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INTERSTITIAL LUNG DISEASE

How the Frequency and Phenotype of Sarcoidosis is Driven by Environmental Determinants

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Abstract

Background Sarcoidosis is a systemic disease in which the personal environment seems to drive a differentiated disease frequency and clinical expression. The main epidemiological studies suggest a key influence of potential environmentally linked exposures related to the type of occupation, the household, life style, socioeconomic status, and region of residence.
Objective To provide an update on how sarcoidosis may be modulated by environmental factors.
Data Sources We searched PubMed for epidemiological studies.
Synthesis The risk of sarcoidosis is enhanced in people working in jobs related to agriculture, water, construction, metal machining, education, and health, and reduced in those working in jobs mainly centered on personal care. Studies have confirmed seasonal-related peaks of sarcoidosis incidence that follow geographical North–South and West–East gradients. Other personal factors include smoking, personal household exposures, and leisure activities. The evidence pointing to the crucial role of the environment in the etiopathogenesis of sarcoidosis is mounting rapidly. Few diseases so strongly combine geography, environment, gender, and ethnicity as key etiopathogenic factors, with susceptibility to any putative agent being modulated by the individual exposome and genome.
Conclusion Geoepidemiological research should focus on evaluating the combined effects of environmental and genetic factors, the identification of clusters of geographically driven exposures, and more precise measurement of all personal exposures (degree of combination, length, and level of exposure).

Keywords Sarcoidosis · Occupational disease · Geolocation · Environment · Seasonality

Introduction

Sarcoidosis, a systemic disease of unknown etiology characterized by non-caseating epithelioid cell granulomas, often develops before 50 years of age, with the incidence peaking at 20–40 years [1, 2]. The clinical presentation is heterogeneous and clearly dominated by thoracic involvement [3], although multiorgan involvement is common. Genetic predisposition and environmental exposures are proposed as epidemiological triggers. Sarcoidosis is one of the systemic diseases with the greatest influence of environmental factors on the frequency and phenotypic expression [4]. Although there are no precise epidemiological studies, several reasons suggest that environmental agents, including occupational, seasonal, and spatial clustering factors, might act as trigger(s) [1].

The infrequency of sarcoidosis (< 20 new cases diagnosed per 100,000 persons/year) [5] means the larger the

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population analyzed, the better the characterization of the influence of geoepidemiological and ethnic factors in the phenotypic disease expression, and the more likely the findings will resemble the real population [6]. The personal environment significantly influences the risk of an individual diagnosis of sarcoidosis. Specific data among the studies included suggest that environmental factors related to the weather, area of residence, workplace, household, life style, and socioeconomic status may be key drivers of the disease phenotype. This review provides an update on how sarcoidosis may be modulated by environmental factors.

Geographical Determinants

Weather

Local weather is a key environmental factor influencing the incidence of sarcoidosis in a specific geographical area, with reports showing the peak of sarcoidosis cases diagnosed varies widely month-by-month. Geoepidemiological analysis [7–18] identifies a specific seasonal distribution following a north–south, west–east pattern in the Northern Hemisphere (Fig. 1). In the US and Europe, the farther north the city, the more frequently the peak incidence occurs in winter, with the lowest incidence overwhelmingly reported in autumn. Only one study in the Southern Hemisphere, from New Zealand [10], found a similar winter/spring clustering to that reported in US/European cities. In contrast, in the two studies carried out in Asia, the peak occurred mainly in summer, suggesting the additional potential influence of ethnic factors. Unfortunately, there was a great heterogeneity in these studies, not only in the study design, but also in the clinical phenotype analyzed, with several studies being focused on a specific clinical feature (erythema nodosum) or phenotypic presentation (Löfgren syndrome), which could be the phenotypic sarcoidosis presentation having the greatest seasonal influence.

Area of Residence

An inverse significant association was found between population density and the regional frequency of sarcoidosis in Switzerland [19], while, in Sweden, the highest prevalences were reported in the less-densely populated areas of the northwest [20], and the ACCESS study reported a reduced risk in US people living in suburbia in the three previous years [21]. However, no significant association with population density was found in studies from Poland, Croatia, Spain, India, or other US studies [22–26]. A higher risk of sarcoidosis is reported in US farm-dwellers [27], and studies have evaluated the influence of rural living, often linked to low-density population and predominantly agricultural activities. A Swiss study [19] reported enhanced disease rates in areas with high rates of agriculture (wheat, potatoes, and artificial meadows) and metallurgy (supply industry,

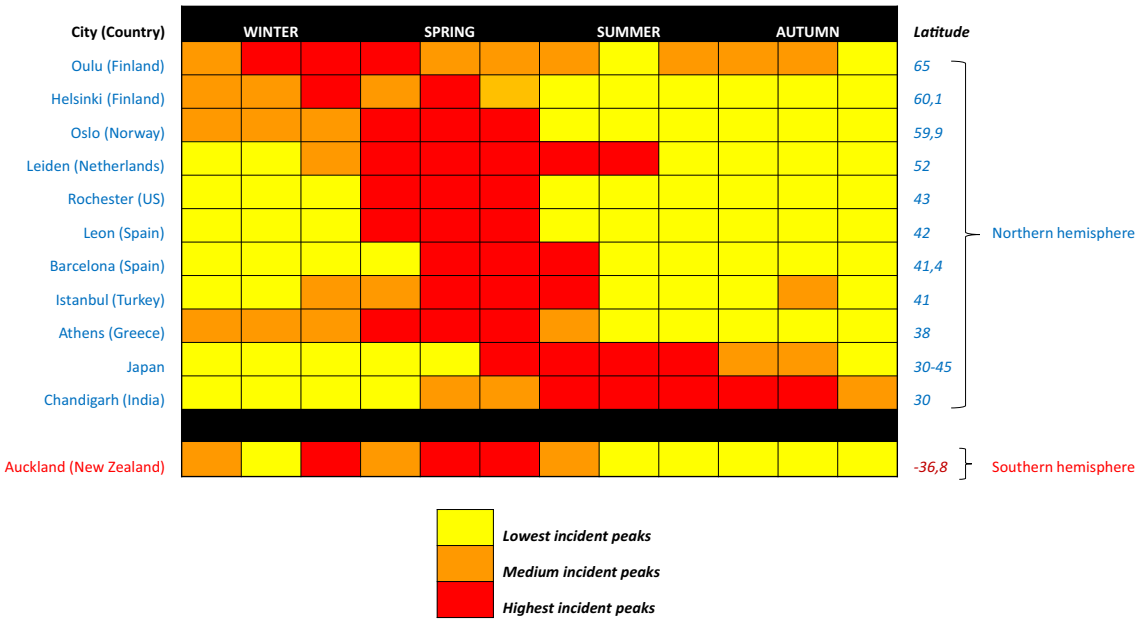

Fig. 1 Influence of the season in incident cases of sarcoidosis: the seasonal peaks of cases diagnosed per year among the different cities follow a specific North–South, West–East geographical gradient

machinery production), and areas with a high density of water supply and air transport factories.

Of studies analyzing the potential influence of air quality (pollution) or living in specific geographical areas near the coast, one found no association between air quality (measuring the highest level of mean annual $PM_{2.5}$ concentrations) and the frequency of sarcoidosis [19], while another [28] analyzed bioaccumulation levels of 12 metals and reported differing deposition patterns in lowland and hilly/mountain areas. Pirozzi et al. [29] studied short-term exposure to particulate matter ($PM_{2.5}$) and ozone (O_3) in 16 patients with fibrotic sarcoidosis with frequent exacerbations and found $PM_{2.5}$ levels were associated with a poor health status in only one of three questionnaires included, with no association with clinical/functional outcomes or ozone exposure. A South Carolina study [30] reported that geographic location appears to be associated with at least one measure of sarcoidosis (multiyear hospitalization rates) in the coastal half of the state, which was highly significant in African-Americans even after adjustment for general hospital usage, suggesting decreasing rates with increasing distance from the Atlantic coastline.

Occupational Determinants

The first reports of a potential influence of the workplace in modifying the risk of sarcoidosis came in the 1960s [31, 32]) Subsequently, all but one main recent epidemiological study have been made in the US, mostly as part of the ACCESS project [21, 23, 27, 33–40], the largest study of the relationship between occupational exposure and sarcoidosis (Table 1; Fig. 2).

Agricultural Employment

The strongest occupational association is in agricultural workers (farmworkers, raising birds, cotton ginning, exposure organic/vegetable dust, or insecticides) and workers in industries related to organic dust exposure, rubber factories, gardening materials, or pesticide-using industries [21, 23, 27, 34, 36]. The long list of potential toxins in agricultural work includes chemicals and aerosolized particulates such as grains, bedding materials, silicates, animal proteins, insect proteins, fungi, bacteria, mycotoxins, endotoxins and, especially, insecticides, and pesticides. Newman et al. [21] confirmed a positive association between agricultural employment and susceptibility to sarcoidosis, although the significance disappeared in the multivariable analysis, which showed insecticide exposure (at any time before study participation and in the 3 years immediately preceding diagnosis) was the key independent associated variable. Ethnicity may modulate the risk (enhanced in Caucasians) [36] and disease severity (lower risk of extrathoracic disease in Blacks exposed to organic dust) [36], as may gender (higher risk in males exposed to industrial organic dust) [36] and some HLA markers (higher risk in HLADRB1*1101 & 1501 carriers exposed to insecticides) [34].

Water Exposure

Another solid positive association is in occupations in contact (direct or indirect) with water (moldy/musty work environments, indoor exposure to high humidity or water damage and firefighters) [21, 23, 33–35]. Newman et al. [21] hypothesized that high-humidity environments may favor the production of bio-aerosols that enhance the sarcoidosis risk. Most fungi exude volatile organic compounds during active growth, causing the “musty” or “moldy” odor associated with fungal contamination [21] and some microorganisms involved in the etiopathogenesis of sarcoidosis-like diseases grow readily in standing water.

Construction

Construction-related jobs are also positively associated with sarcoidosis (hardware workers, building material suppliers, garden supplies and mobile homes, firefighters and others dealing with debris piles, such as those involved in the World Trade Center (WTC) response) [33, 34, 36, 41]. Jordan et al. [38] reported an enhanced risk in people working in the WTC debris pile, but not in those exposed to the dust cloud. Gender may modulate the risk, with a higher frequency in male manual construction workers [23].

Educational work has been linked to a higher risk of sarcoidosis [35, 36], especially in elementary/secondary schools [21, 34, 36] and colleges/universities, but only for Whites [36], while a higher risk is reported in healthcare workers (physicians [21], exposure to radiation [21] and laboratory workers in contact with animals) [21]. US death certificates showed a higher rate of sarcoidosis-related mortality in teachers and healthcare workers [39].

Metal Exposure

Other occupational expositions heterogeneously associated with the risk of sarcoidosis include an enhanced risk associated with metal machining, automotive manufacturing/fitters, and exposure to metal-working fluids, including a higher rate of sarcoidosis-related mortality in metal machinists [21, 23, 35, 39]; in contrast, a reduced risk has been reported in workers exposed to metal dust, fumes, or welding [21, 34, 36], who also have a low risk of extrapulmonary disease [37]. Studies of the risk of exposure to specific metals show titanium exposure (paint, plastics, inks) is associated with a higher risk [35] and

Table 1 Job exposures and risk of developing sarcoidosis: increased and decreased risk (OR > or < 1); in bold, statistically significant results from multivariate adjusted analysis; in italic, results reported for specific epidemiological subsets (gender, ethnicity) [21, 23, 27, 33–38, 40]

Job exposures	Increased risk (OR > 1)	Decreased risk (OR < 1)	Number of studies (references)
Agriculture			
Insecticides	**1.61/1.8**		[21, 34]
Pesticide-using industry	1.41		[21]
Agricultural employment/farms	1.46/**3.7**		[21, 27]
Job in cotton ginning	2.57/**4.98**		[21, 36]
Industrial organic/vegetable dust exposures	**3.5**/*1.82*		[34]
Rubber factory	**14.57**		[34]
Raising birds	3.73		[34]
Water			
Bioaerosol exposure (moldy, musty environments)	**1.49/1.62**/*1.75*		[21, 34, 35]
Indoor exposure high humidity	*1.34*		[35]
Exposures water damage	*1.35*		[35]
Construction			
Suppliers of building materials/garden supplies/hardware/mobile homes	3.2/**3.23**		[34, 36]
WTC debris pile	9.1		[38]
Metal			
Metal machining	*7.47*		[35]
Metal dust/metal fume exposures	*1.8*	**0.61/0.62**/0.69	[34, 36, 37]
Metal working	*2.05/2.2*		[35, 36]
Automotive manufacturing	**13.38**		[21]
Gold exposure		**0.26**	[21]
Exposure to welding		**0.4**	[21]
Titanium exposure	*3.15*		[35]
Military			
Military service		**0.53**	[37]
Ship's servicemen US Navy	*2.3*		[40]
Aviation structural mechanics specializing in structures US Navy	*2.1*		[40]
Mess management specialists US Navy	*2*		[40]
National security		*0.3*	[40]
Others			
Transportation services industry	*2.18/12.71*		[35, 36]
Electric energy		0.5	[36]
Personal			
Waiter/waitress		0.68	[21]
Retail trade industry	*2.41*	*0.49*	[35, 36]
Dusty trades with crustal dust	*2.57*		[36]
General merchandise stores	*1.73*	*0.24*	[36]
Data processor, typist, computer programmer		**0.57–0.70**	[21, 34]
Real estate	*3.38*		[36]
Information clerks		0.65	[36]
Personal service		0.48	[36]
Business services		*0.35*	[35]
Executive, legislative and general government except finance	*3.34*		[35]
Education			
Elementary/secondary schools	1.43/**1.80**		[21, 36]
Educators	1.42/**1.98**/*2.18*		[34–36]
Colleges/universities	*1.74*		[36]

Table 1 (continued)

Job exposures	Increased risk (OR > 1)	Decreased risk (OR < 1)	Number of studies (references)
Exposure to children at work		0.7	[21]
Work providing childcare		**0.57/0.64**/0.65	[21, 34, 36]
Health			
Social and rehabilitation services		**0.59/0.62**	[34, 36]
Hospital volunteer		**0.55/0.6**	[21, 34]
Physician	11		[21]
Radiation exposure	**2.28**		[21]
Job in animal lab	**32.79**		[34]

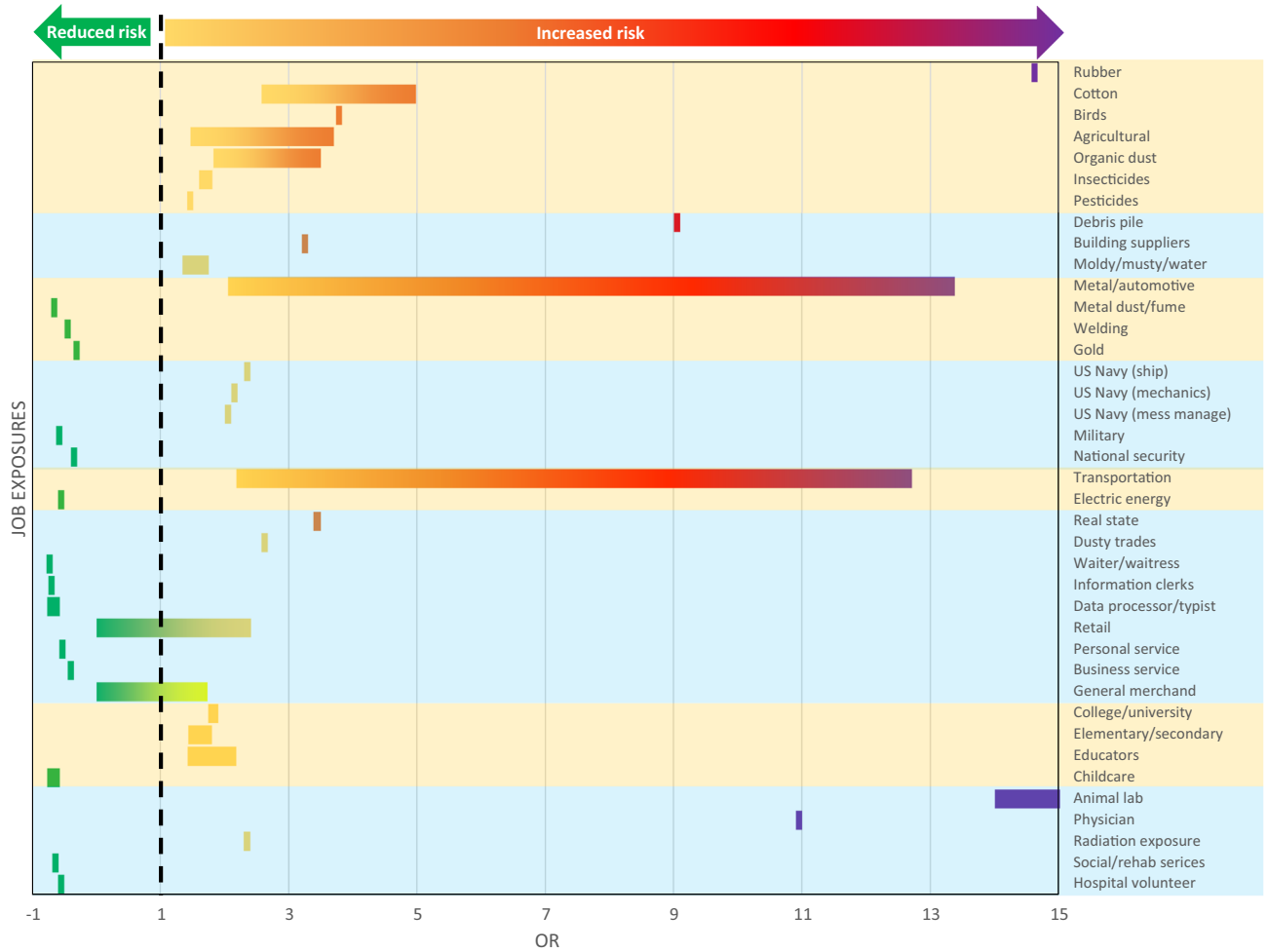

Fig. 2 Jobs and risk of sarcoidosis: enhanced versus reduced risk

gold exposure with a lower risk [21]. Finally, a higher ethnically driven risk was reported in BAA workers exposed to metal-working fluids [36] and a reduced risk in White workers exposed to metal dust/fumes [36].

Miscellanea

In military jobs, specific clusters of lower risk in women and higher risk in White and BAA people have been reported.

Other studies have reported a higher risk in male drivers and transportation workers [23, 35], especially in BAA people [36], and a reduced risk in persons exposed to children [21], providing childcare [36], working in social and rehabilitation services [34, 36] and being hospital volunteers [21]. Service jobs have also been overwhelmingly associated with a low risk of sarcoidosis, including waiters [21], retail/general trade workers [35] and business services like banking and administration [36], and service jobs without personal contact (data processing, typists, and computer programmers) [21, 34] and electrical supply industry workers [36]. The low-risk contrasts with the higher rate of sarcoidosis-related mortality reported for some of these jobs, including people working in sales and banking/administration [39].

Personal Determinants

Household Environment

A greater sarcoidosis risk is reported in people living with central air conditioning or using coal/wood stoves, fireplaces, humidifiers, and private water supplies, while domestic insecticide use does not enhance the risk [21, 27, 34]. Other household exposures are negatively associated with sarcoidosis, including household feather/down pillow stuffing, domestic exposure to children (including homecare of people's own or other children), household pets (cats, fish tanks, and animal dust) [21, 34, 35], and passive smoking exposure [21].

Lifestyle Determinants

Lifestyle determinants also influence the frequency and phenotypic expression of sarcoidosis, with smoking the most frequently reported protective factor. However, worldwide analysis of reported studies shows a potential influence of geographic factors. An inverse relationship between smoking and the sarcoidosis incidence rate has been consistently reported by most case–control studies from the Netherlands [12, 42], France [43–45], UK [46], and US [21, 34, 47], with a higher frequency of extrathoracic involvement in smokers [48, 49]. However, in Asia, no significant differences were found in India [50] and a higher reported prevalence of smoking in Japanese sarcoidosis patients in all age groups except men in their thirties was reported [51].

Studies have linked sarcoidosis with obesity. Ungprasert et al. [47] reported a 2.54-fold higher odds ratio for sarcoidosis in obese subjects (BMI $\geq$ 30 kg/m^2) compared with normal/low BMI individuals, while Cozier et al. [52] reported an increased incidence of sarcoidosis in BAA women with BMI > 30 kg/m^2. Outside the US, Gvozdenovic et al. [53] reported a higher frequency of Serbians with BMI $\geq$ 25 kg/m^2 in patients with sarcoidosis compared with healthy volunteers (78% vs. 47%, $p < 0.01$). Only one study has evaluated the association between alcohol consumption and sarcoidosis, with negative results [42]. The main epidemiological studies have reported some leisure activities as protective factors including having fish tanks or household cats, bird watching/keeping, exposure to indoor pools/hot tubs, exposure to auto/truck repair or printing as hobbies, or being hospital volunteers [21, 34].

Socioeconomic Determinants

Studies have evaluated the relationship between socioeconomic factors and the risk of sarcoidosis, and the association with educational levels varies by country. In Sweden, the lowest incidence rates were reported among the best-educated [20], in India [26] sarcoidosis was less frequent in people with lower educational levels, and in Brazil no association with educational levels was found [54]. A US study made by telephone interview [55] found a more advanced radiographic stage in lower-income individuals and more severe dyspnea in those with low socioeconomic status. Socioeconomic racial disparities may have influenced some of these results [56].

Other Environmental Determinants

Studies have reported spatial, familial, or microbiological sarcoidosis clusters in individuals with other shared environments [57]. The best example of spatial clustering is probably in the Isle of Man (located in the Irish Sea between Great Britain and Ireland, with around 85,000 inhabitants), where a case–control study identified 96 cases of sarcoidosis [58], of which 40% were exposed to $\geq$ 1 other person with sarcoidosis, 16% occurred in the same household (> 50% were blood relatives), 20% were associated with work (predominantly nurses), and 15% were friends; unfortunately, the study examined a limited list of occupations and provided limited analysis of home exposures [57].

Studies have focused on the occurrence of sarcoidosis in families, suggesting the heritable risk is complex and polygenic; siblings had the highest risk, together with Whites (compared with African-Americans) [57]. Family studies have almost exclusively focused on genetics and paid little attention to shared environmental exposures. One study [35] reported that African-American siblings with sarcoidosis were more likely to report indoor exposure to high humidity, water damage, or musty odors than their unaffected siblings. Stewart and Davidson [59] reported a cluster of sarcoidosis cases in two sisters and two unrelated social contacts, including one sister's employer, while other reports of husband–wife occurrences of sarcoidosis support the hypothesis

that a shared household environment may be a key etiopathogenic determinant in some cases [57].

A recent meta-analysis [60] suggests that some infectious agents (probably more than one) may be associated with sarcoidosis, with the geographical location being associated with the specific microorganisms involved. Some occupational case clusters suggesting a microbiological etiology are reported. An outbreak of cases was identified in an automotive manufacturing plant using metal-working fluids contaminated with various bacteria, and mycobacterially contaminated water sources may create aerosols that, when inhaled, produce sarcoidosis [57, 61].

Combining Epidemiological and Environmental Factors

Several examples shown how the increased or reduced risk of the epidemiological association may change for jobs with a similar exposure or according to gender or ethnicity [23, 34–37, 40]. A differentiated risk is reported for some jobs with common exposures, including construction/building materials (enhanced risk in workers in the WTC debris pile but not for those exposed to the dust cloud), metals (enhanced risk for machining, manufacturing, and exposure to metal-working fluids, reduced for exposure to metal dust, fumes, or welding), childcare (enhanced risk for educators, reduced risk for childcare), or health-related occupations (enhanced risk for physicians, reduced risk for workers in social and rehabilitation services). The risk may differ according to the location of the exposure, as reported for insecticides (enhanced risk for occupational exposure, no influence for home use), animals (risk enhanced for occupational exposure and reduced for household pets), children (risk enhanced risk for educators and reduced for domestic exposure to children), water-related environments (risk enhanced for occupational/household exposures and reduced for leisure exposures in indoor pools/hot tubs), metal (risk enhanced for vehicle manufacturing/fitters and reduced for auto/truck repair as a hobby), and health-related environments (risk enhanced for physicians and reduced for hospital volunteers). This suggests that the personal or environmental factors involved act in different combinations and/or at different levels of exposure. Environmental agents may be involved at very low doses of exposure, with a long latent period between the exposure and the disease diagnosis, while exposure to a specific toxin might be a surrogate for environmental exposures to uninvestigated antigens, which could hamper identification of the causative agent/s [21]. Measuring potential co-dependence statistically could identify the degree of overlap between risk factors. For example, a positive association with sarcoidosis is reported in residents of areas with predominantly agriculture, metal, water-related, and transport industries, which are the activities reported as positive occupational associations. Likewise, the potential gender preponderance in some jobs may differ between countries and cultures, and the close relationship between ethnicity, socioeconomic status, and lifestyle determinants.

Some studies have investigated the association between phenotypic disease expression and types of exposure. The ACCESS project investigated whether environmental exposures and genetic factors were associated with particular phenotypes of the disease and found that exposures to agricultural organic dusts and wood burning were associated with a reduced risk of having extrapulmonary sarcoidosis; in addition, the effects of some exposures were significantly different in patients of different ethnicities, with Whites with agricultural dust exposure and African-Americans exposed to wood-burning stoves being less likely to have extrapulmonary disease [37]. Liu et al. [39] reported significant epidemiological differences in risk for sarcoidosis mortality by occupational exposures being more significant in women than in men, and in black than in white individuals; although these findings are associative, they may suggest potential interactions between occupational exposures and epidemiological features that could boost the greater risk of death noted.

Limitations of Epidemiological Studies in Sarcoidosis

The etiopathogenesis of sarcoidosis is complex. Probably, as Max Michael Jr stated in 1956 [62], "perhaps the term syndrome rather than disease should be used, for it is probable that several etiologic agents can produce the disease picture of what is now known as sarcoidosis," or as Newman stated, etiopathogenically, "sarcoidosis is a family of diseases" [57]. This complex clinical scenario requires an equally complex clinical and methodological approach, which has limitations and biases.

Clinical Limitations

Unfortunately, the lack of an internationally accepted set of criteria for a homogeneous diagnosis of sarcoidosis makes it impossible to ensure the stringency of the sarcoidosis diagnosis. Most studies based the diagnosis on a clinical/radiologic picture consistent with sarcoidosis together with a tissue biopsy with histologic evidence of non-caseating granulomas in the absence of other causes of granulomatous disease (Supplementary Table 1). Even using these criteria, sarcoidosis may be misdiagnosed, since other environmental-related pulmonary diseases (chronic beryllium disease, hypersensitivity pneumonitis) may be clinically

and pathologically similar, especially when the disease is confined to the lungs without lymph node involvement [63]. Recent studies are requiring that a diagnosis of sarcoidosis should be maintained for at least 6 months in order to allow time for a misdiagnosis to be corrected [64].

Methodological Limitations

Not all epidemiological studies have evaluated the effect of the intensity, timing, and duration of putative environmental exposures [65]. The rarity of some potentially important exposures requires appropriate sample-size calculation [65]. In the ACCESS study, most associations had OR of < 2.0 (Fig. 2), and for those > 2.0, the numbers were small [66], suggesting some significant results may be due to chance [21]. Recall bias is also an issue, since sarcoidosis patients might have spent more time and attention recalling past exposures [21, 65]. Large numbers of a priori hypotheses and difficulties in disease misclassification and definition of the phenotype of resolved versus persistent sarcoidosis may hamper interpretation of the results [66]. Therefore, environmental determinants in sarcoidosis should be studied using well-designed cohort, case–control, or family-based designs, taking into account their strengths and weaknesses [65].

Conclusion

Environmental factors play a key role in the phenotypic disease expression of sarcoidosis, since the three organs most frequently affected (the lungs, skin, and eyes) are in direct contact with the external environment [67]. Environmental exposure histories should be carefully collected to identify potential workplace triggers for sarcoidosis [63]. Occupational exposures are one of the most solid personal factors reported, and there is rising evidence that sarcoidosis can occur in workplace settings in which there is exposure to environmental triggers of inflammation that promote an abnormal granulomatous immune response [63]. The risk of sarcoidosis is enhanced in people working in agriculture, water-related, construction, metal machining, education, and health activities, and reduced in those working in jobs involving personal care. The influence of geoepidemiological features (gender, ethnicity) and the local/regional environment, including climate and predominant local industries, may also be modulating cofactors. Studies have confirmed seasonal-related peaks of sarcoidosis incidence according to a geographical west–east gradient. Other personal factors include smoking (associated with a lower risk of sarcoidosis except in Japanese studies), personal household exposures, and some leisure activities. The study of environmental factors must be lead by multidisciplinary teams involving disciplines such as epidemiology, immunology, microbiology, and toxicology [63].

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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