Acute Sarcoidosis Clusters in Cold Season and Is Associated with Ambient Air Pollution: A Retrospective Clinical-Meteorological Study

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ANNALSATS Articles in Press. Published February 10, 2021 as 10.1513/AnnalsATS.202008-1083RL

Sarcoidosis is a systemic granulomatous disease of unknown orign. Differences in prevalence, phenotype and severity depending on geographical location and populations have been reported, indicating an influence of genetic and environmental factors (1-2). Acute sarcoidosis is defined by a rapid onset of symptoms including bihilar lymphadenopathy, ankle swelling and/or erythema nodosum and has an overall favourable prognosis (3).

Current concepts of pathogenesis involve an aberrant immune response in genetically susceptible individuals to unknown antigens, stimulating macrophages and dendritic cells with subsequent activation of primarily CD4+ Th1 cells and granulomatous inflammation (reviewed by Grunewald *et al (4)*). Seasonal clustering of sarcoidosis in late winter and spring months has been described (5–11). The further north and the colder the climate, the earlier the incidence of sarcoidosis peaks in the year (12, 13). Risk factors for sarcoidosis include exposure to airborne particles through, for instance, metalworking (14, 15), employment in transportation services (16) and exposure to vegetable dust or wood-burning (17). Increased sarcoidosis frequencies among firefighters (18), as well as the high sarcoidosis incidence in individuals exposed to the World Trade Center collapse (19–21), further point towards the pathogenetic involvement of particulate matter.

The key manifestations of lung and skin, certain risk populations and seasonal clustering suggest an importance of seasonal airborne antigens for acute sarcoidosis. We hypothesized that air pollution plays a role in acute sarcoidosis and its seasonal clustering and north-south gradients.

For this retrospective chart review we searched records of the University Medical Center Freiburg for all patients in the region Baden-Wuerttemberg, Germany diagnosed with acute

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sarcoidosis as defined by bihilar lymphadenopathy combined with ankle swelling and/or erythema nodosum plus a corresponding physician's diagnosis. Disease onset was set as the date of first symptoms (month/year). The study was approved by the local ethics committee of the University of Freiburg (approval number: 11/19). Measured particulate matter (PM_{10}) and nitrogen dioxide (NO_2) concentrations data were provided by the State Institute for the Environment, Measurements and Nature Conservation Baden-Wuerttemberg (LUBW). Monthly medians of the air pollutant time series were calculated from hourly NO_2 concentrations measured at 27 stations and from daily PM_{10} concentrations available at 38 stations located in Southwest Germany. Air temperature data for the same area was sourced from the climate data centre of the German Meteorological Service (ftp://opendata.dwd.de/climate_environment/CDC/).

The seasonal components in the air pollutant, air temperature and sarcoidosis time series were extracted by applying singular spectrum analysis (SSA). The SSA enables the decomposition of time series into a slowly varying, non-linear trend, oscillatory components and noise (22). It combines the phase-space reconstruction technique of a time series and the singular value decomposition (23). We chose an embedding dimension of twelve months to separate the oscillatory, seasonal component from non-linear trends and noise. Based on the seasonal SSA component, we calculated the mean annual variation of air temperature, PM_{10} and NO_2 concentrations and the occurrence of sarcoidosis. To measure similarity, we calculated lagged cross-correlation functions up to 24 lags. The decomposition of the time series was based on SSA routines implemented in Matlab® software (The MathWorks, Natick,

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Massachusetts, United States) by Eric Breitenberger; the routines were downloaded from http://www.atmos.ucla.edu/tcd/ssa/matlab.

Over a period of 25 years (1994-2018) we found 185 patients diagnosed with acute sarcoidosis; 136 (73.5%) displayed complete Löfgren triad, see table 1 for a detailed description of the study cohort. The onset of disease showed a pattern of seasonality: symptoms started predominantly in the first half of the year (73.5% of cases), and peaked in January,. A particularly high incidence was observed in the first third of the year (January 17.8%, February 11.3%, March 12.4%, April 13.0%, 54.5% in total), as shown in figure 1. Monthly median PM_{10} values were highest from December to April with values ranging between 15 and 40 µg/m^3. Monthly median NO_2 levels were measured highest from November to March (45 µg/m^3) and lowest between April and August (25 µg/m^3), as shown in figure 2a. Monthly sarcoidosis incidence correlated with the course of PM_{10} and NO_2 with cross-correlation coefficients ranging between 0.7 and 0.9 (see figure 2c). Time series analysis over 17 years (2000-2016) showed that the maximum number of acute sarcoidosis cases is reached shortly after the peak of particulate matter (median time shift between the maxima within each year was 4 weeks, range -8 to 20 weeks, figure 2a) and the minimum of air temperature (cross-correlation coefficients 0.4-0.9, median time shift 12 weeks, range 0 to 44 weeks, figure 2b).

This is the first demonstration of associations between the seasonal dynamics of air temperature, air pollution, and the incidence of acute sarcoidosis. The relevance of air pollution in the pathogenesis of sarcoidosis is indicated by risk populations (e.g., firefighters (18), exposure to vegetable dust, wood-burning etc. (14)), the observation of regional sarcoidosis clusters in areas with intense metal industry, agriculture (15) or heavy traffic (24), the World

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Trade Center studies (19) and by case reports describing sarcoidosis following intensive dust exposure (25). Furthermore, sarcoidosis patients reported increased severity of respiratory symptoms after short term air pollution exposure (26). In clinical practice, we also consulted patients who developed acute sarcoidosis days after cleaning their pellets storage, after demolition work close to their homes or clearing out their attic without dust masks. Air pollution has been described as a risk factor for disease with negative impacts on health already at low concentration (27). Particulate matter has been linked directly to the development of respiratory diseases and malignancies (28) and plays a potential role in autoimmune disorders (29).

We found an acute sarcoidosis onset pattern which is comparable to those of northern European countries, whereas the incidence peaks later in the year in Mediterranean countries. Hence, in colder regions, sarcoidosis incidence might peak earlier, for example, due to an earlier start of the heating period. Residential furnaces represent a major source of particulate matter and their emissions may affect human health (30). In line with these observations, in our study, low air temperature was associated with increased sarcoidosis incidence.

This study is limited by the single-center retrospective approach, covering one federal state in Germany. Although during the relatively long study period of 25 years, exposures and health care coverage may have changed, we did not observe a significant variation in the seasonality of sarcoidosis and the relative seasonal burden of air pollution. Air pollution has a high spatiotemporal variability and monitoring stations may not fully reflect individual or indoor exposure. We did not had the possibility to assess possible job exposures. We applied PM_{10} instead of $PM_{2.5}$, as indicator of particulate matter. Even though $PM_{2.5}$ is typically used to

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estimate the burden of air pollution on population health, PM_{10} can be regarded a valid surrogate for $PM_{2.5}$ given the strong correlation of the two. Overall, our study suggests that air pollution plays a role in the etiology of acute sarcoidosis and gives a possible explanation for seasonal clustering, north-south gradients and risk populations.

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Table 1: Clinical characteristics of the study cohort.

	Acute sarcoidosis patients
Patients enrolled	185
Median age (years, range)	37.4 (20 - 76)
Female n (%)	90 (48.7%)
X-ray type type 1/2 n (%)	105 (67.3%)/51 (32.7%)
Erythema nodosum n (%)	148 (80%)
Arthritis n (%)	173 (93.5%)
Ankle n (%)	143 (88.3%)
Knee n (%)	29 (18.0%)
Elbow n (%)	9 (5.6%)
Wrist n (%)	25 (15.5%)
Finger n (%)	8 (5.0%)
Histologic confirmation n (%)	70 (37.6%)
Never smokers n (%)	68 (50.0%)
Former smokers n (%)	45 (33.1%)
Current smokers n (%)	23 (16.9%)

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Figure Legends:

Figure 1: Distribution of disease onset of 185 patients diagnosed with acute sarcoidosis shows significant clustering in the first third of the year ($p < 0.005$, Kendall $\tau = -0.68$). The average monthly proportion without the influence of seasonality is 8.3% (dashed line).

Figure 2: (a) Annual cycle showing the temporal relationship between of PM_{10}, NO_2 and the proportion of cases with acute sarcoidosis. Seasonal components derived from singular spectrum analysis for the period 2000-2016 are shown and display that the peak of acute sarcoidosis incidence is reached shortly after air pollution maxima. (b) SSA derived seasonal components of sarcoidosis frequency and temperature shows highest sarcoidosis frequency after the air temperature minimum is reached (period 1994-2018). (c) Results of the lagged cross-correlation functions to measure the similarity between the course of acute sarcoidosis occurrence and PM_{10}, NO_2 and air temperature. For visualisation results were centred and scaled to have mean 0 and standard deviation 1.

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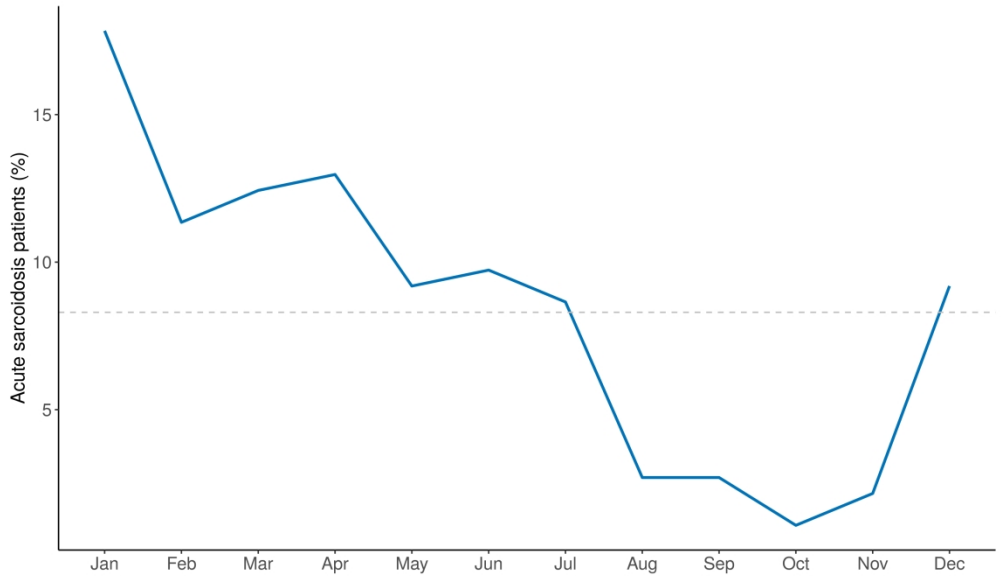

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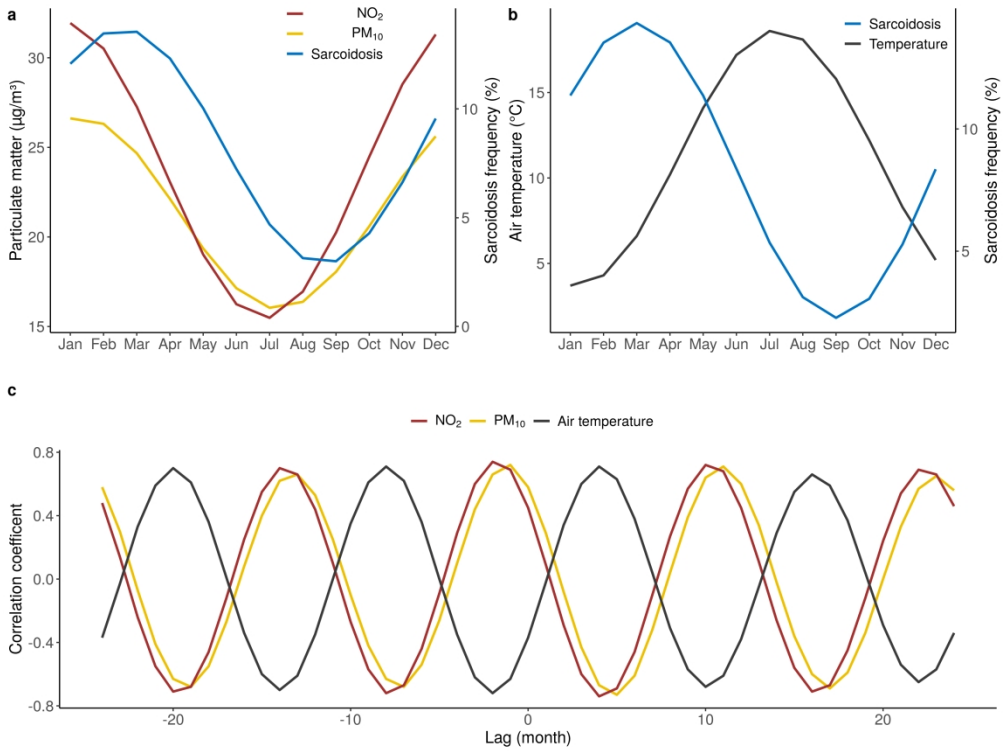

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