Obesity and Weight Gain in Relation to Incidence of Sarcoidosis in US Black Women

Data From the Black Women's Health Study

Yvette C. Cozier, DSc; Patricia F. Coogan, DSc; Praveen Govender, MD; Jeffrey S. Berman, MD; Julie R. Palmer, ScD; and Lynn Rosenberg, ScD

BACKGROUND: Sarcoidosis, a systemic disorder characterized by chronic granulomatous inflammation, occurs more frequently among US black women, as do overweight and obesity. Little is known about the relation of overweight and obesity, which induce chronic inflammation, to incidence of sarcoidosis.

METHODS: We assessed the relation of obesity and weight gain to the incidence of sarcoidosis in the Black Women's Health Study, a follow-up study of 59,000 US black women aged 21 to 69 years at baseline in 1995. Information on weight at age 18 years, height, current weight, incident sarcoidosis, and covariates was collected at baseline and on biennial follow-up questionnaires. Cox regression models adjusted for age, education, geographic region, smoking, alcohol consumption, and physical activity were used to estimate incidence rate ratios (IRRs) and 95% CIs.

RESULTS: From 1995 through 2011, 454 incident cases of sarcoidosis occurred during 707,557 person-years of follow-up. The incidence of sarcoidosis increased with increasing BMI and weight gain. The IRR was 1.40 (95% CI, 0.88-2.25) for BMI ≥ 30 kg/m² at age 18 years relative to 20 to 24 kg/m² (*P* trend = .18), 1.42 (95% CI, 1.07-1.89) for BMI ≥ 35 kg/m² at baseline relative to 20 to 24 kg/m² (*P* trend = .01), and 1.47 (95% CI, 1.10-1.97) for a weight gain between age 18 years and baseline of ≥ 30 kg relative to 0 to 9 kg (*P* trend = .16). In stratified analyses, there were significant trends of sarcoidosis incidence with increasing BMI and weight gain in women aged ≥ 45 years and ever smokers.

CONCLUSIONS: The present study provides evidence that weight gain and obesity during adulthood are associated with increased sarcoidosis incidence.

CHEST 2015; 147(4):1086-1093

Manuscript received May 13, 2014; revision accepted September 26, 2014; originally published Online First November 20, 2014.

ABBREVIATIONS: BWHS = Black Women's Health Study; IRR = incidence rate ratio

AFFILIATIONS: From the Slone Epidemiology Center (Drs Cozier, Coogan, Palmer, and Rosenberg), Boston University; and Pulmonary Center (Drs Govender and Berman), Boston University School of Medicine, Boston, MA.

FUNDING/SUPPORT: This work was supported by the National Heart, Lung, and Blood Institute [Grant K01HL088709] and the Division of Can-

cer Control and Population Science, National Cancer Institute (www.cancercontrol.cancer.gov) [Grants CA058420 and CA164974].

CORRESPONDENCE TO: Yvette C. Cozier, DSc, Slone Epidemiology Center, Boston University, 1010 Commonwealth Ave, Boston, MA 02215; e-mail: yvettcec@bu.edu

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-1099

Sarcoidosis is a multisystem disease of unknown etiology. It is associated with a wide spectrum of disease manifestations but typically affects the lung.¹⁻³ In the United States, patterns of sarcoidosis differ by race and sex,²⁻⁵ with black women experiencing the highest incidence of the disease. The estimated lifetime risk of sarcoidosis is 2.7% for black women compared with 1.0% for white women.^{4,5}

The prevalence of obesity is also disproportionately high in US black women.⁶⁻⁸ Obesity is characterized by a state of low-grade systemic inflammation.⁹ Sarcoidosis is characterized by chronic granulomatous inflammation,

which is believed to be a result of a persistent T-helper 1 polarized immune response targeted to an as-yet-unidentified antigen.¹⁰ We hypothesized that the inflammation associated with obesity partly explains the higher incidence of sarcoidosis in black women.

We prospectively assessed the associations of obesity and weight gain with the incidence of sarcoidosis over a 16-year period in the Black Women's Health Study (BWHS), a prospective follow-up of 59,000 US black women. To our knowledge, this epidemiologic study is the first to examine the relation of these factors to incident sarcoidosis in black women.

Materials and Methods

The human subjects protocol for this study was approved by the Boston University Medical Center Institutional Review Board (H-31125). The BWHS is a follow-up study of US black women that began in 1995 when 59,000 women aged 21 to 69 years (median, 38 years) enrolled through postal health questionnaires.¹¹ Participants indicated their informed consent by completing the questionnaire. At baseline, 97% of the participants had completed high school, and 44% had completed college. More than 80% were from California, Georgia, Illinois, Indiana, Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, South Carolina, Virginia, and the District of Columbia. Participants are mailed biennial questionnaires to obtain updated health information.

On the 1995 baseline questionnaire, BWHS participants provided data on demographics, medical and reproductive history, smoking and alcohol use, physical activity, height, weight, use of selected medications such as oral contraceptives and female hormone supplements, diet, and use of medical care. Participants complete biennial follow-up questionnaires to update these and other exposures and report new occurrences of disease. Follow-up of the baseline cohort is 80% after eight questionnaire cycles.

Ascertainment and Validation of the Diagnosis of Sarcoidosis

On the 1995 baseline questionnaire, BWHS participants were asked whether a physician had ever told them that they had any of a list of medical conditions. The list of diagnoses did not specify sarcoidosis, but numerous women wrote it in under other conditions. All subsequent follow-up questionnaires asked specifically about sarcoidosis and whether the participants had received a new diagnosis in the past 2-year period.

All participants who reported incident sarcoidosis are asked for permission to contact their physicians for information on diagnosis and treatment.¹² The physicians are asked to complete a questionnaire regarding the study participant's condition and treatment or, alternatively, to provide a copy of the participant's medical records pertaining to sarcoidosis. The diagnosis of sarcoidosis was confirmed for 96% of the 160 participants for whom physician questionnaires or medical records were obtained to date. Among the six disconfirmed cases, one had asthma and one had keloids; alternative diagnoses were not provided for the four others. In addition, a supplemental sarcoidosis questionnaire sent to participants with incident sarcoidosis assessed disease severity by asking whether the participants had experienced any of the following nine symptoms at the time of diagnosis: shortness of breath, cough, chest pain, fatigue, palpitations, nasal/sinus congestion, joint pain/muscle aches, numbness, and headaches.¹² We considered women with two or more symptoms at the time of diagnosis to have more-severe disease. Based on the high level of agreement between self-report and

physician report and records, all participants who reported sarcoidosis during follow-up were included as cases of sarcoidosis unless the diagnosis was disconfirmed by medical records.

Exposure Variables and Covariates

Information on adult height (feet and inches), weight at age 18 years (pounds), prudent dietary pattern, recent medical visit, and comorbid illness (eg, hypertension, type 2 diabetes mellitus, asthma) was collected at baseline in 1995. Information on health insurance status for the previous 2-year period was collected in 1997. Current weight, age, geographic region, smoking status, alcohol consumption, and vigorous physical activity were ascertained at baseline in 1995 and on each follow-up questionnaire. Years of education were ascertained on the 1995 and 2003 questionnaires.

BMI at age 18 years and at baseline was calculated as weight measured in kilograms at each time divided by height squared measured in meters. Weight change was calculated as the difference between weight at age 18 years and weight at baseline (1995), converted to kilograms. We assessed the validity of self-reported height and weight in a physical activity validation study among 115 BWHS participants residing in the Washington, DC, metropolitan area.¹³ Correlation coefficients for self-reported and technician measures of weight and height were 0.97 and 0.93, respectively ($P < .01$).¹⁴

Data Analysis

Follow-up for the current analysis was from 1995 to 2011. Potential participants were 55,840 women with complete data on weight at age 18 years and at baseline whose cumulative weight change between age 18 years and baseline was ≥ 0 kg. We excluded prevalent cases of sarcoidosis ($n = 687$) and cancer ($n = 1,402$), women whose baseline weight was ≤ 36 or ≥ 136 kg ($n = 677$), women who were currently pregnant in 1995 ($n = 1,012$), and women who underwent gastric bypass surgery ($n = 100$), leaving 51,452 women in the analytic sample.

Incidence rate ratios (IRRs) and 95% CIs for incident sarcoidosis were estimated for categories of BMI at age 18 years, BMI at baseline, and weight gain from age 18 years to 1995 using Cox proportional hazard models in PROC PHREG of SAS 9.1 (SAS Institute, Inc). Person-time was calculated from baseline to year of sarcoidosis diagnosis, loss to follow-up, death, or end of follow-up, whichever occurred first. We constructed two analytic models to control for potential confounders. Model 1 adjusted for age (1-year intervals) and questionnaire cycle (2-year intervals). Model 2 adjusted for model 1 covariates plus education (≤ 12 , 13-15, ≥ 16 years), geographic region (Northeast, South, Midwest, West), pack-years of smoking (never smoked, < 5 , 5-14, 15-24, ≥ 25 years), alcohol consumption (never, < 1 , 1-6, 7-13, ≥ 14 drinks/week), and hours of vigorous physical activity per week (none, < 5 , and ≥ 5 h/week). All variables in the model, with the exception of BMI, were treated as time varying using the Anderson-Gill data structure.¹⁵

We did not treat BMI as time varying because of the possibility that symptoms of sarcoidosis would have affected weight during follow-up. In further analyses, we controlled for additional potential confounders, including prudent dietary pattern (quintiles), health insurance status (yes, no), recent medical visit (yes, no), hypertension with medication (yes, no), type 2 diabetes mellitus (yes, no), and asthma (yes, no). Tests

of trend were performed by entering each variable in its ordinal form into a single term in the model.¹⁶ We assessed whether associations between BMI and sarcoidosis were consistent across age (< 45 years, ≥ 45 years) and smoking status (ever smoker, never smoker). We obtained *P* values for interaction by comparing models with and without cross-product terms between the covariate and the exposure variable.

Results

Table 1 shows baseline characteristics in 1995 in relation to baseline BMI. Age, BMI at age 18 years, < 16 years of education, residence in the midwest, and physical inactivity were positively associated with BMI in 1995. We observed a positive association between baseline BMI and disease severity among women with sarcoidosis. The percentage of participants reporting two or more symptoms for normal weight (BMI < 25 kg/m²), overweight

(BMI 25-29 kg/m²), and obesity (BMI ≥ 30 kg/m²) were 53%, 53%, and 62%, respectively.

Over the follow-up period, 454 cases of sarcoidosis occurred during 707,557 person-years. As shown in Table 2, there was a positive association with each measure of BMI and for weight gain. After adjustment for behavioral risk factors (model 2), the multivariable IRR for obesity (BMI ≥ 30 kg/m²) at age 18 years relative to 20 to 24 kg/m² was 1.40 (95% CI, 0.88-2.25; *P* trend = .18);

TABLE 1 Baseline Characteristics According to BMI at Baseline (1995) in the Black Women's Health Study (N = 51,452)

Variable	BMI at Baseline, kg/m ²				
	< 20	20-24	25-29	30-34	≥ 35
No. women	2,597	16,342	16,575	8,769	7,169
Median age, y	31	36	40	41	39
Median BMI at age 18 y, kg/m ²	17.5	19.4	20.6	22.3	25.1
Education, y ^a					
≤ 12	18	15	20	23	24
13-15	33	34	37	38	39
≥ 16	49	51	43	39	37
Geographic region ^a					
Northeast	28	27	27	28	27
South	31	30	31	31	31
Midwest	22	22	24	24	26
West	20	21	18	17	16
Alcoholic drinks/wk ^a					
< 1	75	73	72	74	78
1-6	19	20	21	20	16
≥ 7	6	6	6	6	5
Pack-y cigarette smoking ^a					
Never smoked	64	66	62	62	62
< 5	13	13	14	13	14
5-14	12	12	13	14	13
≥ 15	8	7	9	9	8
Vigorous physical activity, h/wk ^a					
None	35	26	30	36	46
< 5	49	54	53	50	44
≥ 5	16	20	17	14	10

Data are presented as percentages unless otherwise indicated. Percentages may not sum to 100% due to missing data.

^aValues are standardized to the age distribution of the Black Women's Health Study cohort in 1995.

TABLE 2] BMI at Age 18 y, BMI at Baseline (1995), and Weight Gain (Age 18 y to Baseline) in Relation to Incidence of Sarcoidosis in the Black Women's Health Study (1995-2011)

Category	No. Cases	Person-y	Incidence Rate Ratio (95% CI)	
			Model 1 ^a	Model 2 ^b
BMI at age 18 y, kg/m ²				
< 20	190	306,742	0.96 (0.78-1.17)	0.96 (0.79-1.17)
20-24	201	316,075	Reference	Reference
25-29	43	62,962	1.12 (0.80-1.55)	1.08 (0.77-1.50)
≥ 30	20	21,778	1.49 (0.93-2.38)	1.40 (0.88-2.25)
<i>P</i> trend value	...	...	.10	.18
BMI at baseline, kg/m ²				
< 20	18	35,633	1.04 (0.63-1.71)	1.03 (0.62-1.69)
20-24	121	226,847	Reference	Reference
25-29	142	228,933	1.13 (0.89-1.44)	1.09 (0.85-1.39)
30-34	87	119,237	1.31 (0.99-1.73)	1.24 (0.93-1.64)
≥ 35	86	96,907	1.55 (1.17-2.05)	1.42 (1.07-1.89)
<i>P</i> trend value	...	...	.002	.01
Weight gain age 18 y to baseline, kg				
0-9	100	208,137	Reference	Reference
10-19	135	223,520	1.13 (0.87-1.47)	1.09 (0.84-1.42)
20-29	113	156,033	1.32 (1.00-1.74)	1.24 (0.94-1.64)
≥ 30	106	119,866	1.60 (1.21-2.13)	1.47 (1.10-1.97)
<i>P</i> trend value	...	...	.05	.16

^aModel 1 adjusted for age and questionnaire period.

^bModel 2 adjusted for model 1 variables plus years of education, geographic region, pack-y smoking, alcohol consumption, and vigorous physical activity.

this estimate was reduced to 1.22 (95% CI, 0.75-2.00) after adjustment for BMI at baseline. The multivariable IRR from model 2 for BMI ≥ 35 kg/m² at baseline relative to 20 to 24 kg/m² was 1.42 (95% CI, 1.07-1.90; *P* trend = .01); after adjustment for BMI at age 18 years, the multivariable IRRs were unchanged. The multivariable IRR from model 2 for cumulative weight gain ≥ 30 kg relative to 0 to 9 kg was 1.47 (95% CI, 1.10-1.97; *P* trend = .16); the estimates were unchanged after simultaneous adjustment for BMI at age 18 years and BMI at baseline. The associations were still present after further adjustment for prudent dietary pattern, health insurance status, recent medical visit, hypertension, type 2 diabetes mellitus, and asthma.

We repeated models 1 and 2 while restricting cases to those confirmed by physician records (*n* = 140). The associations were stronger, with IRRs of 2.13 (95% CI, 1.09-4.17; *P* trend = .01) for BMI ≥ 30 kg/m² at age 18 years; 1.52 (95% CI, 0.90-2.56; *P* trend = .01) for baseline BMI ≥ 30 kg/m²; 1.49 (95% CI, 0.87-2.54; *P* trend = .10) for weight gain ≥ 30 kg. In a subanalysis of women who were lean at age 18 years (BMI < 20 kg/m²),

the multivariable IRR for obesity (BMI ≥ 30 kg/m²) at baseline relative to 20 to 24 kg/m² was 1.81 (95% CI, 0.86-3.83; *P* trend = .018).

In stratified analyses, we assessed the associations across age categories (< 45 years, ≥ 45 years) and categories of smoking (never smoker, ever smoker) (Table 3). There were significant trends of increasing incidence with increasing BMI at age 18 years, BMI at baseline, and weight gain in women aged ≥ 45 years, with weaker associations among women aged < 45 years. The trends for the risk to increase with increasing BMI at baseline and with weight gain were statistically significant among ever smokers but not among never smokers.

Discussion

In this first study, to our knowledge, of obesity and weight gain in relation to incident sarcoidosis in black women, we observed elevated risks of sarcoidosis among those who were obese at age 18 years, obese at baseline in 1995, or gained a considerable amount of weight between age 18 years and baseline. The results are consistent with those from a follow-up study in Danish

TABLE 3 BMI at Age 18 y, BMI at Baseline (1995), and Weight Gain (Age 18 y to 1995) in Relation to Incidence of Sarcoidosis According to Age and Smoking Status in the Black Women's Health Study (1995-2011)

Category	Age				Smoking Status					
	No. Cases	< 45 y	No. Cases	≥ 45 y	P Value for Interaction	No. Cases	Never Smoker	No. Cases	Ever Smoker	P Value for Interaction
BMI at age 18 y, kg/m ²										
< 20	108	1.29 (0.98-1.70)	82	0.71 (0.53-0.94)	...	122	1.00 (0.78-1.29)	65	0.88 (0.63-1.22)	...
20-24	94	Reference	107	Reference	...	120	Reference	80	Reference	...
25-29	24	1.13 (0.72-1.77)	19	1.05 (0.65-1.72)	...	29	1.29 (0.86-1.94)	14	0.79 (0.45-1.40)	...
≥ 30	9	1.18 (0.59-2.35)	11	1.83 (0.95-3.51)	...	8	1.02 (0.50-2.10)	12	1.98 (1.04-3.74)	...
P trend value	...	.30	...	.001	.01	...	.48	...	.16	.16
BMI at baseline, kg/m ²										
< 20	14	1.05 (0.60-1.87)	4	0.85 (0.31-2.38)	...	15	1.27 (0.73-2.21)	3	0.52 (0.16-1.69)	...
20-24	77	Reference	44	Reference	...	83	Reference	38	Reference	...
25-29	70	1.01 (0.73-1.40)	72	1.21 (0.83-1.77)	...	85	1.03 (0.76-1.40)	53	1.10 (0.72-1.67)	...
30-34	42	1.16 (0.79-1.69)	45	1.35 (0.89-2.06)	...	56	1.26 (0.89-1.78)	31	1.19 (0.74-1.92)	...
≥ 35	32	0.99 (0.65-1.51)	54	1.97 (1.30-2.96)	...	40	1.04 (0.70-1.54)	46	2.07 (1.33-3.22)	...
P trend value	...	.83	...	.001	.16	...	.72	...	.0004	.04
Weight gain age 18 y to 1995, kg										
0-9	67	Reference	33	Reference	...	71	Reference	29	Reference	...
10-19	73	1.10 (0.79-1.54)	62	1.06 (0.70-1.63)	...	89	1.07 (0.78-1.47)	45	1.13 (0.71-1.82)	...
20-29	55	1.31 (0.90-1.89)	58	1.15 (0.74-1.77)	...	59	0.98 (0.68-1.40)	51	1.69 (1.06-2.71)	...
≥ 30	40	1.37 (0.91-2.06)	66	1.50 (0.98-2.31)	...	60	1.24 (0.86-1.79)	46	1.96 (1.21-3.18)	...
P trend value	...	.08	...	.04	.81	...	.38	...	.001	.16

Data are presented as incidence rate ratio (95% CI) unless otherwise indicated. Models are adjusted for age, questionnaire period, years of education, geographical region, pack-y smoking, alcohol consumption, and vigorous physical activity.

women with autoimmune disease¹⁷ in which prepregnancy BMI was associated with an increased risk of sarcoidosis and a number of other autoimmune diseases, including erythema nodosum, psoriasis, rheumatoid arthritis, and type 1 diabetes. For sarcoidosis specifically (140 cases), the hazard ratios for BMI 25 to 29 kg/m² and ≥ 30 kg/m² were 1.90 (95% CI, 1.27-2.84) and 3.59 (95% CI, 2.31-5.57), respectively.

Laboratory studies support the possibility that obesity and weight gain increase inflammation. Pohl et al¹⁸ observed enhanced and prolonged inflammatory responses to acute systemic challenge with lipopolysaccharide in diet-induced obese adult rats. Similarly, challenged rats that experienced induced cumulative weight gain from birth to adulthood resulting in adult overweight or obesity were found to have elevated plasma levels of proinflammatory cytokines, including tumor necrosis factor- α , IL-1 β , and IL-6.¹⁹ Pohl et al²⁰ also showed that a weight increase of 11% was adequate to increase the number and duration of inflammatory symptoms in response to lipopolysaccharide challenge.

Over the past decade, there has been a shift in understanding the nature of adipose tissue²¹ such that it is now believed to be a highly active endocrine organ able to mediate biologic effects on inflammation.²² In addition to adipocytes, adipose tissue consists of several types of innate and adaptive immune cells^{23,24} that contribute to the metabolic and immune function of adipose tissue.^{22,24,25} Obese adipose tissue is quite different from lean adipose tissue. As adipose tissue expands with obesity, it undergoes tissue remodeling characterized by adipocyte hypertrophy; tissue fibrosis; and, importantly, a change in the populations of resident immune cells.^{26,27} The net result of these changes is the production of adipokines that influence the metabolic syndrome; loss of cytokines, such as IL-10, that suppress inflammation; and secretion of cytokines tumor necrosis factor- α , IL-6, and interferon- γ that promote inflammation.²⁸ These cytokines alter the immune phenotype of the adipose tissue toward a T-helper 1 proinflammatory phenotype. It is now appreciated that these changes have broad-reaching effects on the lung. Immune cells in the lungs of obese individuals also undergo a switch toward a proinflammatory phenotype, likely in response to the changes in adipose tissue.²⁹ Sarcoidosis in particular is characterized by chronic granulomatous inflammation, which is believed to be a result of a persistent T-helper 1 polarized immune response. These immunologic mechanisms are likely to be operating in different racial groups, and the present results might be generalizable

to white women. However, because the BWHS includes only black women, we could not assess this possibility.

To our knowledge, only one human study has addressed the impact of obesity on the severity of sarcoidosis. In that clinical study of 184 Serbian patients with sarcoidosis and age- and sex-matched control subjects, higher BMI was associated with lower FVC %, higher fatigue, and poorer self-reported health status.³⁰ Although the BWHS lacks detailed immunologic and clinical data, we observed a positive association between BMI at baseline and the number of participants with sarcoidosis reporting two or more symptoms at diagnosis.

The associations of obesity with sarcoidosis incidence in the present study were more apparent in older women and smokers. Older age represents a low-risk category for sarcoidosis relative to younger ages, and relative increases in risk are easier to detect in low-risk populations. In addition, lung function decreases with age,^{31,32} and perhaps the immune and inflammatory effects of weight gain and obesity manifest more strongly in the aging lung. There is evidence that smokers are at low risk for sarcoidosis as shown by inverse associations between cigarette smoking and sarcoidosis risk.³³⁻³⁷ The stronger associations of obesity and weight gain with sarcoidosis among ever smokers may reflect the lower background risk of sarcoidosis in that group compared with never smokers. There was no evidence in the current data that the protective effects of smoking could be a result of the lower BMIs in smokers vs nonsmokers. Smoking was not materially associated with BMI in this cohort. Cigarette smoking may produce profound changes in the numbers, types, and activities of immune and inflammatory cells,^{34,38} altering the immune reactions responsible for initiating disease. It is, therefore, possible that smoking and obesity might interact to increase sarcoidosis risk through adverse effects on the immune system.

Weight in this study was reported prospectively prior to sarcoidosis diagnosis, establishing the temporal sequence between exposure and outcome and obviating recall bias. Important potential confounding factors, including age, smoking, physical activity, education, alcohol consumption, geographic region, diet, insurance status, recent medical visit, and comorbid illness, were taken into account. Follow-up rates within the cohort were high, reducing the likelihood of losses related to both exposure and outcome. Sarcoidosis cases were identified by self-report because it is infeasible and prohibitively expensive to examine all

participants for disease in large observational studies. However, the present validation results in a subset of women showed a high degree of accuracy of self-report.¹²

The present study has several limitations. We relied on self-reported weight and height. Results from a validation study of BWHS participants showed strong correlations between self-reported and technician-measured current weight.¹⁴ We did not have validation data on weight at age 18 years, which was self-reported in 1995 when participants were aged 21 to 69 years, but research in another study indicated acceptable self-report.³⁹ Random errors in reporting or systematic under-reporting of weight by heavier women would have diluted the observed associations of obesity and weight gain with sarcoidosis. We excluded women with very low or high weights to avoid distortion of results by the relatively small number of women with extreme weight values. Because weight loss may be an indication of illness, we excluded women who lost weight between age 18 years and baseline. Furthermore, the results may have been confounded to some degree by steroid use in women for symptoms of sarcoidosis that preceded diagnosis. We do not have comprehensive medical data detailing the timing of steroid use, and this could have biased the relative risk estimates upward.

BWHS participants are volunteers. Participants must be sufficiently literate to complete detailed health questionnaires, and thus, study participants underrepresent the 15% of black women nationally of the same ages who did not graduate from high school.⁴⁰ Conversely, study participants represent most US black women and are residents of many regions of the United States.

In summary, this study provides the first evidence, to our knowledge, that obesity during adulthood is associated with increased sarcoidosis incidence in black women. Excess weight gain may represent a modifiable risk factor for a disease of essentially unknown etiology. The prevalence of obesity has been increasing rapidly in the United States, with the greatest increases among black women.⁶ It has been estimated that obesity will affect up to 70% of US black women by 2020⁶; thus an association between obesity and sarcoidosis incidence is of public health importance. In addition, given the higher prevalence of obesity in black women, it may contribute to the greater incidence of sarcoidosis in black women than in white women. Further prospective studies of weight gain and obesity are needed to clearly establish whether these factors affect the risk of sarcoidosis.

Acknowledgments

Author contributions: Y. C. C. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y. C. C. contributed to originating the idea for this study, supervising the data collection, analyzing and interpreting the data, and writing the manuscript; P. F. C., P. G., and J. S. B. contributed to originating the idea for this study, analyzing and interpreting the data, and writing the manuscript; and J. R. P. and L. R. contributed to originating the idea for this study, designing the BWHS, supervising data collection, analyzing and interpreting the data, and writing the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Other contributions: Data collection and analyses were performed at the Slone Epidemiology Center, Boston University. We thank the participants of the BWHS and the entire BWHS staff.

References

1. Bresnitz EA, Strom BL. Epidemiology of sarcoidosis. *Epidemiol Rev*. 1983;5(1):124-156.
2. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med*. 1997;336(17):1224-1234.
3. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA*. 2011;305(4):391-399.
4. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. *Am J Epidemiol*. 1997;145(3):234-241.
5. Rybicki BA, Maliarik MJ, Major M, Popovich J Jr, Iannuzzi MC. Epidemiology, demographics, and genetics of sarcoidosis. *Semin Respir Infect*. 1998;13(3):166-173.
6. Beydoun MA, Wang Y. Gender-ethnic disparity in BMI and waist circumference distribution shifts in US adults. *Obesity (Silver Spring)*. 2009;17(1):169-176.
7. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010;303(3):235-241.
8. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012;307(5):491-497.
9. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science*. 1993;259(5091):87-91.
10. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med*. 2007;357(21):2153-2165.
11. Rosenberg L, Palmer JR, Rao RS, Adams-Campbell LL. Risk factors for coronary heart disease in African American women. *Am J Epidemiol*. 1999;150(9):904-909.
12. 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.
13. Carter-Nolan PL, Adams-Campbell LL, Makambi K, Lewis S, Palmer JR, Rosenberg L. Validation of physical activity instruments: Black Women's Health Study. *Ethn Dis*. 2006;16(4):943-947.
14. Wise LA, Palmer JR, Spiegelman D, et al. Influence of body size and body fat distribution on risk of uterine leiomyomata in US black women. *Epidemiology*. 2005;16(3):346-354.
15. Therneau TM. *Extending the Cox model*. New York, NY: Springer Verlag; 1997.

16. Breslow NE, Day NE. Statistical methods in cancer research. Volume II—the design and analysis of cohort studies. *IARC Sci Publ.* 1987;(82):1-406.
17. Harpsøe MC, Basit S, Andersson M, et al. Body mass index and risk of autoimmune diseases: a study within the Danish National Birth Cohort. *Int J Epidemiol.* 2014;43(3):843-855.
18. Pohl J, Woodside B, Luheshi GN. Changes in hypothalamically mediated acute-phase inflammatory responses to lipopolysaccharide in diet-induced obese rats. *Endocrinology.* 2009;150(11):4901-4910.
19. Clarke MA, Stefanidis A, Spencer SJ. Postnatal overfeeding leads to obesity and exacerbated febrile responses to lipopolysaccharide throughout life. *J Neuroendocrinol.* 2012;24(3):511-524.
20. Pohl J, Sheppard M, Luheshi GN, Woodside B. Diet-induced weight gain produces a graded increase in behavioral responses to an acute immune challenge. *Brain Behav Immun.* 2014;35:43-50.
21. Denison FC, Roberts KA, Barr SM, Norman JE. Obesity, pregnancy, inflammation, and vascular function. *Reproduction.* 2010;140(3):373-385.
22. Wozniak SE, Gee LL, Wachtel MS, Frezza EE. Adipose tissue: the new endocrine organ? A review article. *Dig Dis Sci.* 2009;54(9):1847-1856.
23. Canello R, Clément K. Is obesity an inflammatory illness? Role of low-grade inflammation and macrophage infiltration in human white adipose tissue. *BJOG.* 2006;113(10):1141-1147.
24. Subramanian V, Ferrante AW Jr. Obesity, inflammation, and macrophages. *Nestle Nutr Workshop Ser Pediatr Program.* 2009;63:151-159.
25. Juge-Aubry CE, Henrichot E, Meier CA. Adipose tissue: a regulator of inflammation. *Best Pract Res Clin Endocrinol Metab.* 2005;19(4):547-566.
26. Schipper HS, Prakken B, Kalkhoven E, Boes M. Adipose tissue-resident immune cells: key players in immunometabolism. *Trends Endocrinol Metab.* 2012;23(8):407-415.
27. Kanneganti TD, Dixit VD. Immunological complications of obesity. *Nat Immunol.* 2012;13(8):707-712.
28. Strissel KJ, DeFuria J, Shaul ME, Bennett G, Greenberg AS, Obin MS. T-cell recruitment and Th1 polarization in adipose tissue during diet-induced obesity in C57BL/6 mice. *Obesity (Silver Spring).* 2010;18(10):1918-1925.
29. Lugogo NL, Hollingsworth JW, Howell DL, et al. Alveolar macrophages from overweight/obese subjects with asthma demonstrate a proinflammatory phenotype. *Am J Respir Crit Care Med.* 2012;186(5):404-411.
30. Gvozdenovic BS, Mihailovic-Vucinic V, Vukovic M, et al. Effect of obesity on patient-reported outcomes in sarcoidosis. *Int J Tuberc Lung Dis.* 2013;17(4):559-564.
31. Degens H, Maden-Wilkinson TM, Ireland A, et al. Relationship between ventilatory function and age in master athletes and a sedentary reference population. *Age (Dordr).* 2013;35(3):1007-1015.
32. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging.* 2006;1(3):253-260.
33. Douglas JG, Middleton WG, Gaddie J, et al. Sarcoidosis: a disorder commoner in non-smokers? *Thorax.* 1986;41(10):787-791.
34. Hance AJ, Basset F, Saumon G, et al. Smoking and interstitial lung disease. The effect of cigarette smoking on the incidence of pulmonary histiocytosis X and sarcoidosis. *Ann N Y Acad Sci.* 1986;465:643-656.
35. Harf RA, Ethevenaux C, Gleize J, Perrin-Fayolle M, Guerin JC, Ollagnier C. Reduced prevalence of smokers in sarcoidosis. Results of a case-control study. *Ann N Y Acad Sci.* 1986;465:625-631.
36. Gupta D, Singh AD, 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.
37. Bresnitz EA, Stolley PD, Israel HL, Soper K. Possible risk factors for sarcoidosis. A case-control study. *Ann N Y Acad Sci.* 1986;465:632-642.
38. Hunninghake GW, Crystal RG. Cigarette smoking and lung destruction. Accumulation of neutrophils in the lungs of cigarette smokers. *Am Rev Respir Dis.* 1983;128(5):833-838.
39. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. *Int J Obes Relat Metab Disord.* 1995;19(8):570-572.
40. Newburger EC, Curry A. *Educational Attainment in the United States, March 1999. Current Population Reports.* Washington, DC: US Department of Commerce; 2000.