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A prospective study of patients diagnosed with sarcoidosis: factors - environmental exposure, health assessment, and genetic outlooks

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Abstract. This original research is a directional study that determined the habits of individuals using four analyses to find statistical significance in the data collected from the surveys of 801 qualified of 1,340 individuals who agreed to participate. Results from the self-reported diagnosis of individuals affected by sarcoidosis produced seven statistically significant indicators of future research needed. The demographics revealed a significantly greater number of women and African-Americans participants than other minorities in the United States and suggested a sense of urgency to find a cure. Most important are the seven statistically significant findings that also gave credence to the researchers' four subdiagnostic classifications. They are acute sarcoidosis (AS) and chronic sarcoidosis with limited dissemination (CSLD), while more severe cases include those with chronic sarcoidosis with full dissemination including cutaneous involvement (CSFDIC) and chronic sarcoidosis with neurosarcoidosis (CSN). The most severe sarcoidosis cases (CSN) were on the "most likely" side of every statistically significant category except drinking alcohol, and the "least likely" to participate in physical activities. Conversely, the least severe case of sarcoidosis (AS) was the opposite. The complete list of statistically significant areas was related to alcohol use, tobacco use, ciprofloxacin use, environmental exposure to metals (copper, iron), infectious diseases (candidiasis), genetics, and physical exercise. Statistically, the most crucial study needed; emerged from the Rh blood grouping of the participants. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (3): 228-242)*

Key words: sarcoidosis, environmental exposure, genetics

Introduction

The modern history of sarcoidosis, an enigmatic multisystem disease, goes back to 1899 when the pioneering Norwegian dermatologist Caesar Boeck coined the term "sarcoid" to describe skin nodules characterized by compact, sharply defined foci of "epithelioid cells with large pale nuclei and a few giant cells (1). Sarcoidosis is a systemic granulomatous disease of unknown cause that primarily affects the lungs; however, the abnormal inflammatory disease process may affect any organ and tissue of the body. The lungs, the lymph nodes of the thorax and the neck, skin, and the liver are the most often involved. The hallmark histological feature of the disease is epithelioid cell granuloma derived from activated T cells and macrophages triggered by unknown immune stimuli such as bacterial protein or beryllium metal (2). There are over 200,000 living individuals with sarcoidosis in the United States. It is hard to say how many worldwide suffer from this disease (2). Globally; the disease is more common in people of Scandinavian, German, Irish, and Puerto Rico de-

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scent (3). No one knows why this occurs. Granulomas of the lachrymal (concerned with the secretion of tears) and salivary glands are found in one-third of patients upon presentation. Since sarcoidosis mimics many other diseases, the number of people who have sarcoidosis is thought to be much higher than the number reported. The cause remains unclear; however, environmental, genetic, ethnic, and familial factors probably modify the expression of the disease. For example, African-Americans are at a greater risk of mortality and morbidity than are white Americans, and more often have a family history of sarcoidosis (4). More females are reported to have sarcoidosis than men. In fact, it is a two to one ratio over African American men. Current reported cases over the last several years show that the gender gap is narrowing. Often most patients that present with acute sarcoidosis (Löfgren syndrome) recover spontaneously, but some develop the chronic debilitating disease. Moreover, sarcoidosis is a multifactor disease of an abnormal immune response to unknown stimuli that produce granulomas in the organs and tissues, also referred to as Boeck's Sarcoid. The proposed study was conducted to identify possible significant factors related to patients diagnosed with sarcoidosis.

Methods

This study used a prospective survey that included nutrition, health history, environmental exposures, lifestyle, genetics, and demographic information. The survey further collected data on both external and internal risk factors that might predispose one to sarcoidosis. The final survey contained 121 questions and took most respondents between thirty and sixty minutes to complete. From the data, statistics were run exceeding the more salient ones included.

Before the start period of the grant, substantial work was done to construct the survey questions to learn more about the causes and effects of sarcoidosis. The first obstacle was to identify commonalities to complete this directional study. Identified were acute, and chronic, with two further distinctions of recurrent or progressive sarcoidosis. In general, published researchers suggested the differentiation of identified cases based on clinical phenotypes of sarcoidosis. Others, not only suggested identifiable subclassifications, they thought them necessary for the treatment of sarcoidosis patients (5). From these documents, four subclassifications seem to capture the manifestations of sarcoidosis that were explicable to participants, with an increase in severity as suggested by the debilitating conditions in the subdiagnostic names given. Subdiagnostic refers to the reliance on the participants to accurately self-report their diagnosis. The first subdiagnostic classification of *acute sarcoidosis* (AS), though called subdiagnostic is recognized, is also called Löfgren syndrome (6). Moreover, the last three are in the recognized chronic category, but not the new subdivision (5). Consequently, the order of increasing severity is the somewhat defined *chronic sarcoidosis with limited dissemination* (CSLD) (7), and *chronic sarcoidosis with full dissemination including cutaneous involvement* (CSFDIC) (8), and the more defined, *chronic sarcoidosis with neurosarcoidosis* (CSN) (9). Prior classification of sarcoidosis was based on chest radiographic features of the disease but didn't fully capture the chronic aspects of the disease (2). Subdiagnostic categories in this paper do not imply lack of lung involvement. The subdiagnostic categories were a way to organize the participants based on the severity of the condition. During this same period of classification, the investigators submitted an application to conduct research using human subjects to the Texas State University Institutional Review Board (IRB) for approval. The application was approved by the Texas State University IRB (IRB application number 2015Z8977) on June 18, 2015.

Participants for the study were recruited by posting a short web-based survey on 31 Sarcoidosis Support Groups on the social network Facebook. The criteria for inclusion in the study was a diagnosis of sarcoidosis as made by a licensed physician or healthcare provider. The short web-based survey explained the purpose of the study and requested that individuals with a diagnosis of sarcoidosis participate in the study. Those who agreed were asked to provide their names and email addresses. Using this technique, 1,340 individuals agreed to participate. Potential participants were later contacted using a custom email with an automatic login link to the research survey. Therefore, no identifying information was needed from this point forward. A sample size of 1000 was targeted. Numerous reminders were provided to participants, and ultimately, 801 individuals responded.

The Principal Investigator of the study developed a bank of possible research questions. From

the bank of questions, the research team refined the questions until everyone agreed on a pilot version. This version was field tested with six individuals diagnosed with sarcoidosis, three health professionals, and one faculty member in health professions. Based on their feedback, the survey was finalized (see Appendix A for a copy of the survey).

The recruitment and main surveys were administered electronically using Snap Surveys© software, which can be used to create and manage web-based surveys. The university subscribes to an Education Enterprise License for this robust software package that includes technical support, software updates, and other application maintenance as needed. Further, this software package allowed the researchers to build a customized data collection instrument while managing and controlling user access. Specifically, when constructing instruments, Snap Survey© software allows for custom design throughout the online instrument, the ability to utilize conditional logic and data entry validations (i.e., question routing), and the creation of distinct participant groupings (e.g., specific classes). Snap Survey© software is installed on a university server, rather than hosted by a third-party cloud storage company. For this specific project, this feature allowed the online version of this survey to be hosted on the Texas State University data center, which brought with it all the security and protection features associated with the university's IT infrastructure. Participants had the option to select a "choose not to answer" response to each question. Participants could also skip a question, resulting in a noted response of missing. Respondents were from all parts of the United States.

Results

Eight hundred and one participants responded to the survey. Demographic information, as well as self-reported subdiagnostic categories, are reported in Tables 1 and 2. Of the 801 respondents, 617 provided valid zip codes as seen in Table 1 along with the state in which respondents live. Representation came from all but two of the 50 states of the US, those being Montana and Nebraska. One respondent lives in the District of Columbia (1, 0.2%). The top five states with the most respondents in the study are Texas (49, 7.9%), New York (48, 7.8%), Michigan (25, 25%), Florida (37, 6.0%) and California (30, 5.0%). Hawaii, New Mexico, South Dakota, and Wyoming, each had one responded (Table 1). Of the 801 respondents, 30 live in the UK, 11 in Canada, seven (7) in Australia, five (5) in Scotland, four (4) in Ireland, one (1) each in Brazil, Netherlands, Slovenia, and New Zealand. Three respondents serve in the military living in the Middle East. Women constituted most of the 801 respondents. Notably, even the least common subdiagnostic classification chronic sarcoidosis with full dissemination, including cutaneous involvement (CSFDIC) was still well-represented among participants, comprising 15.9% of all responses. Chronic sarcoidosis with limited dissemination (CSID) was the largest group which represented 28.5% of all responses. Acute sarcoidosis represented the next largest at 20.7% (Table 2).

Table 3 summarizes responses related to eating habits. Participants questions about their eating habits were prospecting for its role in causing sarcoidosis in addition to its known ability to exacerbate conditions of sarcoidosis (10, 11). About half of the respondents ate breakfast (48.6%) with only 8.2% reporting never eating breakfast. Slightly more than half ate lunch (50.6%) with 2.4% reporting never eating lunch. The largest meal eaten by respondents daily was dinner (78.7%) (12).

Table 4 summarizes responses related to participants smoking habits and alcohol use. Of the 801 subjects in the study, 700 (87.4%) reported not to be a smoker. Of the 801 subjects in the study, 433 (54.1%) reported alcohol use, whereas 367 (45.8%) report no use. Medical marijuana was used by 47 (5.9%); the majority did not report using it (753, 94%).

Table 5 summarizes responses related to exposure to heavy metals. Exposure was defined to participants with the statement, "exposure means that one work or have worked in an industry where this metal was used, in an environmental contamination exposure situation, or that one had any contact inhalation or skin contact with the metal."

Table 6 begins the genetic look at 438 self-reported blood phenotypes matched to their subdiagnosis. Another 84 self-reported their phenotypes but not their subdiagnosis. Associations between subdiagnostic classification and responses to the other questions in the survey were explored for the 663 participants who reported a subdiagnostic classification. Only those associations that were statistically

Table 1. Frequencies and percentages of states in which respondents live

State	N	%	State	N	%
Alabama	8	1.3	Missouri	18	2.9
Alaska	3	0.5	Nevada	5	0.8
Arizona	7	1.1	New Hampshire	5	0.8
Arkansas	8	1.3	New Jersey	14	2.3
California	31	5.0	New Mexico	1	0.2
Colorado	9	1.5	New York	48	7.8
Connecticut	8	1.3	North Carolina	28	4.5
Delaware	3	0.5	North Dakota	3	0.5
District of Columbia	1	0.2	Ohio	27	4.4
Florida	37	6.0	Oklahoma	8	1.3
Georgia	23	3.7	Oregon	10	1.6
Hawaii	1	0.2	Pennsylvania	20	3.2
Idaho	3	0.5	Rhode Island	3	0.5
Illinois	18	2.9	South Carolina	20	3.2
Indiana	14	2.3	South Dakota	1	0.2
Iowa	5	0.8	Tennessee	12	1.9
Kansas	7	1.1	Texas	49	7.9
Kentucky	13	2.1	Utah	6	1.0
Louisiana	9	1.5	Vermont	2	0.3
Maine	4	0.6	Virginia	14	2.3
Maryland	15	2.4	Washington	12	1.9
Massachusetts	17	2.8	West Virginia	7	1.1
Michigan	25	4.1	Wisconsin	13	2.1
Minnesota	15	2.4	Wyoming	1	0.2
			Total	**617**	

significant are reported. Table 7 report crosstabulations of subdiagnosis with the response to those questions that were statistically significant at the .05 level. Neither gender nor race/ethnicity variables were significantly associated with the subdiagnostic category.

Cross Tabulations and Chi-Square Analyses (Table 7): The following are the results from the statistical analysis of the 663 participants who reported a subdiagnostic classification. Ciprofloxacin exposure was relatively common across all groups, with 47.8% of the total sample having reported some exposure. The past or present use of ciprofloxacin was statistically significantly associated with the subdiagnostic classification, $\chi^2(3) = 8.49$, $p = .037$. Table 7 shows this association. Comparison of observed cell counts with cell counts expected under the null hypothesis of statistical independence reveals that those with *acute sarcoidosis* (AS) reported the least exposure, followed by those with *limited dissemination* (CSLD).

Table 2. Sample of self-reported demographic characteristics and subdiagnostic categories

Variable	N	%
Subdiagnostic Category		
Acute sarcoidosis	166	20.7
Chronic sarcoidosis with limited dissemination	228	28.5
Chronic sarcoidosis with full dissemination, including cutaneous involvement	127	15.9
Chronic sarcoidosis with neurosarcoidosis	142	17.7
Choose not to answer	116	14.5
Missing	22	2.7
Gender		
Female	654	81.6
Male	143	17.9
Self-Identified	2	0.2
Missing	2	0.2
Hispanic		
No	744	92.9
Yes	40	5
Missing	17	2.1
Race		
American Indian/Eskimo/Aleut Alaskan Native	8	1
Asian/Pacific Islander	9	1.1
Black/African American	103	12.9
White	603	75.3
Two or More	28	3.5
Other	23	2.9
Missing	27	3.4

Those with a diagnosis of *chronic sarcoidosis with full dissemination, including cutaneous involvement* (CSFDIC) or *chronic sarcoidosis with neurosarcoidosis* (CSN) reported the greatest exposure.

Receiving a diagnosis of candidiasis was also associated with the subdiagnostic classification, $\chi^2(3) = 9.34$, $p = .025$. This association is shown in Table 7. As was the case with ciprofloxacin usage, the more severe the subdiagnostic classification, the more likely diagnosis of candidiasis was to be reported.

The association of subdiagnostic classification with tobacco usage (Table 7) was statistically significant, $\chi^2(3) = 7.89$, $p = .048$. Those with diagnoses of AS, CSLD, and CSFDIC reported the roughly equal incidence of tobacco usage, around 10%. Those with a diagnosis of CSN reported a higher incidence of usage at 19.0%.

The association of alcohol use with subdiagnostic classification was statistically significant, $\chi^2(3) = 10.87$, $p = .012$. Table 7 shows this association. Comparison of observed cell counts with cell counts expected under the null hypothesis of statistical independence reveals that those with either *acute sarcoidosis* (AS) or *chronic sarcoidosis with limited dissemination* (CSLD) are more likely to report the use of alcohol than would be expected by chance. Whereas those with *chronic sarcoidosis with full dissemination, including cutaneous involvement* (CSFDIC) or *chronic*

Table 3. Sample of self-reported eating habits

Variable	N	%
How often do you eat breakfast		
1-2 days a week	185	23.1
3-5 days a week	159	19.9
6-7 days a week	389	48.6
Never	66	8.2
Missing	2	0.2
How often do you eat lunch		
1-2 days a week	110	13.7
3-5 days a week	258	32.2
6-7 days a week	405	50.6
Never	19	2.4
Missing	9	1.1
How often do you eat dinner		
1-2 days a week	30	3.7
3-5 days a week	131	16.4
6-7 days a week	630	78.7
Never	2	0.2
Missing	8	1

Table 4. Key Variables related to substance use

Variable	N	%
Use of tobacco		
No	700	87.4
Yes	100	12.5
Missing	1	0.1
Use of medicinal marijuana		
No	753	94
Yes	47	5.9
Missing	1	0.1
Use of alcohol		
No	433	54.1
Yes	367	45.8
Missing	1	0.1

sarcoidosis with neurosarcoidosis (CSN) are less likely to use alcohol.

The association of copper exposure with subdiagnostic classification was statistically significant, $\chi^2(3) = 9.81$, $p = .020$. As shown in Table 7, those with AS and CSLD reported between four and five percent incidence of exposure, whereas those with

Table 5. Sample of self-reported exposure to metals

Variable	N	%
Have you ever been exposed to…		
Arsenic	20	2.50
Barium	19	2.40
Beryllium	21	2.60
Cadmium	16	2.00
Chromium	17	2.10
Cobalt	16	2.00
Copper	59	7.40
Iron	64	8.00
Lead	95	11.90
Mercury	57	7.10
Nickel	31	3.90
Platinum	14	1.70
Selenium	6	0.70
Thallium	5	0.60
Tungsten	12	1.50
Uranium	5	0.60
Zinc	34	4.20

CSFDIC and CSN reported the considerably higher incidence of exposure at 11.8% and 9.9%, respectively.

Iron exposure was also associated with subdiagnostic classification, $\chi^2(3) = 10.51$, $p = .015$. As shown in Table 7, the pattern of reported exposure by classification was highly similar to the pattern observed for copper exposure. Those with AS and CSLD reported the relatively low incidence of exposure at 4.8% and 6.1%, respectively. In contrast, those with CSFDIC and CSN reported the noticeably higher incidence of exposure at 12.6% and 12.7%, respectively.

Cross Tabulations and Odds Ratio Analyses (Table 8): The statistically significant Chi-Squares in the above six subdiagnostic classifications warranted additional analyses. Specifically, we were interested in analyzing if there were differences based on the severity of sarcoidosis and if the person had an acute versus the chronic case of sarcoidosis. This study was a case-control because we started with the outcome and looked back to see which individuals in the two groupings were exposed or used alcohol, tobacco, and so on. The first grouping divided the 663 participants into artificial categories of "Less" and "More" severe cases of sarcoidosis. Less severe cases included those with *acute sarcoidosis* (AS) and

Table 6. Sample of self-reported blood groups and subdiagnostic categories

Cases of sarcoidosis	Blood Type								Total
	A Positive	A Negative	B Positive	B Negative	AB Positive	AB Negative	O Positive	O Negative	
AS	21	5	16	2	7	2	47	14	114
CSLD	46	6	19	2	6	2	53	21	155
CSFDC	21	4	15	2	1	6	26	10	85
CSN	12	5	13	3	4	1	34	12	84
Total	100	20	63	9	18	11	160	57	438

Table 7. Cross tabulations and chi-square of subdiagnostic classification from exposure, usage, or infection

Exposures / Usages / Infection	Ciprofloxacin			Candida Albicans			Tobacco			Alcohol			Copper			Iron		
Statistical Differences (AS, CSLD, CSFDIC, CNS)	$\chi^2(3) = 8.49$, ***p* = .037**			$\chi^2(3) = 9.34$, ***p* = .025**			$\chi^2(3) = 7.89$, ***p* = .048**			$\chi^2(3) = 10.87$, ***p* = .012**			$\chi^2(3) = 9.81$, ***p* = .020**			$\chi^2(3) = 10.51$, ***p* = .015**		
Subdiagnostic Classifications	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
1. Acute sarcoidosis (AS)																		
Count	66	100	166	17	149	166	20	146	166	80	86	166	7	159	166	8	158	166
Expected Count	79.4	86.6	166	22	144	166	21	146	166	76.4	89.6	166	11.8	154	166	14	152	166
% within row	39.8	60.2	100	10.2	89.8	100	12	88	100	48.2	51.8	100	4.2	95.8	100	4.8	95.2	100
2. Chronic sarcoidosis with limited dissemination (CSLD)																		
Count	106	122	228	24	204	228	22	206	228	120	108	228	11	217	228	14	214	228
Expected Count	109	119	228	31	197	228	28	200	228	105	123	228	16.2	212	228	19	209	228
% within row	46.5	53.5	100	10.5	89.5	100	9.6	90.4	100	52.6	47.4	100	4.8	95.2	100	6.1	93.9	100
3. Chronic sarcoidosis with full dissemination, including cutaneous involvement of the disease (CSFDIC)																		
Count	68	59	127	19	108	127	13	114	127	45	82	127	15	112	127	16	111	127
Expected Count	60.7	66.3	127	17	110	127	16	111	127	58.4	68.6	127	9	118	127	11	116	127
% within row	53.5	46.5	100	15	85	100	10.2	89.8	100	35.4	64.6	100	11.8	88.2	100	12.6	87.4	100
4. Chronic sarcoidosis with neurosarcoidosis (CSN)																		
Count	77	65	142	29	113	142	27	115	142	60	82	142	14	128	142	18	124	142
Expected Count	67.9	74.1	142	19	123	142	18	124	142	65.3	76.7	142	10.1	132	142	12	130	142
% within row	54.2	45.8	100	20.4	79.6	100	19	81	100	42.3	57.7	100	9.9	90.1	100	12.7	87.3	100

chronic sarcoidosis with limited dissemination (CSLD), while more severe cases include those with *chronic sarcoidosis with full dissemination including cutaneous involvement* (CSFDIC) and *chronic sarcoidosis with neurosarcoidosis* (CSN). The second grouping divided the participants into two groups of acute sarcoidosis, which included only individuals in the AS classification versus chronic sarcoidosis, which included all other participants in the CSLD, CSFDIC, and CSN classifications. Table 8 report crosstabulations, the odds ratios, and Chi-Square based on severity and acute versus chronic. Alpha was set at the .05 level.

Table 8 presents the association of ciprofloxacin use with the severity of sarcoidosis. The result was statistically significant, with an Odds Ratio (OR) of 0.66 and confidence interval (CI) 0.49 to 0.91. This result indicates that the odds an individual with a less severe case of sarcoidosis is 0.66, or there is a 34% less chance of them reporting the use of ciprofloxacin than an individual with a more severe case of sarcoidosis.

Table 8 presents the association of ciprofloxacin use with the acute versus chronic sarcoidosis was also statistically significant, with an OR of 0.65 (CI

Table 8. Cross tabulations, odds ratio, and chi-square of severity and disease onset from subdiagnostic classification of exposure, usage, or infection

		Exposures / Usages / Infection	Ciprofloxacin			Candida Albicans			Tobacco			Alcohol			Copper			Iron		
			Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total	Yes	No	Total
AS, CSLD	Less Severe	Count	172	222	394	41	353	394	42	352	394	200	194	394	18	376	394	22	372	394
		% within Exposure Case	43.7	56.3	100	10.4	89.6	100	10.7	89.3	100	50.8	49.2	100	4.6	95.4	100	5.6	94.4	100
CSFDIC, CNS	More Severe	Count	145	124	269	48	221	269	40	229	269	105	164	269	29	240	269	34	235	269
		% within Exposure Case	53.9	46.1	100	17.8	82.2	100	14.9	85.1	100	39	61	100	10.8	89.2	100	12.6	87.4	100
	Total	Count	317	346	663	89	574	663	82	581	663	305	358	663	47	616	663	56	607	663
		% within Exposure Case	47.8	52.2	100	13.4	86.6	100	12.4	87.6	100	46	54	100	7.1	92.9	100	8.4	91.6	100
				95% CI			95% CI			95% CI			95% CI			95% CI			95% CI	
			Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper
	Odds Ratio for Exposure Case (Less Severe / More Severe)		**0.66**	0.49	0.905	**0.535**	0.341	0.838	1.464	0.921	2.328	**1.61**	1.176	2.206	**0.396**	0.215	0.729	**0.409**	0.233	0.716
			$\chi^2(3) = 6.729, p = .009$			**$\chi^2(3) = 7.609, p = .006$**			$\chi^2(3) = 2.614, p = .106$			**$\chi^2(3) = 8.852, p = .003$**			**$\chi^2(3) = 9.366, p = .002$**			**$\chi^2(3) = 10.291, p = .001$**		
AS	Acute	Count	66	100	166	17	149	166	20	146	166	80	86	166	7	159	166	8	158	166
		% within Exposure Case	39.8	60.2	100	10.2	89.8	100	12	88	100	48.2	51.8	100	4.2	95.8	100	4.8	95.2	100
CSLD, CSFDIC, CNS	Chronic	Count	251	246	497	72	425	497	62	435	497	225	272	497	40	457	497	48	449	497
		% within Exposure Case	50.5	49.5	100	14.5	85.5	100	12.5	87.5	100	45.3	54.7	100	8	92	100	9.7	90.3	100
	Total	Count	317	346	663	89	574	663	82	581	663	305	358	663	47	616	663	56	607	663
		% within Exposure Case	47.8	52.2	100	13.4	86.6	100	12.4	87.6	100	46	54	100	7.1	92.9	100	8.4	91.6	100
				95% CI			95% CI			95% CI			95% CI			95% CI			95% CI	
			Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper	Value	Lower	Upper
	Odds Ratio for Exposure Case (Acute / Chronic)		**0.65**	0.45	0.924	0.673	0.385	1.18	1.04	0.608	1.781	1.125	0.791	1.599	0.503	0.221	1.146	0.474	0.219	1.023
			$\chi^2(3) = 5.757, p = .016$			$\chi^2(3) = 1.930, p = .165$			$\chi^2(3) = .021, p = .885$			$\chi^2(3) = .427, p = .513$			$\chi^2(3) = 2.773, p = .096$			$\chi^2(3) = 3.768, p = .052$		

0.45 to 0.92). This result indicates that the odds an individual with an acute case of sarcoidosis is 0.65, or there is a 35% less chance of them reporting the use of ciprofloxacin than an individual with a chronic case of sarcoidosis.

Table 8 presents the association of candidiasis with the severity of sarcoidosis. The result was statistically significant, with an OR 0.54 (CI 0.34 to 0.84). This result indicates that the odds an individual with a less severe case of sarcoidosis is 0.54, or there is a 46% less chance of them reporting having candidiasis than an individual with a more severe case of sarcoidosis.

Table 8 presents the association of candidiasis with the acute versus chronic sarcoidosis with an OR 0.67 (CI 0.39 to 1.18). Since the confidence interval (CI) crosses the line of no effect (1), it is not statistically significant. In other words, no statistical difference exists between acute and chronic candidiasis at 95% confidence.

Table 8 presents the association of tobacco use with the severity of sarcoidosis with an OR of 1.46 (CI 0.92 to 2.33). Since the CI crosses the line of no effect (1), it is not statistically significant. In other words, no statistical difference exists between the severity of sarcoidosis for tobacco use at 95% confidence.

Likewise, Table 8 presents the association of tobacco use with acute versus chronic sarcoidosis with an OR 1.04 (CI 0.61 to 1.78). Since the CI crosses the line of no effect (1), it is not statistically significant. In other words, no statistical difference exists between the acute versus chronic sarcoidosis for tobacco use at 95% confidence.

Table 8 presents the association of alcohol use with the severity of sarcoidosis. The result was statistically significant, with an OR 1.6 (CI of 1.2 to 2.2). These results indicate that the odds an individual with a less severe case of sarcoidosis use of alcohol is 1.6 times that of the odds an individual with a more severe case of sarcoidosis. In other words, those with less severe cases are more likely to report the use of alcohol than those with more severe cases.

However, Table 8 presents the association of alcohol use with the acute versus chronic sarcoidosis with an OR 1.1 (CI 0.8 to1.6). Since the CI crosses the line of no effect (1), it is not statistically significant. In other words, no statistical difference exists between the acute versus chronic sarcoidosis for alcohol use at 95% confidence.

Table 8 presents the association of copper exposure with the severity of sarcoidosis. The result was statistically significant, with an OR 0.40 (CI 0.22 to 0.73). This result indicates that the odds an individual with a less severe case of sarcoidosis is 0.40, or there is a 60% less chance of them reporting exposure to copper than those with a more severe case of sarcoidosis.

Table 8 presents the association of copper exposure with the acute versus chronic sarcoidosis with an OR 0.50 (CI 0.22 to 1.15). Since the confidence interval (CI) crosses the line of no effect (1), it is not statistically significant. In other words, no statistical difference exists between acute and chronic association with copper exposure at 95% confidence.

Table 8 presents the association of iron exposure with the severity of sarcoidosis. The result was statistically significant, with an OR of 0.41 (CI 0.22 to 0.73). This result indicates that the odds an individual with a less severe case of sarcoidosis is 0.41, or there is a 59% less chance of them reporting exposure to iron than those with a more severe case of sarcoidosis.

Table 8 presents the association of iron exposure with the acute versus chronic sarcoidosis with an OR 0.47 (CI 0.22 to 1.02). Since the confidence interval (CI) crosses the line of no effect (1), it is not statistically significant. In other words, no statistical difference exists between acute and chronic association with iron exposure at 95% confidence.

Goodness of Fit Chi-Square Analyses (Table 10): We also ran the goodness of fit, Chi-Square analysis comparing the frequency of blood types in the sarcoidosis cases to that of the United States (US) general population. An initial check was statistically significant for the self-identified subdiagnostic classifications matched with their self-reported blood grouping; $\chi^2(3) = 30.511$, $p < 0.01$ at $\alpha = .05$ (table not shown) but did not reveal the root cause. Then a statistical analysis compared the ABO and Rh blood grouping of sarcoidosis participants to that in the United States (US) according to the American Red Cross (ARC) frequency distribution and Stanford School of Medicine (SSM) at $\alpha = .05$ (13, 14). The ARC gave the frequency distribution of eight phenotypes for four ethnic groups (Caucasian, African-American, American-Latino, and Asian), with slightly different percentages than SSM that had the

same eight phenotypes, but an unknown percentage compilation.

Matching the combined ABO and Rh blood types with self-identified subdiagnostic classifications were possible for 438 of the 663 participants (Table 6) and were statistically significant. ARC, $\chi^2(7) = 146.448$, $p < 0.01$, SSM, $\chi^2(7) = 95.852$, $p < 0.01$; at $\alpha = .05$. However, attempts to understand the phenomena resulted in the separation of the phenotypes and analyzing the assumed more important ABO phenotype, resulted in conflicting results. The ARC frequencies were NOT statistically significant for the 438 participants, $\chi^2(3) = 7.033$, $p = 0.071$, but was for the SSM, $\chi^2(3) = 50.975$, $p < 0.01$; at $\alpha = .05$.

Efforts to explain the apparent contradiction resulted in the comparison of the 438 participants Rh blood grouping alone and was statistically significant. ARC, $\chi^2(1) = 101.764$, $p < 0.001$ (Table 10), which was greater than SSM, $\chi^2(1) = 17.543$, $p < 0.01$; at $\alpha = .05$. The significant finding of the Rh blood grouping compelled the final comparison of all 522 self-reported Rh blood grouping (Table 9), without regards to the subclassifications, that included 84 unknown subdiagnosis, resulted in the greatest statistical significance. ARC, $\chi^2(1) = 126.128$, $p < 0.001$ (Table 10), again, greater than SSM, $\chi^2(1) = 22.503$, $p < 0.01$; at $\alpha = .05$.

Subclassification Association with Exercise: The Godin Leisure-Time Exercise Questionnaire (1985) was used to allow participants to self-report their level of physical activity (12). Of the 663 participants who reported a subdiagnostic classification, 659 provided sufficient information for the calculation of total physical activity (PA) score using Godin and Shephard's (1985) formula, $m = 19.03$, $sd = 21.59$. Inspection of a histogram of PA scores revealed a continuously distributed variable with many zeros (Figure 1). This pattern suggested that an important distinction among these participants was whether they reported any physical activity at all. In other words, the PA scores observed for these $n = 659$ participants could be parsimoniously conceptualized as a mixture of two distributions. One distribution with only the value of zero ($n = 218$), and separate, continuous distribution of PA scores for those participants who actually engaged in physical activity ($n = 441$, $m = 28.44$, $sd = 20.71$).

A dichotomous variable was thus created to indicate whether (1) or not (0) each participant with a non-missing PA score had a PA score that was greater than zero. The association of this dichotomous variable with subdiagnostic classification was statistically significant, $\chi^2(3) = 15.48$, $p = .001$. Inspection of means of this dichotomous variable (i.e., the proportion of individuals reporting greater than zero physical activity) for each subdiagnostic classification showed that AS ($n = 165$, $m = .72$), CSLD ($n = 227$, $m = .71$), and CSFDIC ($n = 126$, $m = .69$) were similar in the proportion of participants reporting some physical activity. In contrast, participants in the CSN subdiagnostic classification were notably less likely to report engaging in any activity ($n = 141$, $m = .53$).

Perhaps unsurprisingly then, while a one-way ANOVA did not show statistically significant variation of mean PA score across subdiagnostic classifications [$F(3, 655) = 1.93$, $p = .12$], means of these PA scores showed a similar descriptive pattern. Those participants with AS ($m = 20.75$, $sd = 23.53$), CSLD ($m = 19.60$, $sd = 19.83$), and CSFDIC ($m = 20.00$, $sd = 22.13$) had similar mean PA scores. Participants in the subdiagnostic classification of CSN had lower PA scores on average ($m = 15.26$, $sd = 21.24$).

Finally, this one-way ANOVA was performed again after excluding those participants with PA

Table 9. Subdiagnostic sarcoidosis vs. us population

	Sarcoid Observed Frequency	US Expected Frequency	Residual	ABO & Rh % <or > Expected	ABO % <or > Expected
A Positive	127	176.8	-49.8	-28%	-42%
A Negative	27	31.2	-4.2	-13%	
B Positive	70	42.1	27.9	66%	115%
B Negative	11	7.4	3.6	49%	
AB Positive	21	16.8	4.2	25%	-38%
AB Negative	11	29.7	-18.7	-63%	
O Positive	187	185.2	1.8	1%	109%
O Negative	68	32.7	35.3	108%	
Total	522				

Table 10. Rh blood grouping observed vs. expected significance

	Self-reported ABO, Rh Matched			Self-reported Rh		
	Observed	Expected	Residual	Observed	Expected	Residual
Positive	341	400.2	-59.2	405	477	-72
Negative	97	37.8	59.2	117	45	72
Total	438			522		
	$\chi^2(1) = 101.764$, $p < 0.001$			$\chi^2(1) = 126.128$, $p < 0.001$		

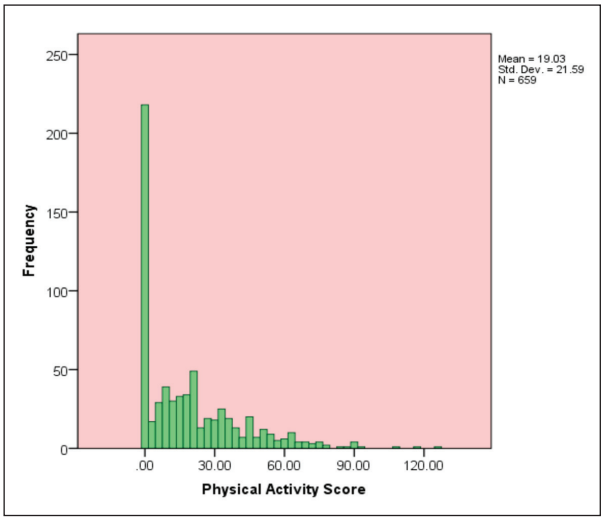

Fig. 1. Self-reported physical activity and activity frequency

scores of zero. There was no statistically significant variation of mean PA score across subdiagnostic classification [$F(3, 437) = .13$, $p = .94$], and mean PA scores across subdiagnostic classifications were descriptively homogeneous (AS, $n = 118$, $m = 29.01$, $sd = 23.11$; CSLD, $n = 161$, $m = 27.63$, $sd = 18.22$; CSFDIC, $n = 87$, $m = 28.97$, $sd = 21.20$; and CSN, $n = 75$, $m = 28.68$, $sd = 21.53$).

Discussion

More than three years are vested in this directional study of sarcoidosis using a prospective survey that covered demographic information, nutrition, environmental exposures, lifestyle, genetics, and health history. The investigators believe it is the single largest directional survey conducted of this population to date. Sarcoidosis is a systemic granulomatous disease of unknown cause that primarily affects the lungs and an abnormal inflammatory disease process that may affect any organ and tissue of the body. The lungs, the lymph nodes of the thorax and the neck, skin, and the liver are the most often involved. Although the hallmark histological feature of the disease is epithelioid cell granuloma derived from activated T cells and macrophages, the triggering stimuli are unknown but have indicators such as bacterial protein or beryllium metal (2).

Researchers of this study identified four subclassifications: *acute sarcoidosis* (AS) and *chronic sarcoidosis with limited dissemination* (CSLD), while more severe cases include those with *chronic sarcoidosis with full dissemination including cutaneous involvement* (CSFDIC) and *chronic sarcoidosis with neurosarcoidosis* (CSN). The subdiagnostic classification allowed further analysis of the data based on severity and, hopefully, can offer future insight into differential diagnoses, management, and additional research. The authors did not compare pulmonary function data to the four subcategories. That has not proven to be useful with past classifications; however, is an area of interest for future studies based on the results of this study (2). This directional study determined the habits of individuals and utilized four analyses to find statistical significance in the data collected from the surveys of 801 participants. Based on our analysis, seven statistically significant results emerged as indicators of future research needed. Namely, the "Cross Tabulations and the Chi-Square Analyses," the "Cross Tabulations and Odds Ratio Analyses," the "Goodness of Fit and Chi-Square Analyses," and the "Godin and Shephard's (1985)" formula were most valuable. These four statistics resulted in the seven statistically significant findings that gave credence to the four subdiagnostic classifications. These seven statistically significant findings are summarized in Figure 2 that reveals statistics that separates the four subcategories into a dichotomy of most likely and least likely occurrences. Six of the seven relates the frequency percentages, while the Rh D blood type reveals a dichotomy based on opposing (72 vs. -71) residual of observed versus expectancy that proved statistically significant. This study did not attempt to ascertain causality of the subcategories; rather, it focused on determining if these categories were statistically feasible. Moreover, the strength of this directional survey was not robust enough to speculate on causality but serves as a Pilot Study for more focused investigations.

Demographic diversity, including ethnicity, presented two points of interest. Considering this study was of those requesting it, the more than 80% of females in our results exceeds recent and robust studies of around 50% and may indicate a greater felt urgency for resolve in that populous (15, 16). While the demographics of those with sarcoidosis mimic that of the 2010 census for Whites (75.2, 72.4) and African-Americans (12.9, 12.6), it is more striking that African-American representation is two to three

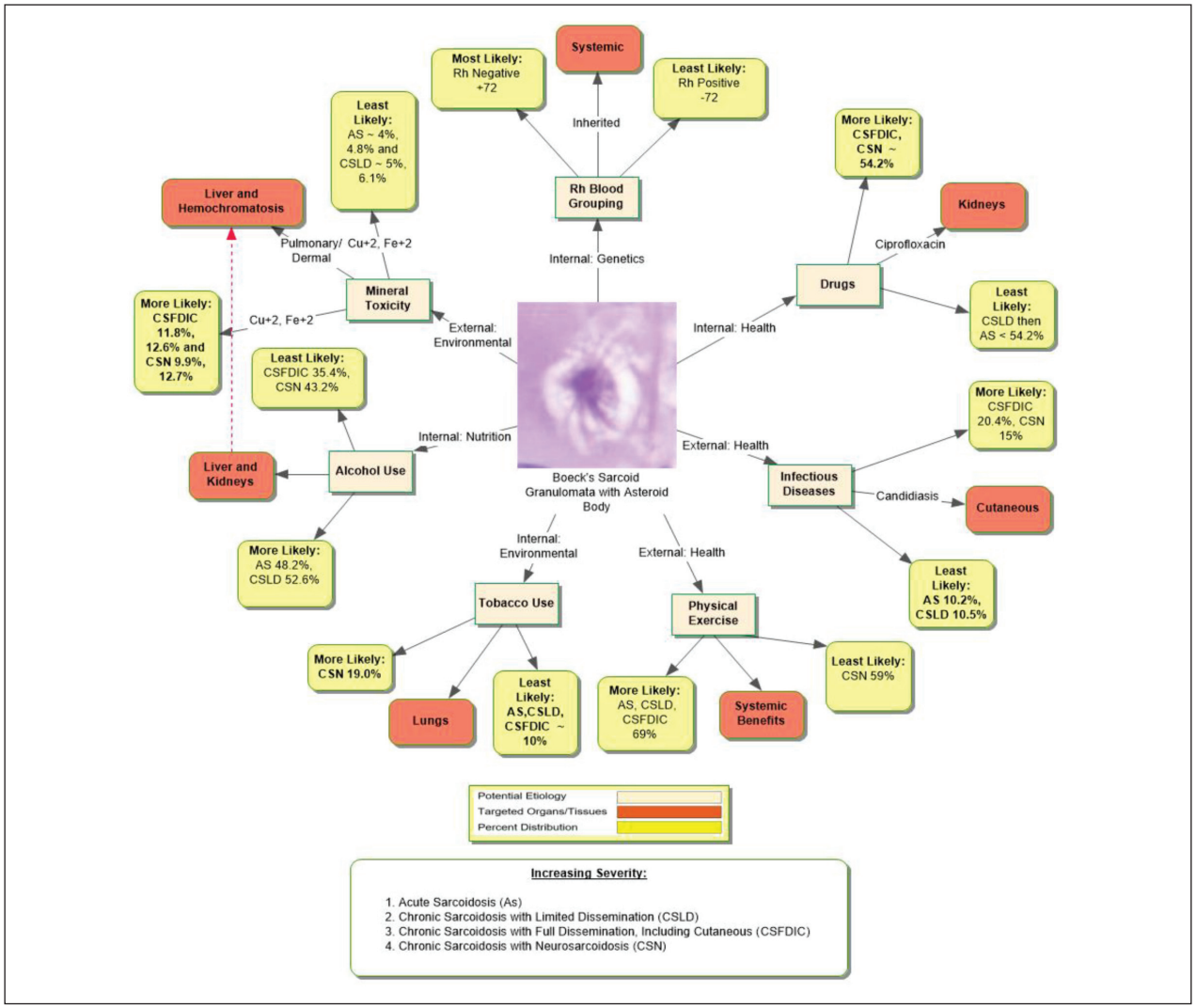

Fig. 2. Seven Statistically Significant Sarcoidosis Linked Dichotomies
*Boeck's Sarcoid – printed by permission of John Lee Sang, M.D., Central Texas Medical Center, San Marcos, Texas

times that of other closed groups such as Mexican Americans and Native Americans (17). It highlights studies demonstrating the disconcerting prevalence among African-American females, and may also reflect their desperation to find a cure (4).

The eating habits of the participants seem like those in the United States, with a greater percentage never missing the last meal of the day and did not reveal any statistical relationship to sarcoidosis. Likewise, 87.4% of the 700 reported nonsmokers is an expected response considering over 85% of people with sarcoidosis have the disease in the lungs. Nevertheless, the subdiagnostic classification with tobacco usage was statistically significant. However, tobacco is the only category that was statistically significant as a subcategory (Table 7) but not at levels of severity, and the acute or chronic onset of the disease (Table 7). Similarly, Gupta et al did not find an effect of tobacco smoke on disease severity in sarcoidosis (19). Perhaps a study with a larger number of participants can shed light on any association between tobacco use and sarcoidosis severity. The link between smoking and chronic obstructive lung disease has been well established. However, there is a dearth of research looking specifically at the impact tobacco use has on sarcoidosis and lung function across acute

and chronic categories. We cannot support the notion that tobacco use is protective against sarcoidosis either. It is known that tobacco affects the immune system among other pathophysiological effects of nicotine toxins and increased serum angiotensin-converting enzyme activity (ACE) tested for in clinical laboratories (20). Whether it is because of the symptoms which mimic COPD or the tendency not to smoke because of the risk of cancer, is not clear. Along with that, the low (5.9%) use of medical marijuana may reflect the same, although some evidence exists for the use of medical marijuana to alleviate the discomfort associated with chronic noncancer pain (21).

On the other hand, alcohol use did not seem to cause an adverse effect. In fact, a null hypothesis of statistical independence revealed that those with AS and CSLD are more likely to use alcohol than would be expected by chance and those with the more severe conditions (CSDIC, CSN) were less likely to use alcohol. Using the same groupings (AS, CSLD versus CSDIC, CSN) provided means of conducting an odds ratio that associated alcohol use with the severity of sarcoidosis. Results indicated that those with less severe cases are more likely to report the use of alcohol than those with more severe cases.

In contrast, environmental exposure presented copper and iron metals with similar statistical significance in the same areas of classification as alcohol, but unfavorable since past research has shown that environmental factors may contribute to sarcoidosis risk. Moreover, researchers associated the risk with individuals who work in occupations with potential metal exposures (22), and association exposure to inorganic particles (16). Workers exposed to beryllium dust or fumes have developed an immune response known as sensitization, a slowly progressive respiratory disease characterized by the formation of lung lesions called granulomas that resemble those found in sarcoidosis patients. These granulomas and accompanying fibrosis impair the lung's ability to expand fully and interfere with the normal gas exchange. Berylliosis has been suggested as a cause of pulmonary sarcoidosis and classified as a type of pneumoconiosis, a systemic granulomatous disease that mainly affects the lungs (17). Exposure to the minerals with statistical significance, copper, and iron, are known to work in tandem in the liver to produce hemochromatosis a condition that causes an iron overload that would affect other organs and tissue (20, 23). Also, high intakes of copper are known to cause gastrointestinal pain, erosion of epithelial cell lining, hemolytic anemia, kidney damage, and death, and therefore cannot be ruled out as contributing factors to sarcoidosis (24). Also, work environments that produce high levels of aerosolized inorganic particles, e.g., wood stoves, fireplaces, talc, human-made mineral fiber, silica dust, intense agricultural activities, continue to be places of higher risk for development of sarcoidosis (25).

Ciprofloxacin, like alcohol, copper, and iron, had similar statistical significance in the same areas of the null hypothesis of statistical independence and those with the more severe conditions (CSDIC, CSN). Unlike those mentioned, ciprofloxacin also has a significant statistical difference in subclassifications of acute and chronic sarcoidosis that revealed increased use of the drug with severity, regardless of the division. Notably, ciprofloxacin is the only category that resulted in a statistically significant difference in all categories. That is, it was statistically significant in subcategorization, levels of severity, and the acute or chronic onset of the disease. Admittedly, when considering the duration of the disease and speculations from the participants that their treatments resulted in other health issues, the relationship between the severity of the disease could be from other drug treatments, requiring additional research. However, ciprofloxacin is a widely used antimicrobial agent to treat bacterial infections of the respiratory and urinary tracts and implicated in cases of induced acute interstitial pneumonitis and hypersensitivity vasculitis (24, 26, 27). Therefore, we surveyed the cohort group to ascertain if ciprofloxacin might have an association with inducing sarcoidosis, and there is a statistically significant relationship between the drug and the severity of the disease.

Furthermore, since the cutaneous effect of candidiasis coincided with this study's greater number of women, where the infection is common, but also the greater number with sarcoidosis, and given its statistical significance (like alcohol, copper, and iron) warrants further investigation (24). In other words, is the drug a stimulus for sarcoidosis and candidiasis? Ciprofloxacin is known to cause an allergic response that results in acute interstitial nephritis (AIN) of the kidney (24). Paone et al. found that kidney granulomas cause interstitial nephritis with an elevated

serum angiotensin-converting enzyme (ACE) activity, and with a bronchoalveolar lavage fluid [BALF] lymphocytes, and a BALF CD4/CD8 ratio could potentially screen for sarcoidosis (28). Also, the fact that increased blood pressure and water retention indirectly results from the ACE activity suggests metabolic influence, and diabetes complication lends to other reasons for investigating the ciprofloxacin sarcoidosis axis.

Genetically, the greatest statistical significance is the Rh blood grouping of all 522 self-reports with an ARC, $\chi^2(1) = 126.128$, $p < 0.001$. This finding suggests the need to investigate the Rh blood group genotypes as the triggering stimuli for sarcoidosis. Specifically, the significantly increased Rh negative grouping suggests that the significantly decreased Rh-positive may have a commonality. To understand the commonality requires a look at the Wiener and Fisher-Race genotype (29). Since the Rh-negative with the greater frequency is "r" or "dce" haplotypes in the respective system, the closest match of Rh-positive with the greater frequency is "R^0" and "Dce" haplotypes respectively in the Wiener and Fisher-Race classification. Therefore, the genotypes of interest are R^0r or Dce/dce, for the Rh-positive participants and the Rh negative is rr or dce/dce respectively for the Wiener and Fisher-Race genotypes.

Concerning physical activity, overall, a statistically significant difference exists between inactivity and activity for those with sarcoidosis. This significance did not carry over to differences between the subcategories. Given that a participant reports engaging in some activity (i.e., the participant's PA score is greater than zero), the four subdiagnostic categories are approximately equal in the mean level of activity reported. Nevertheless, there was a decrease in activity with increased severity, with the first three categories exhibiting the least difference. Strikingly, the analyses together reveal that *chronic sarcoidosis with neurosarcoidosis* (CSN) participants are notably more likely than other participants to report engaging in no physical activity at all.

Because of the four subcategorical classifications (AS, CSLD, CSFDIC, CNS) by the researchers, through four statistical analysis, seven statically significant areas are of interest for future studies. Namely, the association with exercise using the Godin and Shephard's (1985) formula that indicated that those with the most severe cases, CSN, were less likely to engage in physical exercise. Although the other three were roughly the same, they exhibited a decrease in activity with the designated increase in severity. Second; drug use, specifically, Ciprofloxacin association with, third, Candidiasis, and their association with sarcoidosis. Fourth, the association of the seemingly positive effect of alcohol, and fifth, the statistical significance of tobacco use. Sixth, environmental exposure to copper and iron as causative stimuli for sarcoidosis. Seventh, and most significant, the association of sarcoidosis with increased Rh-negative grouping and the significantly decreased Rh-positive and what they have in common.

These seven findings reveal the benefit, if not the need, to standardize the classifications of sarcoidosis. It also indicates that the subclassification in this study is as valid and perhaps simpler than any identified and maintained throughout any single study. A simpler standard classification like the one presented, or the same seems more likely to advance researchers' ability to compare participants within and without the subcategories. Conceivably, such a standard subclassification could lead to other categories within them and assist in definitively proving or disproving causative, the exacerbating, or disabling agents, such as the seven (Figure 2) suggested (especially Rh genetics) having statistical significance in this study.

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References

1. Boek C. Multiple benign sarcoid of the skin J. Cutan Genitourin Dis 1899; 17: 543-550.
2. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-2165.
3. Sarcoidosis. In: World Book, Inc.; 2017: 1p. 1.
4. Gerke AK, Judson MA, Cozier YC, Culver DA, Koth LL. Disease Burden and Variability in Sarcoidosis. Annals of the American Thoracic Society 2017; 14: 421-428.
5. Lawson W, Jiang N, Cheng J. Sinonasal sarcoidosis: A new system of classification acting as a guide to diagnosis and treatment. American Journal Of Rhinology & Allergy 2014; 28(4): 317-322.
6. Saltman AP, Kuriya B. Löfgren syndrome in acute sarcoidosis. CMAJ: Canadian Medical Association Journal = Journal De L'association Medicale Canadienne 2017; 189(39): E1230-E1230.
7. Treatment of the Bilateral Severe Uveitis by IVT of Regulator T-cells: Study of Tolerance of Dose (UVEREG). In: Assistance Publique - Hôpitaux de Paris; 2017.
8. Infection - Fungal: Cutaneous alternariasis with suspected dissemination in a patient with sarcoidosis on immunosuppression. Journal of the American Academy of Dermatology 2016; 74 (Supplement 1): AB156.
9. Culver DA, Ribeiro Neto ML, Moss BP, Willis MA. Neurosarcoidosis. Seminars in Respiratory and Critical Care Medicine 2017; 38(4): 499-513.
10. Schaflein E, Schaeflein E, Wettach I, et al. Extensive interactions between eating and weight disorder, major depression, pain, and sarcoidosis.
11. Byard RW, Manton N, Tsokos M. Sarcoidosis and mechanisms of unexpected death. Journal Of Forensic Sciences 2008; 53(2): 460-464.
12. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 1985; 10: 141-146.
13. Cross AR. 2017; http://www.redcrossblood.org/learn-about-blood/blood-types.html. Accessed September 1, 2017.
14. Stanford Blood Center. How rare is my type? Available from https://bloodcenter.stanford.edu/learn/blood-types/. Accessed September 1, 2017.
15. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of sarcoidosis 1946-2013: a population-based study. Mayo Clinic Proc 2016; 91(2): 183-188.
16. Baughman RP, Field S, Costabel U, et al. Sarcoidosis in America. Analysis Based on Health Care Use. Ann Am Thorac Soc 2016; 13(8): 1244-1252.
17. Rastogi S, Johnson TD, Hoeffel EM, Drewery MP. (2011). The Black Population: 2010 census briefs. Retrieved from Washington, DC: http://www.census.gov/prod/cen2010/briefs/c2010br-06.pdf
18. Cozier YC, Berman JS, Palmer JR, Boggs DA, Serlin DM, Rosenberg L. Sarcoidosis in black women in the United States: data from the Black Women's Health Study. Chest 2011; 139(1): 144-150.
19. Gupta D, Singh DA, Agarwal R, Aggarwal AN, Joshi K, Jindal SK. Is tobacco smoking protective for sarcoidosis? A case-control study from North India. Sarcoidosis Vasc Diffuse Lung Dis 2010; 27(1): 19-26.
20. Burtis CAA, Edward R.; Bruns, David E. Tietz Fundam Clin Chem. 6 ed. 2008.
21. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician Medecin De Famille Canadien 2015; 61(8): e372-e381.
22. Kucera GP, Rybicki BA, Kirkey KL, et al. Occupational risk factors for sarcoidosis in African-American siblings. Chest 2003; 123: 1527.
23. Public Health Service Agency for Toxic Substances and Disease Registry. In: Services UDOHAH, ed: Agency for Toxic Substances and Disease Registry (ATSDR); September 2004.
24. Rifai NH, Andrea; Wittwer, Carl T. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 6 ed: Elsevier; 2018.
25. Newman KL, Newman LS. Occupational causes of sarcoidosis. Curr Opin Allergy Clin Immunol 2012 April; 12(2): 145–150. doi:10.1097/ACI.0b013e3283515173.
26. D. Steiger, L. Bubendorf, M. Oberholzer, M. Tamm, J.D. Leuppi. Ciprofloxacin-induced acute pneumonitis. European Respiratory Journal 2004; 23: 172-174.
27. Beuselinck B, Devuyst O. Ciprofloxacin-induced hypersensitivity vasculitis. Acta Clin Belg 1994; 49(3-4): 173-6.
28. Paone GC, Ilio; Di Tanna, Gian Luca; Leone, Alvaro; Batzella, Sandro; Belli, Francesco; Galluccio, Giovanni; Sebastiani, Alfredo; Conti, Vittoria; Terzano, Claudio. Potential Usefulness of a Combination of Inflammatory Markers in Identifying Patients With Sarcoidosis and Monitoring Respiratory Functional Worsening. Am J Clin Pathol 2012; 137: 494-502.
29. Pincus MR, McPherson RA, Henry JB. Henry's Clinical Diagnosis and Management by Laboratory Methods 21st ed. United States of America: Saunders Elsevier; 2007.