. Age- and sex-standardised prevalence by county of residence (21 counties total) was mapped using the Statistics Sweden software Statistikatlasen ([www.scb.se/statistikatlasen](http://www.scb.se/statistikatlasen)). In a sensitivity analysis, prevalent sarcoidosis cases who were registered in a well-characterised clinical cohort at Karolinska University Hospital were examined to determine what percentage would be considered sarcoidosis cases using our different definitions.

Age- and sex-standardised incidence was estimated by education level among individuals aged 30–74 years with available data on education (98.5%). This age group was used because people aged 30 years and older have had the chance to complete their education and information was not available for individuals aged 75 years and older. SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses. Ethical approval was obtained by the Ethical Review Board of Karolinska Institutet.

**Results**

**Prevalence**
16,547 individuals had a history of sarcoidosis in 2013. When defined as at least two sarcoidosis-coded visits, the prevalence of sarcoidosis was 160 per 100,000. It did not differ greatly when additionally requiring at least one visit with a specialist (152 per 100,000). When using the most liberal definition, requiring only one visit, the prevalence increased to 215 per 100,000. 89 per 100,000 had at least two visits and a history of medication dispensing (figure 1 and table 2). 62–70 per 100,000 were prevalent sarcoidosis cases who had at least one visit in 2013 (figure 1). Approximately two-thirds had a history of a sarcoidosis-related medication dispensing (47 per 100,000). In the sensitivity analysis examining definitions among registered cases from the Karolinska University Hospital clinical cohort, 95% of the individuals in the cohort had two or more sarcoidosis-coded visits in the patient register (see online supplementary table E2).

The average age of individuals living with sarcoidosis in Sweden in 2013 was 56 years and 56% were male (table 2). The prevalence was higher in males than in females (179 versus 141 per 100,000, respectively). The age- and sex-standardised prevalence estimates by county ranged from 105 to 278 per 100,000, with the highest observed in some northern less densely populated counties (figure 2). The lowest prevalence was observed in counties in the southeast. This pattern was similar when examining prevalent sarcoidosis using different definitions of prevalence.

**Incidence**
There were on average 1079 new cases of sarcoidosis diagnosed each year from 2003 through 2012. When defined by at least two visits, the incidence of sarcoidosis was 11.5 per 100,000 per year (table 3). Requiring a visit with a specialist or two visits within 1 year did not greatly change this estimate (11.0 and 10.4 per 100,000 per year, respectively). The most liberal definition, requiring only one visit, increased the
incidence to 14.8 per 100 000 (table 3). One-third of new cases were dispensed a sarcoidosis-related medication within 6 months of diagnosis. The incidence did not appear to vary over time (figure 3).

55% of the incident cases were male and the average age at diagnosis was 50 years (table 3). Regardless of case definition, males had a higher incidence compared with females (table 3). On average, males had a younger age at diagnosis compared with women (median age: males 44.9 years versus females 54.0 years).

The peak incidence in males occurred between the ages of 30 and 50 years, whereas the peak in females was between 50 and 60 years (figure 4). Among 30–74 year olds, the age- and sex-standardised incidence per 100 000 per year was 14.2 for those with less than a high school education, 14.8 for those with a high school education and 12.9 for those with more than a high school education.

Discussion

Prevalent sarcoidosis in 2013 ranged from 152 to 215 per 100 000 depending on the definition used. The annual incidence of sarcoidosis in Sweden during 2003–2012 was 11.5 per 100 000 and differed by –10% to +30% when varying the number of visits, requiring specialist care or requiring two visits within 1 year. One-third of the incident cases were treated with glucocorticoids, antimalarials or immunomodulating medications within 6 months of first sarcoidosis-coded visit in specialty care.

The incidence of 11.5 per 100 000 reported here is lower than a previous report from Sweden by HILLERDAL et al. [3] (19 per 100 000 in 1966–1980), who identified sarcoidosis cases from radiographic screenings in a regional health survey. One-third of the cases in the report by HILLERDAL et al. [3] were identified because of symptoms and the rest were diagnosed through the health survey or by chance. In contrast, we identified individuals with sarcoidosis who received a diagnosis in inpatient or outpatient care, which likely includes more symptomatic cases at the expense of overlooking cases that would have remained clinically undetected. The study population investigated by HILLERDAL et al. [3] also had a different age distribution, capturing cases with a median age 10 years younger than in our study. We cannot rule out that the age at onset has increased over time, which has been suggested by previous studies [19, 20]. However, the older mean age at diagnosis observed in our study may be due to differences in age of onset of symptomatic versus asymptomatic disease or the inclusion of older age groups in our study. HILLERDAL et al. [3] had low rates of screening for older residents, whereas we used a population-based design that captured all Swedish adult residents’ sarcoidosis diagnoses. A report from Denmark also using register-based nationwide data estimated an incidence of 7.2 per 100 000 [10]. Unlike our study, they based their estimates exclusively on hospitalisations, likely underestimating the incidence of sarcoidosis which can often be managed in outpatient care.

The incidence of sarcoidosis did not vary over time between 2003 and 2012. This was consistent with findings from previous studies from the UK, Japan and Australia [8, 15, 21]. Two studies from the USA observed an increase in hospitalisations with sarcoidosis between 1996 and 2000 [19] and 1998 and 2008 [22].
indicate that improved detection and diagnostic procedures over time led to an increased number of identified cases during hospitalisation in the USA. A major limitation to these hospitalisation studies is that they could not identify unique individuals and therefore the same individuals could be counted more than once [22]. In contrast, our study included outpatient specialist care and the use of individual-level data, which likely better identifies the majority of new cases of clinical disease.

Approximately 55% of the incident cases were male, indicating no large difference between the sexes, as has been observed in previous reports [6–11, 13]. Other studies have, however, observed a slight female predominance [4, 5]. This may be due to differences in data sources or due to true differences in the populations under study in terms of age distribution, genetics or sarcoidosis phenotype.

We found that the peak age at onset in males was 10 years earlier than in females, which is consistent with most previous studies [3, 5, 7, 10, 13, 23, 24], but not all [4, 14]. The earlier onset in men could be due to an environmental factor which is more common in men and experienced at a younger age, such as an occupational exposure. In the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study, men were more likely to have pulmonary compared with systemic disease, which was associated with exposure to wood burning and agricultural organic dust [25]. Therefore, the two different peaks in men and women may represent two unique subtypes of sarcoidosis driven by sex-specific exposures. Alternatively, the onset could be delayed in women due to endogenous hormones which may protect against the occurrence of the disease. This is supported by the observation that pregnancy appears to have a favourable effect on sarcoidosis in some patients [26] and that later age at menopause is associated with a lower incidence of sarcoidosis [27].

The observed geographical variation could also be explained by the genetic composition of the individuals living in different regions in Sweden [29]. The southern regions of Sweden include Sweden’s most populated cities, i.e. Stockholm, Gothenburg and Malmö, which are more urban and ethnically diverse than northern regions. Genetics play a role in sarcoidosis aetiology, as demonstrated by the familial aggregation observed in multiple studies and the identification of several susceptibility loci [30]. Whether

### Table 2

<table>
<thead>
<tr>
<th>Characteristics of adults identified with prevalent sarcoidosis in Sweden using different register-based definitions, December 31, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more visit</td>
</tr>
<tr>
<td>Subjects</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age in 2013 years</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
</tbody>
</table>

Data are presented as n, % or mean±SD. Visits defined as having an International Classification of Disease code listing sarcoidosis in inpatient or outpatient care. #: department of internal medicine, dermatology, respiratory medicine, rheumatology or neurology; ¶: medication dispensing data available from July 2005 through December 2013, therefore if medication was dispensed before July 2005 it was not captured in the data.
familial risk explains the geographic variation observed here should be investigated further. Our results do not support the hypothesis that tick-borne bacteria such as *Borrelia burgdorferi* or *Rickettsia helvetica* cause sarcoidosis [31, 32] because ticks are more common in the southern and coastal regions where we see the lowest prevalence [33].

Due to our reliance on ICD codes to identify sarcoidosis and the difficulty in diagnosing some cases, some misclassification likely exists and we were unable to examine different subtypes such as Löfgren’s syndrome.

**FIGURE 2** Age- and sex-standardised prevalence of sarcoidosis per 100 000 by Swedish county, December 31, 2013. Prevalent cases defined as having two or more sarcoidosis-coded visits in inpatient or outpatient care before December 31, 2013.

**TABLE 3** Characteristics of adults identified with incident sarcoidosis in Sweden during 2003–2012 using different register-based definitions

<table>
<thead>
<tr>
<th></th>
<th>One or more visit</th>
<th>Two or more visits</th>
<th>Two or more visits, one or more with specialist*</th>
<th>Two or more visits, within 1 year</th>
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</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>10 787</td>
<td>8 395</td>
<td>8 006</td>
<td>7 627</td>
</tr>
<tr>
<td>Male</td>
<td>53.4</td>
<td>55.0</td>
<td>55.3</td>
<td>55.4</td>
</tr>
<tr>
<td>Age at diagnosis years</td>
<td>51.2±16.0</td>
<td>50.2±15.3</td>
<td>49.8±15.1</td>
<td>49.7±15.2</td>
</tr>
<tr>
<td>Incidence per 100 000 per year</td>
<td>14.8</td>
<td>11.5</td>
<td>11.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Males</td>
<td>16.0</td>
<td>12.8</td>
<td>12.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Females</td>
<td>13.5</td>
<td>10.2</td>
<td>9.7</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Data are presented as n, % or mean±SD. Visits defined as having an International Classification of Disease code listing sarcoidosis in inpatient or outpatient care. *: department of internal medicine, dermatology, respiratory medicine, rheumatology or neurology.
We were limited by the use of the first sarcoidosis-coded visit date as a proxy for date of incidence, and there is likely a lag between onset and diagnosis of a few months. Despite this potential misclassification, our estimates were quite robust and do not change greatly when varying the incidence and prevalence definitions. In a clinical cohort of well-characterised sarcoidosis cases from Karolinska University Hospital, 95% had two or more sarcoidosis-coded visits. This indicates that we capture the large majority of cases, but does not provide a positive predictive value of the ICD-10 diagnosis, which must be obtained from a validation study. Data on primary care visits for sarcoidosis were not included in this study, but most cases are referred to a specialist in Sweden, therefore these missing cases are likely few. Lastly, our prevalence estimate may include people who no longer suffer from sarcoidosis, therefore overestimating the burden of the disease on the population. However, this estimate represents a group that may have a reactivation of disease in the future and are therefore still of interest. The number of prevalent cases who were seen for care in 2013 may more realistically reflect those individuals living with sarcoidosis currently requiring clinical care; however, it misses individuals who still live with the disease but visit the doctor infrequently.

The generalisability of our study is excellent due to the population-based nationwide data used. However, it is uncertain whether our findings are generalisable to other populations with different genetic and racial compositions. The identification of over 16 000 prevalent cases and over 10 000 incident cases makes our investigation the largest study of individual-level data on sarcoidosis occurrence to date. Our study is further strengthened by the inclusion of cases diagnosed in both inpatient and outpatient care, which gives a clear picture of the occurrence of clinical disease in Sweden. Our register-based estimates were reasonably robust when using different combinations of ICD codes, care providers and treatments, demonstrating that these data are valuable for future investigations into the aetiology of sarcoidosis.

In conclusion, we observed a geographical variation in Sweden that has not been reported before and must be investigated further with regard to familial clustering of disease and environmental exposures. Data show that men and women are affected by the disease at different ages, with the age at diagnosis in men 10 years younger than in women. This indicates that sex plays a role in sarcoidosis occurrence through genetics, hormones, occupational exposures or another as-yet unidentified factor. Future studies should investigate risk factors for sarcoidosis in women and men separately to clarify the reasons for these differences.
Acknowledgements

Author contributions: E.V. Arkema, J. Grunewald, S. Kulberg, A. Eklund and J. Askling designed the study. E.V. Arkema and J. Askling acquired the register data. J. Grunewald, S. Kulberg and A. Eklund acquired the clinical cohort data. E.V. Arkema drafted the manuscript and performed the statistical analyses. E.V. Arkema, J. Grunewald, S. Kulberg, A. Eklund and J. Askling interpreted the results, revised the manuscript and approved the final version to be published.

References

