ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

Prevalence and characteristics of self-reported hypothyroidism and its association with nonorgan-specific manifestations in US sarcoidosis patients: a nationwide registry study

Bashar N. Alzghoul[1], Farah N. Amer[2], Diana Barb[3], Ayoub Innabi[1], Mamoun T. Mardini[4,5], Chen Bai[4], Bara Alzghoul[6], Tamara Al-Hakim[7], Noopur Singh[7], Mindy Buchanan[7], Leslie Serchuck[7], Diana Gomez Manjarres[1], Whitney W. Woodmansee[3], Lisa A. Maier[8,9] and Divya C. Patel[1]

ABSTRACT Little is known about the prevalence, clinical characteristics and impact of hypothyroidism in patients with sarcoidosis. We aimed to determine the prevalence and clinical features of hypothyroidism and its relation to organ involvement and other clinical manifestations in patients with sarcoidosis.

We conducted a national registry-based study investigating 3835 respondents to the Sarcoidosis Advanced Registry for Cures Questionnaire between June 2014 and August 2019. This registry is based on a self-reported, web-based questionnaire that provides data related to demographics, diagnostics, sarcoidosis manifestations and treatment. We compared sarcoidosis patients with and without self-reported hypothyroidism. We used multivariable logistic regression and adjusted for potential confounders to determine the association of hypothyroidism with nonorgan-specific manifestations.

14% of the sarcoidosis patients self-reported hypothyroidism and were generally middle-aged white women. Hypothyroid patients had more comorbid conditions and were more likely to have multiorgan sarcoidosis involvement, especially with cutaneous, ocular, joints, liver and lacrimal gland involvement. Self-reported hypothyroidism was associated with depression (adjusted odds ratio (aOR) 1.3, 95% CI 1.01–1.6), antidepressant use (aOR 1.3, 95% CI 1.1–1.7), obesity (aOR 1.7, 95% CI 1.4–2.1), sleep apnoea (aOR 1.7, 95% CI 1.3–2.2), chronic fatigue syndrome (aOR 1.5, 95% CI 1.2–2) and was borderline associated with fibromyalgia (aOR 1.3, 95% CI 1–1.8). Physical impairment was more common in patients with hypothyroidism.

Hypothyroidism is a frequent comorbidity in sarcoidosis patients that might be a potentially reversible contributor to fatigue, depression and physical impairment in this population. We recommend considering routine screening for hypothyroidism in sarcoidosis patients especially in those with multiorgan sarcoidosis, fatigue and depression.

@ERSpublications
Hypothyroidism is a frequent comorbidity in sarcoidosis patients, is often associated with sarcoidosis multiorgan involvement, and might be a potentially reversible contributor to fatigue, depression and physical impairment in this population https://bit.ly/2XGdjKg

Cite this article as: Alzghoul BN, Amer FN, Barb D, *et al.* Prevalence and characteristics of self-reported hypothyroidism and its association with nonorgan-specific manifestations in US sarcoidosis patients: a nationwide registry study. *ERJ Open Res* 2021; 7: 00754-2020 [https://doi.org/10.1183/23120541.00754-2020].

This article has supplementary material available from openres.ersjournals.com.

Received: 16 Oct 2020 | Accepted: 24 Dec 2020

Introduction

Sarcoidosis can pose a devastating impact on healthcare-related quality of life (HRQoL) and can have significant manifestations that appear to be nonorgan specific, such as fatigue and depression [1]. Due to multiorgan involvement and the frequent comorbidities associated with sarcoidosis and its treatment, it can be challenging to determine whether such manifestations are related to sarcoidosis or another comorbid condition [2].

Autoimmune diseases are known to be associated with sarcoidosis; some have theorised that sarcoidosis itself may be an autoimmune process [3, 4]. This link with autoimmune conditions perhaps explains the association previously described between sarcoidosis and autoimmune thyroid disorders, albeit in small studies or case series [5]. The exact prevalence and characteristics of hypothyroidism in sarcoidosis is unknown [5–7]. A recent nationwide Taiwanese study found that 12% of sarcoidosis patients had an autoimmune thyroid disorder [3].

Hypothyroidism has been linked to depression [8, 9], obesity [10], sleep apnoea [11], chronic fatigue [12] and fibromyalgia [13] in the general population. Many patients with sarcoidosis suffer from these same problems that are thought to be nonorgan specific. Interestingly, in a study evaluating idiopathic pulmonary fibrosis patients, another type of interstitial lung disease, 17% had hypothyroidism and it was found to be a predictor of mortality [14]. However, the contribution of hypothyroidism to the disease manifestations, morbidity and mortality in sarcoidosis is unknown. Understanding the links between hypothyroidism and sarcoidosis may lead to clearer understanding of the pathogenesis of sarcoidosis. It may also help clinicians to understand the factors affecting HRQoL in sarcoidosis.

In this study, we sought to determine the prevalence of hypothyroidism in a self-reported nationwide sarcoidosis registry from the United States. We also aimed to characterise the clinical features and cluster of organ involvement in sarcoidosis patients who also have hypothyroidism and to study the possible association of self-reported hypothyroidism with nonorgan-specific manifestations such as depression and fatigue.

Methods

Study population

We conducted a national registry-based study investigating 3835 respondents to the Foundation for Sarcoidosis Research (FSR) Sarcoidosis Advanced Registry for Cures Questionnaire (SARC) [15]. This registry from FSR was open to all English-speaking patients self-identifying as having sarcoidosis *via* a web-based questionnaire that includes 72 questions. Respondents were either directly recruited through their treating physicians, by the FSR or *via* national and international organisations. It provides an observational cohort platform to collect cross-sectional and longitudinal self-reported data related to demographics, diagnostics, organ involvement, treatment and the physical and psychosocial impact of sarcoidosis. We included patient surveys completed between June 2014 and August 2019. Respondents were able to update their surveys longitudinally with time. Data from the most recent survey for each respondent were used for our analysis. We excluded 13 patients who were reported to be deceased or had missing information regarding the question "is the patient living" bringing the final cohort to a total of 3822 respondents. The study was approved by the University of Florida Institutional Review Board (no. 201902211).

Objectives and data management

The primary objective of the study was to define the prevalence of self-reported hypothyroidism in patients with sarcoidosis. Secondary objectives were to determine the demographic and clinical characteristics of the sarcoidosis patients who reported hypothyroidism; and to study the association of hypothyroidism with the physical and nonorgan-specific manifestations of sarcoidosis. We divided the

Affiliations: [1]Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, Gainesville, FL, USA. [2]Dept of Internal Medicine, University of Central Florida/North Florida Regional Medical Center, Gainesville, FL, USA. [3]Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL, USA. [4]Dept of Health Outcomes and Biomedical Informatics, College of Medicine, University of Florida, Gainesville, FL, USA. [5]Dept of Aging and Geriatric Research, College of Medicine, University of Florida, Gainesville, FL, USA. [6]Dept of Internal Medicine, University of Kentucky, Lexington, KY, USA. [7]Foundation for Sarcoidosis Research, Chicago, IL, USA. [8]Division of Environmental and Occupational Health Sciences, National Jewish Health, Denver, CO, USA. [9]Division of Pulmonary Sciences and Critical Care Medicine, Dept of Medicine, School of Medicine, Dept of Environmental/Occupational Health, Colorado School of Public Health, University of Colorado Anschutz Campus, Aurora, CO, USA.

Correspondence: Divya C. Patel, PO BOX 10025, Gainesville, FL 32610-0225, USA.
E-mail: divya.patel@medicine.ufl.edu

patients into two groups: those who self-reported hypothyroidism and those who did not report hypothyroidism based on a response to a question in the survey regarding hypothyroidism (supplementary table 1). We compared the following data between the two groups and reported it in three categories: 1) patient characteristics, diagnosis and treatment of sarcoidosis; 2) organ involvement and comorbidities developed after the diagnosis of sarcoidosis; and 3) data regarding the physical impairment and nonorgan-specific manifestations of the disease. The responses "unsure" or "prefer not to answer" were labelled as missing information. Only complete cases were analysed for each variable. In each table, we presented the nominator (positive cases) and denominator (complete cases) for each categorical variable. Data missingness was <2% for demographics, <1% for insurance status, 19.8% for education, 22.7% for income, 9.7% for hospitalisation history, <1% for steroid use history, 35.7% for cytotoxic agent use history, 47% for tumour necrosis factor (TNF) inhibitor use history and <2% for comorbid conditions. Missing data regarding organ involvement ranged from 11% for lung involvement to 36.8% for bone involvement. The question regarding endocrine and vitamin D disorders was a tick-box format so cases with empty boxes were regarded as negative (supplementary table 1).

Patients reported comorbidities that have newly developed after the diagnosis of sarcoidosis. We divided newly developed comorbidities into those probably related to sarcoidosis itself (cancer, chronic fatigue syndrome, chronic pain syndrome, congestive heart failure, depression, fibromyalgia, lymphoma and sleep disorders) and those probably related to the use of corticosteroids (diabetes mellitus, cataracts, glaucoma, obesity, hypertension, osteoporosis/osteopenia and sleep apnoea) [16]. Multiorgan sarcoidosis was defined by the reported presence of three or more organs affected by sarcoidosis [1, 17]. Systemic medications used to treat sarcoidosis were divided into four categories: 1) steroids (prednisone, methylprednisolone, dexamethasone); 2) cytotoxic agents (hydroxychloroquine, chloroquine, methotrexate, azathioprine, leflunomide, mycophenolate, cyclophosphamide); 3) TNF inhibitors (infliximab, adalimumab, certolizumab, golimumab, etanercept); and 4) other systemic therapies (rituximab, pentoxifylline, intravenous Ig, thalidomide, adrenocorticotropic hormone).

We studied the association between self-reported hypothyroidism and the following comorbidities: self-reported depression, chronic fatigue syndrome, fibromyalgia, sleep apnoea, sleep disorders and obesity. We also looked at whether hypothyroidism was associated with patient reports of feeling depressed always or often, using antidepressant medications and reporting feeling tired always or often. To investigate physical impairment and social impact, questions regarding use of any mobility assistive device, employment-based disability, missing more than seven work days in the past year and impact on job termination were analysed (survey question details in supplementary table 1).

Validation cohort

To validate our results, we queried the University of Florida integrated data repository from January 2011 until September 2020 and identified patients who carry the diagnosis of sarcoidosis with and without hypothyroidism and compared the presence and absence of depression, fatigue, fibromyalgia, obesity and obstructive sleep apnoea based on International Classification of Diseases (ICD) codes. The following ICD codes were used: sarcoidosis (ICD-9=135; ICD-10=D86); hypothyroidism (ICD-9=244; ICD-10=E03); depression (ICD-9=311, 296.2 and 296.3; ICD-10=F32, F33); fatigue (ICD-9=780.7 and ICD-10=R53); fibromyalgia (ICD-9=729.1 and ICD-10=M79.7); obesity (ICD-9=278, ICD-10=E65-E68) and obstructive sleep apnoea ((OSA) ICD-9=327.23 and ICD-10=G47.33).

Data analysis

The distribution of patient characteristics and outcomes were summarised as percentages for categorical variables and mean ±SD for continuous variables. To compare differences between groups, we used an independent sample t-test for continuous variables and Chi-squared test for categorical variables. A clustered bar chart was created to demonstrate the frequencies of other endocrine and vitamin D disorders and different skin manifestations between groups. To study the association between self-reported hypothyroidism and potential nonorgan-related and social manifestations in sarcoidosis patients, multivariable logistic regression was performed adjusted for sex, race, age at diagnosis, use of steroids, multiorgan involvement (as a binary variable) and whether the patient had other sarcoidosis-related comorbidities (as a binary variable). These confounders were selected on an *a priori* basis. We also adjusted for healthcare insurance status with the noted disparity between the two groups and its potential impact on the outcomes. Based on this multivariable logistic regression analysis, we constructed a forest plot to illustrate the odds ratio with 95% confidence intervals of the likelihood of nonorgan-related manifestations in sarcoidosis patients with and without self-reported hypothyroidism. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (released 2015, IBM Corp, Armonk, NY, USA).

Results

Demographics and baseline characteristics

Among the 3822 sarcoidosis patients identified for our analysis, 538 reported hypothyroidism with a prevalence of 14.1%. The patients with self-reported hypothyroidism were generally middle-aged and were slightly older than the nonhypothyroidism patients at the time of sarcoidosis diagnosis (45.1±12.5 *versus* 43.1±13.7 years, p=0.001). The hypothyroidism patients were predominantly white women (table 1). Subgroup analysis showed that the prevalence of hypothyroidism in all white females enrolled in the study was 20% (supplementary table 2). Patients with hypothyroidism were more frequently seen by endocrinologists and other specialised healthcare providers before the diagnosis of sarcoidosis was made. During the course of sarcoidosis, patients with hypothyroidism received systemic corticosteroids more frequently as well as chloroquines, pentoxifylline and intravenous Igs, when compared to patients without hypothyroidism. No significant difference was noted in the use of TNF inhibitors or other cytotoxic agents (table 1 and supplementary figure 1).

Sarcoidosis organ involvement and comorbidities

Sarcoidosis patients with self-reported hypothyroidism also reported more multiorgan involvement (51% *versus* 44%, p<0.001). Other self-reported endocrine and vitamin D disorders are presented in figure 1.

TABLE 1 Baseline demographics and clinical characteristics of sarcoidosis patients with hypothyroidism as compared with patients with no hypothyroidism[#]

	Hypothyroidism	No hypothyroidism	p-value
Demographics			
Patients	538	3284	
Age years[¶]	45.1±12.5	43.1±13.7	0.001
Duration of disease years[¶]	12.3±10.8	11.6±10.9	0.136
Women	486/538 (90)	2326/3284 (71)	<0.001
Race			
African American	41/530 (8)	667/3222 (21)	<0.001
White	480/530 (91)	2521/3222 (78)	<0.001
Other races[+]	10/530 (2)	74/3222 (2)	0.55
Healthcare insurance			
Private health insurance	332/531 (62.5)	1816/3256 (56)	0.004
Government insurance	211/531 (40)	1078/3256 (33)	0.003
No health insurance	55/531 (10)	621/3256 (19)	<0.001
Graduated college or university	284/473 (60)	1394/2594 (54)	0.01
Income USD			0.50
<35000	127/442 (29)	656/2513 (26)	
35000–99999	197/442 (44.5)	1173/2513 (47)	
>100000	118/442 (26.5)	684/2513 (27)	
Healthcare providers seen before sarcoidosis diagnosis was made[§]			
Endocrinologist	115/538 (21)	241/3284 (7)	<0.001
Primary care provider	436/538 (81)	2623/3284 (80)	0.53
Other specialists	451/538 (83)	2569/3284 (78)	0.003
Family history of sarcoidosis	81/446 (18)	476/2707 (18)	0.77
Ever admitted to hospital in relation to sarcoidosis	185/498 (37)	1158/2995 (39)	0.52
Sarcoidosis-specific therapy[f]			
Steroids	416/536 (78)	2356/3262 (72)	0.009
Cytotoxic agents	254/382 (66.5)	1339/2076 (64.5)	0.45
Tumour necrosis factor inhibitors	79/312 (25)	376/1712 (22)	0.19
Others	38/291 (13)	142/1616 (9)	0.007

Data are presented as n, mean±SD or n/N total (%), unless otherwise stated. [#]: Missing values were excluded for each variable. [¶]: Age when the diagnosis of sarcoidosis was made or was extremely likely is reported here. Duration is based on time difference in years between age at time of diagnosis and age at time of survey answering. [+]: Other races include American Indian/Alaska Natives (127), Asian (32), Native Hawaiian/Pacific Islander (9) and others (57). [§]: Primary care providers include family medicine doctors, internists and/or general paediatricians. Other specialists include cardiologists, pulmonologists, dermatologists, gastroenterologists, neurologists, ophthalmologists, psychiatrists and/or rheumatologists. [f]: Steroids: prednisone, methylprednisolone and dexamethasone. Cytotoxic agents: hydroxychloroquine, chloroquine, methotrexate, azathioprine, leflunomide, mycophenolate and cyclophosphamide. Tumour necrosis factor inhibitors: infliximab, adalimumab, certolizumab, golimumab and etanercept. Others: rituximab, pentoxifylline, intravenous Ig, thalidomide, adrenocorticotropic hormone.

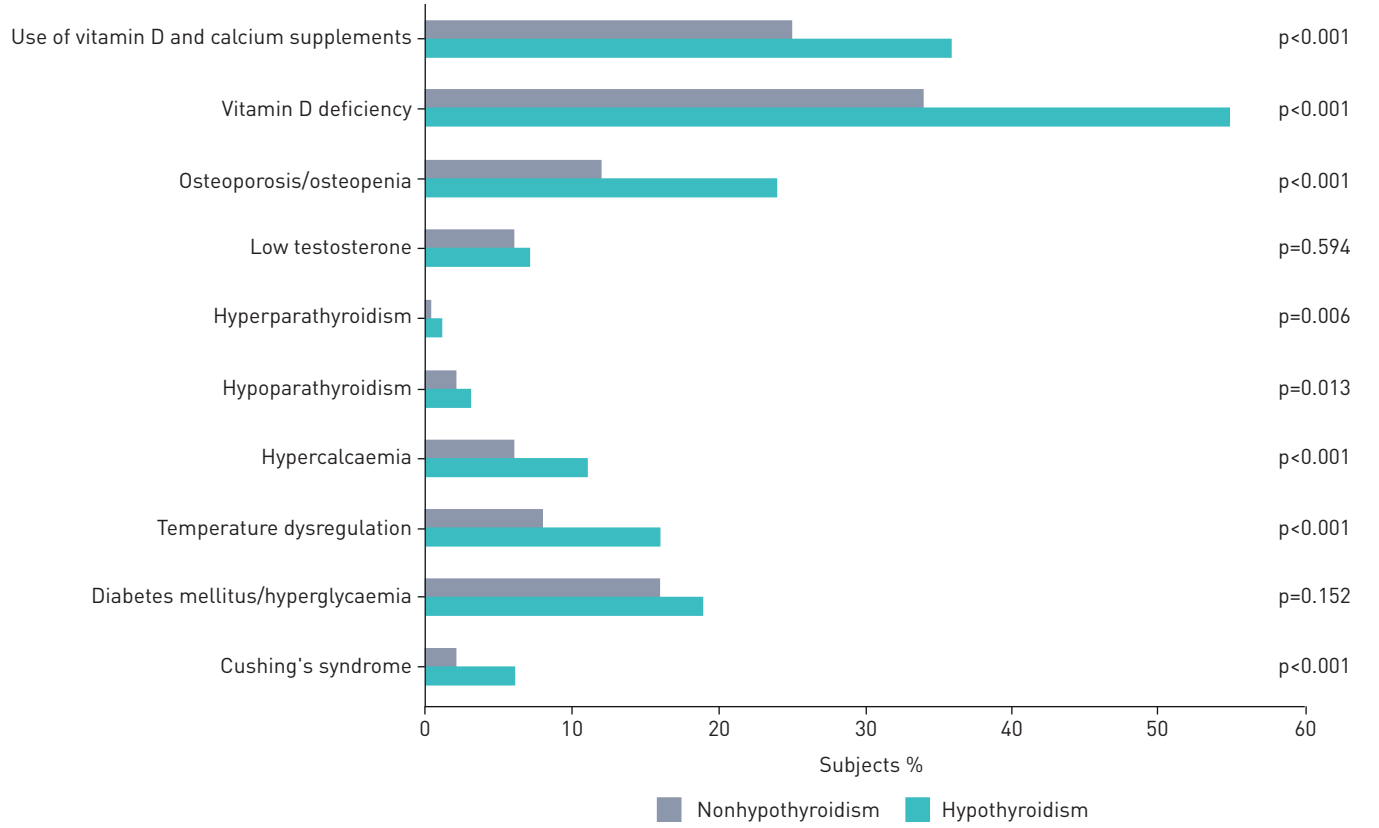

FIGURE 1 Clustered bar chart demonstrating the frequencies of other endocrine and vitamin D disorders in sarcoidosis patients with hypothyroidism as compared with those with no hypothyroidism.

These included disorders related to corticosteroid use and calcium metabolism. Furthermore, hypothyroid patients had more skin, joint, eye, liver and lacrimal gland sarcoidosis-related manifestations (table 2). Although there was no difference in the prevalence of pulmonary sarcoidosis, respondents with self-reported hypothyroidism reported more use of home ventilators and noninvasive positive pressure ventilation machines (31% *versus* 24%, p=0.001; data not shown). The cutaneous sarcoidosis manifestations that were more common in the hypothyroid group included abnormal skin pigmentation, erythema nodosum, lupus pernio, papules, plaques and *s.c.* nodules around scars and tattoos (supplementary figure 2). Additionally, the hypothyroid group had more frequent comorbidities either related to sarcoidosis disease or to steroids use (table 2).

Physical impairment and nonorgan-specific manifestations

On univariable analysis, when compared to patients with absence of hypothyroidism, patients with self-reported hypothyroidism were more likely to report depression, obesity, sleep disorders, sleep apnoea, chronic fatigue syndrome and fibromyalgia. They also reported using antidepressants, feeling depressed most of the time and feeling tired most of the time more frequently when compared to patients without hypothyroidism (table 3). Adjusting for baseline demographics and potential confounders including corticosteroids use in multivariable logistic regression analysis, self-reported hypothyroidism was associated with depression (adjusted odds ratio (aOR) 1.3, 95% CI 1.01–1.6), antidepressant use (aOR 1.3, 95% CI 1.1–1.7), obesity (aOR 1.7, 95% CI 1.4–2.1), sleep apnoea (aOR 1.7, 95% CI 1.3–2.2), chronic fatigue syndrome (aOR 1.5, 95% CI 1.2–2) and was borderline associated with fibromyalgia (aOR 1.3, 95% CI 1–1.8) (table 3 and figure 2). Furthermore, hypothyroidism was associated with employment-based disability, missing work days and disease-related job termination in univariable analysis but only with missing work days when adjusting for potential confounders (table 3).

Validation cohort results

Using the University of Florida database, we identified 2189 adult sarcoidosis patients, of which 1324 (60.5%) were female, 834 (38%) were African American and 328 (15%) also carried the diagnosis of hypothyroidism. Hypothyroidism patients were mainly female (75%) and white (65%). Compared to

TABLE 2 Sarcoidosis involvement of other organs as reported by sarcoidosis patients with hypothyroidism as compared to those with no hypothyroidism[#]

	Hypothyroidism	No hypothyroidism	p-value
Patients	538	3284	
Multiorgan sarcoidosis ⩾3 organs[¶]	276/532 (52)	1444/3154 (46)	0.009
Lungs	377/492 (77)	2201/2909 (76)	0.64
Bones or vertebrae	43/352 (12)	234/2062 (11)	0.64
Brain or cranial nerves	51/351 (14.5)	275/2077 (13)	0.51
Peripheral nerves	105/387 (27)	518/2234 (23)	0.09
Central lymph nodes[+]	282/431 (65)	1431/2457 (58)	0.005
Peripheral lymph nodes[§]	122/391 (31)	623/2210 (28)	0.23
Eyes	138/405 (34)	604/2318 (26)	0.001
Cardiac	59/384 (15)	335/2196 (15)	0.96
Joints	141/408 (35)	632/2314 (27)	0.003
Kidneys	33/350 (9)	163/2047 (8)	0.36
Parotid or lacrimal glands	35/351 (10)	130/1985 (6.5)	0.02
Stomach/intestines	34/360 (9)	153/2080 (7)	0.17
Liver	72/367 (20)	312/2125 (15)	0.02
Spleen	51/356 (14)	287/2064 (14)	0.83
Muscles	39/355 (11)	209/2079 (10)	0.59
Sinuses	45/363 (12)	216/2149 (10)	0.18
Skin	167/412 (40.5)	750/2308 (32.5)	0.001
Newly arising comorbidities after sarcoid diagnosis[f]			
Probably sarcoid-related	274/498 (55)	1352/3284 (41)	<0.001
Probably steroid-related	284/498 (57)	1377/3284 (42)	<0.001

Data are presented as n or n/N total (%), unless otherwise stated. [#]: Patients were asked whether or not the organ involvement is a confirmed diagnosis, suspected or if they were unsure. Prevalence presented in this table is based on confirmed diagnosis only as reported by the patients. For this analysis, answers suspected or "not involved" were regarded as "not involved". "Unsure" or missing were regarded as missing values. [¶]: Multiorgan sarcoidosis defined if three or more organs were involved. [+]: Lymph nodes in the chest and abdomen. [§]: Axillary, cervical and inguinal lymph nodes. [f]: Probably sarcoid-related: cancer, chronic fatigue syndrome, chronic pain syndrome, congestive heart failure, depression, fibromyalgia, lymphoma and sleep disorders; probably steroid-related: diabetes mellitus, cataracts, glaucoma, obesity, hypertension, osteoporosis/osteopenia and sleep apnoea.

sarcoidosis patients without hypothyroidism, hypothyroidism patients significantly had more depression (OR 2.6, 95% CI 2–3.4), fatigue (OR 2.1, 95% CI 1.7–2.7), fibromyalgia (OR 2.8, 95% CI 2–3.9), obesity (OR 1.7, 95% CI 1.3–2.2) and OSA (OR 1.9, 95% CI 1.4–2.4) (supplementary table 3).

Discussion

To our knowledge, this is the largest study in the published literature to assess the prevalence, characteristics and potential impact of hypothyroidism in sarcoidosis patients [3, 6, 7, 18–24]. Our study shows that 14% of sarcoidosis patients reported hypothyroidism. These patients were mainly middle-aged white females. Hypothyroidism was more likely to be reported in sarcoidosis with multiorgan involvement, especially when involving the skin, joints, eyes, liver and/or the lacrimal glands. Furthermore, self-reported hypothyroidism was associated with depression, fatigue, obesity, sleep apnoea and physical impairment.

In this nationwide sarcoidosis cohort, the reported prevalence of self-reported hypothyroidism is remarkably higher than what is reported in the general population, which ranges between 3% and 7% in the United States [12]. Notably, sarcoidosis patients with hypothyroidism had a similar demographic profile as the general population of hypothyroidism patients [12]. Our prevalence is similar to what has been observed in other smaller sarcoidosis cohorts. Antonelli *et al.* [6] reported 17% prevalence of subclinical hypothyroidism and 5% prevalence of overt hypothyroidism in sarcoidosis patients from Italy. Malli *et al.* [7] reported a 15% prevalence in a cohort from Greece. In a nationwide case–control study from Taiwan looking at sarcoidosis comorbid conditions, the prevalence of autoimmune thyroid disease was around 12% [3].

Our study does not answer the question of whether hypothyroidism is caused by autoimmune thyroiditis, direct sarcoidosis infiltration of the thyroid gland, other causes or is multifactorial. Although direct evidence of autoimmunity as the cause of sarcoidosis is lacking, associations with autoimmune conditions,

TABLE 3 Physical impairment and psychosocial impact of hypothyroidism in patients with sarcoidosis

	Hypothyroidism	No hypothyroidism	Adjusted odds ratio (95% CI)[#]
Patients n	538	3284	
Psychosomatic impact			
Depression[¶]	141/489 (29)	748/3284 (23)	1.3 (1.01–1.6)
Feeling depressed[+]	167/504 (33)	794/2781 (29)	1.1 (0.9–1.4)
Use of antidepressants[§]	204/530 (39)	872/3210 (27)	1.3 (1.1–1.7)
Obesity	125/489 (26)	544/3284 (17)	1.7 (1.4–2.1)
Sleep apnoea	132/489 (27)	559/3077 (18)	1.7 (1.3–2.2)
Chronic fatigue syndrome	138/491 (28)	590/3284 (18)	1.5 (1.2–2)
Feeling tired[+]	434/508 (85)	2218/2801 (79)	1.1 (0.8–1.5)
Fibromyalgia	89/484 (18)	325/3284 (10)	1.3 (0.97–1.8)
Physical impairment and social impact			
Use of mobility assistive devices[f]	99/538 (18)	478/3277 (15)	1.1 (0.8–1.4)
Employment-based disability	164/514 (32)	747/3207 (23)	1.2 (0.95–1.5)
Missing more than 7 work days in the past year	155/280 (55)	796/1749 (46)	1.2 (1.02–1.6)
Job termination due to illness	159/391 (41)	791/2321 (34)	1.1 (0.9–1.4)

Data are presented as n or n/N total (%), unless otherwise stated. [#]: Multivariable logistic regression analysis adjusted for sex, race, age at diagnosis, healthcare insurance status, use of steroids, multiorgan involvement and other sarcoidosis-related comorbidities (cancer, chronic pain syndrome, congestive heart failure and lymphoma). The effective sample size that was kept in the adjusted complete-case analyses was 92% for depression, 81% for "feeling depressed", 90% for antidepressants use, 92% for obesity, 87% for sleep apnoea, 92% for chronic fatigue syndrome, 82% for "feeling tired", 92% for fibromyalgia, 92% for "use of mobility device", 90% for disability, 51% for work days missing and 67% for job termination. [¶]: Depression disorder developed after the diagnosis of sarcoidosis as reported by respondents. [+]: Feeling depressed or feeling tired defined if patient answered feeling tired/depressed often or always. [§]: Antidepressants reported include citalopram (Celexa), fluoxetine (Prozac), escitalopram (Lexapro), fluvoxamine (Luvox), duloxetine (Cymbalta), venlafaxine (Effexor), paroxetine (Paxil) and sertraline (Zoloft). [f]: Mobility assistive devices include canes, scooters, walkers and wheelchairs.

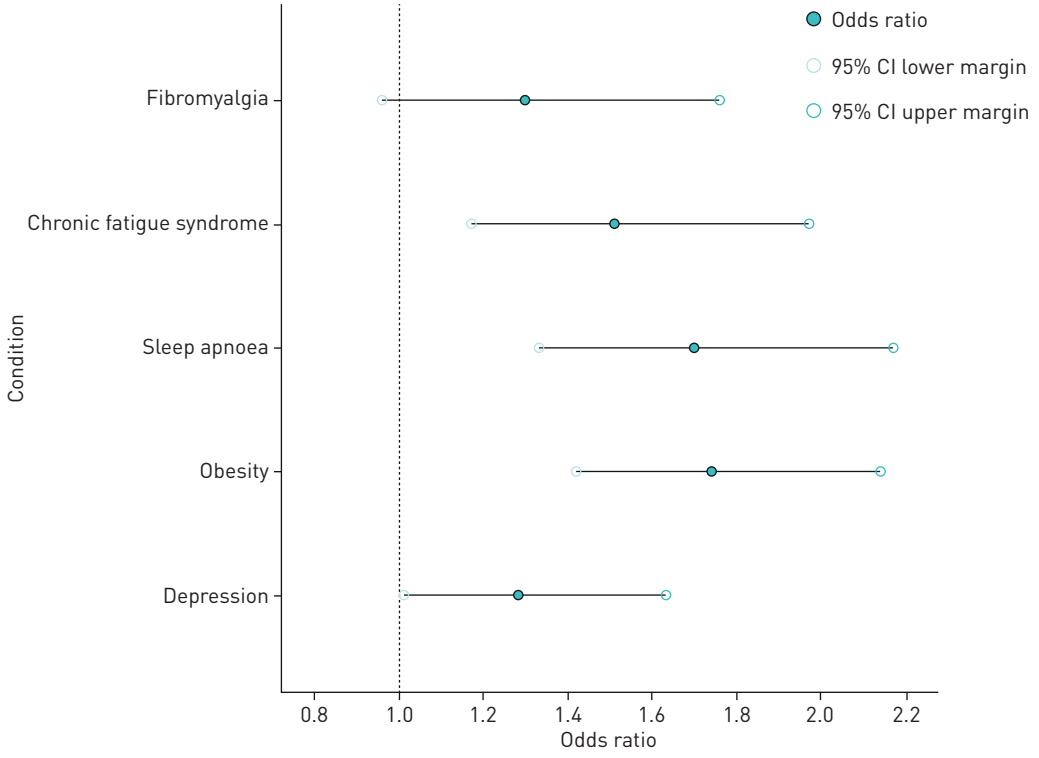

FIGURE 2 Forest plot showing the adjusted odds ratio of the likelihood of different nonorgan-specific conditions in patients with sarcoidosis who also have hypothyroidism *versus* those with no hypothyroidism. Odds ratio with confidence intervals are based on multivariable logistic regression analysis adjusted for sex, race, age at diagnosis, healthcare insurance status, use of steroids, multiorgan involvement and other sarcoidosis-related comorbidities (cancer, chronic pain syndrome, congestive heart failure and lymphoma).

including thyroid disease, have been noted [3, 4, 24]. Enhanced T-cell immunity along with loss of T-cell tolerance to self-antigens and possible exogenous antigenic exposure have all been proposed to play a role in the pathophysiology of sarcoidosis [4, 25]. Additionally, the increase in circulating Igs and the possible response to B-cell-depleting therapy in refractory cases might also suggest a role of the humoral immune system [26]. Recently, sarcoidosis patients were found to have elevated levels of age-associated B-cells in their blood and bronchoalveolar lavage as compared to healthy subjects, supporting the role of B-cell immunity [27]. This autoimmune phenomenon in sarcoidosis might explain the higher prevalence of hypothyroidism noted in our sarcoidosis cohort as compared to the general population. Previous studies have also shown that sarcoidosis patients have higher levels of thyroid peroxidase antibodies [19] and/or thyroglobulin antibodies [19, 20] when compared to control subjects, which might have a pathophysiological role in the association between sarcoidosis and autoimmune thyroid disease [5]. Another possible mechanism of hypothyroidism in sarcoidosis is direct granulomatous thyroid infiltration, which is reported in around 4% in autopsy studies of systemic sarcoidosis patients [5, 28]. Various treatments for sarcoidosis, including systemic use of steroids or other immunosuppression treatments, can alter thyroid function tests [29]. High doses of systemic steroids can reduce thyroid-stimulating hormone levels but this effect is usually transient and reversible and not typically associated with clinical central hypothyroidism [29]. Other immune suppressing agents such as cyclophosphamide [30], infliximab [31] and chloroquine [32] have been reported to cause hypothyroidism. In our analysis, patients with self-reported hypothyroidism were more likely to have received corticosteroids, chloroquines, pentoxifylline and intravenous Ig when compared to sarcoidosis patients without hypothyroidism, which might suggest a potential contribution from medications in hypothyroidism, and or to treat associated organ involvement.

A novel finding in our study is the link that we noted between self-reported hypothyroidism and multiorgan involvement of sarcoidosis. It is unclear from our analysis whether the same mechanism underlying the development of multiorgan sarcoidosis also underlies the development of hypothyroidism; autoimmunity has been postulated as a mechanism for development of nonpulmonary disease although an exuberant antigen-driven immune response is often noted in multiorgan disease [33]. Other than the lungs and lymphatic system, the most common organ systems reported to be involved with sarcoidosis in the self-reported hypothyroid group were the skin, joints and eyes. The association with cutaneous sarcoidosis was previously reported by Anolik *et al.* [22] who linked the development of thyroid disorders with cutaneous sarcoidosis, although the underlying mechanisms of this association are not clear.

Nonorgan-specific symptoms and social and physical impairment related to sarcoidosis can have a large burden on the patients' HRQoL. Sarcoidosis-associated fatigue is a challenging problem that is common in sarcoidosis [2]. It is likely multifactorial in origin and often very difficult to treat [2]. Several studies evaluated pharmacological and nonpharmacological approaches to treat fatigue in sarcoidosis; however, none of these studies looked at hypothyroidism and fatigue in this patient population [34–39]. In one study of German patients evaluating excessive daytime sleepiness and fatigue predictors in sarcoidosis, Bosse-Henck *et al.* [40] found an increased prevalence of "thyroid disorders" in patients with fatigue and excessive daytime sleepiness. Interestingly, in a recently published article phenotyping sarcoidosis organ involvement, fatigue was linked to female sex in sarcoidosis and to cardiac, central nervous system and skin sarcoidosis involvement. However, hypothyroidism was not included in that model [41]. In our analysis, sarcoidosis patients with hypothyroidism were 1.5-times more likely to report fatigue when compared to sarcoidosis patients without hypothyroidism. Chronic fatigue was previously reported to be associated with other comorbidities, including depression, obesity, sleep apnoea and fibromyalgia [2, 40]. We found an association between self-reported hypothyroidism and all four conditions even after controlling for corticosteroid use, suggesting that fatigue in sarcoidosis is multifactorial and may also be linked to hypothyroidism.

We acknowledge several limitations. Despite the extensive recruitment efforts and the relatively large sample size, the participation is still limited by access, awareness and ability to take an online survey. It is clear that the data disproportionately represented white patients (80%) and women (73.6%), which limits the generalizability of our results. However, our reported prevalence of hypothyroidism is in the range with what has been reported in other smaller but more defined sarcoidosis cohorts. Furthermore, using the University of Florida database of sarcoidosis patients, including 40% men and 38% African American people, the prevalence of hypothyroidism was 15%, which was also associated with depression, fatigue, fibromyalgia, obesity and obstructive sleep apnoea, suggesting that our results may have generalizability despite these limitations. Another limitation is the recruitment process, given the platform in which the survey is administered, which leads to referral bias. Furthermore, patients who chose to participate in the survey may not necessarily represent the general sarcoidosis population as those with more severe disease were likely over-represented. Also, the self-reported nature of the data opens the door for nondifferential misclassification of exposure and outcomes. This may explain the higher rates of extrathoracic sarcoidosis

in almost all organ systems when compared to published literature. Unfortunately, self-reported registry studies are commonly subject to this bias; however, the large participant number, statistical adjustment for demographics and potential confounders and the external validation that we performed may address this limitation to some degree. Finally, we cannot establish a causality relationship between hypothyroidism and the tested outcomes due to the self-reported observational nature of this study. However, our study highlights the importance of considering hypothyroidism as a potentially treatable factor among other factors contributing to the physical and nonorgan-related disability in sarcoidosis.

Conclusion

In conclusion, self-reported hypothyroidism is prevalent in sarcoidosis and may be an important potentially treatable contributor of disabling symptoms. It is often associated with multiorgan involvement. Based on our findings, routine screening for hypothyroidism should be considered in sarcoidosis patients, especially in those with multiorgan involvement, fatigue and depression. Further investigation is needed to determine common pathogenic pathways and to assess the impact of treatment of hypothyroidism has on the nonorgan-specific symptoms in sarcoidosis.

Acknowledgment: The authors would like to thank the FSR for the use of FSR-SARC Patient Registry data to conduct this study.

Data availability: Data are available upon request through the FSR-SARC Registry Committee. You can contact the committee at datarequests@stopsarcoidosis.org. Restrictions on access to data are to ensure patient privacy for all persons in the FSR-SARC Registry.

Author contributions: B.N. Alzghoul: study conception and design, project administration, IRB protocol preparation, statistical analysis, initial draft writing and manuscript reviewing and editing; F.N. Amer: study conception and design, figures and tables preparation and manuscript reviewing and editing; A. Innabi and B. Alzghoul: manuscript reviewing and editing; M.T. Mardini and C. Bai: statistical analysis and manuscript reviewing and editing; T. Al-Hakim, N. Singh, M. Buchanan and L. Serchuck: registry design and enrollment, manuscript reviewing and editing; D. Barb, D. Gomez Manjarres, W.W. Woodmansee, and L.A. Maier: study conception and design and manuscript reviewing and editing; D.C. Patel: study conception and design, study administration, supervision and manuscript reviewing and editing. B.N. Alzghoul and D.C. Patel are the guarantors of the study. All authors reviewed and approved the final manuscript.

Conflict of interest: B.N. Alzghoul has nothing to disclose. F.N. Amer has nothing to disclose. D. Barb has nothing to disclose. A. Innabi has nothing to disclose. M.T. Mardini has nothing to disclose. C. Bai has nothing to disclose. B. Alzghoul has nothing to disclose. T. Al-Hakim reports helping with the FSR-SARC registry design and enrollment. N. Singh reports helping with the FSR-SARC registry design and enrollment. M. Buchanan reports helping with the FSR-SARC registry design and enrollment. L. Serchuck reports helping with the FSR-SARC registry design and enrollment. D. Gomez Manjarres has nothing to disclose. W.W. Woodmansee has nothing to disclose. L.A. Maier reports being a nonpaid member of the Scientific Advisory Board of the FSR, and receives grant funding for research as a member of the FSR-Clinical Studies Network. She helped with the FSR-SARC registry design and enrolment. D.C. Patel has nothing to disclose.

Support statement: This study received nonmonetary support from the FSR.

References

1 Sauer WH, Stern BJ, Baughman RP, *et al.* High-risk sarcoidosis. Current concepts and research imperatives. *Ann Am Thorac Soc* 2017; 14: S437–S444.
2 Drent M, Lower EE, Vries JD. Sarcoidosis-associated fatigue. *Eur Respir J* 2012; 40: 255–263.
3 Wu C-H, Chung P-I, Wu C-Y, *et al.* Comorbid autoimmune diseases in patients with sarcoidosis: a nationwide case–control study in Taiwan. *J Dermatol* 2017; 44: 423–430.
4 Korsten P, Tampe B, Konig MF, *et al.* Sarcoidosis and autoimmune diseases: differences, similarities and overlaps. *Curr Opin Pulm Med* 2018; 24: 504–512.
5 Fazzi P, Fallahi P, Ferrari SM. Sarcoidosis and thyroid autoimmunity. *Front Endocrinol (Lausanne)* 2017; 8: 177.
6 Antonelli A, Fazzi P, Fallahi P, *et al.* Prevalence of hypothyroidism and Graves disease in sarcoidosis. *Chest* 2006; 130: 526–532.
7 Malli F, Bargiota A, Theodoridou K, *et al.* Increased primary autoimmune thyroid diseases and thyroid antibodies in sarcoidosis: evidence for an under-recognised extrathoracic involvement in sarcoidosis? *Horm Athens Greece* 2012; 11: 436–443.
8 Wekking EM, Appelhof BC, Fliers E, *et al.* Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. *Eur J Endocrinol* 2005; 153: 747–753.
9 Dayan CM, Panicker V. Hypothyroidism and depression. *Eur Thyroid J* 2013; 2: 168–179.
10 Biondi B. Thyroid and obesity: an intriguing relationship. *J Clin Endocrinol Metab* 2010; 95: 3614–3617.
11 Thavaraputta S, Dennis JA, Laoveeravat P, *et al.* Hypothyroidism and its association with sleep apnea among adults in the United States: NHANES 2007–2008. *J Clin Endocrinol Metab* 2019; 104: 4990–4997.
12 Chaker L, Bianco AC, Jonklaas J, *et al.* Hypothyroidism. *Lancet* 2017; 390: 1550–1562.
13 Haliloglu S, Ekinci B, Uzkeser H, *et al.* Fibromyalgia in patients with thyroid autoimmunity: prevalence and relationship with disease activity. *Clin Rheumatol* 2017; 36: 1617–1621.
14 Oldham JM, Kumar D, Lee C, *et al.* Thyroid disease is prevalent and predicts survival in patients with idiopathic pulmonary fibrosis. *Chest* 2015; 148: 692–700.

15 Sarcoidosis Advanced Registry for Cures (FSR-SARC). 2020. www.stopsarcoidosis.org/fsr-sarc/ Date last updated: December 10, 2020.
16 Harper LJ, Gerke AK, Wang X-F, *et al.* Income and other contributors to poor outcomes in US patients with sarcoidosis. *Am J Respir Crit Care Med* 2020; 201: 955–964.
17 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: 1885–1889.
18 Papadopoulos KI, Hörnblad Y, Liljebladh H, *et al.* High frequency of endocrine autoimmunity in patients with sarcoidosis. *Eur J Endocrinol* 1996; 134: 331–336.
19 Nakamura H, Genma R, Mikami T, *et al.* High incidence of positive autoantibodies against thyroid peroxidase and thyroglobulin in patients with sarcoidosis. *Clin Endocrinol* 1997; 46: 467–472.
20 Ilias I, Panoutsopoulos G, Batsakis C, *et al.* Thyroid function and autoimmunity in sarcoidosis: a case-control study. *Croat Med J* 1998; 39: 404–406.
21 Reynolds HY. Sarcoidosis: impact of other illnesses on the presentation and management of multi-organ disease. *Lung* 2002; 180: 281–299.
22 Anolik RB, Schaffer A, Kim EJ, *et al.* Thyroid dysfunction and cutaneous sarcoidosis. *J Am Acad Dermatol* 2012; 66: 167–168.
23 Martusewicz-Boros MM, Boros PW, Wiatr E, *et al.* What comorbidities accompany sarcoidosis? A large cohort (n=1779) patients analysis. *Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 115–120.
24 Terwiel M, Grutters JC, van Moorsel CHM. Clustering of immune-mediated diseases in sarcoidosis. *Curr Opin Pulm Med* 2019; 25: 539–553.
25 Grunewald J, Kaiser Y, Ostadkarampour M, *et al.* T-cell receptor-HLA-DRB1 associations suggest specific antigens in pulmonary sarcoidosis. *Eur Respir J* 2016; 47: 898–909.
26 Sweiss NJ, Lower EE, Mirsaeidi M, *et al.* Rituximab in the treatment of refractory pulmonary sarcoidosis. *Eur Respir J* 2014; 43: 1525–1528.
27 Phalke S, Aviszus K, Rubtsova K, *et al.* Age associated B cells appear in patients with granulomatous lung diseases. *Am J Respir Crit Care Med* 2020; 202: 1013–1023.
28 Okuma H, Hashimoto K, Wang X, *et al.* Systemic sarcoidosis with thyroid involvement. *Intern Med* 2017; 56: 2181–2186.
29 Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 793–800.
30 Reinhardt W, Sauter V, Jockenhövel F, *et al.* Unique alterations of thyroid function parameters after *i.v.* administration of alkylating drugs (cyclophosphamide and ifosfamide). *Exp Clin Endocrinol Diabetes* 1999; 107: 177–182.
31 Cerniglia B, Judson MA. Infliximab-induced hypothyroidism: a novel case and postulations concerning the mechanism. *Case Rep Med* 2013; 2013: 216939.
32 Munera Y, Hugues FC, Le Jeunne C, *et al.* Interaction of thyroxine sodium with antimalarial drugs. *BMJ* 1997; 314: 1593.
33 Grunewald J, Grutters JC, Arkema EV, *et al.* Sarcoidosis. *Nat Rev Dis Primer* 2019; 5: 1–22.
34 Lower EE, Harman S, Baughman RP. Double-blind, randomized trial of dexmethylphenidate hydrochloride for the treatment of sarcoidosis-associated fatigue. *Chest* 2008; 133: 1189–1195.
35 Erckens RJ, Mostard RLM, Wijnen PAHM, *et al.* Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol* 2012; 250: 713–720.
36 Heij L, Niesters M, Swartjes M, *et al.* Safety and efficacy of ARA 290 in sarcoidosis patients with symptoms of small fiber neuropathy: a randomized, double-blind pilot study. *Mol Med* 2012; 18: 1430–1436.
37 Lower EE, Malhotra A, Surdulescu V, *et al.* Armodafinil for sarcoidosis-associated fatigue: a double-blind, placebo-controlled, crossover trial. *J Pain Symptom Manage* 2013; 45: 159–169.
38 Strookappe B, Elfferich M, Swigris J, *et al.* Benefits of physical training in patients with idiopathic or end-stage sarcoidosis-related pulmonary fibrosis: a pilot study. *Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 43–52.
39 Atkins C, Wilson AM. Managing fatigue in sarcoidosis – a systematic review of the evidence. *Chron Respir Dis* 2017; 14: 161–173.
40 Bosse-Henck A, Koch R, Wirtz H, *et al.* Fatigue and excessive daytime sleepiness in sarcoidosis: prevalence, predictors, and relationships between the two symptoms. *Respir Int Rev Thorac Dis* 2017; 94: 186–197.
41 Schupp JC, Freitag-Wolf S, Bargagli E, *et al.* Phenotypes of organ involvement in sarcoidosis. *Eur Respir J* 2018; 51: 1700991.