Published in final edited form as:

Semin Arthritis Rheum. 2019 June ; 48(6): 1030–1034. doi:10.1016/j.semarthrit.2018.10.004.

A Prospective Study of Obesity and Risk of Systemic Lupus Erythematosus (SLE) among Black Women

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Abstract

Background: Obesity may influence systemic lupus erythematosus (SLE) pathogenesis via stimulation of systemic inflammation, but the relationship between obesity and SLE risk is unclear. Past studies have predominantly assessed White women, while Black women have higher prevalence of both obesity and SLE.

Methods: We prospectively assessed the relationship between body mass index (BMI, kg/m²) and incident SLE within the Black Women's Health Study (median age 38 at entry in 1995). Height and weight at age 18 and during follow-up were self-reported. We confirmed incident SLE cases by updated American College of Rheumatology criteria and collected covariates prospectively. Cox proportional hazards regression models, adjusted for potential confounders, estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for categories of updated BMI and risk of SLE, relative to BMI 20–24.9 ("normal" BMI). Secondary analyses investigated BMI at age 18, BMI in 1995 at cohort entry, cumulative updated BMI and "lagged" BMI (4 years prior to outcome window to address possible reverse causation).

Results: Adult obesity was not related to SLE risk: HR for BMI ≥30 ("obesity") relative to normal BMI at 4 years prior to SLE diagnosis was 0.90 (95% CI 0.53–1.54). However, obesity at age 18 was associated with increased risk: HR 2.38 (95% CI 1.26–4.51) for ≥30 vs. normal BMI.

Conclusions: Among these Black women, obesity as a teenager was associated with increased SLE risk in adulthood. Further studies are necessary to understand the biologic mechanisms and windows of exposure for the relationship of obesity to SLE pathogenesis.

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Keywords

Obesity; body mass index; systemic lupus erythematosus; prospective; risk factor; Black women

Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease with a complex and yet to be elucidated pathogenesis. Environmental exposures are thought to contribute to or accelerate the onset of SLE and other autoimmune diseases among genetically-predisposed individuals. Obesity has been associated with increased risk of several related autoimmune diseases, including rheumatoid arthritis, type 1 diabetes, psoriasis and inflammatory bowel disease [1–7]. There is strong biologic plausibility for a role of obesity in accelerating SLE pathogenesis. Adipose tissue is an essential endocrine organ, secreting adipokines[8], complement components[9], and other pro-inflammatory mediators[9], contributing to a systemic inflammation in obese subjects[8, 10]. Additionally, adipose tissue increases circulating estrogen concentrations via the conversion of androgen to estrogens by aromatase enzymes[11]. Estrogen accelerates disease in murine models of lupus and associations of early age at menarche, oral contraceptive use, and menopausal female hormone use with increased risk of SLE point to a role of estrogen in disease pathogenesis [12, 13].

Recently, obese women followed from 1989 in the Nurses' Health Study II (NHSII), who were 25–42 years old at cohort entry, were found to have a significantly increased risk of developing SLE (hazard ratio, HR, 1.85 [95% CI 1.17–2.91]) compared to normal weight women, based on 115 incident SLE cases (N =116,430)[14]. However, obesity did not significantly increase SLE risk (HR 1.11 [95% CI 0.65–1.87]) among older women (age 30–55 years old at cohort entry) in the Nurses' Health Study (NHS) which began in 1976, based on 153 incident cases (N=121,700)[14]. In a follow-up study of 75,000 women participating in the Danish National Birth Cohort (median age: 30 years), no association between obesity and incident SLE was found, based on 46 incident cases[6]. These studies were based largely on White women, who comprised >95% of the studies' participants [6, 14].

In the U.S., SLE occurs more commonly among Black women, who also have poorer SLE-specific long-term outcomes than White patients [15]. In addition, the prevalence of obesity is disproportionately high among American Black women [16–18]. In the present report, we have assessed obesity as a potential risk factor for SLE, based on 127 incident cases that occurred in a large cohort of Black women in the U.S.

Methods

The Black Women's Health Study (BWHS). The BWHS began in 1995 when 64,500 Black women enrolled by completing a 14-page health questionnaire. The 59,000 women whose addresses were considered to be valid a year later comprise the cohort that has been followed. Participants provided information on demographic characteristics, health status, and medical and lifestyle variables [19, 20]. Women were enrolled from across the continental U.S., with the largest numbers residing in California, Georgia, Illinois, Indiana,

Louisiana, Maryland, Massachusetts, Michigan, New Jersey, New York, South Carolina, and the District of Columbia. The women were 21 to 69 years of age at cohort entry, with a median of 38 years. Participants have been followed from baseline using biennial health questionnaires and yearly linkage with the National Death Index. Follow-up of the original cohort has been successful for >85% of potential person-years through 2015.

The study was approved by the Institutional Review Board of Boston University Medical Center. Participants indicated their consent by filling out the questionnaires and signing consents for obtainment of medical records.

Data collection.

On the baseline 1995 questionnaire, participants provided data on demographics, current weight, current height, weight at age 18, medical and reproductive history, vigorous physical activity, cigarette smoking, alcohol use, and dietary intake. Information was also collected on use of select medications including oral contraceptives and menopausal female hormone supplements. Follow-up questionnaires have updated all variables other than height.

SLE cases.

Cases of SLE were identified through self-report. The baseline (1995) questionnaire asked about a list of diagnoses that included “lupus”. Every biennial questionnaire since then has asked about “lupus (systemic lupus erythematosus)” and the date of diagnosis. The physicians of women who gave consent were asked to provide medical records relevant to SLE or to fill out a check list which asked about the presence of American College of Rheumatology criteria for the diagnosis [21, 22]. We obtained medical records or check lists for 240 women, of which 127 were confirmed by study rheumatologists as being SLE after medical record review confirmed the presence of at least 4 ACR SLE classification criteria. Brigham and Women’s Hospital rheumatologists (including MB, KC, CL and ST) reviewed medical records for all ACR criteria manifestations for a random sample of 62 incident and prevalent cases and compared results with prior abstractions. For these cases, we confirmed a very high Kappa agreement level between any two different reviewers (0.96, 95%CI 0.89 to 1.00). An additional 30 cases were reviewed due to inconsistencies noted within their prior abstraction, and any records with discrepancy between the result of the original and new abstractions were adjudicated by a Brigham and Women’s Hospital rheumatologist (n=13). Lastly, 4 new cases were reviewed independently by 2 Brigham and Women’s Hospital rheumatologists, followed by a third review to adjudicate any discrepancies. Anti-dsDNA and anti-Smith (anti-Sm) antibody status at SLE diagnosis was also determined by medical record review. We assessed SLE overall and a secondary outcome comprised of cases classified as anti-dsDNA+ and/or anti-Sm+ (anti-dsDNA+/Sm+).

BMI.

BMI at age 18, at baseline and during biennial follow-up were calculated as weight measured in kilograms (kg) at each time divided by height squared measured in meters (m²). We assessed the validity of self-reported height and weight in a physical activity validation study among 115 BWHS participants residing in the metropolitan Washington, DC area [23]: correlation coefficients for self-reported and technician measured weight and height

were 0.97 and 0.93, respectively ($p<0.01$) [24]. 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 the Nurses' Health Study II has indicated acceptable self-report [25].

Covariates.

We collected data on a number of health- and BMI-related variables. Data on age, vigorous physical activity, smoking status, alcohol consumption, oral contraceptive use, use of female hormone supplements, age at menarche and menopausal status, and years of education were obtained in 1995 and updated on subsequent questionnaires. Parental education was collected in 2009. Information was also collected on dietary intake in 1995 using the short-form National Cancer Institute-Block food frequency questionnaire [26], and was updated in 2001; from these data, we calculated daily energy intake (kcal) and Western dietary pattern (high in meat/fried foods)[27]. Higher scores indicate higher daily caloric intake and poorer diet quality, respectively. The Western dietary pattern has been positively associated with inflammatory biomarkers in previous research [28]. Finally, a neighborhood socioeconomic status score was derived from socioeconomic data obtained by linking the women's addresses to U.S. Census block data on wealth, income, and education; lower scores denote lower socioeconomic status [29] Neighborhood SES has been inversely associated with obesity in the BWHS [30].

Analytic cohort.

From the original (baseline) cohort of 59,000 women, we excluded 755 women who reported prevalent SLE at baseline. We also excluded 1765 women with missing information on weight or height at baseline and 37 women with BMI less than 16, leaving an analytic cohort of 56,443 women.

Statistical analysis.

We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of BMI with risk of SLE. HRs approximate the incidence rate ratio; thus, we use the term "risk" to imply hazard. Women contributed person-time from baseline (1995) until SLE diagnosis, death, loss to follow-up, or end of follow-up (2015), whichever occurred first. Women who reported SLE but for whom we were unable to obtain medical records to confirm the diagnosis were censored at the reported age at diagnosis. BMI was updated each questionnaire cycle, as were other time-varying variables. The Cox models were jointly stratified by age in 1-year intervals and questionnaire cycle (Model 1). In addition to terms for BMI, multivariable models included terms for age at menarche (<11, 11, 12–14, 15 years), use of oral contraceptives (current, never/past), menopausal status and ever use of menopausal female hormones, cigarette smoking (never, past, current), alcohol consumption (never, past, current), quintiles of energy intake (quintile 1=low; quintile 5=high), quintiles of Western diet [27] (quintile 1=low; quintile 5=high), vigorous physical activity (none, <5, 5 hours/week), years of education (12, 13–15, 16, 17), and quintiles of neighborhood socioeconomic status score (quintile 1=low; quintile 5=high) (Model 2). In the primary analysis, the risks of SLE for categories of BMI were compared to that of BMI 20–24.9 ("normal" BMI) and time-varying updated exposures were used. In secondary analyses, we examined baseline (1995) BMI in

categories carried forward, cumulative average BMI in categories. These analyses considered the variables of interest in relation to the occurrence of SLE at least 2 years subsequently. Because SLE can develop insidiously over a period of years and weight loss can occur in active SLE prior to diagnosis, we also conducted analyses in which the exposure of interest was “lagged” with respect to the outcome; thus we considered obesity in relation to SLE onset at least four years later. We also examined BMI at age 18, as well as joint categories of BMI at age 18 with BMI at the start of the cohort. The multivariable models for the latter analyses included terms for age began alcohol consumption (<20 years, 20 years/never), age began smoking (<18 years, ≥18 years/never), age began oral contraceptive use (<18 years, ≥18 years/never), hours of vigorous activity at age 21 (none, <5, ≥5 hours/week), age at menarche (<11, 11, 12–14, ≥15 years), and completed parental education (neither parent attended college, at least one parent some college, at least one parent college graduate).

Results

Among 56,443 BWHHS participants with BMI data available at cohort entry in 1995, over 30% of were obese (BMI ≥30 kg/m²). Age-adjusted baseline characteristics of study participants categorized by BMI category are shown in Table 1. Obesity at entry was positively associated with age and energy intake and inversely associated with educational attainment, neighborhood socioeconomic status, current oral contraceptive use, and vigorous physical activity. Obesity status did not differ appreciably by smoking or drinking habits, menopausal status, and menopausal female hormone use.

We confirmed 127 cases of incident SLE. Mean age at diagnosis was 43 years; mean number of ACR criteria for the classification of SLE was 5.1 (±1.3); 48% were anti-dsDNA or anti-Smith antibody positive; 64% had a hematological disorder and 31% had a renal disorder. In an analysis of updated BMI in relation to SLE risk (Table 2), the multivariable HR was non-significantly elevated for BMI <20 relative to BMI 20–24.9 (reference) (HR 1.57, 95% CI 0.75–3.27), although relatively few SLE cases comprised the BMI <20 category. No significant association was demonstrated for the overweight (BMI 25–29.9) or obese (BMI ≥30) categories compared to the reference (HR was approximately 0.8 and compatible with 1.0). In lagged analyses in which the exposure occurred at least 4 years prior to the time window for outcome assessment, the HRs for all categories of BMI, including that for BMI <20, were all close to and compatible with 1.0. Results were similar when cumulative averaging of BMI was carried out. In a subgroup analysis stratifying by anti-dsDNA or anti-Smith status, the HR for updated BMI ≥30 kg/m² (13 cases) was 0.69 (95% CI: 0.31–1.55) (data not shown) based on 41 SLE cases positive for anti-dsDNA or anti-Smith compared to those cases negative for these antibodies.

We examined BMI at age 18 (n=55,951). Self-reported obesity at age 18, reported by 4.2% of the cohort, was associated with more than doubling in SLE incidence (HR 2.38, 95% CI: 1.26–4.51) (Table 3). In analyses stratifying by the risk of anti-dsDNA or anti-Smith positive SLE, the HR for BMI ≥30 relative to normal BMI was 1.41 (95% CI 0.42–4.80) among 61 cases with positive antibodies compared to those without these antibodies (data not shown).

We also considered the joint effects of BMI at two points in time (Table 4): age 18 and in 1995 (cohort entry). The HR was significantly increased for women who were obese both at age 18 and in 1995, relative to women who were non-obese at both time points (HR 2.03 [95% CI 1.04–3.95]). For women who were non-obese at age 18, but became obese by 1995, the HR was 0.78 (95% CI, 0.50–1.22). Too few women lost weight and moved from obese to non-obese for informative analysis.

Discussion

In the present prospective study of Black women (with a median age 38 years at cohort entry), our assessment of obesity in adulthood using updated, cumulative average, and lagged analyses, was not associated with incident SLE. In contrast, obesity at age 18 was associated with more than a doubling in SLE incidence. This risk remained doubled in women who were persistently obese from age 18 to time of cohort entry in 1995.

Within the NHSII female cohort consisting mainly of White women, cumulative average obesity in adulthood (mean age 34.4 years) was associated with a significantly increased risk of SLE, with a HR of 1.85 ([95% CI: 1.17–2.91])[14]. However, among the nurses in the earlier cohort, NHS, who were older at enrollment (mean age 42.5 years), there was only a small non-significant increase in SLE risk [14]. While obesity during follow-up in the BWHS was not associated with increased SLE risk, it should be noted that 30% of the cohort were obese at study baseline. This contrasts to 8% of NHS and 11% of NHSII who were obese at cohort entry. In both BWHS and NHS/NHSII studies, there was no evidence of an association of obesity with increased risk of anti-dsDNA/anti-Smith positive SLE.

While there was no association of obesity during adulthood with SLE in the present study, obesity earlier in life, at age 18, was associated with a more than doubling in risk of SLE. In the analysis of obesity at age 18 and in 1995, the risk of SLE was most elevated among obese women at cohort entry who had also been obese at age 18. In NHS and NHSII, self-reported obesity at age 18 was not associated with SLE risk, but there were very few women in the two cohorts who were obese at age 18. Among the combined total of 256 cases in the two cohorts of nurses, only 4 cases were obese at age 18 (1.56%) [14]; the comparable number among the 127 SLE cases in the BWHS was 12 (9.44%).

There has been a shift in our understanding of the nature of adipose tissue over the past decade[31]. Once thought to be an inert energy storage tissue, this tissue is now recognized as a highly active endocrine organ able to mediate biologic effects on inflammation [32]. Adipose tissue produces more than 50 adipokines [33, 34], and compared to non-obese individuals, obese individuals exhibit higher levels of C-reactive protein and TNF-alpha receptor 2 [35]. Obesity may predispose induction of T-helper 17 cells, a subset of CD4 effector T lymphocytes, through an IL-6 dependent process known to exacerbate conditions such as multiple sclerosis and colitis in mouse models [36]. Animal data support an association between obesity and SLE as SLE-prone mice (NZB/WF1) have higher body weight and visceral fat in comparison to control mice (NZW/LacJ) [37]. Obesity is also a risk factor for other autoimmune conditions including rheumatoid arthritis [2, 38, 39], psoriasis [40], inflammatory bowel disease [41], and sarcoidosis [42–44].

The BWHS is the first study to assess BMI in relation to incidence of SLE specifically among Black women. Compared to previous cohorts primarily of white women, the BWHS has a higher overall incidence of SLE, a higher proportion of obesity at age 18, and a higher proportion of obesity in adulthood, making the BWHS an appropriate cohort for studying the hypothesis that obesity may adversely affect the incidence of SLE. A strength of the study was the confirmation of the SLE diagnoses through medical records. We also explored BMI in multiple ways using updated, cumulative average, and lagged analyses. In addition, numerous potential confounders were collected prospectively and time-varying analyses accounted for changes in the variables of interest and potential confounders over time. Prospective data collection reduced the possibility that the reporting of the exposures of interest was influenced by SLE disease status. A validation study in the BWHS in which self-report of weight and height were compared with technician measurements demonstrated that both weight and height are reported with a high degree of accuracy by BWHS participants [23]. Obesity has been associated with increased risk of type 2 diabetes in the BWHS[29], providing further support for the validity of reporting of weight and height in the BWHS. Weaknesses of the current study include the relatively small number of confirmed cases in the cohort, which limited statistical power, and potential residual confounding by unmeasured factors. Self-reported BMI at age 18 is subject to recall bias and has not been directly validated in the BWHS, but research by others has demonstrated acceptable accuracy [25].

Conclusion

The current BWHS results suggest that although obesity in adulthood does not seem to increase SLE risk, obesity during the teenage years may be associated with elevated risk of SLE later in life among Black women. These findings are in contrast to those from the NHSII, which suggest that obesity at age 25 and after may be an SLE risk factor, whereas results from NHS suggest little or no association. Past studies have confirmed that the mean age at onset of SLE is younger among Black than White women in the U.S [45]. The mean age at onset of SLE in the BWHS was 43 compared to 49.2 years in NHS/NHSII, and it is theoretically possible that higher prevalence of obesity at early ages could influence the younger age at onset of SLE among Black women. Further and larger studies of these and other populations are required to clarify the time windows of vulnerability and biologic mechanisms by which obesity may influence the pathogenesis of SLE.

Acknowledgments

Each author contributed to the analysis and interpretation of the data and writing of the manuscript with the most input and time from YCC, MB, KC, and LR. Each author has approved the final version and will take public responsibility.

Research reported in this publication was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases R01 AR0573727; National Cancer Institute R01 CA058420, U01CA164974; Dr. Barbhaiya is supported by the Rheumatology Research Foundation Scientist Development Award; Dr. Tedeschi is supported by the Lupus Foundation of America Career Development Award. The funders had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the view of the National Institutes of Health.

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

Abbreviations:

SLE	systemic lupus erythematosus
BMI	body mass index
BWHS	Black Women's Health Study
NHS	Nurses' Health Study
NHSII	Nurses' Health Study 2
HR	hazard ratio
CI	Confidence Interval
dsDNA	double-stranded deoxyribonucleic acid
Sm	Smith
ACR	American College of Rheumatology
U.S.	United States

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Table 1.Baseline Characteristics of Women in the BWHS¹ According to Body Mass Index, N=56,443.

Characteristics	Underweight/ Normal BMI < 25 kg/m ² n=21,547 (38.2%)	Overweight BMI 25-<30 kg/m ² n=17,823 (31.6%)	Obese BMI ≥ 30 kg/m ² n=17,073 (30.2%)
Mean age, years, mean SD	36.3 ± 10.2	40.8 ± 11	40.9 ± 10.7
Mean BMI, kg/m ² , SD	22.3 ± 1.9	27.3 ± 1.4	36.2 ± 5.8
Mean BMI at age 18, kg/m ² , SD	19.5 ± 2.4	21.2 ± 3.0	24.7 ± 5.1
Energy intake, kcal/day, mean, SD	1,406 ± 923	1,475 ± 937	1,725 ± 1,258
Education ≥ 16 years, %	51	43	38
Quintiles of neighborhood SES, %			
1, low	15	18	23
2	16	19	21
3	18	19	18
4	20	18	17
5, high	23	18	13
Alcohol intake status, %			
Never	57	55	55
Past	16	18	21
Current	26	27	24
Smoking status, %			
Never	66	63	63
Past	17	20	21
Current	17	17	16
Age at menarche, %			
< 11	7	11	17
11	14	17	20
12–14	66	63	55
15+	12	8	7
Premenopausal, %	77	75	74
Current oral contraceptive use, %	28	25	21
Ever female hormone use, %	15	16	17
Vigorous activity ≥ 5 hours/week, %	17	14	9

¹Percentages standardized to the age distribution of the cohort at baseline (1995).

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Table 2.

Relationship of Body Mass Index (BMI) with Risk of SLE among 56,443 women in the Black Women's Health Study (1995–2015).

BMI (kg/m ²)	Cases/person-years	Age and questionnaire period-adjusted HR (95%CI)*	Multivariable-adjusted HR (95%CI)**
	Updated analysis		
< 20	9/27,561	1.67 (0.80, 3.46)	1.57 (0.75, 3.27)
20–24.9	38/224,870	Ref.	Ref.
25–29.9	35/302,860	0.80 (0.50, 1.27)	0.79 (0.50, 1.26)
30+	45/370,484	0.89 (0.57, 1.38)	0.82 (0.52, 1.30)
	Lagged analysis***		
< 20	4/25,049	0.99 (0.34, 2.86)	0.95 (0.33, 2.73)
20–24.9	27/202,360	Ref.	Ref.
25–29.9	29/266,782	0.95 (0.56, 1.62)	0.93 (0.55, 1.59)
30+	35/319,709	1.01 (0.61, 1.68)	0.90 (0.53, 1.54)

HR=hazard ratio; CI=confidence interval

* Model 1: adjusted for age and questionnaire period

** Model 2: adjusted for age, period, alcohol intake, smoking status, neighborhood SES (quintiles), education, energy intake (quintiles), menopausal status, current use of oral contraceptives, ever use of female hormone, vigorous activity, age at menarche, Western diet (quintiles).

*** Lagged analysis: exposure occurred at least 4 years prior to the time window for outcome assessment

Table 3.

Relationship between Body Mass Index (BMI) at Age 18 and Risk of SLE among 55,951 women in the Black Women's Health Study

BMI at age 18 (kg/m ²)	Cases/person-years	Age and questionnaire period- adjusted HR (95%CI)*	Multivariable-adjusted HR (95%CI)**
< 20	49/378,566	1.10 (0.74, 1.63)	1.05 (0.71, 1.56)
20–24.9	51/412,108	Ref.	Ref.
25–29.9	15/90,642	1.28 (0.72, 2.28)	1.25 (0.70, 2.23)
30+	12/37,132	2.48 (1.32, 4.67)	2.38 (1.26, 4.51)

HR=hazard ratio; CI=confidence interval

* Model 1: adjusted for age and period

** Model 2: adjusted for age, period, age began alcohol intake (< 20 years), age began smoking (< 18 years), age began use of oral contraceptives (< 18 years of age), vigorous activity at age 21, age at menarche, and parental education.

Table 4.

Relationship between obesity trend from age 18 to 1995 (Time of cohort entry) and Risk of SLE among 55,951 women in the Black Women's Health Study.

Obesity trend	Cases/person-years	Age and questionnaire period-adjusted HR (95%CI)*	Multivariable-adjusted HR (95%CI)**
Obese-obese	10/32,229	2.09 (1.08, 4.02)	2.03 (1.04, 3.95)
Obese-non obese	2/4,903	2.81 (0.69, 11.5)	2.81 (0.69, 11.5)
Non obese-obese	25/240,418	0.76 (0.49, 1.19)	0.78 (0.50, 1.22)
Non obese-non-obese	90/640,898	Reference	Reference

HR=hazard ratio; CI=confidence interval

* Model 1: adjusted for age and period

** Model 2: adjusted for age, period, age began alcohol intake (> 20 years), age began smoking (> 18 years), age began use of oral contraceptives (> 18 years of age), vigorous activity at age 21, age at menarche, and parental education.