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Prevalence of sarcoidosis in Switzerland is associated with environmental factors

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ABSTRACT: The current study aimed to investigate incidence, prevalence and regional distribution of sarcoidosis in Switzerland with respect to environmental exposures.

All sarcoidosis patients hospitalised between 2002 and 2005 were identified from the Swiss hospital statistics from the Swiss Federal Office for Statistics (Neuchâtel, Switzerland). Regional exposure characteristics included the regional distribution of different industrial sectors, agriculture and air quality. Co-inertia analysis, as well as a generalised linear model, was applied.

The prevalence of "ever-in-life" diagnosed sarcoidosis, currently active sarcoidosis and sarcoidosis requiring hospitalisation was 121 (95% CI 93–149), 44 (95% CI 34–54) and 16 (95% CI 10–22) per 100,000 inhabitants, respectively. The mean annual incidence of sarcoidosis was 7 (95% CI 5–11) per 100,000 inhabitants. The regional workforce in the metal industry, water supply, air transport factories and the area of potato production, artificial meadows (grassland) and bread grains were positively associated with the frequency of sarcoidosis.

The prevalence of sarcoidosis was higher than assumed based on former international estimates. Higher frequency was found in regions with metal industry and intense agriculture, especially production of potatoes, bread grains and artificial meadows.

KEYWORDS: Agriculture, air pollution, berylliosis, epidemiology, metal industry

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The reported prevalence of sarcoidosis varies considerably across different countries and studies. Usually, it is estimated that 1–40 per 100,000 inhabitants are affected by sarcoidosis [1, 2]. There are no reliable data on the annual incidence of the disease, which is more common in adulthood, typically with an onset of disease before the age of 50 yrs. Sarcoidosis is observed throughout the world and affects all races and ages, as well as both sexes.

Different epidemiological studies have investigated environmental risk factors for the development of sarcoidosis. Exposure to bio-aerosols, as well as mold/mildew exposures and contact with insecticides, were described to be associated with a higher sarcoidosis frequency by the ACCESS (A Case-Control Etiologic Study of Sarcoidosis) study [3]. Along these lines, exposure to high humidity, mold/mildew, water damage or musty odour were associated with a higher frequency of sarcoidosis in African–American siblings [4]. Fire fighters in New York (NY, USA) seem to have a higher risk of developing sarcoidosis than the rest of the population [5]. However, to our knowledge there is no study investigating the country-wide frequency of sarcoidosis in respect to the vicinity to specific industries, types of agriculture or of meteorological and air quality measures.

Sarcoidosis is a multisystem disorder characterised by the presence of non-caseating granulomata and an accumulation of T-lymphocytes and macrophages in multiple organs [6]. The central enigma of sarcoidosis, *i.e.* its aetiology, still remains an unsolved problem. Many features of the disease suggest sarcoidosis is an antigen-driven disease. This is also supported by the fact that other granulomatous disorders with known antigens, such as berylliosis, have a very similar immunopathological and clinical presentation. It is conceivable that patients with sarcoidosis have hypersensitivity to one or more likely, many as yet not identified antigen(s). Recently, MÜLLER-QUERNHEIM *et al.* [7] "screened" their sarcoidosis patients with contact history to beryllium for hypersensitivity to beryllium using a lymphocyte proliferation test with different concentrations of beryllium sulphate; a soluble form of beryllium. They found that up to 40% of these patients with sarcoidosis and a history of beryllium exposure did have a sensitisation to beryllium. None of these individuals were employed at a factory that exposed them directly to beryllium or beryllium alloys; however, all of them had an identifiable "down-stream" source of exposure. The importance of down-stream exposure to agents such as beryllium is not known [7, 8].

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The prevalence and incidence of sarcoidosis vary between ethnic groups [9, 10]. In the USA, sarcoidosis is three to four times more frequently associated with a more severe phenotype in African–Americans [11]. The differences in the occurrence and presentation of sarcoidosis between ethnicities underline the importance of the genetic background. In European countries sarcoidosis is more prevalent in northern regions compared to Mediterranean countries [10, 12, 13]. Familial clustering and case aggregation have been reported [14, 15]. Differences in the genetic background as well as differences in environmental exposure might be responsible for this observation [10].

The aim of the current study was to investigate the incidence, prevalence and regional distribution of sarcoidosis in Switzerland. Furthermore, our hypothesis was that there might be an association between the distribution of metal-processing industry and the frequency of sarcoidosis. Therefore, we studied correlations between the regional incidence of sarcoidosis and the regional distribution of metal related as well as other industrial occupations. We also studied potential associations with the population density, different types of agriculture and the availability of medical resources, as well as with measures of air quality.

MATERIAL AND METHODS

Regional distribution of sarcoidosis cases

Figure 1 summarises the flow of patient selection for the calculation of regional incidence and frequency of sarcoidosis. Patients with sarcoidosis were identified with the aid of the statistics from Swiss hospitals obtained by the Swiss Federal Office for Statistics (Neuchâtel, Switzerland), which has nationwide coverage of all hospitalised patients since 1998. For each canton of Switzerland a specific validation of the coding accuracy was performed with the help of a coding specialist and by plotting the number of diagnoses per year. It generally took 3–5 yrs from the start of coding until satisfactory coding quality was reached. For the sake of consistency and data quality, in each canton these early years with a ''learning curve'' were deleted and the data from the 2002–2005 were used for further analyses.

Patients whose diagnosis list contained the word ''sarcoidosis'' (International Classification of Disease code D86) were selected. The anonymised dataset included a list of up to eight final diagnoses for each patient, together with the patient's area of residency (''Med-Stat'' regions). The patients were coded into one of the 612 Med-Stat regions according to their area of residency. Thus, the hospital in which their diagnosis was recorded was not relevant.

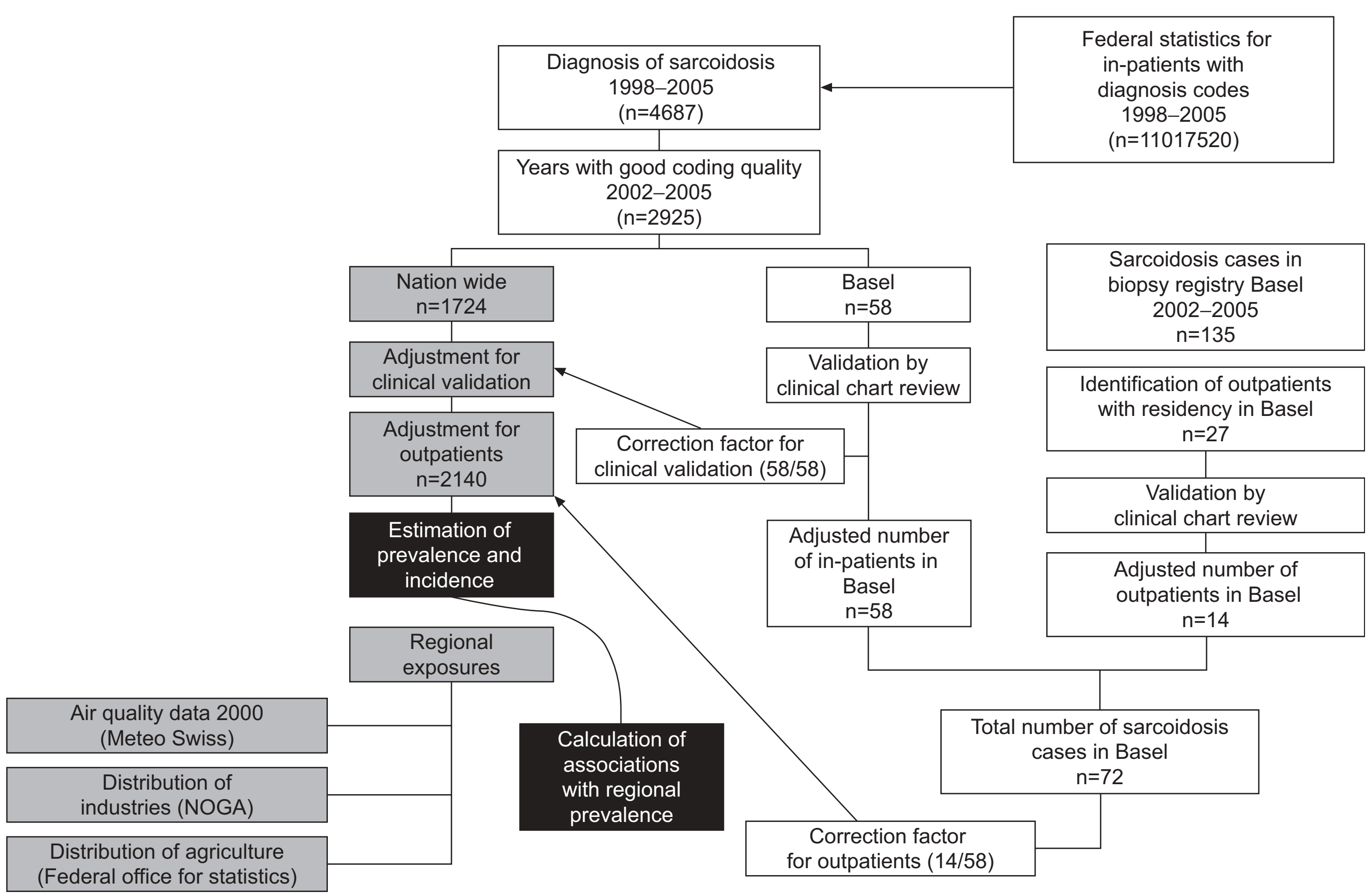

FIGURE 1. Flowchart explaining the selection process of sarcoidosis cases for the calculation of disease frequency and incidence. NOGA: Nomenclature Générale des Activités économiques. ■: estimation of true incidence, prevalence and distribution; □: clinical validation and correction for outpatients in Basel (Switzerland).

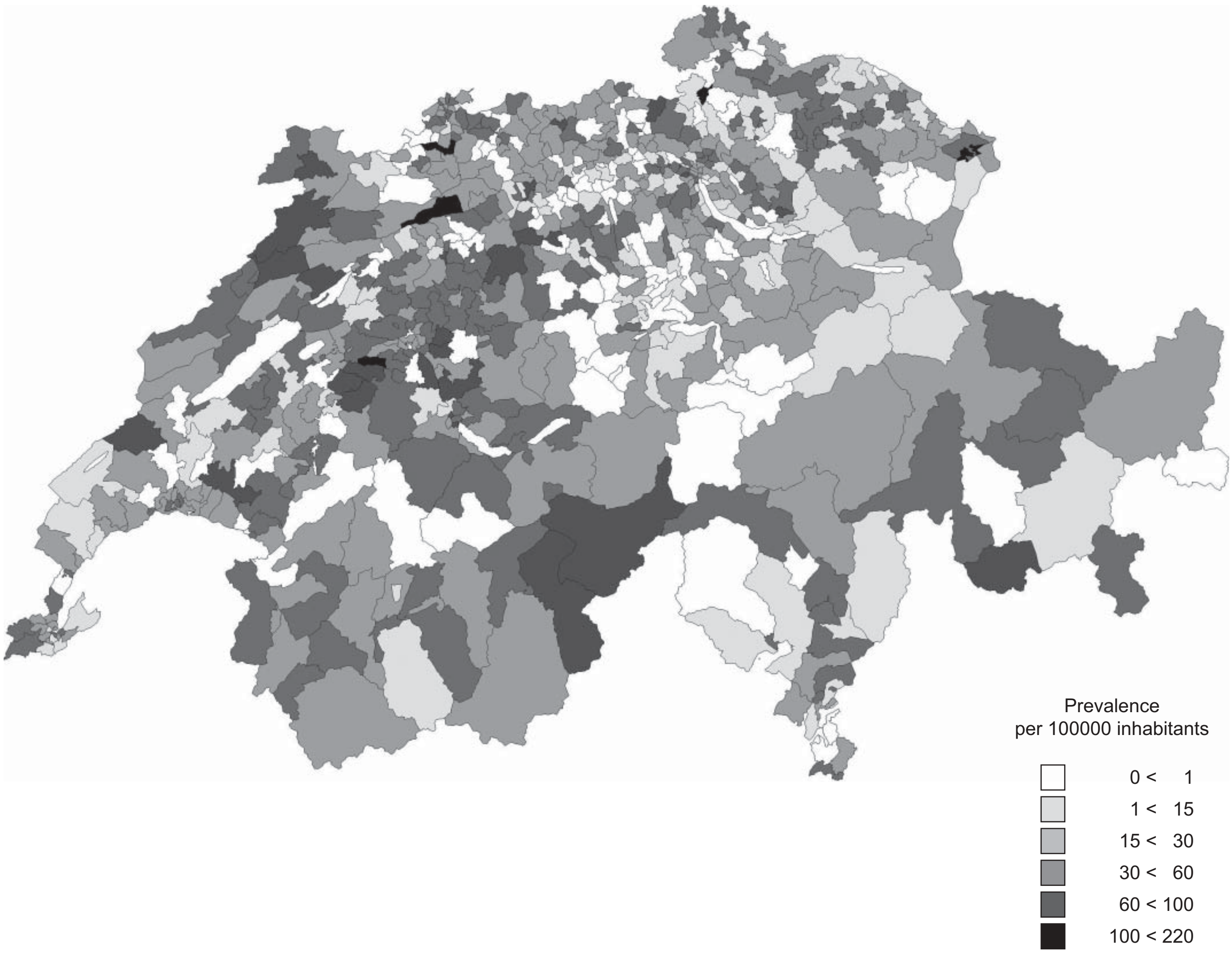

FIGURE 2. Map of Switzerland showing a significant regional heterogeneity in the prevalence of sarcoidosis in Switzerland ($p<0.001$). The prevalence is given as number of cases per 100,000 inhabitants. The geographic resolution was determined by Med-Stat regions, which represent aggregates of zip codes. Switzerland is divided into 612 Med-Stat regions.

In general the first diagnosis listed described the main reason for hospitalisation. Patients with a main diagnosis of sarcoidosis were considered to have active sarcoidosis. Further diagnoses represent health issues which are active but were diagnosed beforehand and/or managed on an outpatient basis. Thus, the list of diagnoses, even if not consistently comprehensive, generally represents a summary of relevant and active health issues independent of the time of diagnosis or whether it was an in- or outpatient problem. Patients who were hospitalised several times during the observation period could be identified through a unique identifier and were counted only once.

For the year 2004 all medical records of patients hospitalised in the University Hospital Basel (Basel, Switzerland) were reviewed in order to validate the quality of the statistics provided by the Federal Office for Statistics. With this we could validate whether or not the diagnosis of sarcoidosis was made and coded according to general recommendations [6].

The basis of the outpatient cases was the 2002–2005 biopsy registry of the Dept of Pathology at the University Hospital Basel. This registry was searched for the term ''sarcoidosis''. In 52% of identified potential sarcoidosis patients the diagnosis could be validated by the clinical records. In the other 48% of cases the diagnosis of saroidosis could not be confirmed and the patients turned out to suffer from other granulomatous disorders, such as tuberculosis. The clinically validated sarcoidosis patients were filtered according to their area of residency. For the outpatient cases of the Basel-Stadt canton, patients were studied who lived in the canton but who had never been hospitalised between the years 2002–2005. On the basis of these patients an outpatient-correction factor was calculated, *i.e.* number of outpatient cases divided by number of inpatient cases. This correction factor was used to estimate the number of outpatient sarcoidosis cases per canton on the basis of the available nationwide data on hospitalised patients. Thus, we were able to estimate the number of in-patient and outpatient cases with a diagnosis of sarcoidosis throughout Switzerland.

TABLE 1 Incidence and prevalence of sarcoidosis according to different definitions

Prevalence of sarcoidosis per year per 100000 inhabitants	Ever-in-life diagnosed sarcoidosis#	Currently active sarcoidosis¶	Hospitalised for active sarcoidosis
All	121 (93–149)	44 (34–54)	16 (10–22)
Males	130 (89–172)	47 (33–62)	18 (9–28)
Females	112 (74–149)	40 (27–53)	14 (5–22)
Incidence	7 (5–11)	7 (5–11)	2 (2–3)

Data are presented as prevalence (95% confidence interval). #: prevalence was calculated from patients with a main or secondary hospital diagnosis of sarcoidosis and with the assumption of a normal life-span for females and males; ¶: only patients with a main diagnosis of sarcoidosis were included and it was assumed that two out of three cases will go into remission after a mean disease duration of 12 months and that one out of three cases will suffer from a chronically active disease.

Regional distribution of specific industries, agriculture and air quality

The geographic resolution was determined by Med-Stat regions, which represent aggregates of zip code areas. Switzerland was divided into 612 Med-Stat regions (fig. 2). In 2002, the number of workers per region in each of the 464 industrial and 17 agricultural branches (Nomenclature Générale des Activités économiques (NOGA)) was determined [16]. As a measure of air quality the highest level of average annual $PM_{2.5}$ (particulate matter with an aerodynamic diameter <2.5 μm) concentration in each respective region from a dispersion model was obtained (reference year 2002). Moreover, analyses were repeated using estimates of source-specific $PM_{2.5}$ levels (*e.g.* $PM_{2.5}$ from traffic, agriculture, industry and households) [17].

Statistical analysis

Throughout the study the hospitalisation rate corrected for the coding quality and the fraction of outpatient cases was taken as an estimate of the true incidence and frequency of sarcoidosis. The frequency of sarcoidosis was estimated according to the method described by GUTZWILLER *et al.* [18]. We presumed that sarcoidosis would not lead to a significantly reduced life time. In the studies by VISKUM and VESTBO [19, 20], they found that sarcoidosis patients had the same survival time compared with the general population. Three different definitions for the prevalence of sarcoidosis were used: 1) prevalence of ''ever-in-life'' diagnosed sarcoidosis; 2) prevalence of currently active sarcoidosis; and 3) prevalence of active sarcoidosis requiring hospitalisation. The prevalence of ever-in-life diagnosed sarcoidosis was estimated by dividing the sum of the life expectancies of all new sarcoidosis patients by the size of the average resident population in Switzerland between the years 2002–2005 [21]. For the estimation of prevalence of currently active sarcoidosis, all patients with a diagnosis of sarcoidosis were included and it was assumed that two third of cases would go into remission after a mean disease duration of 12 months and that one third of cases would suffer from a chronically active disease. For the prevalence of active sarcoidosis requiring hospitalisation, only in-patients with a main diagnosis of sarcoidosis were included in the analysis.

Data were analysed using the SPSS software package (version 15.0; SPSS Inc., Chicago, IL, USA), as well as R-project version 2.9.0 (open-source software program). Associations between the geographic distribution of patients with sarcoidosis and industry, agriculture and air quality were first analysed with a co-inertia analysis; an unsupervised hypothesis-generating multivariate technique [22]. Co-inertia analysis is closely related to the method of partial least squares. It provides a global measure of the co-structure of two datasets. Let us define X and Y, two data matrices with the same number rows, the same row weights (Dr is the diagonal matrix of row weights). Q and R are the diagonal matrix of the column weights of X and Y, respectively. The co-inertia analysis of tables X and Y is given by the eigenvalue decomposition of the statistical triplet (Y^tD_rX, Q, R). The concordance between the two datasets is given by the RV-coefficient, a multivariate extension of the Pearson correlation coefficient, whose significance is obtained by the Monte-Carlo permutation test. Co-inertia analysis is able to summarise graphically highly complex data. The closeness between the vector representing the regional frequency of sarcoidosis and the vector representing a specific regional factor indicates the strength of the respective statistical association. The vectors of relevant factors approximate the direction of the vector of sarcoidosis: the longer the vector, the stronger the respective association.

To assess the association between the regional frequency of sarcoidosis and the different regional covariates, Poisson regression models with the natural logarithm of the regional population size as offset variable were computed. All significant co-variables from univariate analyses from 464 industrial, 17 agricultural and

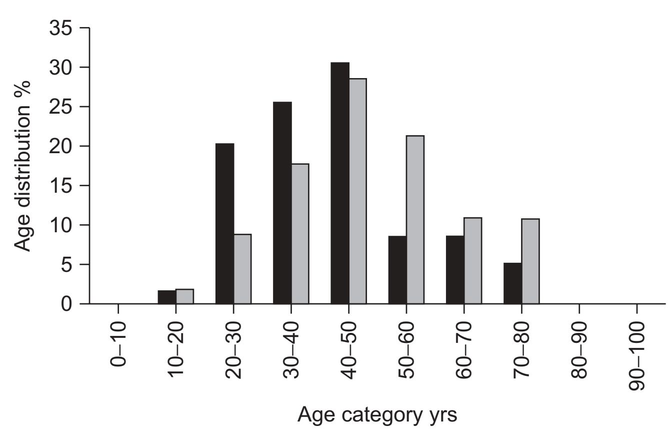

FIGURE 3. Age- and sex-distribution of patients hospitalised for active sarcoidosis. For this analysis only patients with a main diagnosis of sarcoidosis were included. ■: male; ■: female.

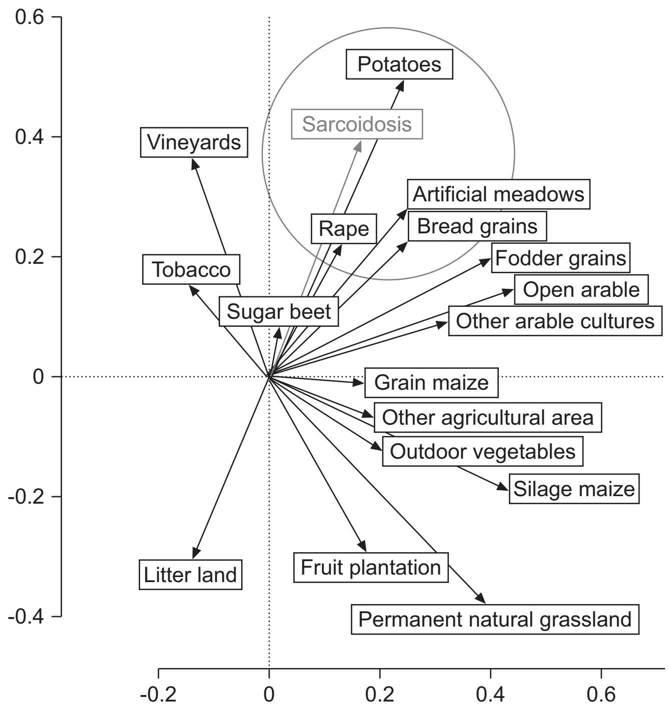

FIGURE 4. Co-inertia analysis of the regional frequency of sarcoidosis and agricultural sectors. The closeness between the vector representing the sarcoidosis prevalence and the vector representing a specific regional factor indicates the strength of the respective statistical association. The vectors of relevant factors approximate the direction of the vector of sarcoidosis; the longer the vector, the stronger the respective association. p=0.004.

11 air pollution factors were collectively scrutinised for interaction and interdependence within the subcategories industry, agriculture, air pollution, healthcare resources and population density. A backward variable selection procedure was used for the final models. At the end only co-variables with a significance level of $p<0.1$ remained.

RESULTS

Demographics, frequency and incidence of sarcoidosis

In total, 5,590,962 in-patient cases were coded in Swiss hospitals from 2002 to 2005. Of these, 2,925 (0.05%) patients were hospitalised with a diagnosis of sarcoidosis. In 899 (31%) cases, sarcoidosis was the first diagnosis. The mean age of patients hospitalised for sarcoidosis was 55 ± 16 yrs, 52 ± 15 yrs for males and 58 ± 17 yrs for females ($p<0.01$). The mean age at the initial diagnosis was 45 ± 15 yrs (41 ± 14 and 48 ± 15 yrs for males and females, respectively; p=0.025). The mean incidence and prevalence of ever-in-life diagnosed sarcoidosis per year was 7 (95% CI 5–11) and 121 (95% CI 93–149) per 100,000 inhabitants (table 1). The sex-specific disease frequency was 130 (95% CI 89–172) for males and 112 (95% CI 74–149) for females. The prevalence of currently active sarcoidosis was 44 (95% CI 34–54) per year and per 100,000 inhabitants. The prevalence of active sarcoidosis requiring hospitalisation was 16 (95% CI 10–22). The age-specific rate of hospitalisation for sarcoidosis started to increase at the age of 25–35 yrs and peaked at the age of 40–45 yrs for males and 50–60 yrs for females (fig. 3).

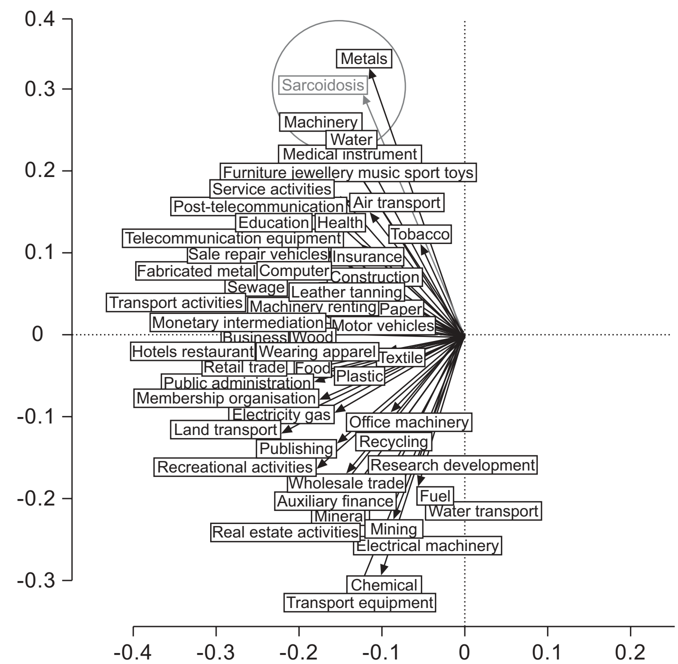

FIGURE 5. Co-inertia analysis of the regional frequency of sarcoidosis and different industrial branches. The closeness between the vector representing the sarcoidosis prevalence and the vector representing a specific regional factor indicates the strength of the respective statistical association. The vectors of relevant factors approximate the direction of the vector of sarcoidosis; the longer the vector, the stronger the respective association. p=0.009.

Geographic distribution and associations with regional characteristics

The co-inertia analysis showed associations between the regional frequency of sarcoidosis and production of bread grain and potatoes (fig. 4), and the regional importance of the metal industry, water supply industry and production of machinery (fig. 5). These results were largely corroborated by the multivariate analysis of the main branches of the NOGA categories, where the area of potato production, artificial meadows and bread grains, as well as the density of water supply industry and air transport factories were positively associated with the regional frequency of sarcoidosis (table 2). The population of sarcoidosis patients was not randomly distributed across the regions ($p<0.001$). This regional heterogeneity was not explained by differences in the local medical services (p=0.43). No significant association was found between the air quality (fig. 6) and the disease frequency of sarcoidosis. A negative significant association was seen between the regional disease frequency of sarcoidosis and the population density (p=0.03). The associations with the metal industry represented trends. Table 3 shows the results of a multivariate analysis of all 464 industrial sub-branches which gave positive associations with the regional frequency of sarcoidosis. Different sub-branches of the metal industry were associated with higher sarcoidosis frequency.

DISCUSSION

We were able to estimate the regional incidence and prevalence of sarcoidosis in Switzerland with the aid of a nationwide hospital database. We were able to give estimates for ever-in-life

TABLE 2 Multivariate analysis showing associations of main industrial Nomenclature Générale des Activités économiques (NOGA) branches#, agricultural sectors, measures of air pollution and population density with the regional frequency of sarcoidosis

	NOGA branches	% change¶ (95% CI)	p-value+
Main industrial branches§			
Other service activities such as hair dressing, washing of textiles, saunas, solariums	93	59 (12–127)	0.010
Collection, purification and distribution of water	41	47 (13–90)	0.004
Manufacture of woods	20	46 (14–88)	0.003
Computer and related activities	72	41 (5–89)	0.022
Manufacture of basic metals	27	40 (-4–105)	0.079
Air transport	62	22 (1–46)	0.035
Real estate activities	70	-32 (-53– -2)	0.041
Wholesale trade and commission trade, expect of motor vehicles and motorcycles	51	-42 (-65– -3)	0.038
Health, veterinary and social workƒ	85		
Veterinary activities	85.2	39 (19–62)	<0.001
Dental practice activities	85.13	27 (-14–90)	0.232++
Social work activities	85.3	24 (-15–82)	0.264++
Hospital and human health activities	85.11, 12, 14	-13 (-42–32)	0.516++
Agriculture##			
Bread grains		690 (120–2735)	0.002
Potatoes		149 (62–281)	<0.001
Fodder grains		134 (-1–452)	0.052
Artificial meadows		97 (35–189)	<0.001
Other arable crop		60 (-4–168)	0.073
Outdoor vegetables		60 (11–131)	0.013
Open arable land		-98 (-100– -86)	<0.001
Air pollution¶¶			
Total $PM_{2.5}$		-5 (-31–33)	0.782++
Population density			
Population density		-29 (-48– -3)	0.033

$PM_{2.5}$: particles with a 50% cut-off aerodynamic diameter of <2.5 μm. #: branches which remained significant after a backward elimination process are presented as adjusted estimates of the percent changes in the frequency of sarcoidosis associated with increments in different covariates from their 1st to their 99th percentile (separate models for different groups of covariates); ¶: for an increment in the respective covariate from the 1st to the 99th percentile; +: a p-value of <0.1 was statistically significant; §: the following were analysed but are not significant NOGA-Industry-categories: 15–19, 21–26, 28–37, 40, 45, 50, 52, 55, 60–67, 71, 73–75, 80, 85, 90–92; ƒ: no backward selection was performed since these results are to demonstrate that sarcoidosis rates are not associated with the regional levels of health services; ##: the following were analysed but are not significant subgroups of agriculture: litter land, permanent natural grassland, outdoor vegetables, fruit plantation, arable land, rape, vineyards, silage maize, tobacco, grain maize, and sugar beet; ¶¶: the following were analysed but are not significant subgroups of air pollution: secondary particle distribution associated with the different main $PM_{2.5}$ sources traffic, agriculture, industry, household, residential emission and secondary particle; ++: these not significant factors and are only illustrated for overview.

diagnosed sarcoidosis, currently active sarcoidosis and currently active sarcoidosis requiring hospitalisation. In Germany, the prevalence calculated from clinical records was reported as 40–50 cases per 100,000 inhabitants, which is comparable to our prevalence of currently active sarcoidosis. In France and Switzerland it was estimated as to be as low as 10–20 cases per 100,000 inhabitants [14]. However, reported prevalences in different studies are highly dependant on the method of study. The study by REID [24] performed in the USA brought up an interesting comparison. Considering comprehensive autopsy results REID [24] estimated a prevalence of 333 cases per 100,000 inhabitants, whereas considering cases from clinical records their prevalence estimate was only 8.3 cases per 100,000 inhabitants. We utilised a nationwide registry and clinical records, as well as data taken from a biopsy registry. To include biopsy data bears the risk of overestimation. Granulomatous lesions are found in different organs and do not necessarily lead to a clinical diagnosis of sarcoidosis. In our study we validated biopsy cases with clinical records and found that only 52% of the biopsies compatible with sarcoidosis were indeed clinically defined cases of sarcoidosis. The other 48% of patients were found to actually suffer from diseases such as drug-induced granulomatous hepatitis, Mycobacterial spp. infections or hypersensitivity pneumonitis. Applying such a correction factor to the 333 cases out of 100,000 cases in the study by REID [24] would provide a prevalence estimate quite close to our prevalence according to the ever-in-life diagnosed sarcoidosis definition. Our incidence rate is comparable to the results reported in Denmark (eight cases per 100,000 inhabitants per year) [25]. With 11 cases a year per 100,000 inhabitants, Finland is the only country to report a higher incidence than Switzerland [26].

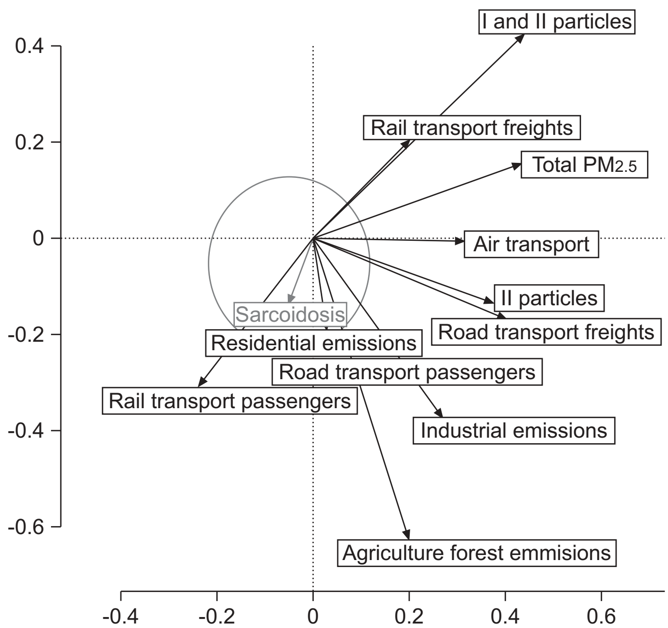

FIGURE 6. Co-inertia analysis of the regional frequency of sarcoidosis and indicators of air quality. The closeness between the vector representing the sarcoidosis prevalence and the vector representing a specific regional factor indicates the strength of the respective statistical association. The vectors of relevant factors approximate the direction of the vector of sarcoidosis; the longer the vector, the stronger the respective association. p=0.20.

The reported incidence and prevalence in our study might yet be an underestimation. We only included outpatient cases identified from the biopsy registry which were clinically validated. It is possible that some of the excluded patients had sarcoidosis, but had not yet reached the necessary clinical criteria to diagnose it. Furthermore, we could only identify outpatients with potential sarcoidosis if they had undergone a biopsy. It is likely that a certain fraction of patients with sarcoidosis were diagnosed in an outpatient basis without histopathological validation. However, we assumed that sarcoidosis would not significantly shorten the lifespan of affected individuals [20], which could result in a slight overestimation of the number of living patients with sarcoidosis.

The mean age at the initial diagnosis in our study was 45±15 yrs. There is a significant variability in the literature, however, the reported age at initial diagnosis varies from <40 yrs [27, 28], to ~40 yrs [29, 30] to 48 yrs [31]. Approximately one-third of the patients in the ACCESS study were ⩾50 yrs of age at the time of diagnosis [32]. It is likely that methodological differences are responsible for the observed age differences between studies.

Several environmental risk factors associated with the frequency of sarcoidosis were identified in epidemiological studies [3–5, 33, 34], mainly exposure to water damage, working in the metal industry, motorcycle manufacture, wood burning and machining. Further exposures that have been associated with sarcoidosis in a number of studies were related to air transport, hair dressing, wood dust, population density, being a dental technician (berylliosis), working in the medical and health sector and manufacture of furniture. We found a heterogeneous distribution of sarcoidosis in Switzerland, which was associated with two main signals: 1) the regional importance of agriculture, and 2) different sub-branches of the metal industry.

As in other studies [35, 36], the highest number of cases per population was observed in rural areas. This association supports the hypothesis that antigens derived from an agricultural setting could be involved in the pathogenesis of sarcoidosis. The association between agriculture and sarcoidosis has already been established in other studies, but the correlation with specific agricultural sectors is new. Only associations with vegetable dust, high humidity, insecticides, plant farming and animals in the workplace have been reported so far [4, 37]. The association with grain mill production is especially interesting, as is the significant relationship with areas of grain cultivation. KUCERA *et al.* [4] proposed that dust exposure or work involving mold/mildew exposure might represent a risk factor. The associations with agricultural sectors found in our study included production of bread grains, potatoes and artificial meadows (grassland). In Switzerland, the production of these crops is located on fertile soils and such farms typically do not have cattle. This leads to exposure to mineral fertilisers as these are used to compensate for the absence of naturally produced manure.

We are the first to report an association between the geographic distribution of sarcoidosis and the regional importance of different types of metal-processing industry. Other studies have sought associations with specific jobs and workplaces within the metal industry [3, 5, 37]. Exposure to a metal-working plant, either by vicinity of residence or professional exposure, could represent a risk factor for the development of sarcoidosis. In addition, living near a metal plant might be a surrogate marker for the likelihood of working in this industry and being exposed to specific pollutants, metals including traces of beryllium and other antigens [38]. A likely, or at least possible, explanation for our observation might be the fact that hypersensitivity to beryllium or other metals is under diagnosed [7]. Recently, MAIER *et al.* [39] reported a series of eight cases of chronic beryllium disease attributable to industry-associated environmental exposure from a community surrounding a beryllium manufacturing facility in Reading (PA, USA). Several of these cases had previously been misdiagnosed with other diseases such as sarcoidosis. The hazard related to beryllium exposure has been well known for many years with the first description being published by HARDY *et al.* [40] in 1948, with additional reports being made by MACHLE *et al.* [41]. However, prevention measures mostly focus on plants which directly work with beryllium metal or alloys. The problem is that the diffusion of beryllium ''downstream'' has resulted in possibly a large number of very diverse workplaces that use beryllium. Some of these workplaces only use it some of the time and many companies are not aware of the risks. As a consequence patients with downstream exposure are not evaluated for the presence of hypersensitivity to berylliosis. This was the case until the study by MÜLLER-QUERNHEIM *et al.* [7] revealed that, in a German cohort of subjects with a diagnosis of sarcoidosis, who were referred because of a potential beryllium exposure, ~40% of patients actually had a positive lymphocyte proliferation test to beryllium and, thus, potentially had berylliosis [7]. Our data

TABLE 3 Multivariate analysis showing associations of all 464 industrial Nomenclature Générale des Activités économiques (NOGA) sub-branches#

	NOGA branch	% change¶ (95% CI)	p-value+
Metal industry	27, 28		
Cold rolling of narrow strip§	2732	578 (174–1578)	<0.001
Manufacture of basic iron and steel and of ferro-alloys§	2710	240 (13–922)	0.029
Copper production§	2744	86 (-3–257)	0.061
Manufacture of light metal packaging	2872	37 (12–67)	0.002
Manufacture of metal tanks, containers and reservoirs	2821	29 (6–57)	0.010
Aluminium production	2742	7 (-1–17)	0.099
Wood industry	20		
Manufacture of products of wood	2051	114 (61–183)	<0.001
Transport industry/type	34, 35, 50, 60–64		
Manufacture of motorcycles§	3541	286 (60–832)	0.003
Transport *via* railways	6010	158 (87–254)	<0.001
Manufacture of railway and tramway locomotives and rolling stock	3520	69 (33–115)	<0.001
Sale, maintenance and repair of motorcycles and related parts and accessories	5040	62 (14–129)	0.007
Scheduled air transport	6210	2 (1–3)	<0.001
Machine industry	29, 51, 52		
Wholesale of agricultural machinery and accessories and implements	5188	67 (19–134)	0.003
Wholesale of other office machinery and equipment	5185	64 (15–133)	0.006
Manufacture of bearings, gears and driving elements	2914	28 (2–60)	0.033
Manufacture of machinery for metallurgy	2951	6 (3–10)	<0.001
Agricultural sector specific industry	15, 16, 51, 85		
Manufacture of fruit and vegetables§	1532	8970 (256–23·10^4)	0.006
Wholesale of agricultural machinery and accessories and implements	5188	67 (19–134)	0.003
Veterinary activities	8520	57 (28–92)	<0.001
Agents involved in the sale of food, beverages and tobacco	5117	55 (20–100)	<0.001
Manufacture of grain mill products	1561	32 (11–58)	0.002
Manufacture of beer	1596	-28 (-44– -7)	0.013
Service sector	22, 52, 70–75, 57, 80, 85, 90–93		
Reproduction of video recording§	2232	75 (-1–208)	0.053
Real estate agencies	7031	60 (15–125)	0.006
Administration of healthcare, education, cultural services and social services	7512	60 (6–141)	0.026
Saunas and solariums	9304	59 (9–131)	0.016
Other services activities	9305	40 (12–75)	0.003
Refuse disposal	9002	29 (2–64)	0.035
Other sporting activities	9262	21 (0–48)	0.052
Correspondents, news agencies	9240	-17 (-32–0)	0.052
Retail sale of books, newspaper and stationery	5247	-20 (-32–6)	0.006
Photographic activities	7481	-35 (-51– -12)	0.005
Retail sale of medical and orthopaedic goods	5232	-39 (-60– -7)	0.022
General civil service	7511	-42 (-60– -14)	0.006
Publishing of newspaper	2212	-42 (-62– -12)	0.010
Accounting, book keeping and auditing activities	7412	-43(-61– -14)	0.007
Labour recruitment and provision of personnel	7450	-43(-63– -13)	0.009
Pre-primary and primary education	8010	-50 (-68– -21)	0.003
Retail sale of hardware, paints and glass	5246	-53 (-72– -23)	0.003
Other manufactures and building sector	21, 22, 25, 45, 46		
Architectural and engineering activities and related technical consultancy	7420	180 (63–382)	<0.001
Manufacture of soap, cleaning, perfumes and toilet preparations	2451	16 (4–30)	0.007
Manufacture of paper and paperboard	2112	1 (0–1)	<0.001
Manufacture of other office and shop furniture	3613	48 (11–97)	0.008
Erection of roof covering and frames	4522	-38 (-59– -6)	0.025
Striking of coins and medals	3621	-12 (-19– -4)	0.003
Manufacture of plastic packing goods	2522	-45 (-68– -5)	0.033

#: sub-branches which remained significant after a backward elimination process are presented as adjusted estimates of the per cent changes in the frequency of sarcoidosis associated with increments in different covariates from their 1st to their 99th percentile for NOGA sub-branches in significant main categories; ¶: for an increment in the respective covariate from the 1st to the 99th percentile; +: a p-value of <0.1 was statistically significant; §: for an increment in the respective covariate from the minimum to the maximum.

appears to support the hypothesis that regions with an increased load of specific metal-processing industry have a higher frequency of sarcoidosis. Whether or not this observation is related to the use of beryllium remains unclear as hypersensitivity reactions to other metals might also play a role. Switzerland imports ~60 kg of unwrought beryllium or beryllium powder and ~1.3 tons of beryllium contained in intermediate and finished goods per year. The annual production of beryllium bound in waste and scrap rises to an estimated amount of 2 tons [42]. In terms of actual weight, the amount of beryllium handled in Switzerland does not seem to be impressive; however, hypersensitivity reactions can arise from very low amounts and concentrations. The real hazardous aspect of beryllium may be its widespread use in different industry branches handling metal, such as engineering, electrical industry, watch manufactures and air transport. More effort is needed with respect to preventative efforts and education.

The coding system used in the current study neither provided the full residential address nor the profession and work place of the individual. Duration of residence and changes of residency were not available either. Thus, it was not possible to assess environmental exposure at an individual level. Neither was it possible to obtain information on individual professional exposure. Due to the anonymised format of the Swiss coding system it was not feasible to contact individuals for a more detailed assessment. However, the Swiss coding system provides nationwide coverage and good quality information of regional indicators, enabling valid comparisons across regions.

In conclusion, we estimated the prevalence of sarcoidosis in Switzerland according to three clinically relevant definitions, which is higher than some previous estimates derived from other countries. The prevalence of sarcoidosis showed a significant regional heterogeneity. Intense agricultural production as well as the presence of specific sub-branches of metal-processing industry in the vicinity of residency were positively associated with the frequency of sarcoidosis and, thus, identified as environmental risk factors. Different studies, including ours, have found ''signals'' from the metal-processing industry and some agricultural sectors. The observed associations do not directly imply causality. Further studies to elucidate the true hazard associated with different types of exposure [34] are required to define the true relationship between such exposures and sarcoidosis.

STATEMENT OF INTEREST

None declared.

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