

Association Between Obesity and Sarcoidosis: A Systematic Review and Meta-analysis

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Abstract: *Background:* Sarcoidosis is a systemic inflammatory disease characterized by epithelioid granuloma formation in various organs. The etiology of sarcoidosis is unknown. Several studies report an increased risk of sarcoidosis in obese patients. The purpose of this study is to conduct a systematic review to assess the risk of sarcoidosis in obese or overweight patients, and to provide a population-based estimate of the risk of sarcoidosis in obese and overweight individuals. *Methods:* Using the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) guidelines, we conducted a comprehensive search of studies (Randomized control trial (RCT), cohort or case-control) studies that estimated the risk of sarcoidosis with body mass index (BMI) between 2009-2019 using keywords and MESH terms related to obesity and sarcoidosis. The search was conducted in MEDLINE, EBSCO, and CINAHL. Three independent investigators reviewed each article and assessed for bias. Data was extracted from each study that met inclusion criteria. Quantitative analysis was performed using Review Manager 5.3 software. *Results:* An initial search yielded 77 potential articles; 73 articles did not meet inclusion criteria and 4 were included in the final analysis. The pooled risk estimate for the incidence of sarcoidosis in obese and overweight individuals was 1.68 [95% confidence interval 1.5-1.87] with a significant statistical heterogeneity, I^2 of 92%. *Conclusion:* From our systematic review, obese and overweight individuals have a 68% (RR 1.68, 95% CI 1.50 to 1.87) increased risk of developing sarcoidosis in comparison with normal or underweight individuals. More studies are needed to further evaluate the role of obesity in the etiopathogenesis of sarcoidosis.

Keywords: Sarcoidosis, Obesity, Pulmonary

1. Introduction

The incidence of obesity is increasing worldwide [1-3] and has been associated with an increasing incidence of autoimmune diseases including rheumatoid arthritis, psoriasis, Lupus and autoimmune thyroiditis. [4-10]. The World Health Organization (WHO) has defined obesity as a Body Mass Index (BMI) ≥ 30 kg/m² and overweight as BMI ≥ 25 Kg/m² to <30 kg/m² [11]. In 2015, over 40% of the world's adult population was overweight and about 13% (over 600 million people) were obese. [1, 2] In 2015-2016, 38% of US men and 41.5% of US women were considered obese. [12] The

prevalence of obesity in the US varies by race, ethnicity and geography. Hispanics and non-Hispanic blacks have the highest age-adjusted prevalence rates of obesity in the US. [12] Geographically, the western states have the lowest prevalence rates of obesity in the country. [13]

Sarcoidosis is a systemic granulomatous inflammatory disease of unknown etiology characterized by non-caseating granulomas which can affect any organ in the body. [14, 15] It involves the lungs in over 90% of cases. [14-16] The incidence of sarcoidosis varies with race, gender and geographic location. [17-20] Worldwide, the highest incidence rates of sarcoidosis are reported in Northern Europe and in the United States. [17, 21] In the US, the

incidence of disease is 2 to 3 times higher in African Americans than in Whites. [19, 20] Geographically in the US, the northeastern states have the highest incidence of disease while the western states have the lowest rates. [20] This geographic variability maybe attributed to various environmental exposures thought to be associated with sarcoidosis [22, 23] however, it is also notable, that the geographic distribution of sarcoidosis in the US mimics that of obesity very closely. [13, 20]

The etiology of sarcoidosis is unknown. However, it has been hypothesized that genetic predisposition, occupational/environmental exposures and infection with certain bacterial antigens may play a role in the etiopathogenesis of disease. [24-26] More recently, obesity has been implicated as a risk factor in the etiology of sarcoidosis. [5, 27-31] Harpsøe *et al* [5] evaluated a prospective cohort of over 75,000 Danish women enrolled in the Danish National Birth Cohort during 1996 – 2002 [5, 32] and found that obese women had a 3.59 fold (HR 3.59, 95% CI 2.31 to 5.57) increased risk of developing sarcoidosis than their non-obese counterparts. Subsequently, Cozier *et. al* [28] using data from the Black Women's Health Study (BWHS), a longitudinal follow-up study of 59,000 US black women aged 21 to 69 years at baseline found that there was a 42% (IRR 1.42, 95% CI 1.07-1.89) increased incidence of sarcoidosis for black/African American women with BMI \geq 35 Kg/m² at study baseline compared to non-obese subjects. That study also showed that significant weight gain between age 18 and study baseline (median age 38 years), was associated with an increased risk of sarcoidosis. Subjects who gained 30kg or more between age 18 and study entry, had a 47% (IRR 1.47, 95% CI 1.10-1.97; *p* trend 0.16) increased risk of developing sarcoidosis. [28] Two additional epidemiological studies done in predominantly white US populations showed similar results. [30, 31] Dumas *et. al.* followed over 110, 000 predominantly white female nurses enrolled in the Nurses Health Study II (NHSII) [31] from 1989 - 2013 and found that subjects who were overweight (BMI 25-29.9) at study entry had a 53% (HR 1.53, 95% CI 1.12-2.10) increased risk of incident sarcoidosis while subjects who were obese at study entry had a 74% (HR 1.74, 95% CI 1.26-2.40) increased risk of developing sarcoidosis.

Both the BWHS and the NHSII had broad subject representations in the USA, and enrolled patients in over 14 US states with representations across the four geographic regions. [33, 34] A case control study done in Olmsted county MN (predominantly White population) compared patients diagnosed with sarcoidosis over a 37-year period from 1976 to 2013 to age and gender matched controls from the same population, and found a 12% increased odds of developing sarcoidosis in overweight subjects (OR 1.12; 95% CI 0.72-1.75) and a 2.5 fold increased odds (OR 2.54, 95% CI 1.58 – 4.06) of developing sarcoidosis in obese subjects. [30]

These studies were done in very select populations (Black females [28], White females [31], Danish women [5, 32], Olmsted County, MN [30]) and a generalizable population-

based risk estimate for the incidence of sarcoidosis in obese subjects is not available. The aim of this study was to further evaluate the incidence of sarcoidosis in obese subjects with a goal of providing a generalizable population-based risk estimate of disease. This primary aim of this study was to review the current literature to evaluate the association between high BMI (>25) and the risk of sarcoidosis. The goal is to provide a population-wide risk estimate of disease in overweight and obese subjects.

2. Methods

2.1. Search Strategy

A comprehensive search of published literature was conducted in MEDLINE, EBSCO, CINAHL and EMBASE databases. The search strategy was restricted to published literature within the past 10 years (January 2009 to September 2019) and available in English language. A hand search of other relevant literature from references of relevant articles was also performed.

2.2. Inclusion Criteria

Inclusion criteria included studies that had the following 1) Randomized Control Trials, Cohort or case-control studies with a well described effect measure that described the risk of developing sarcoidosis based on body weight or BMI. 2) Well defined sarcoidosis cases in line with acceptable international disease-classification codes. For case-control studies, cases must have been matched with the controls on various demographics of importance such as age, race and gender. Matching was important because the incidence and clinical presentation of sarcoidosis has been shown to vary with race, age, gender and geo-ethnicity. [16, 19, 20, 35-40] Eligible studies included in this review were independently reviewed and determined by the three investigators. In case of disagreements, a consensus was built to resolve them.

2.3. Data Extraction

A systematic data extraction form as provided by the PRISMA statement was used to extract important information from the selected articles. The information collected included 1) article title 2) authors 3) publication year 4) study participants 5) average follow-up time 6) effect of outcome measure and 7) estimated risk or odds ratio. To ensure objectivity, this process was supervised by the senior author. The study was exempted from IRB review since it involved review of secondary data.

2.4. Statistical Analysis

Quantitative data analysis was performed using Review Manager (v5.3) software from the Cochrane Collaboration (London, UK). Cases among obese (BMI \geq 30) or overweight BMI \geq 25 to <30) individuals and those among normal (BMI 18.5 – 24.9) or underweight individuals (BMI <18.5) were extracted from individual articles. Relative risk

ratios and weights were computed for individual studies and a pooled estimate was calculated. Cochrane Q test and a test of heterogeneity (I^2) test were performed.

3. Results

Our search yielded 75 articles as shown in the PRISMA flow diagram in Figure 1. The search on databases yielded 64 potential articles. Search from other sources including review of references in some key papers yielded another 13 articles. After excluding two duplicated articles, there were 75 articles

that went through initial review of relevant titles and abstracts. This initial review excluded 62 articles that did not meet the standards of our inclusion criteria. Some of these studies were case reviews or were on other topics on sarcoidosis other than the relationship between obesity and sarcoidosis. 13 articles went under full review after which 9 were excluded since they were either review articles or case reports and were not cohort or case-control studies. Four articles [5, 28, 30, 31] that measured the effect of obesity on the incidence of sarcoidosis satisfied our eligibility criteria and were included in the meta-analysis.

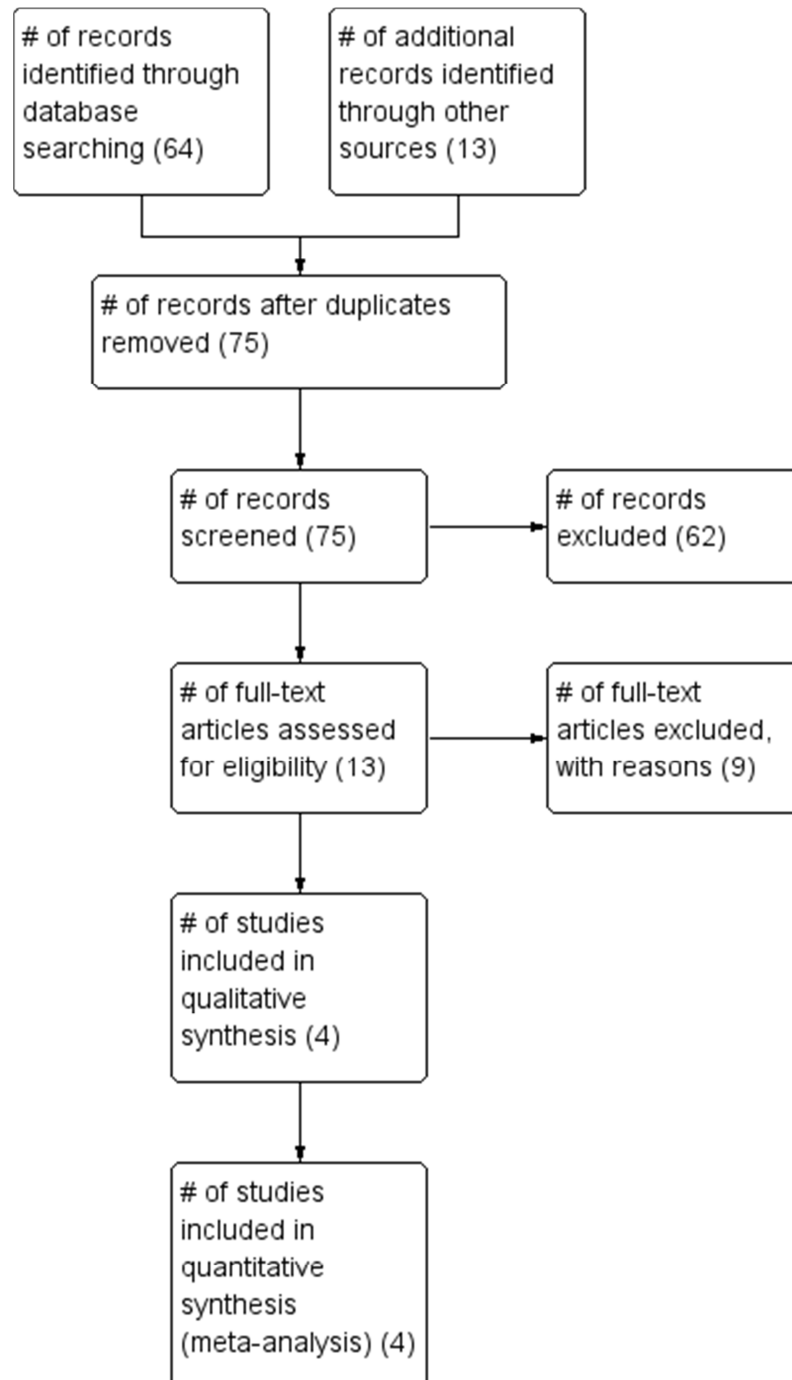


Figure 1. PRISMA flow diagram.

These studies measured the risk of developing sarcoidosis based on body mass index categorized as underweight, normal weight, overweight and obese. One study [28] included an extra category of morbidly obese subjects with BMI ≥ 35 and restricted the group with obesity to BMI 30 to

34 [28]. Two of the studies [28, 31] reported BMI at age 18 as well as baseline BMI at study entry. To be consistent across all four studies, we used only the baseline BMI at study entry for those two studies. The summary of included studies is shown in Table 1.

Table 1. Characteristics of studies included.

	Harpsoe et al. 2014 [5]	Cozier et al. 2015 [28]	Ungprasert et al. 2016 [30]	Dumas et al. 2017 [31]
Study design	Prospective cohort	Prospective cohort	Nested Case-Control	Prospective cohort
Publication year	2014	2015	2016	2017
Case definition	Sarcoidosis cases were defined as outlined in the ICD-8 and ICD-10 codes and physician diagnosis.	Cases were patients who reported being diagnosed with sarcoidosis in the preceding 2 years of a biennial questionnaire survey. Cases were validated from patient medical records.	Cases were identified from diagnostic codes and confirmation from physician diagnosis.	Cases were identified from self-reported physician diagnosed sarcoidosis.
Year (s) of study	1996 to 2002	1995 to 2011	1976 to 2013	1989 to 2013
Follow-up period	11.4 years	16 years	*16 years	24 years
Number of Cases	140	454	345	270
Number of Controls	-	-	345	-
Total number in study population	75,008	51,452	690	116,312
Average Age (range) at study enrollment	30.2 years (27 - 33)	38 years (21 - 69)	**45.5 years (± 13.65)	34 years (25 - 44)
Study Population	Danish Females enrolled in the Danish National Birth Cohort between 1996 to 2002 [32].	Black Women's Health study [33].	Population based cohort study of residents in Olmsted county MN diagnosed with sarcoidosis between 1976 to 2013 [82].	The Nurses Health study II [34]
Country	Denmark	USA	USA	USA
Gender and Racial distribution	White Danish Females only	Black Females only	50% Males; 91% Caucasian, 3% AA, 2% Asian, 3% others	Females only, 96% White
Age at BMI check	Pre-pregnancy BMI	BMI at age 18 and baseline BMI in 1995.	BMI within 1 year before to 3 months after date of diagnosis of sarcoidosis	BMI at age 18 and baseline BMI in 1989.
Relative Risk Estimate (95% CI)	HR:	IRR (for baseline BMI):	OR:	HR (for baseline BMI):
BMI 25-29 kg/m ²	1.90 (1.27-2.84)	1.09 (0.85 - 1.39)	1.12 (0.72-1.75)	1.53 (1.12 - 2.10)
BMI ≥ 30 kg/m ²	3.59 (2.31-5.57)	1.24 (0.93 - 1.64);	2.54 (1.58-4.06)	1.74 (1.26 - 2.40)
BMI ≥ 35 kg/m ²	-	BMI 30-34: 1.42 (1.07 - 1.89)	-	-

*computed as an average of the follow up times for cases and controls from table 1 of that paper.

**Mean age reported – computed as the mean of the ages of cases and controls in the paper.

AA=African American.

Our study included over 243,400 subjects (Table 2). The study population was predominantly female (99%). The average age of study participants at study enrollment was 36.9 years with an age range of 21 to 69 years. 77% of the study population were White/Caucasian and 23% were Black/African American. 63% had a Low/Normal BMI, 21.9% were overweight and 14.8% were obese. For the final analysis, we grouped overweight, obese and morbidly obese subjects together, and underweight and normal weight subjects together. There were 751 cases of incident sarcoidosis in overweight or obese subjects (0.84%) and 418 cases of incident sarcoidosis in normal or underweight subjects (0.27%).

Table 2. Population characteristics.

Total Number	N (%)
Total Population Size (N)	243, 462
Average Age in Years (range)	36.9 (21 – 69)
Females N (%)	243, 120 (99.9%)
Ethnicity N (%)	5

Total Number	N (%)
Black/AA	6, 125 (23%)
White	187,295 (77%)
Others	40 (<1%)
BMI Categories	
Normal/Low	153,814 (63%)
Overweight	53,329 (21.9)
Obese	36,142 (14.8%)
Unknown	177 (<1%)

As shown in Figure 2 there is an increased risk of developing sarcoidosis among overweight, obese and morbidly obese subjects compared to those who are underweight or have normal BMI. The pooled relative risk estimate was 1.68 [95% confidence interval, 1.5-1.87]. This suggests that there is a 68% increased risk of developing sarcoidosis in obese and overweight subjects when compared to their non-obese or underweight counterparts. This was consistent with the findings in the individual studies that were included in the meta-analysis. The included studies showed heterogeneity with an I^2 of 92% which indicates that

the variation in effect estimates is not by chance.



Figure 2. Meta-analysis results.

4. Discussion

While it is well known that obesity and high BMI are associated with poor health outcomes for patients with chronic diseases [2, 41-44] including sarcoidosis, [45-47] their role in the etiology of these chronic diseases has only recently begun to be explored. [29, 43, 48-53] Studies in the past two decades have shown that obesity is associated with an increased incidence of autoimmune diseases, and have expounded on the biological plausibility of that association. [4-10, 54, 55]

The relationship between obesity and sarcoidosis has been characterized both as “posing twin problems for patients” [47] as well as a “chicken vs. egg scenario”. [29] It is well known that treatment with corticosteroids, the first line treatment option for patients with sarcoidosis can be complicated by obesity, [56-62] and that obese patients with sarcoidosis are more likely to have added health problems, decreased lung function and poorer perceived health status and health related quality of life than non-obese patients with sarcoidosis. [45, 46, 63-66] Recent epidemiological studies have reported an increased incidence of sarcoidosis in obese subjects and suggest that obesity is a risk factor for disease incidence. [5, 28-31] These studies include longitudinal cohort studies [5, 28, 31, 32] that enrolled subjects prospectively, and collected data on BMI prior to the development of sarcoidosis or initiation of corticosteroids for treatment. These studies showed that there is a 42% to 3.5 fold (RR 1.42 to 3.59) increased incidence of sarcoidosis in obese and overweight subjects when compared to their lean and non-obese counterparts. [5, 28, 31] In addition to their longitudinal design and evidence of temporality, they also demonstrated a graded effect of BMI on the incidence of sarcoidosis suggesting a “dose-response” relationship. [5, 28, 30, 31] Harpsøe et al [5] found a 90% (95% CI 1.27-2.84) increased risk of developing sarcoidosis in overweight women in the Danish National Birth Cohort and a 3.6 fold (95% CI 2.31 to 5.57) increased risk of incidence of sarcoidosis in obese Danish women compared to those with normal BMI. Similarly, Cozier *et al.* [28] found that compared to African American females with normal BMI, overweight subjects (BMI 25-29.9) had a 13% increased incidence of sarcoidosis, obese subjects (BMI 30-34 kg/m²) had a 31% increased incidence, and morbidly obese subjects (BMI > 35 kg/m²)

had a 55% increased incidence of sarcoidosis. [28] These findings are replicated in the other two studies included in this analysis and lend credence to the postulation that obesity may play a role in the etiology of sarcoidosis. [30, 31]

Although the etiology of sarcoidosis remains unknown, the immunological mechanisms underlying granuloma formation and disease progression have been described. [24-26, 67, 68] It is biologically plausible that obesity may play a role in the etiopathogenesis of disease by influencing the immunological mechanisms of granuloma formation.

The sarcoid granuloma is thought to result from an aberrant CD4+ Th1/Th17 immune mediated response to a yet unidentified antigen. [25, 26, 67-69] Antigen presenting cells (macrophages and dendritic cells) bind to and present this putative antigen to T cells via HLA class II CD4+ T cell receptors. [67] Activation of macrophages by this putative antigen results in release of large amounts of pro-inflammatory cytokines such as Tumor Necrosis Factor- α (TNF- α), interleukin (IL)-1, and IL-6. TNF- α induces transformation of macrophages into epithelioid and multinucleated giant cells (MGC) and activates natural killer cells (NK cells) causing release of interferon gamma (IFN- γ) which in turn stimulates activated macrophages to produce several chemokines that attract Th1/Th17 cells, monocytes and T-regulatory cells (Tregs) to the site of inflammation. Activated macrophages, MGC and clonal CD4+ Th1/Th17 cells constitute the core of the sarcoid granuloma with a few scattered B-cells and Tregs in the periphery. It has been suggested that an impaired immunosuppressive function of Tregs in sarcoidosis plays a role in the development of chronic persistent disease. [67, 70-73]

Adipose tissue once thought to be inert, is now known to be a metabolically active “immuno-endocrine” organ that secretes a wide variety of pro-inflammatory mediators known as adipokines (adipocytokines) that induce a chronic inflammatory state in obese subjects. [6, 74] The adipokines secreted in obesity include IL-6, TNF- α , leptin and adiponectin. [74, 75] IL-6 has been associated with deregulation of the Th-17/T-reg balance in obese patients, a state known to promote autoimmunity [74, 76]. Leptin is a potent pro-inflammatory immunomodulator that enhances the proliferation and activation of NK cells, and differentiation of naïve T cells to Th1 cells. Circulating levels of leptin are directly correlated with the adipose tissue

mass and are upregulated by TNF- α [6]. Leptin induces macrophages to produce increased amounts of pro-inflammatory cytokines (TNF- α , IL-6 and IL-12), and has been shown to inhibit the proliferation of Treg cells. [6, 75] Leptin mediated inhibition of Treg cells has been proposed as a mechanism that may promote the development of chronic persistent disease in obese patients. [67, 70-73] Adiponectin is an anti-inflammatory adipokine whose levels are decreased in obesity [6, 75]. It works in concert with various resident innate and adaptive immune cells in adipose tissue to dampen the inflammatory process. [77, 78] It has been shown, that as adipose tissue expands, there is a progressive decline in the anti-inflammatory cytokines [79, 80] and a net gain in pro-inflammatory cytokines. The net result favors a pro-inflammatory state with increased amounts of Th-1 cells, TNF- α , IL-6, IL-12 and IFN- γ . [29, 79, 80] This cytokine milieu represents the same cytokine milieu that initiates and drives sarcoid granuloma formation and could hypothetically account for the increased incidence of sarcoidosis in obesity.

Our study sought to provide a generalizable population-wide risk estimate for the incidence of sarcoidosis in obese and overweight subjects. It is based on epidemiologic studies and reflects all the current information available on this topic. We aggregated all available data from the studies available and conducted a meta-analysis that demonstrated an overall significant positive association between obesity and incident sarcoidosis. We found that subjects who are overweight or obese have a 68% [RR 1.68, 95% CI 1.50 - 1.87] increased risk of developing sarcoidosis when compared to normal and underweight subjects.

Our study has several strengths. First, it includes a large number of subjects (over 243,400) with long follow-up periods (11 to 24 years) recruited from population-based studies with broad geographic representation in the US and Netherlands. Second, participants were from the two countries that have the highest incidence of sarcoidosis worldwide, and within the US, there was a broad representation of subjects from all the various regions and across a broad range of age groups. [81] Third, we included only studies with a longitudinal design and excluded case reports and review articles so as to avoid any confounding by indication.

There are however several limitations to our study. First, our study population was over 99% females and was predominantly (77%) White/Caucasian therefore, our study results may not be generalizable to males or other racial groups that are not well represented in our study. This is a reflection of the racial, gender and geo-ethnic distribution of the cohorts included in our analysis and does not represent what is known about the current epidemiology of sarcoidosis worldwide [19, 20]. Three of the four studies [5, 28, 31] included in our analysis were conducted in cohorts of women and our predominant female population reflects this. It is to be noted, that these cohorts were not originally designed for the study of sarcoidosis, and so do not reflect the gender or racial distribution that has been reported for sarcoidosis. Sarcoidosis is a rare disease and there are currently no

cohorts designed for the study of the disease. Secondly, although we screened a large number of studies, only four studies met eligibility criteria for inclusion in the meta-analysis. This is a small number of studies; however, it represents all the studies available in this area and speaks to the need for more studies of obesity and sarcoidosis in more representative cohorts.

In conclusion, this is the first meta-analysis of its kind. It shows that there is a 68% (RR 1.68, 95% CI 1.50 to 1.87) increased incidence of sarcoidosis in overweight and obese subjects when compared to normal and underweight individuals. More studies are needed to further evaluate the role of obesity in the etiopathogenesis of sarcoidosis. Future studies should focus on populations with a large representation of males and other geo-ethnic groups. Studies evaluating the role of leptin and adiponectin in sarcoidosis are also needed to further explore the biologic plausibility of this association.

Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

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