



Original Article

# Negative Association of Smoking History With Clinically Manifest Cardiac Sarcoidosis: A Case-Control Study

Chenchen Xu, BHSc,<sup>a</sup> Pablo B. Nery, MD,<sup>a</sup> Christiane Wiefels, MD,<sup>b,c</sup> Rob S. Beanlands, MD,<sup>a</sup> Stewart D. Spence, MD,<sup>a</sup> Daniel Juneau, MD,<sup>d</sup> Steven Promislow, MD,<sup>a</sup> Kevin Boczar, MD,<sup>a,e</sup> Robert A. deKemp, PhD,<sup>a</sup> and David H. Birnie, MD<sup>a</sup>

<sup>a</sup> Department of Medicine (Cardiology), University of Ottawa Heart Institute, Ottawa, Ontario, Canada

<sup>b</sup> Department of Medicine, Division of Nuclear Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada

<sup>c</sup> Postgraduate Program in Cardiovascular Sciences, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

<sup>d</sup> Department of Radiology and Nuclear Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada

<sup>e</sup> Faculty of Medicine, School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

## ABSTRACT

**Background:** The etiology of sarcoidosis is still unknown and is likely related to a genetic susceptibility to unidentified environmental trigger(s). Our group and others have extensively described a specific phenotype of primarily Caucasian patients who have clinically manifest cardiac sarcoidosis (CS). In this study, we sought to explore whether smoking is associated with this specific phenotype of sarcoidosis.

**Methods:** We performed a case-control study. Cases with clinically manifest CS were prospectively enrolled in the Cardiac Sarcoidosis Multi-Center Prospective Cohort Study (CHASM-CS registry; NCT01477359) and answered a standardized smoking history questionnaire. Cases were matched 10:1 with controls from the Ontario Health Study. Pretreatment positron emission tomography scans with <sup>18</sup>F-fluorodeoxyglucose were compared for smokers vs nonsmokers.

**Results:** Eighty-seven cases met the inclusion criteria. A total of 82 of

## RÉSUMÉ

**Introduction :** L'étiologie de la sarcoïdose est encore inconnue et est possiblement liée à une susceptibilité génétique à un ou des déclencheurs environnementaux inconnus. Notre groupe et d'autres groupes ont exposé sous tous ses aspects un phénotype particulier chez des patients principalement blancs qui ont une sarcoïdose cardiaque (SC) manifeste sur le plan clinique. Dans la présente étude, nous avons cherché à explorer si le tabagisme est associé à ce phénotype particulier de la sarcoïdose.

**Méthodes :** Nous avons réalisé une étude cas témoins. Les cas qui avaient une SC manifeste sur le plan clinique ont été inscrits de façon prospective à l'étude CHASM-CS (Cardiac Sarcoidosis Multi-Center Prospective Cohort Study, registre CHASM-CS; NCT01477359) et ont répondu à un questionnaire standardisé sur les antécédents de tabagisme. Les cas ont été appariés 10:1 aux témoins de l'Étude sur la

Sarcoidosis is characterized by infiltration of non-caseating granulomas, most commonly resulting in pulmonary disease.<sup>1</sup> This multi-system disease can affect people of any age and ethnicity. Less-common sites of disease involvement include the splenic, renal, dermatologic, neurologic, and cardiac systems.<sup>1</sup> Up to 5% of the time, patients with sarcoidosis present with

one or more clinical signs of cardiac sarcoidosis (CS), including ventricular arrhythmia, heart failure, and conduction abnormalities.<sup>2,3</sup>

Currently, the cause of sarcoidosis is not known. With ongoing research efforts, several hypotheses have been proposed to explain the etiology of this disease, with the most common hypothesis suggesting a susceptibility to unknown environmental triggers, due to genetic predisposition.<sup>1</sup> Studies such as **A Case Control Etiologic Study of Sarcoidosis: Environmental and Occupational Risk Factors (ACCESS)** examined various environmental exposures that may be associated with sarcoidosis.<sup>4</sup> In the study, triggers such as occupational exposure to musty odors and insecticides were found to have positive associations with sarcoidosis. A negative association was found between smoking and sarcoidosis.<sup>4</sup> A number of other publications have examined the association between extracardiac sarcoidosis and smoking, but the results have not been

Received for publication April 7, 2022. Accepted June 5, 2022.

**Ethics Statement:** Institutional ethics approval was obtained at the onset of the registry. Additionally, a second ethics approval was obtained for the questionnaire and data linkage. The institutional review board was the Ottawa Health Science Network Research Ethics Board, and associated approval numbers are, CHASM-CS registry: 20120365-01H, and 20200624-01H.

Corresponding author: Dr David Birnie, 40 Ruskin Street, University of Ottawa Heart Institute, Ottawa, Ontario K1Y 4W7, Canada.

E-mail: [dbirnie@ottawaheart.ca](mailto:dbirnie@ottawaheart.ca)

See page 761 for disclosure information.

87 (94.3%) answered the questionnaire and were matched with 820 controls. A clear negative association of sarcoidosis and smoking was found, with 23 of 82 CS cases (28.0%) being current or ex-smokers, vs 392 of 820 controls (47.8%;  $P = 0.0006$ ). CS patients with a smoking history had significantly less lifetime consumption ( $8.31 \pm 9.20$  pack-years) than the controls ( $15.34 \pm 10.84$  pack-years;  $P < 0.003$ ). On  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography scan, the mean standardized uptake value of the left ventricle was  $4.2 \pm 8.98$  in lifetime nonsmokers vs  $2.89 \pm 2.07$  in patients with a smoking history ( $P < 0.0001$ ).

**Conclusions:** We describe a strong negative association between smoking history and clinically manifest CS. Nonsmokers had more severe myocardial inflammation (greater mean standardized uptake value of the left ventricle) than did patients with a smoking history. Further research is needed to understand these associations and whether they have therapeutic potential.

consistent.<sup>5-10</sup> Previous work is of variable methodologic quality, and studies are limited by small sample sizes, inclusion of a broad range of sarcoidosis phenotypes, and issues pertaining to the selected control populations. Our group and others have described extensively a specific phenotype of primarily Caucasian patients with clinically manifest CS.<sup>11,12</sup> In this phenotype, cardiac manifestations are usually the first presentation of sarcoidosis in any organ, and other organ involvements are usually modest. In the current study, we sought to explore whether smoking is associated with this specific phenotype of clinically manifest CS. We also examined whether the disease had different clinical features (in patients with vs without a history of smoking).

## Methods

### Study design

**Case-control: cases.** This study is a single-centre substudy of the ongoing Cardiac Sarcoidosis Multi-Center Prospective Cohort Study (CHASM-CS registry, NCT01477359) at the University of Ottawa Heart Institute (UOHI). CHASM-CS is a multicentre, Canadian and Japanese prospective registry of patients with CS. The registry was created to answer clinical questions about diagnosis and treatment for the specific group of patients who have clinically manifest CS. The registry includes baseline assessment of patients with clinically manifest CS, including the following factors: history, echocardiogram, electrocardiogram (ECG), chest computed tomography (CT) scan,  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography (FDG-PET) scan, blood test for biomarkers within 2 months of the PET scan, cardiac magnetic resonance imaging, and biopsy. For this substudy, all patients with clinically manifest CS<sup>2</sup> from the CHASM-CS registry were included.

santé Ontario. Nous avons comparé avant le traitement la tomographie par émission de positons au  $^{18}\text{F}$ -fluorodéoxyglucose des fumeurs vs des non-fumeurs.

**Résultats :** Quatre-vingt-sept cas répondaient aux critères d'inclusion. Un total de 82 sur 87 (94,3 %) cas ont rempli le questionnaire et ont été appariés à 820 témoins. Nous avons observé une association négative claire entre la sarcoïdose et le tabagisme, soit 23 sur 82 cas de SC (28,0 %) qui fumaient actuellement ou étaient des ex-fumeurs vs 392 sur 820 témoins (47,8 % ;  $P = 0,0006$ ). Les patients atteints de SC qui avaient des antécédents de tabagisme avaient une consommation significativement moindre durant leur vie ( $8,31 \pm 9,20$  paquets-années) que les témoins ( $15,34 \pm 10,84$  paquets-années ;  $P < 0,003$ ). À la tomographie par émission de positons au  $^{18}\text{F}$ -fluorodéoxyglucose, la valeur moyenne de fixation normalisée du ventricule gauche était de  $4,2 \pm 8,98$  chez les non-fumeurs de toujours vs  $2,89 \pm 2,07$  chez les patients qui avaient des antécédents de tabagisme ( $P < 0,0001$ ).

**Conclusions :** Nous démontrons une forte association négative entre les antécédents de tabagisme et la SC manifeste sur le plan clinique. Les non-fumeurs avaient plus d'inflammation myocardique grave (une plus grande valeur moyenne de fixation normalisée du ventricule gauche) que les patients qui avaient des antécédents de tabagisme. D'autres recherches sont nécessaires pour comprendre ces associations et savoir s'ils ont un potentiel thérapeutique.

**Criteria for inclusion in CHASM-CS.** Clinically manifest CS was defined as the presence of one or more of the following clinical features:

- (i) positive biopsy for sarcoid (either endomyocardial biopsy or extracardiac); AND/OR
- (ii) chest CT scan highly suggestive of pulmonary sarcoidosis; AND
- (iii) one or more of the following clinical features:
  - advanced conduction system disease (sustained Mobitz II AV (atrioventricular) block or third-degree atrioventricular block);
  - nonsustained or sustained ventricular arrhythmia; and
  - ventricular dysfunction (left ventricular ejection fraction  $< 50\%$  and/or right ventricular ejection fraction  $< 40\%$ ); AND
- (iv) no alternative explanation for clinical features; AND
- (v) FDG-PET suggestive of active CS.

### Questionnaire

A standardized smoking history questionnaire was sent to all cases (see [Supplemental Appendix S1](#)). If the patient did not respond to the mailing, then research staff made 2 follow-up calls. Questionnaire results were linked to patient clinical data already in the CHASM-CS registry.

### FDG-PET scanning

Full details on the imaging protocols and image interpretation methods have been published elsewhere.<sup>12</sup> In brief, the imaging protocol included a whole-body acquisition (from the base of the cranium to mid-thigh) 60 minutes after the intravenous injection of 5 MBq/kg of FDG, followed immediately by a dedicated cardiac acquisition with ECG gating for evaluation of left ventricle (LV) function. To achieve adequate

suppression of physiological myocardial FDG uptake, all patients were instructed to follow a low-carbohydrate, fat-rich, protein-permitted diet the day before the examination, followed by a fast of at least 12 hours immediately before the examination. Unless contraindicated, patients also received a low dose (15 IU/kg) of intravenous unfractionated heparin before FDG injection, per our local protocol, in order to increase plasma levels of free fatty acid. All patients also underwent rest ECG-gated myocardial perfusion imaging studies using PET/CT with either  $^{82}\text{Rb}$  or  $^{13}\text{N}$ -ammonia on the same day.

### PET-scan analysis

All images were interpreted by an experienced nuclear cardiologist/medicine specialist with significant experience in reporting CS scan results. Readers were blinded to all clinical data and to whether patients were smokers or not. Sites of disease involvement were defined as “active” when abnormal FDG uptake in a pattern consistent with sarcoidosis was present. The number of discrete areas with increased FDG uptake was counted. The maximum standardized uptake value (SUV) of the left ventricle (LV) was measured on axial images of the whole-body PET scan, and the mean SUV of the LV and a summed rest perfusion score were calculated using FlowQuant automated software (Ottawa, ON). Significant right ventricular FDG uptake was evaluated visually as being present or absent. On the whole-body scans, sites of extracardiac disease involvement were defined as “active,” when abnormal FDG uptake in a pattern consistent with sarcoidosis was present, or “inactive,” in the presence of CT findings consistent with sarcoidosis, but normal FDG uptake. Lymph nodes were considered positive for sarcoidosis if they had a maximum SUV above mediastinal blood pool value, were enlarged ( $> 10$  mm in the short axis), and followed a pattern of distribution characteristic for sarcoidosis.

### Controls

Cases were matched 10:1 with controls from the Ontario Health Study (OHS). The OHS is an ongoing research study and database that prospectively collects health information from over 225,000 Ontario residents. The OHS aims to investigate how lifestyle, environment, and family history factors increase the risk of chronic diseases such as cancer, diabetes, and heart disease (<https://www.ontariohealthstudy.ca>). The data were collected using a Web-based questionnaire consisting of demographic and health-related questions. Cases were matched on sex, age (within 2 years), postal code (3-digit), ethnicity, history of diabetes, and hypertension.

### Ethics

Institutional ethics approval was obtained at the onset of the registry. Additionally, a second ethics approval was obtained for the questionnaire and data linkage. The institutional review board was the Ottawa Health Science Network Research Ethics Board, and associated approval numbers from the CHASM-CS registry are 20120365-01H and 20200624-01H.

### Sample-size estimation

Sample size was based on the primary objective (to determine if smoking history is associated with the development of

clinically manifest CS). We estimated that if 93 CS patients are matched to 930 controls, and the cases had a rate of smoking of 18.6%, based on our previous work,<sup>10</sup> then it can be estimated that we have 80% power (1-sided alpha of 5%) to detect an odds ratio of  $\leq 0.55$ .

### Statistics

Categorical variables are presented as counts and percentages, and continuous variables are presented as means ( $\pm$  standard deviation). We compared categorical variables using the  $\chi^2$  test, and continuous variables using *t*-tests. In a subset of patients, specifically cases and controls with a history of previous or current smoking and the development of sarcoidosis, logistic regression analysis was used to calculate the odds ratios and corresponding 95% confidence intervals (Cis) for the multivariable analysis. The following variables were used in the logistic regression analysis: age, sex, history of diabetes, and hypertension. Lifetime smoking pack-year history was also included as a continuous variable in the analysis. Statistical analysis was subsequently performed using SAS software (version 9.4, TS Level 1M6; SAS Institute, Cary, NC), and statistical significance was defined as a *P* value of  $< 0.05$ .

## Results

### Cases and controls

A total of 87 patients met the inclusion criteria, of whom 82 of 87 (94.3%) completed the questionnaire. These 82 patients (45.1% female) met the inclusion criteria and were matched with 820 controls. Study flow is shown in [Figure 1](#), and baseline demographics of the cases and controls are shown in [Table 1](#).

### Association with smoking

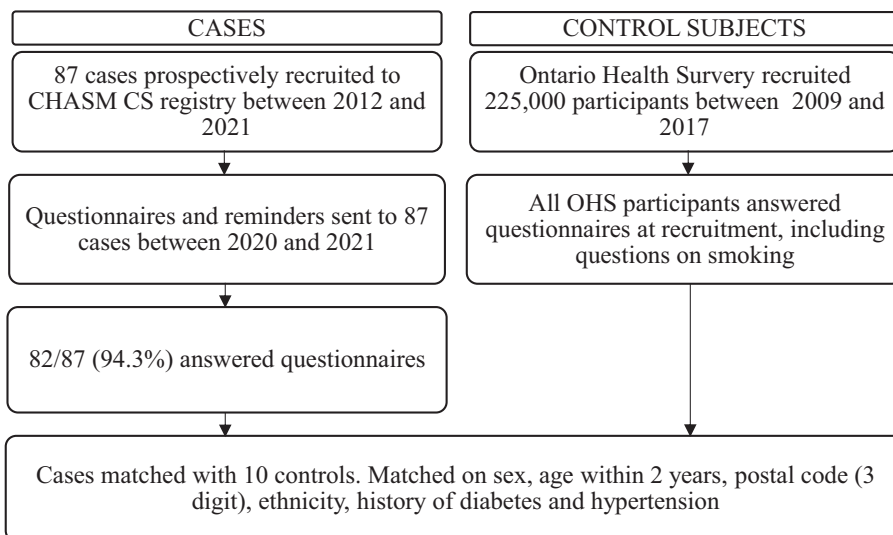
The results are shown in [Table 2](#). A clear negative association with smoking was seen, with 23 of 82 CS patients (28.0%) being current or ex-smokers, vs 392 of the 820 controls (47.8%;  $P = 0.0006$ ). In the subset of CS cases who had a history of smoking, their estimated lifetime consumption ( $8.31 \pm 9.20$  pack-years) was significantly less than that of the controls ( $15.34 \pm 10.84$  pack-years,  $P < 0.003$ ). [Table 3](#) shows the multivariable analysis in all cases and controls who did have a history of smoking; the odds ratio for development of sarcoidosis was 0.94 (95% CI, 0.89, 0.99) per pack-year of smoking.

### FDG-PET scan analysis stratified by smoking history

Pretreatment scans were available for analysis in 78 of 82 of the cases (95.12%), and these data are shown in [Table 4](#). Nonsmokers had more severe myocardial inflammation; the mean SUV of the LV was  $4.2 \pm 8.98$  in the lifetime nonsmokers, vs  $2.89 \pm 2.07$  in patients with a smoking history ( $P < 0.0001$ ).

## Discussion

We found a strong and consistent negative association between smoking history and a very specific phenotype of sarcoidosis (clinically manifest CS). Additionally, nonsmokers had more severe myocardial inflammation on pretreatment FDG-PET scans (greater mean SUV of the LV) compared to



**Figure 1.** Summary of cases and controls. CHASM-CS, Cardiac Sarcoidosis Multi-Center Prospective Cohort Study; OHS, Ontario Health Study.

that of patients with a smoking history. Only one previous publication has looked at the association between smoking and CS. Our group previously published a paper on the finding of a negative association between smoking history and the diagnosis of CS in a case-control study with 43 patients and 36 controls.<sup>10</sup> The controls were patients with cardiac presentations similar to those of the cases who were investigated, and CS was excluded. A point of criticism of the study was that these controls were not “normal” subjects. Hence, the current study follows the approach of the previous study that compared CS risks/exposures to cardiac risks/exposures.<sup>10</sup> Our current findings extend these observations by using a larger number of cases and a control population that is more representative of the source population from which cases were selected. Further, our current study shows the additional novel findings of a dose-dependent relationship of lifetime pack-years of smoking and the risk of CS and important findings on FDG-PET scans.

**Table 1. Baseline demographics of the cohort included in the study**

Characteristics	Cases (n = 82)	Controls (n = 820)	P value
Age, y	54.68 ± 8.72	54.66 ± 8.710	0.988
Race (Caucasian)	79 (96.34)	799 (97.44)	0.473
Sex (female)	37 (45.12)	370 (45.12)	1.000
Hypertension	28 (34.15)	280 (34.15)	1.000
Diabetes	12 (14.63)	120 (14.63)	1.000
Presenting cardiac feature			
VT or cardiac arrest	17 (20.73)		
Sustained Mobitz II and/or third-degree AV block	51 (62.20)		
LV dysfunction	8 (9.76)		
Sustained Mobitz II and/or third-degree AV block + VT	3 (3.66)		
VT + LV dysfunction	2 (2.44)		
All 3	1 (1.22)		

Values are n (%), or mean ± standard deviation, unless otherwise indicated.

AV, atrioventricular; LV, left ventricle; VT, ventricular tachycardia.

Several previous publications have reported on the association between extracardiac sarcoidosis and smoking; the results have not been consistent. Newman et al. recruited 706 newly diagnosed patients with sarcoidosis from 10 centres, and an equal number of age-, race-, and sex-matched control subjects.<sup>4</sup> An independent negative association was found between sarcoidosis and a history of smoking cigarettes (odds ratio 0.65, CI 0.51-0.82).<sup>4</sup> Carlens et al. performed a cohort study of 277,777 men within a cohort of Swedish construction workers who had provided information about tobacco use in 1978-1993.<sup>5</sup> Cross-linkage to the nationwide Swedish Hospital Discharge Register identified 342 cases of sarcoidosis up to 2004. Ever-smoking was associated with a decreased risk of sarcoidosis (risk ratio 0.5; 95% CI, 0.4-0.5).<sup>5</sup> Ungprasert et al. identified 345 incident cases of sarcoidosis and 345 controls.<sup>6</sup> The odds ratio of sarcoidosis, comparing current smokers with never smokers, adjusted for age and sex, was 0.34 (95% CI, 0.23-0.50). The odds ratio of sarcoidosis comparing current smokers with never smokers and former smokers, adjusted for age and sex, was 0.38 (95% CI, 0.26-0.56). The odds of sarcoidosis were not significantly different for former vs never smokers.

The association of sarcoidosis with smoking has not been found in other studies.<sup>7-9</sup> Rivera et al. performed a gene-

**Table 2. Smoking history in cases and controls**

Characteristics	Cases (n = 82)	Controls (n = 820)	P value
History of ever smoking cigarettes (defined as lifetime consumption of > 100 cigarettes)	23 (28.05)	392(47.80)	0.0006
Smoking at time of diagnosis (cases) or age-matched controls)	6 (7.32)	100 (12.20)	0.191
Years of daily smoking	16.07 ± 13.71	19.93 ± 12.92	0.167
Daily quantity of cigarettes	10.75 ± 8.65	16.33 ± 4.21	0.006
Total pack-years	8.31 ± 9.20	15.34 ± 10.84	0.003

Values are n (%) or mean ± standard deviation, unless otherwise indicated.

**Table 3. Multivariable analysis in cases (n =23) and controls (n =392) with history of previous smoking or current smoking and the development of sarcoidosis**

Parameter	Point estimate	95% confidence interval		P value
Age	0.97	0.92	1.03	0.30
Sex (male referent)	0.81	0.34	1.93	0.63
Diabetes	1.78	0.55	5.80	0.34
Hypertension	0.86	0.34	2.23	0.76
Per pack year	0.94	0.89	0.99	0.03

environment interaction study in a Swedish case-control study of 3713 individuals.<sup>9</sup> Prior to adjusting for genes, no association was found between ever smoking and never smoking and sarcoidosis. Patients with certain alleles who also had a smoking history were at significantly increased risk of having sarcoidosis. A point to note is that smoking habits in cases and controls were assessed by 2 different questionnaires, and the authors did not use the 100-cigarette cutoff for defining never smoking.<sup>9</sup> A study from India matched (age, sex, and religion) 98 newly diagnosed cases of sarcoidosis and 196 controls and found that smoking was not associated with sarcoidosis.<sup>7</sup> Hattori et al. retrospectively identified 388 patients newly diagnosed with sarcoidosis between 2000 and 2008.<sup>8</sup> The results of 2 surveys of smoking prevalence in Japan provided reference data. Apart from men in their 30s, the prevalence of smoking in patients with sarcoidosis was higher, compared with that in the general Japanese population.<sup>8</sup>

The conflicting results may, at least in part, be explained by differences in race between cohorts, the heterogeneity of sarcoidosis populations, and methodologic issues. However, of note, is that the results in the studies with higher-quality methodology show a consistent negative association of smoking with sarcoidosis.<sup>4-6</sup> The explanation for this association is unclear; it may be due to residual confounding. However, a number of additional pieces of evidence suggest that there is a direct association. Perhaps the most important is a recent, randomized, double-blind, controlled pilot trial of daily nicotine transdermal patch treatment or placebo patch use for 24 weeks, in 50 patients with active pulmonary sarcoidosis.<sup>13</sup> Nicotine treatment was associated with a clinically significant, approximately 2.1% (70 mL) improvement in forced vital capacity from baseline to 26 weeks.<sup>13</sup> Additional findings supporting the association between sarcoidosis and smoking come from observations of similar autoimmune diseases, and results from basic science laboratories. For example, a consistent negative association has been found between smoking and ulcerative colitis,<sup>14</sup> along with data suggesting a positive benefit of nicotine replacement.<sup>15,16</sup> Evidence does suggest that smoking may reduce macrophage activation post-dust exposure.<sup>15,17</sup> Smoking may also exert its protective effects through lymphocyte modulation, as studies have shown that lymphocyte activation may be associated with pulmonary sarcoidosis.<sup>18,19</sup> Supporting this theory are data suggesting that cluster of differentiation CD4/CD8 lymphocyte counts in bronchoalveolar lavage specimens are lower in smokers with sarcoidosis, compared with those in

**Table 4. Patients stratified by lifetime smoking status**

Characteristic	Never smoker (n = 59)	Current or ex-smoker (n = 23)	P value
Age at presentation of CS y	55.05 ± 8.80	55.03 ± 10.33	0.95
Race (Caucasian)	26/59 (44.07)	11/23 (47.83)	0.76
Sex (Female)			
Prior history of extracardiac sarcoidosis			
Hypertension	21/59 (35.59)	7/23 (30.43)	0.66
Diabetes	8/59 (13.56)	4/23 (17.39)	0.66
Presenting cardiac feature			
Sustained Mobitz II and/or third-degree AV	24 (40.68)	12 (52.17)	0.56
VT	11 (18.64)	4 (17.39)	0.91
Both	2 (3.39)	0 (0.00)	0.37
Other	26 (44.07)	7 (30.43)	0.45
Pre-immunosuppressant cardiac PET data			
Discrete LV areas with increased FDG uptake	5.11 ± 3.49	4.36 ± 4.02	0.41
LV SUV <sub>max</sub>	8.20 ± 4.25	6.86 ± 3.85	0.65
Mean SUV of the LV	4.20 ± 8.98	2.89 ± 2.07	< 0.001
RV FDG uptake	20/53 (36.36)	7/22 (31.82)	0.05
SPRS	4.64 ± 5.32	6.50 ± 6.54	0.23
LVEF	45.71 ± 14.47	46.86 ± 12.84	0.51
Pre-immunosuppressant whole-body FDG uptake			
Cervical lymph nodes	17/53 (32.08)	6/22 (27.27)	0.68
Thoracic lymph nodes	42/53 (79.25)	17/22 (77.27)	0.85
Abdominal lymph nodes	23/53 (43.40)	9/22 (40.91)	0.84
Lymph nodes (any)	43/53 (81.13)	18/22 (81.82)	0.94
Lungs	23/53 (43.40)	10/22 (45.45)	0.87
Spleen	12/53 (22.64)	4/22 (18.18)	0.67
Liver	5/53 (9.43)	4/22 (18.18)	0.29
Bone	11/53 (20.75)	7/22 (31.82)	0.31
Neurologic	0/53	0/22	1.00
Skin/subcutaneous (PET findings)	1/53 (1.89)	0/22	0.52
Number of organs involved	2.11	1.95	0.26

Values are n (%), n/N (%), or mean ± standard deviation, unless otherwise indicated.

AV, atrioventricular; CS, cardiac sarcoidosis; FDG, <sup>18</sup>F-fluorodeoxyglucose; LV, left ventricle; LVEF, left ventricular ejection fraction; PET, positron emission tomography; RV, right ventricle; SPRS, summed perfusion rest score; SUV<sub>max</sub>, maximum standard uptake value; VT, ventricular tachycardia.

nonsmokers with sarcoidosis.<sup>18,19</sup> In addition, nicotine has been linked with regulation of T cell-mediated inflammation via the cholinergic pathway.<sup>20</sup>

We also found in the current study that nonsmokers had more severe myocardial inflammation (greater mean SUV of the LV) than did patients with a smoking history. This relationship between disease severity assessed by FDG-PET scanning and smoking status has not been previously reported. However, other studies have explored the severity of sarcoidosis, using other metrics and smoking status. Valeyre et al. assessed 64 patients with pulmonary sarcoidosis, at presentation and after a 1-year follow-up period and found that clinical, radiographic, and functional abnormalities were similar in smokers and nonsmokers.<sup>19</sup> In a study of 384 newly diagnosed sarcoidosis patients from Japan, a trend for lung parenchymal involvement was found to be greater in current smokers than in never smokers.<sup>8</sup> In a US study of 518 patients, smokers also were found to have a higher incidence of extrapulmonary involvement, compared with that of nonsmokers.<sup>21</sup>

Our study has several limitations. First, we cannot exclude the possibility that the observation is because of residual confounding. Second, we attempted to control for socioeconomic status by matching postal codes, an approach that is somewhat controversial. Unfortunately, we did not have access to appropriate data to allow use of reliable measures such as income or education level. Another issue is the moderate sample size. We did, however, have a quite distinct and very homogeneous phenotype to study, in marked contrast to other epidemiologic studies that have included a broad range of phenotypes, geographies, and racial groupings.<sup>22,23</sup> Finally, we cannot exclude the differential effects of recall bias (and other forms of bias) in the cases and controls; the case group, for example, may be more likely to underestimate their smoking levels, owing to feelings of shame.

## Conclusions

We found a strong negative association between smoking history and a very specific phenotype of sarcoidosis (clinically manifest CS). Additionally, nonsmokers had more severe myocardial inflammation (greater mean SUV of the LV) than patients with a smoking history. Further research is needed to understand these associations and whether they have therapeutic potential (eg, nicotine-replacement therapy).

## Funding Sources

This work has been supported partially by the Canadian Institute of Health Research (D.H.B., Nominated Principal Investigator; grant no. 342139, NCT01477359). R.B. holds the Vered Chair in Cardiology at the University of Ottawa Heart Institute and is a distinguished Chair of Cardiovascular Research at Ottawa Faculty of Medicine. D.B. holds a University of Ottawa Faculty of Medicine Tier 1 Clinical Research Chair in Cardiac Electrophysiology. The other authors have no funding sources to declare.

## Disclosures

R.B. has received grants and honoraria in the past 2 years from General Electric Healthcare Systems, Lantheus Medical

Imaging, and Jubilant DraxImage; these are not related directly to this project. The other authors have no conflicts of interest to disclose.

## Acknowledgements

The authors thank the participants in the Ontario Health Study (OHS). The data used for this research were made available by the OHS with financial support from the Canadian Partnership Against Cancer and Health Canada, and the Ontario Institute for Cancer Research. The authors express gratitude to the Cardiac Sarcoidosis Multi-Center Prospective Cohort Study (CHASM-CS) team, including Janine Ryan, Keri O'Reilly, Karen MacDonald, Sali Kalif, Tammy Knight, and Owen Clarkin. Thanks to Jordan Bernick for statistical support.

## References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007;357:2153-65.
2. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;11:1305-23.
3. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. *J Am Coll Cardiol* 2016;68:411-21.
4. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med* 2004;170:1324-30.
5. Carlens C, Hergens MP, Grunewald J, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. *Am J Respir Crit Care Med* 2010;181:1217-22.
6. Ungprasert P, Crowson CS, Matteson EL. Smoking, obesity and risk of sarcoidosis: a population-based nested case-control study. *Respir Med* 2016;120:87-90.
7. Gupta D, Singh AD, Agarwal R, et al. Is tobacco smoking protective for sarcoidosis? A case-control study from North India. *Sarcoidosis Vasc Diffuse Lung Dis* 2010;27:19-26.
8. Hattori T, Konno S, Shijubo N, Ohmichi M, Nishimura M. Increased prevalence of cigarette smoking in Japanese patients with sarcoidosis. *Respirology* 2013;18:1152-7.
9. Rivera NV, Patasova K, Kullberg S, et al. A gene-environment interaction between smoking and gene polymorphisms provides a high risk of two subgroups of sarcoidosis. *Sci Rep* 2019;9:18633.
10. Spence SD, Medor MC, Nery PB, et al. Exploring occupational, recreational, and environmental associations in patients with clinically manifest cardiac sarcoidosis. *CJC Open* 2020;2:585-91.
11. Juneau D, Nery P, Russo J, et al. How common is isolated cardiac sarcoidosis? Extra-cardiac and cardiac findings on clinical examination and whole-body (18)F-fluorodeoxyglucose positron emission tomography. *Int J Cardiol* 2018;253:189-93.
12. Kandolin R, Lehtonen J, Airaksinen J, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation* 2015;131:624-32.
13. Crouser ED, Smith RM, Culver DA, et al. A pilot randomized trial of transdermal nicotine for pulmonary sarcoidosis. *Chest* 2021;160:1340-9.

14. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006;81:1462-71.
15. Pullan RD, Rhodes J, Ganesh S, et al. Transdermal nicotine for active ulcerative colitis. *N Engl J Med* 1994;330:811-5.
16. Julian MW, Shao G, Schlesinger LS, et al. Nicotine treatment improves Toll-like receptor 2 and Toll-like receptor 9 responsiveness in active pulmonary sarcoidosis. *Chest* 2013;143:461-70.
17. Moller W, Barth W, Kohlhauf M, Haussinger K, Kreyling WG. Motion and twisting of magnetic particles ingested by alveolar macrophages in the human lung: effect of smoking and disease. *Biomagn Res Technol* 2006;4:4.
18. Moller W, Barth W, Pohlitz W, et al. Smoking impairs alveolar macrophage activation after inert dust exposure. *Toxicol Lett* 1996;88:131-7.
19. Valeyre D, Soler P, Clerici C, et al. Smoking and pulmonary sarcoidosis: effect of cigarette smoking on prevalence, clinical manifestations, alveolitis, and evolution of the disease. *Thorax* 1988;43:516-24.
20. Drent M, van Velzen-Blad H, Diamant M, Hoogsteden HC, van den Bosch JM. Relationship between presentation of sarcoidosis and T lymphocyte profile. A study in bronchoalveolar lavage fluid. *Chest* 1993;104:795-800.
21. Krell W, Bourbonnais JM, Kapoor R, Samavati L. Effect of smoking and gender on pulmonary function and clinical features in sarcoidosis. *Lung* 2012;190:529-36.
22. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001;164:1885-9.
23. Schupp JC, Freitag-Wolf S, Bargagli E, et al. Phenotypes of organ involvement in sarcoidosis. *Eur Respir J* 2018;51:1700991.

### Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2022.06.001>.