Racial Differences in Sarcoidosis Incidence: A 5-Year Study in a Health Maintenance Organization

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Reports of racial differences in the incidence of sarcoidosis, a granulomatous disorder of unknown etiology, are primarily based on studies of military and veteran populations. To determine racial differences in sarcoidosis incidence in a metropolitan population, the authors conducted a study of newly diagnosed cases that occurred between 1990 and 1994 among members of the Health Alliance Plan health maintenance organization in Detroit, Michigan. The study population was racially heterogeneous, was limited to individuals aged 20–69 years, and comprised about 5% of the Detroit metropolitan area population in that age group Annual age-adjusted incidence, in number of new cases per 100,000, was highest in African-American females (39.1 cases). The next highest incidence was found in African-American males (29.8 cases), followed by Caucasian females (12.1) and Caucasian males (9 6). African-American females aged 30–39 years were at the greatest risk, with an annual incidence of 107/100,000 Overall, African Americans had about a threefold higher age-adjusted annual incidence (35.5/100,000) compared with Caucasians (10 9/100,000). Additional adjustment for sex, area of residence, and year of study resulted in 3.8-fold greater risk for African Americans compared with Caucasians This study further confirmed the higher incidence of sarcoidosis in African Americans compared with Caucasians, but the racial difference was lower than previously reported The results should be more generalizable than previous studies done with select populations and should serve as a useful frame of reference for future epidemiologic research of sarcoidosis. Am J Epidemiol 1997;145:234–41.

African Americans; biopsy; pulmonary disease (specialty), risk; sex, whites

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology. Although often detected by incidental chest x-ray in asymptomatic individuals, the disease can range from an acute self-limiting process to progressive organ dysfunction with substantial morbidity (1, 2). In the United States, sarcoidosis has been reported to be 10–17 times more common in African Americans compared with Caucasians (3–6). Wide variation in the occurrence of sarcoidosis has also been reported among other ethnic groups. For example, the prevalence of sarcoidosis is about 1–5 per 100,000 in Argentina and Brazil compared with 50–60 per 100,000 in Denmark and Sweden (1, 2). In addition, sarcoidosis is thought to be more common in females (7–10), but this difference is not as well established (1, 11, 12) and may vary in different ethnic groups.

While sarcoidosis risk appears to be associated with age, race, and sex (1), the interaction of all three factors has not been examined. Racial variation in disease incidence with respect to age and sex is an important factor to consider in the search for possible genetic and environmental causes of this disease. We previously found that African-American sarcoidosis patients have a threefold higher prevalence of family history of sarcoidosis compared with Caucasian patients (13). This difference in familial aggregation may be due to an environmental exposure and/or to an inherited susceptibility found more frequently in African Americans. Alternatively, it could be due to the different age and size structure of African-American families or to a different incidence of sarcoidosis in African Americans compared with Caucasians (14). An accurate assessment of the underlying population risk of sarcoidosis for specific age, race, and sex groups can aid in studies aimed at determining why racial disparities in prevalence and familial aggregation exist (13, 15).

In our study, we identified incident cases of sarcoidosis over a 5-year period from a population who belonged to the same health maintenance organization (HMO) and were served by one large medical system.

In recent years, incidence studies have benefited from the use of HMOs (16–18), which usually provide a well-defined, large population base. The use of an HMO to study sarcoidosis has an added advantage that members may be more likely to follow through with the tests and procedures needed to confirm the diagnosis. Our results include age-, race-, and sex-specific incidence estimates that should be useful in studies of other sarcoidosis risk factors.

MATERIALS AND METHODS

Study population

The study population consisted of individuals aged 20–69 years who were members in the Health Alliance Plan HMO from 1990 to 1994 and were served exclusively by the Henry Ford Hospital medical group, which comprises more than 900 primary and specialty care physicians. We restricted our study population to individuals who lived in the three counties that comprise the metropolitan Detroit, Michigan, area. Since the population at risk was a dynamic cohort, with individuals enrolling and leaving, the denominator for each calendar year was based on the population enrolled at midyear. The variables examined for association with development of sarcoidosis included sex, age (10-year intervals from ages 20–69 years), residence (urban vs. suburban), and race (African American vs. Caucasian). Data on race were unavailable for 16 percent of the study population; therefore, for the whole study population, upon which incidence calculations were based, the racial distribution was estimated from the 84 percent with complete demographic data.

The population from which incidence rates between 1990 and 1994 were calculated and the base population from which the study population was drawn are presented in table 1. The HMO study population included about 5 percent of the total metropolitan De-

troit population in the age range 20–69 years. Apart from an increase in enrollment between 1990 and 1992, the HMO population was stable in size and demographic pattern. The demographic differences in the HMO study population compared with the population at large included a slight overrepresentation of the age group 40–49 years, an underrepresentation of the age group 60–69 years, and a higher percentage of urban residents (33 vs. 24 percent), females (55 vs. 51 percent), and African Americans (31 vs. 22 percent).

Case ascertainment

Incident cases of sarcoidosis were identified through a retrospective search of pulmonary clinic and pathology records. To ensure a thorough detection of sarcoidosis cases, we also searched an outpatient database for all individuals who were given the *International Classification of Diseases,* Ninth Revision, code for sarcoidosis (135.0) at any visit from 1990 to 1994. All cases were confirmed by medical chart review. The diagnosis of sarcoidosis had to be noted and supported by either histologic confirmation or a chest x-ray report of bilateral hilar adenopathy accompanied by the exclusion of other disorders (e.g., neoplasms, tuberculosis, or histoplasmosis), which can mimic the signs and symptoms of sarcoidosis. Cases were categorized as either definite (histologic confirmation) or probable (without histologic confirmation). The date of diagnosis for definite cases was the date of biopsy, whereas for probable cases the first date of a physician's diagnosis of presumptive sarcoidosis was used. After the diagnosis date and medical criteria were confirmed, incident cases were linked back to the study population defined above. To be included in the numerator for incidence estimates, all incident cases had to be enrolled in the HMO subset served by the Henry Ford medical group at the time of their diagnosis.

TABLE 1. **Demographics of study population from 1990 to 1994 compared with the metropolitan Detroit, Michigan, area population***

Year	No †	Race/sex				Age distribution (years)					Urban resident
		CM‡	CF‡	AAM‡	AAF‡	20–29	30–39	40–49	50–59	60–69	
1990	148,716	31.2	36.3	12.4	18.6	23.3	29 3	23 1	13.5	10 7	31 1
1991	166,847	31.1	36.4	12.1	18.7	23.5	29.4	23.6	13.2	10 3	30 9
1992	170,259	30.8	36.1	12.1	19.1	23.1	29.3	24.1	13.5	10.0	31 1
1993	172,635	30.7	35.8	12.2	19.4	22.5	29.0	24.6	14.1	9.9	31 1
1994	172,434	30 1	35 2	12 4	20.3	21.7	28.7	25.3	14.6	9.7	31.9
1990 study area§	2,485,925	37.0	38 4	9 7	12 4	24 7	27 0	20.4	14 0	13.6	24.4

* Numbers represent percentages in respective categories.
† Population totals for individuals aged 20–69 years
‡ CM, Caucasian males, CF, Caucasian females, AAM, African-American males, AAF, African-American females.
§ 1990 US Census estimates for the Detroit metropolitan area

Characterization of cases

Additional data collected on incident cases included the chest radiograph stage at presentation, presence of symptoms (e.g., fever, cough, or dyspnea) at time of diagnosis, and extrathoracic involvement. Radiographic stages were stratified into five levels as previously defined (19): zero, a normal chest x-ray; one, the presence of bilateral hilar adenopathy only; two, adenopathy with pulmonary infiltrates; three, pulmonary infiltrates without adenopathy; and four, pulmonary fibrosis with loss of lung volume. Extrathoracic involvement included any disease manifestation that occurred outside the lungs as noted by a physician.

Statistical analysis

Annual and average annual incidence rates were calculated for each race (African American vs. Caucasian)/sex group over the 5-year study period. All incidence estimates, except age-specific estimates, were adjusted to the 1990 United States population by using the direct method. The crude and adjusted risk estimates of developing sarcoidosis over the 5-year study period for race (African American vs. Caucasian), sex, age, and area of residence (urban vs. suburban) were calculated from a Poisson regression model. Using the generalized linear interactive modeling (GLIM) statistical package (20), we assumed the number of new cases in each stratum to follow a Poisson distribution with mean $n\lambda$, where n was the number of individuals in the stratum and λ was the risk of developing sarcoidosis. Parameterization was done

with a log-linear model, in which each term was first fit individually to obtain crude relative risk estimates, and then all terms were included in a main effects model to obtain adjusted estimates. Using the main effects model, we then tested all possible two-way interactions on the basis of the change of the log-likelihood of the model after the introduction of each interaction term. Associations between race-/sex-specific sarcoidosis incidence and disease characteristics at presentation were analyzed using chi-square tests.

RESULTS

Sarcoidosis incidence

Over the 5-year study period, we identified 259 newly diagnosed sarcoidosis cases that were part of our defined study population. Among these patients, four were neither Caucasian nor African American and were excluded, since our analysis was restricted to these two races. The average time of enrollment for the incident cases in the HMO study population was 3.08 ± 2.99 years compared with 3.17 ± 3.26 for the entire study population. Although there was some fluctuation in annual incidence over the 5-year period, incidence was consistently higher for African-American females compared with African-American males and for African-American males compared with Caucasian males and females (figure 1). Race- and sex-specific, age-adjusted average annual incidence over the 5-year period was 9.6/100,000 for Caucasian males, 12.1/100,000 for Caucasian females, 29.8/100,000 for
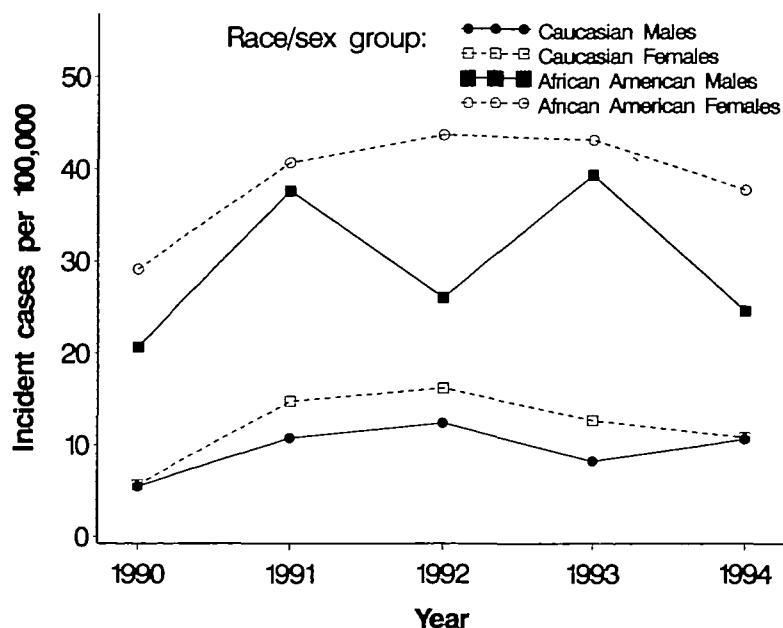
FIGURE 1. Annual average, age-adjusted sarcoidosis incidence for Caucasian males, Caucasian females, African-American males, and African-American females in a health maintenance organization, Detroit, Michigan, 1990–1994.

African-American males, and 39.1/100,000 for African-American females (table 2). When incident cases were limited to those with biopsy confirmation, pulmonary involvement (radiographic stage one or greater), or symptoms at presentation, the race/sex pattern of disease incidence was unchanged (table 2). In both races, the female:male ratio was approximately 1.3:1. When the sexes were combined, the 5-year age-adjusted annual incidence was 10.9/100,000 for Caucasians and 35.5/100,000 for African Americans.

The highest sarcoidosis incidence was in the age range 20–49 years (figure 2). The highest annual age-specific incidence, 107/100,000, was found in African-American females aged 30–39 years, followed by African-American males aged 30–39 years (89/100,000). For Caucasians, sarcoidosis incidence peaked a decade later (ages 40–49 years) in both males and females. After age 60, the annual incidence in all the race/sex groups except African-American males fell to approximately 10 cases per 100,000. While African-American males aged 60–69 years had a much higher incidence (22.4/100,000) than did the other race/sex groups in this age stratum, this estimate also had a large standard error (±12.9/100,000) since it was based on only three incident cases. Sarcoidosis before age 20 or after age 70 is so infrequent that the disease incidence can be considered negligible. Therefore, based on cumulative incidence estimates between ages 20 and 69 years, the lifetime risk of sarcoidosis for African-American males and females was 2.1 and 2.7 percent, respectively, whereas the lifetime risk for Caucasian males and females was 0.7 and 1.0 percent, respectively.

Sarcoidosis risk factors

Of the risk factors examined for sarcoidosis (table 3), African-American race had the highest unadjusted relative risk, at 3.23 (95 percent confidence interval (CI) 2.51–4.15). Females were at an increased risk for sarcoidosis, with an unadjusted relative risk of 1.43 (95 percent CI 1.11–1.84). The greatest unadjusted

relative risk in the five decades of life was in the age group 30–39 years (relative risk (RR) = 1.68, 95 percent CI 1.20–2.37), and the smallest was in the age group 60–69 years (RR = 0.49, 95 percent CI 0.26–0.94). When all of these factors were placed in the same model, including a variable for year of study to adjust for secular trends, race became an even stronger predictor of sarcoidosis (RR = 3.81, 95 percent CI 2.69–5.40), but the relative risk for female sex decreased to 1.29 and was only marginally significant. Urban residence, which had a statistically significant crude relative risk that was protective (RR = 0.48; 95 percent CI 0.38–0.62), reversed direction (RR = 1.29) in the multivariate model. Of all of the possible two-way interaction terms tested, race by age (χ^2 = 12.06; p = 0.017 with 4 degrees of freedom) and sex by age (χ^2 = 9.57; p = 0.048 with 4 degrees of freedom) were statistically significant.

Disease presentation

Table 4 shows the race/sex differences between patients at the time of disease presentation. African Americans had more radiographically advanced disease compared with Caucasians; Caucasians more often presented with stage 1 disease (bilateral hilar adenopathy only), whereas African Americans more often presented with more advanced disease. African Americans had a 2- to 3-year younger mean age at diagnosis compared with Caucasians. Both symptomatic disease and extrathoracic involvement were more prevalent in females and African Americans. Of the 102 cases with extrathoracic involvement, cutaneous sarcoid was most common (48 percent), followed by eye (31 percent) and joint (29 percent) involvement. African Americans had more biopsy-confirmed disease compared with Caucasians (71 vs. 61 percent; p = 0.094). Statistically significant race/sex heterogeneity was found for radiographic stage (0 and 1 vs. 2–4; p = 0.020), extrathoracic involvement (p = 0.030), and symptomatic disease (p = 0.044).

TABLE 2. Age-adjusted sarcoidosis incidence by case definition and race/sex group in a health maintenance organization population, Detroit, Michigan, 1990–1994

| Type of sarcoidosis | Caucasians | | | | African Americans | | | |
| | Males | | Females | | Males | | Females | |
	Incidence	95% CI*	Incidence	95% CI	Incidence	95% CI	Incidence	95% CI
Biopsy confirmed	5.9†	2 9–8.9	7 3	4.3–10.4	20 1	11 4–28.8	28.7	20.4–37.0
Pulmonary	9.0	5 3–12.7	11.7	7.8–15.6	28 2	17 9–38.5	36.2	26.8–45.5
Symptomatic	6 8	3 6–10 0	8.9	5.6–12.3	23 8	14.3–33.2	34.4	25.4–43.5
All cases	9.6	5.8–13.3	12.1	8.2–16 1	29.8	19 2–40.4	39.1	29.4–48.8

* CI, confidence interval.
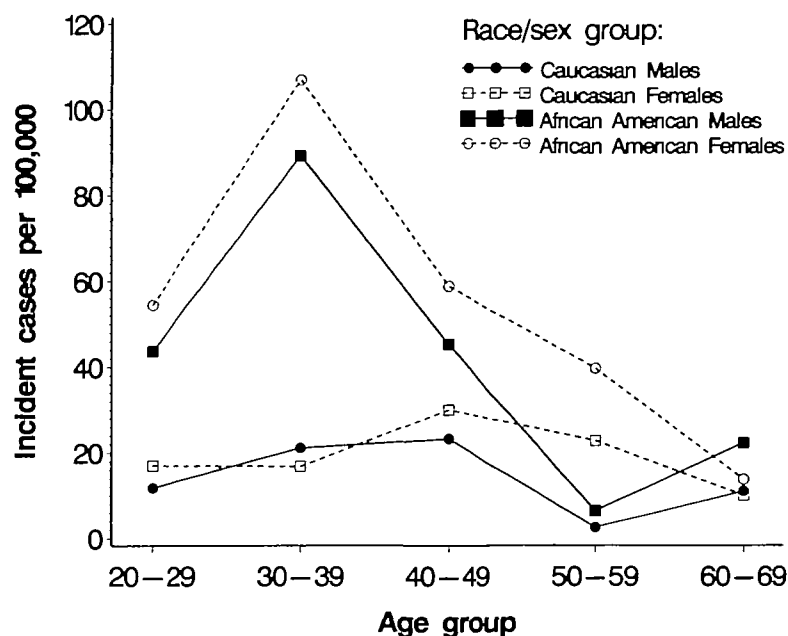† Per 100,000 person-years age adjusted to the 1990 US population.

FIGURE 2. Annual average, age-specific sarcoidosis incidence for Caucasian males, Caucasian females, African-American males, and African-American females in a health maintenance organization, Detroit, Michigan, 1990–1994

TABLE 3. Crude and adjusted relative risk of developing sarcoidosis in a health maintenance organization population, Detroit, Michigan, 1990–1994

Variable	Unadjusted risk estimates		Adjusted risk estimates	
	RR*	95% CI*	RR	95% CI
African-American race	3.23	2.51–4.15	3.81	2.69–5.40
Female sex	1.43	1 11–1 84	1.29	1.00–1 67
Age (years)				
20–29	1		1	
30–39	1 68	1.20–2.37	1.71	1.22–2.42
40–49	1.34	0 93–1 94	1 35	0.94–1 96
50–59	0 63	0 37–1.08	0 66	0.39–1.12
60–69	0 49	0 26–0 94	0.51	0 27–0.98
Urban residence	0 48	0 38–0.62	1 29	0 92–1.81

* RR, relative risk; CI, confidence interval

DISCUSSION

Our study represents the first report of differences in age- and sex-specific sarcoidosis incidence between African Americans and Caucasians. We found that African-American females aged 30–39 years had a 20 percent higher risk of sarcoidosis compared with African-American males of the same age, who had the next highest sarcoidosis risk. Apart from the higher disease incidence in African Americans compared with Caucasians, African Americans had a higher frequency of extrathoracic and symptomatic disease and were diagnosed at a slightly earlier age. These findings are consistent with past studies of racially heterogeneous populations that found African Americans to be more severely affected (21–24). Our age-adjusted, race-specific incidence estimates show that African

Americans have a three- to fourfold greater risk for disease compared with Caucasians. While this racial difference is lower than found in other studies of racially heterogeneous populations (3–6, 25), it more likely represents racial differences in sarcoidosis incidence in the general population.

Most population-based incidence studies of sarcoidosis were confined to racially homogeneous European populations (7, 10, 11, 26–29), and the one population-based study done in the United States was limited to Caucasians (12). In general, the incidence studies that used mass radiographic screening resulted in a higher incidence (7, 29), probably because of inclusion of more asymptomatic cases, many of which would likely have gone undetected in an observational study. While radiographic screening may give a better idea of

TABLE 4. Characteristics of incident sarcoidosis cases at presentation by race and sex in a health maintenance organization population, Detroit, Michigan (n = 255), 1990-1994

Race/sex	No	Age			Radiographic stage*								Extrathoracic		Symptomatic		Biopsy proven	
		Mean	(SD†)	Median	0 No	0 %‡	1 No	1 %	2 No	2 %	3 or 4 No	3 or 4 %	No	%	No	%	No	%
Caucasians																		
Males	41	39.8	(9 3)	38 2	2	4.9	27	65.9	8	19.5	4	9.8	13	31.7	29	70.7	28	68.4
Females	60	40.9	(10 7)	40 6	2	3.3	40	66.7	11	18.3	7	11.7	22	36.7	45	75.0	36	60.0
African Americans																		
Males	49	37 8	(9 6)	37.0	3	6.1	27	55.1	14	28.6	4	8.2	14	28.6	39	79.6	33	67.3
Females	105	37 3	(8 8)	38 0	6	5.7	45	42.9	37	35.2	16	15.2	53	50.5	93	88.6	77	73.3

* One African-American male and one African-American female had missing chest x-rays
† SD, standard deviation
‡ Percentage within race/sex group.

the total number of sarcoidosis cases in a population, most asymptomatic cases spontaneously resolve within 2 years (7, 30) and thus have limited public health implications. This is especially true when racial differences in sarcoidosis are considered, since allocation of resources and disease prevention and treatment are best addressed in studies of cases that result in morbidity. Our study included asymptomatic cases in the estimation of incidence, but case detection was done in the usual care setting and should therefore reflect the impact of sarcoidosis on the health care system. The age-adjusted incidence of sarcoidosis in Caucasians in our study (10.9 per 100,000) was consistent with those in other studies that relied on diagnosis through usual clinical care (10–12, 26–28) (table 5).

Racial comparisons of incidence, while previously confined to primarily male military or veteran populations (3–6, 24, 25), have been helpful in pointing out the greater risk of sarcoidosis in African Americans. For studies that used active military personnel (3, 5, 6), case detection benefited from routine screening, which ensures high case ascertainment. However, the populations at risk in these studies were not well defined, particularly with regard to race. The studies done in veteran populations relied on case ascertainment through veterans' hospitals (4, 24, 25), which would lead to both underestimates and possible selection biases in incidence rates. Moreover, the underrepresentation of female subjects in these studies and the selection criteria for military service give an incomplete picture of the disease spectrum in the general population.

While some studies have found risks of two or greater for female sex (9, 10), others have found no difference between the sexes (11, 12). In our study, the unadjusted risk for female sex was 1.4, but after adjustment for other demographic factors, it fell to 1.3 and was not statistically significant. This nominal additional risk for female sex is consistent with several other reports (7, 8) but, unfortunately, sheds no new light on whether females are at increased risk for sarcoidosis. Our findings do show that any additional risk to females does not differ between African Americans and Caucasians.

An HMO provides a well-defined cohort for epidemiologic research. Past incidence studies involving HMOs have included such diverse disorders as gestational diabetes (16), prostate cancer (17), and gastric ulcers (18). Since sarcoidosis is uncommon and occurs primarily in young adults, our large cohort of HMO members provided an ideal population to study sarcoidosis incidence. The disadvantage of an HMO is that our results may not be reflective of the general

TABLE 5. Selected incidence studies of sarcoidosis in Caucasian and African-American populations

Study (reference no)	Area	Time period	Incidence per 100,000		Comments
			Caucasians	African Americans	
Gundelfinger and Britten (5)	US Navy and Marine Corps	1954–1958	4.4	47.8	Case ascertainment from statistical reports of hospitalizations
British Thoracic and Tuberculosis Association (28)	Great Britain	1961–1966	3.3		Active case finding in four distinct geographic areas
Sartwell and Edwards (3)	US Navy	1958–1971	7.6	81.8	65 of 134 cases detected as a result of a routine chest x-ray
Hillerdal et al. (7)	Sweden	1966–1980	19		Over 50% of cases detected at health screen
Parkes et al (11)	Isle of Man, Great Britain	1977–1983	14.7		Active case finding in a well-defined population
Henke et al. (12)	Rochester, MN	1946–1975	6.1		Case finding in a well-defined population cohort
Poukkula et al. (29)	Finland	1970–1981	15		Mass radiographic screening done every 3 years
Mana et al. (26)	Spain	1986–1988	1.36		Histologically confirmed cases from 3 hospitals
Fazzi et al. (27)	Tuscany, Italy	1977–1990	1 2		94% of patients detected by galium scan
Kolek (10)	Moravia and Silesia	1981–1990	3 3–4.4		Patients detected at 24 regional clinical centers
Present study	Detroit, MI	1990–1994	10.9	35.5	Patients in a large health maintenance organization diagnosed in one health care system

population, since only individuals with health insurance were included in this study. Employment is directly related to socioeconomic status (SES), and most people obtain HMO membership through their own or a spouse's employer. Therefore, our HMO study population probably underrepresented individuals with lower SES, despite the high percentage of urban Detroit residents. If SES is a risk factor for sarcoidosis, then our risk estimates for race, based on racial differences in SES, would be biased. This could explain the less-striking racial differences we found compared with other studies (3–6, 24, 25). To our knowledge, no studies to date have shown an association of SES with sarcoidosis risk, but given the racial differences in risk, this issue needs to be further examined. Once an individual became part of our defined study population, selection should not have been an issue. We did not require membership in the HMO for any length of time, and preferred selection into the study population for cases was unlikely since the mean time since enrollment for sarcoidosis cases and the entire study population was similar.

Our method of case finding relied on accurate physician diagnosis and reporting of cases. It is unlikely that many cases were misclassified since most were confirmed by tissue diagnosis (67 percent), and over half (66 percent) were referred to a specialty clinic for more thorough diagnostic procedures. Since our large HMO study cohort was encompassed in one health care system that served a metropolitan population, our results should represent Caucasian and African-American sarcoidosis incidence in other large metropolitan populations.

Previous studies have identified African-American race as an important risk factor for sarcoidosis (3–6, 24, 25), and we found a 3.8-fold greater incidence in African Americans after adjustment for other factors. This race differential in sarcoidosis incidence is smaller than has been previously reported in more select populations (3–6, 24, 25). In addition, our results provide the first quantitative summary of the risk in African-American females compared with African-American males and show that the sex differential (1.3:1) was the same in both races. These age, race,

and sex incidence estimates should allow more accurate adjustment for these demographic factors in studies of sarcoidosis aimed at quantifying the effect of other putative environmental and genetic risk factors.

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