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DOI:
10.1136/oemed-2022-108632

This article has been accepted for publication in OEM following peer review.
The definitive copyedited, typeset version is available online at 10.1136/oemed-2022-108632

Airborne Occupational Exposures associated with Pulmonary Sarcoidosis: A Systematic Review and Meta-Analysis

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Word Count: 4,600

Abstract

Background

The aetiology and pathophysiology of sarcoidosis is ill-defined – current hypotheses centre on complex genetic-immune-environmental interactions in an individual, triggering a granulomatous process.

Aim

To define and describe which airborne occupational exposures (aOE) are associated with and precede a diagnosis of pulmonary sarcoidosis.

Methods

Systematic review and meta-analyses of odds ratios (OR) for specified aOE associated with pulmonary sarcoidosis (DerSimonian Laird random effects model [pooled log estimate of OR]). Standard search terms and dual review at each stage occurred. A compendium of aOE associated with pulmonary sarcoidosis was assembled, including mineralogical studies of sarcoidosis granulomas.

Results

N=81 aOE were associated with pulmonary sarcoidosis across all study designs. Occupational silica, pesticide and mould or mildew exposures were associated with increased odds of pulmonary sarcoidosis. Occupational nickel and aluminium exposure were associated with a non-statistically significant increase in the odds of pulmonary sarcoidosis. Silica exposure associated with pulmonary sarcoidosis was reported most frequently in the compendium (n=33 studies) and was the commonest mineral identified in granulomas.

Conclusion

Airborne occupational exposure to silica, pesticides and mould or mildew is associated with increased odds of pulmonary sarcoidosis. Equipoise remains concerning the association and relationship of metal dusts with pulmonary sarcoidosis.

Keywords

Sarcoidosis; Occupational exposures; Minerals; Epidemiology; Chemicals; Silica; Organic dusts; Metal

Key Messages

What is already known on this topic?

1. Sarcoidosis is likely the result of a complex genetic-immune-environmental interaction.
2. Environmental and occupational exposures have been linked with the onset of sarcoidosis, but equipoise persists.

What this study adds

1. Occupational silica, pesticides and mould and mildew exposure are associated with increased odds of pulmonary sarcoidosis.
2. Numerous airborne occupational exposures have been associated with pulmonary sarcoidosis - it is highly unlikely pulmonary sarcoidosis is the result of a single environmental antigen.

How might this study affect research, practice or policy?

1. An environmental and occupational exposure history is important in the work-up of sarcoidosis, given the similarities with other granulomatous diseases and pneumoconiosis.
2. Equipoise remains concerning the role of metal dusts amongst other exposures in the onset of sarcoidosis.
3. Studies investigating the interaction of genetic and environmental factors are required in sarcoidosis.
4. Larger mineralogical studies of granulomas found in sarcoidosis are likely to improve understanding of the role of the environment in the onset of sarcoidosis.

Sarcoidosis is a multisystem disease characterised by non-caseating granulomas that can affect any organ, with approximately 90% of cases involving the lungs (pulmonary parenchyma or hilar lymph nodes) [1]. The diagnosis of sarcoidosis is yet to be standardised, but is made using three main features: a compatible clinical presentation, histological presence of non-necrotising granulomatous inflammation and exclusion of alternative causes of granulomatous disease (e.g. drug-induced and immune deficiency syndromes) [2]. The aetiology and pathophysiology of sarcoidosis is yet to be fully defined, but current hypotheses suggest an exaggerated and dysregulated immune response to environmental exposures in genetically predisposed individuals [3].

Airborne exposures are particles that are suspended in the air and can be inhaled into the respiratory tract through the nose or mouth [4]. These particles can be described based on their diameter which determines the region of lung that they can deposit:

- extra-thoracic – particles that cannot penetrate beyond the larynx, typically <100µm in diameter;
- thoracic – particles that penetrate below the larynx, typically <10µm in diameter; or,
- respirable – particles that penetrate the gas exchange regions of the lung, typically <4µm in diameter [4].

When airborne particles present in the alveoli as foreign antigens, they are phagocytosed by antigen presenting cells (APC) that display specific peptides to recruit immune system cells. T-helper cells ($CD4^+$ lymphocytes) attach to these peptides, stimulating cytokine release, which in turn recruit other immune cells to the site [3]. Following antigen clearance, the immune response should self-regulate and cease. However, in sarcoidosis a persistent immune reaction leads to the formation of granulomas [5].

Human leukocyte antigen (HLA) genotypes are located at chromosome 6 and encode cell surface molecules of major histocompatibility complex (MHC) cells, to present antigen peptides to T-cell receptors. Various HLA genotypes such as HLA-DRB1 and -DRB3 [6] are associated with an increased risk of sarcoidosis. There is an increased risk of sarcoidosis amongst first degree relatives [7] and monozygotic and dizygotic twins [8], suggestive of a genetic component in the onset of sarcoidosis. Likewise, sarcoidosis prevalence varies across ethnicity, with prevalence higher in black populations [1, 9]. However, not all individuals with these genetic variations develop sarcoidosis, suggesting other factors influence disease onset.

Geographical variation in the prevalence of sarcoidosis occurs both internationally [10] and regionally within individual countries [11]. Two studies hypothesised differences in the prevalence of sarcoidosis were linked to predominant industries – in Sweden, it was highest in northern counties [12]; in Switzerland, higher prevalence was observed regions with prominent metal and intense agriculture industries [13]. Similarly, seasonal clustering of acute sarcoidosis [14] has been demonstrated, suggesting an environmental component.

Specific occupational groups have an increased risk of sarcoidosis, including firefighters [15], nurses [16] and military personnel [17], whilst occupational exposure to silica [18, 19], metal dust [20]

and pesticides [21] amongst others have been associated with an increased risk of developing granulomatous lung disease. It is estimated that workplace exposures contribute to approximately 30% of the burden of sarcoidosis [22].

Studies assessing granuloma composition in sarcoidosis have applied techniques like electron microscopy. Transmission electron microscopy (TEM) passes a beam of electrons through a human tissue sample, producing an image of the internal structures of a cell. Scanning electron microscopy (SEM) directs an electron beam across the surface of a sample, creating an image of cell structures in tissues and allowing measurement of particle size and number. SEM may be combined with other techniques, such as TEM (scanning transmission electron microscopy, STEM) and energy dispersive X-ray spectroscopy (EDXA). EDXA provides an elemental and compositional analysis of a sample. Each element has a unique atomic structure which when excited by X-ray in EDXA will produce a unique set of peaks on the electromagnetic emission spectrum, enabling identification of specific elements in the sample. The application of such techniques to identify elemental components of granulomas in sarcoidosis may help determine any specific causative occupational exposures. Similarly, Lymphocyte proliferation tests (LPT) have been studied in sarcoidosis, assessing immune responses to specific antigens.

This systematic review with meta-analyses aims to define and describe which airborne occupational exposures precede and are associated with an increased odds of pulmonary sarcoidosis. Additionally, we intend to produce a compendium of all studies reporting an association between airborne occupational exposures and a diagnosis of pulmonary sarcoidosis and discuss mineralogical and immunological studies relating to occupational exposures, to inform future research.

Methods

This systematic review with meta-analyses was performed in accordance with MOOSE guidelines and reported in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) [23, 24]. The protocol was registered and can be viewed in full on the PROSPERO international database (PROSPERO ID: CRD42020199054). A summary of the methodology is presented as follows.

Studies were eligible if they included only adult patients (18 years and older) and met eligibility criteria (*table S1*). Sarcoidosis and sarcoid-like reactions are included in this review, given the lack of clinical criteria defining and differentiating the two entities. Studies reporting pulmonary sarcoidosis with beryllium exposure and a positive Beryllium LPT (BeLPT) were excluded as this meets criteria for a diagnosis of Chronic Beryllium Disease (CBD) [25]. Mineralogical analysis studies of granulomas in sarcoidosis are included.

Search Strategy

Medline, Embase, ZETOC, Cochrane library, PROSPERO and Open Grey electronic databases were searched between 1st January 1958 (year of the first international conference on sarcoidosis) to 31st December 2022. Searches applied a combination of index terms and text words related to occupational exposures and sarcoidosis in the English language (*table*

S2a-b). No language restrictions were applied at the initial screening stage. All study designs were eligible for inclusion in the compendium (including conference abstracts), but only observational studies were included in the meta-analyses.

Study Selection, Data Extraction and Quality Assessment

Study selection against pre-determined inclusion and exclusion criteria (*table S1*) of titles and abstracts was performed independently by two reviewers (CH and KP). Eligible studies underwent a full-text review completed by two reviewers independently (CH and KP/ AM). Disagreements were resolved by discussion with or review by a third independent reviewer (GW). Studies must report a specified occupational exposure and associate the exposure with the diagnosis of sarcoidosis – studies reporting an occupation group or job title only and not a specific exposure were excluded, as it is not be possible to identify the occupational exposure from this information, due to regional and time-specific variations in workplaces and the processes occurring.

Data was extracted using a pre-determined standardised, piloted data extraction sheet (including a risk of bias tool) by one reviewer (CH), with 10% of studies checked by a second reviewer (GW) for accuracy. Any discrepancies arising were reviewed by both reviewers and resolved. For studies not published in the English language, study selection and data extraction were performed by a healthcare professional (SC, AMT) fluent in the relevant language – it was not possible to translate nine manuscripts which were excluded. Authors of studies with unclear, incomplete or missing data were contacted to clarify or provide additional information and excluded if no response was returned.

If the same study population was reported across multiple published papers, these were combined, with outcomes only reported once per exposure. After the World Trade Center (WTC) disaster, surveillance programs such as the WTC-health program and WTC-health registry have published results regularly. Therefore, to avoid duplicate publication bias in the WTC dust exposure category, only the latest publications from these cohorts reporting odds ratios (or providing data where this is calculable) were included in analysis. Additionally, studies reporting community, not occupational exposure to the WTC dust were excluded.

Risk of bias and quality assessment was performed using the Newcastle-Ottawa scale for cohort and case-control studies and adapted for longitudinal or cross-sectional studies, whilst the Joanna Briggs Institute critical appraisal tool for case series and case reports were used for corresponding study designs.

Statistical Analysis

Studies were grouped nominally by the occupational exposure reported and study design – if a study reported more than one exposure, all were included. Demographic data (gender, age, ethnicity) were extracted, along with the sarcoidosis diagnostic criteria used. The odds ratio (OR) for specific occupational exposures was extracted or calculated (from available data) for case-control and cohort studies. Meta-analysis was conducted when two or more studies reported an OR for an individual occupational exposure, applying a random effects model (pooled log estimate of OR; DerSimonian Laird). The I^2 statistic was used to evaluate

statistical heterogeneity. Meta-analyses were conducted using STATA (Stata statistical software: Release 16; StataCorp LP, College Station, TX, USA).

The compendium created categorises all studies by the reported occupational exposure. Like the meta-analyses, an association between specific occupational exposures and the onset of pulmonary sarcoidosis must be inferred by the authors. The frequency or proportion of cases of pulmonary sarcoidosis with specific exposures, the odds ratios of specific occupational exposures in pulmonary sarcoidosis and the incidence or prevalence of occupational exposures in pulmonary sarcoidosis are reported from the data extracted. Studies applying mineralogical analysis techniques on sarcoidosis or sarcoid-like granulomas are described.

Results

Database searches identified 9,952 studies, with 12 observational (11 case control and 1 cohort) studies of 22 occupational exposures eligible for meta-analyses (*Figure 1*) - a summary of the design of these studies is available in *table 1* and their results in *Table S5*. A list of excluded studies at full-text review is available from the authors at request. 76 studies were eligible for inclusion in the compendium of occupational causes of sarcoidosis (*tables S3-S4*). 81 individual occupational exposures had been associated with a diagnosis of pulmonary sarcoidosis, most commonly silica (n=33 studies), followed by iron (n=13), aluminium (n=12), World Trade Center (WTC) dust (n=9), chromium (n=8) and titanium (n=8) (*Figure S1*). Sources of exposure were divided in to 6 groups: Mineral dust; Mixed dusts +/- fumes; Organic; Metals; Chemicals; and Radiation. A risk of bias assessment was completed for all included studies (*tables S6a-e*).

[insert Figure 1]
[insert Table 1]

Meta-Analyses

Meta-analyses were conducted for 12 occupational exposures (*Figure S2*). Occupational silica exposure was associated with a diagnosis of pulmonary sarcoidosis (OR 1.26 [1.02 – 1.56], I^2 33.7%; *Figure 2*), as was occupational pesticide (OR 1.42 [95% CI 1.09 – 1.85], I^2 14.3%) and mould or mildew exposure (OR 1.52 [95% CI 1.21 – 1.91], I^2 0%) (*Figure 3*). Non-statistically significant associations were observed between occupational aluminium (OR 1.89 [95% CI 0.72 – 4.95], I^2 90.5%; *Figure 2*) and nickel (OR 1.18 [95% CI 0.65 – 2.14], I^2 0%) exposure with a diagnosis of pulmonary sarcoidosis. A non-statistically significant reduced odds of occupational gold exposure (OR 0.39 [95% CI 0.14 – 1.09], I^2 11.8%; *Figure 2*) with a diagnosis of pulmonary sarcoidosis was observed.

[insert Figure 2]
[insert Figure 3]

Subgroup analysis of silica exposure by source of the control group was performed to explore the impact of the recruitment strategy on observed heterogeneity (*Figure 3*). Heterogeneity existed in the at risk of exposure population control studies, likely influenced

by the wide confidence interval of one study [18] resulting from the low participant numbers. Otherwise, all studies across both the community controls and at risk of exposure population control demonstrated a similar observed increased odds ratio of pulmonary sarcoidosis after silica exposure, with low overall heterogeneity in the meta-analysis (I^2 33.7%).

Some occupational exposures were reported in a single case control study only – occupational exposure to organic dust (OR 2.57 [95% CI 1.35 – 5.16]) [26], titanium (OR 3.15 [95% CI 1.02 – 9.68]) [32], vegetable dust (OR 1.82 [95% CI 1.01 – 3.27]) [32], radiation (OR 1.83 [95% CI 1.00 – 3.46]) [21] and photocopier toner (OR 2.91 [95% CI 1.71 – 4.94]) [33] were associated with increased odds of pulmonary sarcoidosis. Occupational welding fume exposure was associated with reduced odds of pulmonary sarcoidosis (OR 0.40 [95% CI 0.16 – 0.96]) [21].

Mineralogical Studies

26 studies reported mineralogical analysis of pulmonary sarcoidosis tissue biopsies (*tables S7-8*). The majority of these were case reports (n=13) and case series (n=4), whilst the remaining studies were case control (n=5) and cross-sectional design (n=4). Analysis techniques were predominantly electron microscopy (TEM, SEM, STEM) with a form of x-ray diffraction analysis or atomic absorption spectroscopy (AAS). Elemental presence varied but all studies matched exposures to workplace environment, with some studies matching spectrum peaks from granulomas to workplace dust samples [35-39]. Silica, silicon and silicates along with metallic elements such as aluminium, titanium, iron, chrome and nickel and various alloys were identified in such studies.

Nine studies investigated sensitisation using specific LPT (*table S9*) in pulmonary sarcoidosis. The majority were case reports (n=4) and case series (n=2), with the remaining studies case control (n=2) or longitudinal (n=1) design. Beryllium LPT was predominantly used to exclude chronic beryllium disease, however, positive LPTs to aluminium compounds, nano silica and zirconium with relevant occupational exposures have been published demonstrating sensitisation.

Discussion

This systematic review with meta-analyses identified occupational exposure to silica, mould or mildew and pesticides are associated with increased odds of pulmonary sarcoidosis. Similarly, single case-control studies demonstrated occupational exposures to inorganic dusts, titanium, vegetable dust, radiation and photocopier toner are associated with increased odds of pulmonary sarcoidosis. Equipoise persists concerning the relationship between occupational aluminium, nickel, metal dust and organic dust exposure and pulmonary sarcoidosis. The types of occupational exposures associated with a diagnosis of pulmonary sarcoidosis have been categorised in to six groups: Mineral dust; Mixed dusts +/- fumes; Organic; Metals; Chemicals; and Radiation.

The large number of airborne occupational exposures associated with a diagnosis of pulmonary sarcoidosis and these meta-analyses results suggest it is highly probable that

there is no single environmental exposure trigger of sarcoidosis. Instead, one could hypothesise that various exposures trigger a common inflammatory pathway stimulating a granulomatous response. Some patients will express identical T-cell receptors in their granulomata, suggesting a common antigen is responsible [40], whilst genetic variations in HLA-genotypes amongst others likely influence the phenotype and progression of disease. Likewise, properties of individual antigens such as aero-diameter size and solubility may influence lung parenchymal clearance and therefore granuloma persistence. Whilst the immunopathogenesis of sarcoidosis is beyond the scope of this review, we explore some potential causation mechanisms of the occupational exposure categories identified in sarcoidosis.

Silica

Minerals are naturally occurring inorganic solid compounds which have a defined chemical composition. They take a crystalline-primary form or are manipulated into a secondary structure. The mechanical breakdown of minerals in industry, through processes such as grinding, cutting and drilling produce mineral dusts which can be inhaled by humans if fine enough.

Silica is the most abundant mineral in the Earth's crust and a common occupational exposure. Silica-exposed occupations, such as iron foundry [41] and construction work [19], mining [42] and tunnelling [43] have been associated with a diagnosis of sarcoidosis, as have occupations and occupational exposures where silica is a component of the exposure, such as crustal dust [26], desert dust [44], cement dust [38] and sandstorms [45].

Silica exposure is associated with other autoimmune inflammatory conditions, such as rheumatoid arthritis [46], with a possible dose-dependent relationship [41]. The exact mechanism in rheumatological conditions is unclear, but silica is felt to be linked to citrullination of peptides (producing antibodies to citrullinated peptides) [47] and disrupted alveolar macrophage function with the resultant prolonged production of pro-inflammatory cytokines [48] – a similar process may occur in sarcoidosis.

Misdiagnosis of silicosis as sarcoidosis is possible when an occupational history is overlooked. Sarcoidosis and silicosis demonstrate overlapping features on thoracic radiology and histologically in early disease (including histiocytic aggregates and granulomatous inflammation) [49]. Animal models have demonstrated that silica induces pulmonary granuloma formation after acute high and chronic low dose silica exposure, with a potential dose-response relationship [50]. Reactive oxygen species (ROS) released in response to silica and silica-activated cells have been shown to increase several inflammatory cytokines, like TNF-α, TGF-β and IL-1β [51], which in turn promote granuloma formation in sarcoidosis [52]. Whether silicosis and sarcoidosis are part of the same disease spectrum remains unclear, as does the impact of the type (i.e. respirable crystalline silica, silicate or silicon compound), dose and duration of silica exposure in sarcoidosis.

Organic Dusts

Organic dusts refer to plant, animal and micro-organism components that may be present in isolation or as part of a mixture. Dependent on the source, organic dust may contain proteins, enzymes, bacteria, fungi, endotoxins, mycotoxins and fibres. Differing components of organic dusts have been associated with a wide variety of pulmonary diseases [53]. Occupational mould or mildew exposure is associated with increased odds of sarcoidosis in our meta-analysis, with similar findings in studies of non-occupational environmental exposures [54]. Mould generally refers to fungal growth which reproduce by generating spores, which can be airborne. Greaves et al [55] recently demonstrated the presence of *Aspergillus nidulans* in HLA-DRB1*03 genotypes in Lofgren Syndrome compared to controls, suggesting the importance of a genetic-environmental interaction in the onset of sarcoidosis.

More widely, meta-analysis demonstrated increased microorganism DNA and protein antigen presence (from *Propionibacterium acnes*, mycobacteria, borrelia and HHV-8) in histological and cellular samples of patients with sarcoidosis [56]. Likewise, patients diagnosed with sarcoidosis have increased serological type-1 t-helper cell immunological responses to several mycobacterium species [57]. Musty and mouldy odours have been associated with micro-organism presence even when there is no visible growth [58] and were associated with sarcoidosis in the ACCESS study [6]. Other forms of organic dust, such as vegetable dust [32] and a generic 'organic dust' [26] are associated with increased odds of pulmonary sarcoidosis in this review, but it is unclear whether this relates to the exposure itself or microbial contamination, comparable to contamination of floor dust, heat pumps and condensation drain tubes seen in building clusters of sarcoidosis [59].

Chemicals

Chemicals are molecular mixtures with constant composition characteristics used or produced in a reaction involving changes to atoms and/ or molecules. Chemicals are diverse with varied pulmonary effects when inhaled. Therefore, in our systematic review, this category refers primarily to pesticides where increased odds of pulmonary sarcoidosis were shown in the meta-analysis. Pesticides is a term that includes over a thousand chemical substances predominantly used on crops and livestock, including insecticides, herbicides and fungicides. Respiratory exposure occurs due to fumigation or mixture preparation and has been associated with asthma [60] and chronic obstructive airways disease (COPD) [61] – potentially mediated by eosinophilic airway inflammation [62] or ROS production [63]. Pesticides such as paraquat [64], organophosphate, carbamate, neonicotinoid insecticides and bipyridylium herbicides have all been associated with impairments in respiratory function [65], whilst in rats, the fungicide hexachlorobenzene when ingested led to microgranuloma formation in the lung [62]. Diverse chemical compositions and mixtures of pesticides along with their varied methods and environments of application (i.e. open fields, greenhouses) make interpretation of dose-response and other relationships challenging.

Chemicals have the potential to damage pulmonary epithelium, triggering inflammation, which produces increased amounts of ROS in the lungs [66]. ROS are elevated in sarcoidosis [67], whilst total anti-oxidant capacity and levels are lowered with increased levels of TNF-α and inteleukin (IL)-8 [68]. Oxidative stress is increasingly associated in the onset of sarcoidosis [69] and could explain why various chemicals are associated with the onset of pulmonary

sarcoidosis, due to the direct insult on the alveolar epithelium which stimulates oxidative stress and damage.

Occupational exposure to photocopier toner increased the odds of pulmonary sarcoidosis in a single study [33]. Whilst this has been categorised as a chemical, copper, iron and silicon within the photocopier toner may be responsible for granulomatous lung disease [70]. Conversely, photocopier toner and ink is widely available, yet no association between exposed occupations and pulmonary sarcoidosis established. This highlights a common challenge epidemiologists and clinicians alike face when attempting to determine if association or causation is present between exposure and disease.

Metals

A metal is an element which under biologically significant conditions may react by losing electrons to form cations. Metals possess properties that stimulate antigen-specific cellular immune responses, which have potential to induce similar clinical and pathological conditions to sarcoidosis [71]. It is likely that a portion of diagnosed sarcoidosis relates to metal induced granulomatosis - aluminium, copper, titanium and zirconium have all been associated with formation of non-caseating granuloma in the lungs [72]. Iron, copper, cadmium, chromium and nickel possess the ability to produce reactive radicals, most notably ROS [73]. In our review, equipoise persists for aluminium, nickel and general metal dust exposure with sarcoidosis, whilst a single case-control study [32] of titanium showed a statistically significant association. It is important to recognise that individuals are rarely exposed to these metals in their elemental form and more likely as a salt or oxide [74] – the physical, biological and toxic properties, intracellular effects and pulmonary antigen clearance times will therefore alter and require consideration in future studies.

Mineralogical studies demonstrate presence of aluminium, titanium and iron in granulomas of pulmonary biopsy samples (*tables S7-8*), which relates to an occupational source and suggest causation. Meanwhile, hypersensitivity has been demonstrated by LPT to aluminium, titanium and zirconium (*table S9*) and is similar to that observed in CBD [75]. However, therein lies a diagnostic conundrum – is this true sarcoidosis, sarcoid-like disease or granulomatous disease of a known cause? The lack of clear diagnostic criteria is exposed throughout this review and as a result, some studies, such as Redline, et al [76] have been excluded where an alternative but similar diagnosis to sarcoidosis has been made.

Mixed Dusts +/- Fumes

This category is a combination of dusts, fibres, particles and fumes, the content of which are difficult to determine. The WTC dust cloud generated after the WTC buildings collapsed on 9/11 was a complex mixture of substances, including, but not limited to cement dust, iron, synthetic organic materials, combustion products, asbestos, silica, glass fibre, heavy metals, polycyclic aromatic hydrocarbons and chlorinated products [77]. A single case-control study of WTC dust [30] met the eligibility criteria for this meta-analysis due to the data available and methodology applied to avoid duplication bias; however, published cohort studies have assessed the longitudinal impact on respiratory health [78-79]. New York firefighters exposed to the WTC dust cloud had significantly elevated incidence rates of sarcoidosis in the

subsequent 12 months from exposure (86 per 100,000 workers) [79] compared to the pre-9/11 incidence rate (15 per 100,000 workers), whilst overall the incidence rate of sarcoidosis increased after WTC dust cloud exposure (229 per 100,000) [78]. A strong association between the onset of sarcoidosis following WTC dust exposure and HLA-DQB1 gene variants has also been identified [80]. Whilst the WTC disaster provided evidence of the environmental role in the onset of sarcoidosis, it is not possible to elicit the underlying mechanism, or indeed the specific exposures responsible. This is not an isolated trend in first responder emergency workers, with a previous study showing higher incidence proportions and point prevalence of sarcoidosis in firefighters, compared with emergency medical services (EMS) health care workers (HCWs) [81].

Mineralogical Studies

Mineralogical studies may develop our understanding of the composition and triggers of granuloma formation in sarcoidosis. Studies that employed EDXA, AAS, TEM and STEM have begun to build a picture of the mineral content of granulomas in sarcoidosis. Mineral and metal elements have been demonstrated in granulomas, including silica, aluminium, titanium, nickel, iron and zinc with some studies identifying the presence of multiple elements in the same granuloma (*tables S7-8*). A suggestion of causation in sarcoidosis is stronger when the peak signals of granulomas are matched to workplace samples [35-39].

Whether elemental properties lead to persistent inflammation or immune dysregulation is unknown, whilst an understanding of the interaction of multiple elements present in granulomas is limited. A study of LPT in sarcoidosis [27] demonstrates sensitisation to elements which have been identified in mineralogical studies (*tables S7-8*), suggesting these minerals might be responsible for stimulating T-cell responses seen in granulomas and subsequent sensitisation. However, the latency period between exposure and granuloma formation, exposure dose and duration remain undefined. It is possible that different exposures lead to different phenotypes of sarcoidosis [20].

Genetic-Immunologic-Environmental Interactions

Many occupational exposures have been associated with sarcoidosis across the literature, suggesting it is highly unlikely there is a single causative antigen of sarcoidosis. It remains probable that sarcoidosis results from a complex genetic-immune-environmental interaction. The ACCESS study remains unique in investigating the relationship of HLA genotypes and occupational exposures (e.g. HLA DRB1*1101 with insecticide exposure and musty odours), relating this to specific sarcoidosis phenotypes (e.g. extra-pulmonary disease or cardiac disease) [32]. Following the WTC-disaster, variants of HLA and non-HLA genotypes were identified in WTC-dust exposed firefighters who had been diagnosed with sarcoidosis compared with exposed colleagues who had no diagnosis of sarcoidosis [82]. More recently, Ronsmans et al [20] demonstrated that the type of occupational exposure was associated with sarcoidosis phenotype (e.g. contact with livestock with pulmonary only, liver or splenic disease). The authors postulated pulmonary antigen clearance mechanisms, as well as particle surface properties, size, chemical composition and solubility, may influence organ involvement. To date, few studies have combined genetic studies with environmental exposures, hence this should be a focus of future research.

Strengths, Limitations and Implications of this Review

This is the first meta-analysis of the association between specific airborne occupational exposures and a diagnosis of pulmonary sarcoidosis. Our inclusion criteria specified that the airborne occupational exposure occurred prior to the diagnosis of sarcoidosis – whilst this meant the exclusion of larger retrospective cohort studies comparing occupations and occupational exposures on death certificates of people with sarcoidosis [83], it enables discussion concerning a causal relationship. The compendium produced will help direct and focus future research on potential environmental causation in sarcoidosis, given the clinical equipoise that remains.

The main limitations inherent in the included studies, were methods of exposure assessment. The majority of studies identified occupational exposures through either the application of a job exposure matrix (JEM) or an expert opinion or review of patient occupational histories. These are pragmatic and well-practiced epidemiological methods for assessing causative exposure in large population-based studies. However, under or over-estimations of the exposures has likely occurred, alongside insufficient information on dose, duration, latency and frequency of the occupational exposure available. The variability in exposure assessment and confirmation, alongside the unknown characteristics of the exposure account for a significant proportion of the heterogeneity seen between studies. Furthermore, many of the included observational studies are vulnerable to a range of biases (*tables S6a-e*). Finally, some population level studies may include cases of pneumoconiosis and other pulmonary granulomatous diseases (such as hypersensitivity pneumonitis) that have been misdiagnosed as sarcoidosis, as a result of their clinical and radiological similarities or oversight of an exposure history. However, inclusion criteria for most studies in this review included a histological diagnosis of sarcoidosis, minimising this effect.

Whilst this review identifies the role of specific occupational exposures in the onset of sarcoidosis, it also generates further questions. It is unclear if patients with an identified occupational exposure should be diagnosed as sarcoidosis, or whether a diagnosis of sarcoid-like reaction or granulomatous disease of known cause should be made, similar to CBD [84]. Alternatively, should the term sarcoidosis be more inclusive but with acknowledgement of various phenotypes, of which occupational causes is one? Finally, it is unclear whether exposure elimination maybe an effective strategy - studies of WTC dust [85] and CBD [86] suggest a potential role.

Conclusion

Occupational silica, mould or mildew and pesticide exposure are associated with increased odds of pulmonary sarcoidosis, whilst equipoise persists with occupational metal and generic organic dust exposure. The number of exposures identified suggests that it is highly unlikely a single antigen is responsible for the onset of sarcoidosis – the onset is far more likely the result of a complex genetic-environment-immunological interaction. Future studies should examine the potentially complex relationship between genetic factors and airborne occupational exposures and the mineralogical composition of sarcoidosis granulomas.

Funding

No funding was received for this study.

Contributorship

CH designed and led this study and was involved with every stage including performing database searches, abstract and full text review, data extraction, data analysis, data validation and manuscript writing and preparation. KP was second reviewer for abstract screening and full-text review. AZM was second reviewer for full text review. SC was second reviewer for full text review and data extraction. PSB was a co-supervisor of this project. AMT was second reviewer for full text review and data extraction and co-supervisor of this project. GIW was the primary supervisor for this project and validated data extracted. All authors have had the opportunity to review, edited and revise draft manuscripts and agree on the final version submitted.

Competing Interests

The authors have no conflicts of interest to disclose related to this study.

Data Sharing/ Availability

Most data extracted relevant to the study is included in the article or uploaded as supplementary information. Additional data on the screening and analysis process is available upon reasonable request.

References

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999; 160(2): 736-55.
2. Crouser ED, Maier LA, Wilson KC, et al. Diagnosis and detection of sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020; 201(8): e26-e51.
3. Moller DR, Rybicki BA, Hamzeh NY, Montgomery CG, Chen ES, Drake W, Fontenot AP. Genetic Immunologic, and Environmental Basis of Sarcoidosis. Ann Am Thorac Soc. 2017; 14 (Supplement_6): S429-S436.
4. European Committee for Standardization (CEN). Workplace atmospheres-size fraction definitions for measurement of airborne particles (Report No. BS EN 481: 1993). London, England: CEN, British Standards Institute; 1993.
5. Miyara M, Amoura Z, Parizot C et al. The immune paradox of sarcoidosis and regulatory T cells. Journal of Experimental Medicine. 2006; 203 (2): 359–70.
6. Rossman MD, Thompson B, Frederick M, Iannuzzi MC, Rybicki BA, Pander JP, et al. HLA and environmental interactions in sarcoidosis. J Sarcoidosis Vasc Diffuse Lung Dis. 2008; 25: 125–32.
7. Rossides M, Grunewald J, Eklund A, Kullberg S, Di Giuseppe D, Askling J, Arkema EV. Familial aggregation and heritability of sarcoidosis: a Swedish nested case−control study. Eur Respir J. 2018; 52 (2): 1800385.
8. Sverrild A, Backer V, Kyvik KO, Kaprio J, Milman N, Svendsen CB, Thomsen SF. Heredity in sarcoidosis: a registry-based twin study. Thorax. 2008; 63(10): 894-6.
9. Hena KM. Sarcoidosis epidemiology: race matters. Front Immunol. 2020; 11: 537382.

10. Arkema EV, Cozier YC. Sarcoidosis epidemiology: recent estimates of incidence, prevalence and risk factors. Curr Opin Pulm Med. 2020; 26(5): 527-34.
11. Arkema EV, Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. Ther Adv Chronic Dis. 2018; 9(11): 227-40.
12. Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. Eur Respir J. 2016; 48: 1545-8.
13. Deubelbeiss U, Gemperli A, Schindler C, Baty F, Brutsche MH. Prevalence of sarocidosis in Switzerland is associated with environmental factors. Eur Respir J. 2010; 35: 1088-97.
14. Demirkok SS, Basaranoglu M, Akbilgic O. Seasonal variation of the onset of presentations in stage 1 sarcoidosis. Int J Clin Pract. 2006; 60(11): 1443-50.
15. Prezant DJ, Dhala A, Goldstein A, Janus D, Ortiz F, Aldrich TK, Kelly KJ. The incidence, prevalence, and severity of sarcoidosis in New York City firefighters. Chest. 1999; 116(5): 1183-93.
16. Edmondstone WM. Sarcoidosis in nurses: is there an association? Thorax. 1988; 43: 342-3.
17. Gorham ED, Garland CF, Garland FC, Kaiser K, Travis WD, Centeno JA. Trends and occupational associations in incidence of hospitalized pulmonary sarcoidosis and other lung diseases in Navy personnel: a 27-year historical prospective study, 1975-2001. *Chest.* 2004; 126(5): 1431–8.
18. Rafnsson V, Ingimarsson, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline and risk of sarcoidosis. Occup Environ Med. 1998; 55: 657-60.
19. Jonsson E, Jarvholm B, Andersson M. Silica dust and sarcoidosis in Swedish construction workers. Occup Med. 2019; 69: 482-6.
20. Ronsmans S, De Ridder J, Vandebroek E, Keirsbilck S, Nemery B, Hoet PHM, et al. Associations between occupational and environmental exposures and organ involvement in sarcoidosis: a retrospective case-case analysis. Respir Res. 2021; 22: 224.
21. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, et al. A Case Control Etiologic Study of Sarcoidosis Environmental and Occupational Risk Factors. Am J Respir Crit Care Med. 2004; 170(12): 1324-30.
22. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, et al. The occupational burden of nonmalignant respiratory diseases. An official American Thoracic Society and European Respiratory Society statement. Am J Respir Crit Care Med. 2019; 199(11): 1312-34.
23. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
25. Newman LS, Kreiss K, King TE Jr, Seay S, Campbell PA. Pathologic and immunologic alterations in early stages of beryllium disease. Re-examination fo diserase definition and natural history. Am Rev Respir Dis. 1989; 139: 1479-86.
26. Barnard J, Rose C, Newman L, Canner M, Martyny J, McCammon C, et al. Job and industry classifications associated with sarcoidosis in a case-control etiologic study of sarcoidosis (ACCESS). Occup Environ Med. 2005; 47: 226-34.
27. Beijer E, Meek B, Bossuyt X, Peters S, Vermeulen RCH, Kromhout H, Veltkamp M. Immunoreactivity to metal and silica associates with sarcoidosis in Dutch patients. Respiratory Research. 2020; 21: 141.
28. Catinon M, Cavalin C, Chemarin C, Rio S, Roux E, Pecquet M, et al. Sarcoidosis, inorganic dust exposure and content of bronchoalveolar lavage fluid: the MINASARC pilot study. Sarcoidosis Vasc Diffuse Lung Dis. 2018; 35: 327-32.
29. Graff P, Larsson J, Bryngelsson I-L, Wiebert P, Vihlborg P. Sarcoidosis and silica dust exposure among men in Sweden: a case-control study. BMJ Open. 2020; 10: e038926.
30. Jordan HT, Stellman SD, Prezant D, Teirstein A, Osahan SS, Cone JE. Sarcoidosis diagnosed after September 11, 2001, among adults exposed to the Wortld Trade Center disaster. J Occup Environ Med. 2011; 53(9): 966-74.
31. Kajdasz DK, Lackland DT, Mohr LC, Judson MA. A current assessment of rurally linked exposures as potential risk factors for sarcoidosis. Ann Epidemiol. 2001; 11: 111-17.
32. Kucera GP, Rybicki BA, Kirkey KL, Coon SW, Major ML, Maliarik MJ, Ianuzzi MC. Occupational Risk Factors for Sarcoidosis in African-American Siblings. Chest. 2003; 123: 1527-35.
33. Rybicki BA, Amend KL, Maliarik MJ, Ianuzzi MC. Photocopier exposure and risk of sarcoidosis in African-American sibs. Sarcoidosis Vasc Diffuse Lung Dis. 2004; 21: 49-55.

34. Levin AM, Chen Y, She R, Adrainto I, Datta I, Iannuzzi MC, et al. Identification of environmental exposures associated with risk of sarcoidosis in African Americans. Am J Respir Crit Care Med. 2018; 197: A5367.
35. Bodokh I, Brun P, Mayaffre C, Majcwrczyk N, Montagne M. Sarcoidose cutanee secondaire a l'inhalation de particules de flocage d'isolation. Ann Dermatol Venereol. 1998; 125: 182-4.
36. Cai H, Cao M, Meng F, Wei J. Pulmonary sarcoid-like granulomatosis induced by aluminium dust: report of a case and literature review. Chin Med J. 2007; 120(17): 1556-60.
37. Checchi L, Nucci MC, Gatti AM, Mattia D, Violante FS. Sarcoidosis in a dental surgeon: a case report. J Medical Case Reports. 2010; 4: 259.
38. Pimentel JC, Menezes AP. Pulmonary and hepatic granulomatous disorders due ot the inhalation of cement and mic dusts. Thorax. 1978; 33: 219-27.
39. Ronsmans S, Verbeken EK, Adams E, Keirsbilck S, Yserbyt J, Wuyts WA, et al. Granulomatous lung disease in two workers making light bulbs. Am J Ind Med. 2019; 62: 908-13.
40. Grunewald J, Grutters JC, Arkema EV, et al. Sarcoidosis. Nat Rev Dis Primers. 2019; 5(1): 45.
41. Vihlborg P, Bryngelsson I-L, Andersson L, et al. Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries: a retrospective cohort study. BMJ Open. 2017; 7: e016839.
42. Oliver LC, Sampara P, Pearson D, Martell J, Zarnke AM. Sarcoidosis in Northern Ontario hard-rock miners: A case series. Am J Ind Med. 2022; 65(4): 268-280.
43. Kawano-Dourado LB, Carvalho CRR, Santos UP, Canzian M, Coletta ENA, Pereira CAC, Kairalla RA. Tunnel excation triggering pulmonary sarcoidosis. Am J Ind Med. 2012; 55(4): 390-4.
44. Patel DC, Jaber J, Krefft SD, Miller RF. Sarcoidosis in military deployers to Iraq, Afghanistan and Southwest Asia. Am J Respir Crit Care Med. 2019; 199: A1869.
45. Silhan LL, Hines SE, Shah NG. Another war syndrome? A case of neuro- and pulmonary sarcoidosis in a solider returning from Iraq. Am J Respir Crit Care Med. 2013; 187: A6143.
46. Wrangel O, Graff P, Bryngelsson I, Fornander L, Wiebert P, Vihlborg P. Silica dust exposure increases risk for rheumatoid arthritis. A Swedish National Registry Case-Control Study. Occ Environ Med. 2021; 63(11): 951-5.
47. Stolt P, Yahya A, Bengtsson C, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA-positive rheumatoid arthirtis. Ann Rheum Dis. 2010; 69: 1072-6.
48. Pollard KM. Silica, Silicosis, and autoimmunity. Front Immunol. 2016; 7: 97.
49. Hoy RF, Chambers DC. Silica-related diseases in the modern world. Allergy. 2020; 75: 2805-17.
50. Castranova V, Porter D, Millecchia L, Ma JY, Hubbs AF, Teass A. Effect of inhaled crystalline silica in a rat model: time course of pulmonary reactions. Mol Cell Biochem. 2002; 234-235(1-2): 177-84.
51. Rimal B, Greenberg AK, Rom WN. Basic pathogenetic mechanisms in silicosis: current understanding. Curr Opin Pulm Med. 2005; 11: 169-73.
52. Patterson KC, Chen ES. The pathogenesis of pulmonary sarcoidosis and implications for treatment. Chest. 2018; 153(6): 1432-42.
53. Simpson JC, Niven RM, Pickering CA, Fletcher AM, Oldham LA, Francis HM. Prevalence and predictors of work related respiratory symptoms in workers exposed to organic dusts. Occup Environ Med. 1998; 55(10): 668-72.
54. Tercelj M, Salobir B, Harlander M, Rylander R. Fungal exposure in homes of patients with sarcoidosis – an environmental exposure study. Eviron Health. 2011; 10: 8.
55. Greaves SA, Ravindran A, Santos RG, Chen L, Falta MT, Wang Y, et al. CD4+ T cells in the lungs of acute sarcoidosis patients recognize an *Aspergillus nidulans* epitope. J Exp Med. 2021; 218(10): e20210785.
56. Esteves T, Aparicio G, Garcia-Patos V. Is there any association between sarcoidosis and infectious agents?: a systematic review and meta-analysis. BMC Pulmonary Med. 2016; 16: 165.
57. Allen SS, Evans W, Carlisle J, Hajizadeh R, Nadaf M, Shepherd BE, et al. Superoxide dismutase A antigens derived from molecular analysis of sarcoidosis granulomas elicit systemic Th-1 immune reponses. Resp Res.2008; 9: 36.
58. Verhoeff AP, van Wijnen JH, Brunekreef B, et al. Presence of viable mould propagules in indoor air in relation to house damp and outdoor air. Allergy. 1992; 47: 83-91.
59. Park J-H, Cox-Ganser JM, White SK, Laney AS, Caulfield SM, Turner WA, Sumner AD, Freiss K. Bacteria in a water-damaged building: associations of actinomycetes and non-tuberculous mycobacteria with respiratory health in occupants. Indoor Air. 2017; 27(1): 24-33.
60. Mamane A, Baldi I, Tessier J-F, Raherison C, Bouvier G. Occupational exposure to pesticides and respiratory health. Eur Resp Rev. 2015; 24: 306-19.

61. De Matteis S, Jarvis D, Darnton L, Consonni D, Kromhout H, Hutchings S, Sadhra SS, et al. Lifetime occupational exposures and chronic obstructive pulmonary disease risk in the UK Biobank cohort. Thorax. 2022. Doi:10.1136/thoraxjnl-2020-216523. Online ahead of print.
62. Michielsen C, Zeamari S, Leusink-Muis A, et al. The environmental pollutant hexachlorobenzene causes eosinophilic and granulomatous inflammation and in vitro airwars hyperreactivity in the Brown Norway rat. Arch Toxicol. 2002; 76: 236-47.
63. Vallyathan V, Shi X, Castranova V. Reactive oxygen species: their relation to pneumoconiosis and carcinogenesis. Environ Health Perspect. 1998; 106: 1151-55.
64. Cha ES, Lee YK, Moon EK, et al. Paraquat application and respiratory health effects among South Korean farmers. Occup Environ Med. 2012; 69: 398-403.
65. Mamane A, Baldi I, Tessier JF, Raherison C, Bouvier G. Occupational exposure to pesticides and respiratory health. Eur Respir Rev. 2015; 24: 306-19.
66. Lakey PSJ, Berkemeier T, Tong H, Arangio AM, Lucas K, Poschl U, et al. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. Sci Rep. 2016; 6: 32916.
67. Bargagli E, Olivieri C, Bennett D, Prasse A, Muller-Quernheim J, Rottoli P. Oxidative stress in the pathogenesis of diffuse lung diseases: A review. Resp Med. 2009; 103: 1245-56.
68. Boots AW, Drent M, Swennen ELR, Moonen HJJ, Bast A, Haenen GRMM. Antioxidant status associated with inflammation in sarcoidosis: A potential role for antioxidants. Resp Med. 2009; 103: 364-72.
69. Fois SS, Canu S, Fois AG. The role of oxidative stress in sarcoidosis. Int. J Mol. Sci. 2021; 22: 11712.
70. Armbruster C, Dekan G, Hovorka A. Granulomatous pneumonitis and mediastinal lymphadenopathy due to photocopier toner dust. The Lancet. 1996; 348: 690.
71. Newman LS. Occupational asthma: diagnosis, management and prevention. Clin Chest Med. 1995; 16: 621-36.
72. Newman LS. Metals that cause sarcoidosis. Seminars in Resp Infections. 1998; 13(3): 212-20.
73. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr. Med. Chem. 2005; 12: 1161-208.
74. Nemery B. Metal toxicity and the respiratory tract. Eur Respir J. 1990; 3: 202-19.
75. Fireman E, Goshen M, Ganor E, Spirer Z, Lerman Y. Induced sputum as an additional tool in the identification of metal-induced sarcoid-like reaction. Sarcoidosis Vasc Diffuse Lung Dis. 2004; 21: 152-6.
76. Redline S, Barna BP, Tomashefski JF, Abraham JL. Granulomatous disease associated with pulmonary deposition of titanium. Br J Ind Med. 1986; 43(10): 652-6.
77. Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenberg J, et al. Characterization of the Dust/ Smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the Collapse of the WTC 11th Septermber 2001. Environmental Helath Perspectivess. 2002; 110(7): 703-14.
78. Crowley LE, Herbert R, Moline JM, Wallenstein S, Shukla G, Schechter C, et al. "Sarcoid like" granulomatous pulmonary disease in world trade center disaster responders. American Journal of Industrial Medicine. 2011; 54: 175-84.
79. Izbicki G, Chavko R, Banauch GI, Weiden MD, Berger KI, Aldrich TK, Hall C, Kelly KJ, Prezant DJ. World trade center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department Rescue workers. Chest. 2007; 131: 1414-23.
80. Cleven KL, Ye K, Zeig-Owens R, Hena KM, Montagna C, Shan J, et al. Genetic variants associated with FDNY WTC-related sarcoidosis. Int. J Environ Res Public Health. 2019; 16: 1830.
81. Prezant DJ, Dhala A, Goldstein A, Janus D, Ortiz F, Aldrich TK, Kelly KJ. The incidence, prevalence, and severity in New York City Firefighters. Chest. 1999; 116 (5): 1183-93.
82. Cleven KL, Ye K, Zeig-Owens R, et al. Genetic variants associated with FDNY WTC-related Sarcoidosis. Int J Environ Res Public Health. 2019; 16: 1830.
83. Liu H, Patel D, Welch, et al. Association between occupational exposures and sarcoidosis: an analysis from death certificates in the United States, 1988-1999. Chest. 2016; 150(2): 289-98.
84. Rossman MD, Kreider ME. Is chronic beryllium disease sarcoidosis of known etiology? Sarcoidosis, Vasc diffuse Lung Dis Off J. WASOG. 2003; 20: 104-9.
85. Hena KM, Yip J, Jaber N, et al. Clinical course of sarcoidosis in World Trade Center-exposed firefighters. Chest. 2007: 131(5): 1414-23.
86. Sprince NL, Kanarek DJ, Weber AL, Chamberlin RI, Kazemi H. Reversible respiratory disease in beryllium workers. Am Rev Respir Dis. 1978: 117; 1011-7.

Table

Case-control Studies						
Study and Year	**Country of Study**	**Sarcoidosis or Sarcoid-like**	**Case description**	**Control description**	**Occupational exposures identified**	**How exposure identified**
Barnard J, et al. 2005 [26]; Newman LS, et al. 2004 [21]	USA	Sarcoidosis	Patients with a new diagnosis of biopsy-proven sarcoidosis within 6 months of recruitment.	Age, gender, ethnicity and geographically matched random controls.	Industrial organic dust; crustal dust; metal dust/ fume; metal working fluids; insecticide exposure at work; exposure to mould/ mildew at work; exposure to musty odors at work; job raising birds; radiation exposure at work; animal dust exposure (vocational and avocational); gold exposure.	SIC/SOC exposure classification determined a priori by experts (not formal JEM).
Beijer E, et al. 2020 [27]	Netherlands	Sarcoidosis	Patients with a diagnosis of sarcoidosis as per ATS/ ERS criteria.	Patients with a diagnosis of obstructive sleep apnoea.	Silica; metals; chromium; nickel.	JEM; LPT.
Catinon M, et al. 2018 [28]	France	Sarcoidosis	Patients with a biopsy-proven diagnosis of sarcoidosis.	Healthy subjects from Dermscan matched by age, gender and smoking status.	Mixed mineral dust	Dust exposure questionnaire; BAL.
Graff P, et al. 2020 [29]	Sweden	Sarcoidosis	Patients diagnosed with sarcoidosis on nationwide patient database.	Age, sex, county matched controls.	Silica	Combination of: updated version of PARCC-JEM; Swedish JEM for Nordic Occupational Cancer Study; and Airway Irritant-JEM.
Jordan HT, et al. 2011 [30]	USA	Sarcoidosis	Patients diagnosed with biopsy- proven sarcoidosis.	Not described.	WTC dust cloud	Registered on the WTC- health registry (registers people exposed to WTC dust cloud).
Kajdasz DK, et al. 2001 [31]	USA	Sarcoidosis	Patients diagnosed with biopsy- proven sarcoidosis.	Age, sex, ethnicity matched community controls.	Insecticides and herbicides at work.	Questionnaire.

Kucera GP, et al. 2003 [32]; Rybicki BA, et al. 2004 [33]	USA	Sarcoidosis	African-american patients with a radiological or histological diagnosis of sarcoidosis identfied through the Henry Ford Health System.	Sibling-matched controls with no diagnosis of sarcoidosis.	Aluminium; beryllium; chromium; cobalt; gold; nickel; platinum; titanium; zirconium; talc; insecticides/ pesticides; silica; vegetable dust; animal dust; hairspray; high humidity; water damage; mould/ mildew; animals in the workplace. Photocopier toner.	Questionnaire derived from ACCESS study [36]; Self report by patient/ questionnaire.
Levin AM, et al. 2018 [34]	USA	Sarcoidosis	Patients diagnosed with sarcoidosis.	No diagnosis of sarcoidosis controls – not described further.	Aluminium	Questionnaire
Rafnsson V, et al. 1998 [18]	Iceland	Sarcoidosis	Patients with a biopsy-proven diagnosis of sarcoidosis identified from a national register.	General population controls.	Silica	Workplace records/ measurements
Cohort Studies						
Study and Year	**Country of Study**	**Sarcoidosis or Sarcoid-like**	**Study Cohort description**		**Occupational exposures identified**	**How exposure identified**
Jonsson E, et al. 2019 [19]	Sweden	Sarcoidosis	Workers registered on the Swedish Construction Workers Cohort database. Construction workers with a diagnosis of sarcoidosis compared to those without a diagnosis.		Silica	JEM

Table 1: Case-control and Cohort Studies of Occupational Exposures associated with a diagnosis with Pulmonary Sarcoidosis
Abbreviations: SIC, Standard Industrial Classifications; SOC, Standard Occupational Code; JEM, Job Exposure Matrix; LPT, Lymphocyte Proliferation Test; OSA, Obstructive Sleep Apnoea syndrome; BAL, Bronchioloalveolar Lavage; TEM, Transmission Electron Microscopy;; PARCC, PARticles and Cardio- and Cerebrovascular diseases; WTC, World Trade Center; ACCESS, A Case Control Etiologic Study of Sarcoidosis [36].
Note: some study populations are included in multiple publications – merging of some information has occurred to reflect this