Prospective study of body mass index and risk of sarcoidosis in US women

Orianne Dumas, Krislyn Boggs, Yvette Cozier, Meir Stampfer, Carlos Camargo

Prospective study of body mass index and risk of sarcoidosis in U.S. women

Orianne Dumas[1,2], Krislyn M Boggs[3], Yvette C Cozier[4], Meir J Stampfer[3], Carlos A Camargo Jr[3,5]

1. INSERM, U1168, VIMA: Aging and chronic diseases. Epidemiological and public health approaches, F-94807, Villejuif, France
2. Univ Versailles St-Quentin-en-Yvelines, UMR-S 1168, F-78180, Montigny le Bretonneux, France
3. Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA
4. Slone Epidemiology Center, Boston University, Boston, USA
5. Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

Contact information for the corresponding author:

Orianne Dumas

Inserm UMRS 1168

VIMA- Aging and chronic diseases - Epidemiological and public health approaches

16, avenue Paul Vaillant Couturier

94807 Villejuif cedex

France

e-mail: orianne.dumas@inserm.fr

Phone: (33) 1 45 59 53 57

Word count: 1061

Take home message:

Higher BMI is prospectively associated with increased risk of developing sarcoidosis in women

To the editor:

Sarcoidosis is a systemic inflammatory disorder, characterized by the formation of immune granulomas that can occur in various organs but typically affects the lungs [1]. Although sarcoidosis resolves spontaneously in many cases, about one-third of patients experience chronic disease associated with significant morbidity [2].

Although the exact causes of sarcoidosis remain unknown, it is thought to result from an exaggerated immune response to as yet unidentified antigens in individuals with genetic susceptibility [1]. Geographical variations in sarcoidosis occurrence support the existence of environmental risk factors [3–5]. Research into the potential causes of sarcoidosis has focused on occupational and environmental exposures [6, 7], but lifestyle-related risk factors are less well examined.

The proinflammatory milieu of obesity appears to favor the development of other inflammation-related diseases, such as asthma [8]. Recently, a study of African-American women found that obesity was prospectively associated with a higher risk of incident sarcoidosis [9]. Black Americans are known to have an increased risk of sarcoidosis compared to whites, and risk factors may differ across these two populations. Although an association between obesity and sarcoidosis has also been suggested in two studies of predominantly white populations [10, 11], data were either cross-sectional or included limited information regarding weight change over time and potential confounders. In the current study, we aimed to investigate the prospective association of body mass index (BMI) and weight change with 24-year incidence of sarcoidosis in a large cohort of US female nurses.

The Nurses' Health Study II (NHSII) began in 1989 when 116,430 female registered nurses from 14 U.S. states, aged 25 to 44 years, completed a mailed questionnaire on their medical

history and lifestyle characteristics [3]. Follow-up questionnaires have been sent every two years since. The active follow-up rate (number of person-years in the cohort when participants are censored after their last questionnaire response) from 1989 to 2013 was 86% of the potential person-years. The study was approved by the local Institutional Review Board.

In all questionnaires, participants were asked to report physician-diagnosed condition(s) that they ever had (baseline) or that were diagnosed since the last questionnaire cycle (follow-up). Although no specific question on sarcoidosis was included, participants were asked to report "other major illness" in a final free-text field. We used this information to identify cases of physician-diagnosed sarcoidosis from 1989-2013. Although cases have not been validated by medical records, the validity of these nurses' health outcomes reports is generally >80% for other conditions [12]. Further, a 96% agreement between self-report of sarcoidosis diagnosis and physician's report has been reported in the Black Women's Health Study [9].

Current height and weight, and weight at age 18 years were reported on the baseline questionnaire. Current weight was updated in all subsequent biennial questionnaires. Race (white, black, others), smoking status (never, ex- or current smoker) and pack-years (continuous), US region (West, Midwest, South, Northeast), household income (>$44,500 vs. ≤$44,500), husband's education (high school or less, college graduate, graduate degree), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, 27-41.9, ≥42 metabolic equivalents [METs] per week) and alcohol consumption (0, 0.01-5, 5.01-10, >10 g/day) were examined as potential confounders [9, 10]. Associations of current BMI (i.e., BMI at the questionnaire cycle before diagnosis), BMI at age 18 years, and weight change since age 18 years, with sarcoidosis incidence were evaluated by Cox proportional hazard models. All Cox models were stratified by age in months and calendar year. A two-sided $P<0.05$ was considered statistically significant. All analyses were run using SAS V.9 (SAS Institute, Cary, NC, USA).

The study population consisted of 116,312 women without a history of sarcoidosis at baseline. At baseline, participants were on average 34 years old, 96% were white, 14% were current smokers and 21% were ex-smokers. BMI at baseline was <20 kg/m^2 in 15% of the participants; 20 to 24.9 kg/m^2 in 54%; 25 to 29.9 kg/m^2 (overweight) in 19%; and ≥30 kg/m^2 (obesity) in 12%.

During 2,457,150 person-years of follow-up, from 1989 to 2013, 270 incident cases were reported. Higher current BMI was associated with increased risk of developing sarcoidosis during follow-up (P-trend<0.001, Table 1). Similar results were observed in multivariable-adjusted models (P-trend<0.001), with significant associations in both overweight (hazard ratio: 1.53, 95% confidence interval; 1.12-2.10) and obese (1.74, 1.26-2.40) women. Results were confirmed in a sensitivity analysis, where sarcoidosis cases were restricted to participants who specifically indicated that the diagnosis occurred within 2 years before the questionnaire cycle where they first reported sarcoidosis (n=174): stronger associations were found for the risk of sarcoidosis incidence in overweight (1.75, 1.18-2.59) and obese (1.94, 1.30-2.91) women.

To rule out potential reverse causation (i.e., symptoms of sarcoidosis before diagnosis affecting weight), we examined the association between BMI at age 18 years and sarcoidosis incidence during follow-up. Although associations were attenuated compared to current BMI, a positive significant trend was observed between BMI at age 18 years and sarcoidosis incidence (P-trend=0.009, Table 1). Higher weight gain since age 18 years was also associated with increased risk of sarcoidosis incidence (P-trend=0.02).

In this large cohort of predominantly white US women, increased risks of sarcoidosis were observed in both overweight and obese participants. Consistent findings were reported in a Danish register-based study examining the association between pre-pregnancy BMI in women and the development of several disorders, including sarcoidosis [10]. Similar results were also reported in a population of US black women [9] but only for those with morbid obesity (BMI ≥35 kg/m^2).

Chronic systemic inflammation associated with adiposity is suspected to have a role in the development of many disorders, including respiratory [8] and autoimmune diseases [10]. Adipokines produced in the obese adipose tissue have broad immunomodulatory effects. In particular, they may induce a proinflammatory process in the lungs [8, 9], which is involved in most sarcoidosis cases. Furthermore, some investigators have suggested that the exaggerated inflammatory response to a causal antigen leading to granulomas formation in sarcoidosis may occur, or be enhanced, in an inflammatory environment [13]. Our results are consistent with the hypothesis that adiposity-related inflammation may contribute to sarcoidosis development.

In summary, this analysis of a large cohort of US women followed-up over 24 years showed that higher BMI and weight gain was prospectively associated with a higher risk of incident sarcoidosis. Given the elevated prevalence of overweight and obesity in the US and other developed countries, and limited understanding of sarcoidoisis etiology, the potential impact of adiposity-related inflammation merits further investigation.

Acknowledgments

The Nurses' Health Study II is coordinated at the Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA. We would like to thank the participants and staff of the Nurses' Health Study II for their valuable contributions.

Funding: National Institutes of Health UM1 CA176726.

Table 1. Prospective association between BMI and sarcoidosis incidence in NHSII women

	Person-years	No. of cases	Age-adjusted HR		Multivariable-adjusted HR	
			HR	95% CI	HR	95% CI
Current* BMI (kg/m^2)						
<20	196,733	15	1.00	0.58-1.74	1.02	0.59-1.78
20 to 24.9 (ref.)	1,042,052	82	1	-	1	-
25 to 29.9	618,960	80	1.65	1.21-2.26	1.53	1.12-2.10
≥30	526,901	85	2.02	1.49-2.75	1.74	1.26-2.40
P-trend			*P <0.001*		*P <0.001*	
BMI at age 18 years (kg/m^2)						
<20	959,879	88	0.81	0.62-1.06	0.82	0.63-1.07
20 to 24.9 (ref.)	1,226,325	139	1	-	1	-
25 to 29.9	188,343	29	1.38	0.92-2.06	1.31	0.87-1.95
≥30	58,877	11	1.67	0.90-3.08	1.50	0.80-2.79
P-trend			*P=0.002*		*P=0.009*	
Weight change since age 18 years† (lb)						
Less than -5	132,685	16	1.34	0.68-2.66	1.36	0.69-2.71
-4.9 to 4.9 (ref)	229,372	18	1	-	1	-
5 to 14.9	403,705	24	0.78	0.42-1.44	0.76	0.41-1.40
15 to 24.9	401,392	46	1.51	0.87-2.61	1.43	0.83-2.48
25 to 34.9	324,565	33	1.31	0.73-2.33	1.20	0.67-2.14
35 to 44.9	246,729	26	1.33	0.72-2.43	1.19	0.65-2.19
45 to 54.9	182,979	24	1.64	0.88-3.04	1.44	0.77-2.68
55 and above	447,156	74	1.97	1.16-3.33	1.63	0.96-2.79
P-trend			*P <0.001*		*P=0.02*	

Abbreviations: BMI, body mass index; HR, hazard ratio; CI, confidence interval.

Multivariable models were adjusted for age, race (white, black, others), smoking status (never, ex- or current smoker) and pack-years (continuous), US region (West, Midwest, South, Northeast), household income (>$44,500 *vs.* ≤$44,500; evaluated in 2001), husband's education (high school or less, college graduate, graduate degree; evaluated in 1999), physical activity (<3, 3-8.9, 9-17.9, 18-26.9, 27-41.9, ≥42 METs/week) and alcohol consumption (0, 0.01-5, 5.01-10, >10 g/day).

* At the questionnaire cycle before time of diagnosis. † Analyses further adjusted for BMI at age 18 years. Observations with missing values for smoking status or region (<0.5%) were excluded from analyses (multivariable-adjusted models). For each other covariates with >0.5% missing values, including current BMI (3.0%), BMI at age 18 years (0.9%), or weight change since age 18 years (3.6%), a "missing" category was included in the model.

REFERENCES

1. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. *Lancet* 2014; 383: 1155–1167.
2. Gerke AK. Morbidity and mortality in sarcoidosis. *Curr Opin Pulm Med* 2014; 20: 472–478.
3. Dumas O, Abramovitz L, Wiley AS, Cozier YC, Camargo CA Jr. Epidemiology of Sarcoidosis in a Prospective Cohort Study of U.S. Women. *Ann. Am. Thorac. Soc.* 2016; 13: 67–71.
4. Jamilloux Y, Maucort-Boulch D, Kerever S, Gerfaud-Valentin M, Broussolle C, Eb M, Valeyre D, Seve P. Sarcoidosis-related mortality in France: a multiple-cause-of-death analysis. *Eur. Respir. J.* 2016; 48: 1700–1709.
5. Arkema E V, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: a nationwide register-based assessment in Sweden. *Eur. Respir. J.* 2016; 7: 113–118.
6. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, Terrin ML, Weinberger SE, Moller DR, McLennan G, Hunninghake G, DePalo L, Baughman RP, Iannuzzi MC, Judson MA, Knatterud GL, Thompson BW, Teirstein AS, Yeager H, Johns CJ, Rabin DL, Rybicki BA, Cherniack R. A case control etiologic study of sarcoidosis: Environmental and occupational risk factors. *Am J Respir Crit Care Med* 2004; 170: 1324–1330.
7. Liu H, Patel D, Welch AM, Wilson C, Mroz MM, Li L, Rose CS, Van Dyke M, Swigris JJ, Hamzeh N, Maier LA. Association Between Occupational Exposures and Sarcoidosis: An Analysis From Death Certificates in the United States, 1988-1999. *Chest* 2016; 150: 289–298.
8. Umetsu DT. Mechanisms by which obesity impacts asthma. *Thorax* 2017; 72: 174–177.
9. Cozier YC, Coogan PF, Govender P, Berman JS, Palmer JR, Rosenberg L. Obesity and

Weight Gain in Relation to Incidence of Sarcoidosis in US Black Women. *Chest* 2015; 147: 1086.

10. Harpsøe MC, Basit S, Andersson M, Nielsen NM, Frisch M, Wohlfahrt J, Nohr EA, Linneberg A, Jess T. Body mass index and risk of autoimmune diseases: A study within the Danish National Birth Cohort. *Int. J. Epidemiol.* 2014; 43: 843–855.
11. Ungprasert P, Crowson CS, Matteson EL. Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study. *Respir. Med.* 2016; 120: 87–90.
12. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am. J. Epidemiol.* 1986; 123: 894–900.
13. Newman KL, Newman LS. Occupational causes of sarcoidosis. *Curr. Opin. Allergy Clin. Immunol.* 2012; 12: 145–150.