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Obesity and the Risk of Systemic Lupus Erythematosus among Women in the Nurses' Health Studies

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Abstract

Background—Obesity is increasingly prevalent and related to increased risk of several autoimmune diseases, likely via generation of inflammatory adipokines. Prior studies have not evaluated obesity in relation to systemic lupus erythematosus (SLE) risk. We prospectively evaluated whether obesity was associated with increased SLE risk among women in the U.S. Nurses' Health Study cohorts.

Methods—We conducted a prospective cohort study among 238,130 women in the Nurses' Health Studies (NHS, 1976–2012; NHSII, 1989–2013). Incident SLE was confirmed by American College of Rheumatology 1997 criteria and validated through medical record review. Body mass index (BMI, kg/m²) was calculated at baseline and on biennial questionnaires. Cox proportional hazards models estimated HRs (95% CIs) for SLE by cumulative average BMI category [18.5 to <25 (normal [reference]), 25 to <30 (overweight), 30 (obese)], adjusting for potential time-varying confounders. Models were performed separately in each cohort; results were meta-analyzed. Sensitivity analyses used simple time-varying BMI, a four-year lag between exposure and SLE risk window to address potential reverse causation, and evaluated BMI at age 18 and weight change since age 18. A secondary analysis started follow-up in both cohorts at similar calendar years when the prevalence of obesity in the U.S. increased most dramatically [1988 (NHS)/1989 (NHSII)].

Results—We identified 153 NHS incident SLE cases and 115 incident NHSII cases during 5,602,653 person-years of follow-up. At baseline, 8.4% of women in NHS and 11.8% in NHSII were obese. Mean age at enrollment was 42.5 (SD 7.2) years in NHS and 34.4 (SD 4.7) years in NHSII. Cumulative average obesity was significantly associated with SLE risk in NHSII (HR 1.85

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[1.17–2.91]), but not in NHS (HR 1.11 [0.65–1.87]) compared to normal BMI. In the meta-analysis of both cohorts, obesity was not significantly associated with increased risk of SLE (HR 1.46 [0.88–2.40]). Simple time-varying BMI and lagging the exposure window by four years produced similar findings to the primary analysis. In NHSII, a 10 pound gain between age 18 and enrollment slightly increased SLE risk (HR 1.09 [1.02–1.18]). In the secondary analysis starting follow-up of both cohorts at similar calendar year, the point estimate for obesity in NHS was higher than the primary analysis (HR 1.67 [0.81–3.45]).

Conclusion—We observed an 85% significantly increased risk of SLE among obese compared to normal BMI women in the more recent NHSII cohort, but no association was observed in the earlier NHS cohort. Secular trends in obesity may account for the differences between the two birth cohorts.

Keywords

systemic lupus erythematosus; body mass index; obesity

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous, chronic autoimmune disease that occurs predominantly in women. SLE is thought to develop in genetically-susceptible individuals after exposure to environmental risk factors. Specific or cumulative environmental exposures may contribute to the initial break in immune tolerance resulting in autoantibody formation and to the subsequent progression to clinical manifestations over time.¹ In a prospective study of U.S. Armed Forces members who were asymptomatic at the time of blood draw, the mean interval between the detection of autoantibodies and onset of SLE was 3.3 years, and was as long as 9.4 years.² Thus, the window during which environmental exposures may contribute to the development of SLE is wide.

Among women, a number of reproductive factors have been associated with increased SLE risk: oral contraceptive use,^{3,4} age 10 at menarche;³ and use of postmenopausal hormone replacement therapy.³ Parity and breastfeeding, however, have not been associated with SLE risk.³ Other environmental risk factors associated with increased SLE risk include current cigarette smoking⁵ and crystalline silica.⁶ Moderate alcohol intake (>0.5 drinks/day) has been associated with a decreased risk of incident SLE.⁷

The prevalence of obesity in the U.S. has been increasing over the past four decades, particularly since the late 1980s.⁸ In 2014, over 40% of U.S. adult women fulfilled the World Health Organization definition of obesity (body mass index [BMI] ≥ 30 kg/m²).⁹ Obesity is a serious public health problem, associated with increased risk for many chronic diseases including hypertension,¹⁰ type 2 diabetes,¹¹ osteoarthritis,¹² coronary artery disease,¹³ and cancer.¹⁴ Adipose tissue secretes inflammatory cytokines, termed adipokines, the presence of which may contribute to the development of chronic diseases in individuals with additional genetic or environmental risk factors. Adipose tissue also increases circulating estrogens via aromatase enzymes, which convert androgens to estrogens.¹⁵ Prospective cohort studies have identified associations between obesity and increased risk of other autoimmune diseases, such as rheumatoid arthritis,^{16–18} psoriatic arthritis,^{19,20} and

type 1 diabetes.^{21,22} However, to our knowledge, no previous study has investigated an association between obesity and risk of incident SLE.

We hypothesized that chronic obesity was associated with increased risk for incident SLE among women, and tested this hypothesis in two prospective cohorts of women: the U.S. Nurses' Health Study and Nurses' Health Study II.

MATERIALS AND METHODS

Study design and population

The Nurses' Health Study (NHS) is a prospective cohort that enrolled 121,700 women living in 11 U.S. states at its start in 1976, while Nurses' Health Study II (NHSII) is a prospective cohort that enrolled 116,430 women living in 14 states in 1989. The cohorts differ by age at enrollment, calendar years of birth, and duration of follow-up and thus comprise two distinct birth cohorts. NHS participants were enrolled at ages 30–55 in 1976, born from 1921–1946, and have been followed for 36 years with most recent follow-up at ages 66–91. NHSII participants were enrolled at ages 25–42 in 1989, born from 1947–1964, and have been followed for 24 years with most recent follow-up at ages 49–62. Thus NHS is an earlier birth cohort exposed to lifestyle and environmental factors dating back to 1921, and NHSII is a more recent birth cohort with exposures dating back to 1947. Participants have completed mailed questionnaires at baseline and every two years in follow-up regarding lifestyle factors, health behaviors, and the development of new diseases. Follow-up rates have been high and only 5% of person-time has been lost to follow-up.²³ The National Death Index is searched every two years for non-responders, to validate mortality.

Identification of cases

In this analysis, NHS participants were followed from 1976 through May 31, 2012, and NHSII participants were followed from 1989 through May 31, 2013. Methods for SLE case identification and validation according to ACR 1997 Classification Criteria have previously been reported.^{3,24} Two rheumatologists independently reviewed medical records for women who self-reported SLE, to confirm whether four of the 11 ACR criteria were met. We excluded participants self-reporting an existing diagnosis of SLE at cohort entry, and censored those who self-reported SLE in follow-up without confirmation by medical record review.

Exposures and covariates

Body mass index (BMI)—BMI was calculated as weight in kilograms divided by squared height in meters (kg/m^2) using self-reported height from the baseline questionnaire and self-reported weight updated on biennial questionnaires. In a previous validation study among 140 NHS participants, self-reported weight and measured weight had high accuracy ($r=0.97$).²⁵ Missing BMI values were imputed by assigning the last BMI carried forward, for up to two consecutive questionnaire cycles. As we hypothesized that long-term obesity, rather than short-term obesity, would be related to SLE risk, cumulative average BMI was the primary exposure. Cumulative average BMI was calculated as the average BMI over all questionnaire cycles prior to the current questionnaire cycle.

BMI in the setting of pregnancy was handled differently, given that weight gain during pregnancy is not primarily due to excess adipose tissue. For questionnaire cycles in which women reported being pregnant, we carried forward BMI from the prior cycle before calculating cumulative average BMI, consistent with prior analyses of BMI and risk of rheumatoid arthritis.¹⁶

We categorized cumulative average BMI according to World Health Organization (WHO) categories: normal (18.5 kg/m² to <25 kg/m² [reference]), overweight (25 kg/m² to <30 kg/m²), and obese (≥30 kg/m²).²⁶ Women with BMI <18.5 kg/m² at baseline were excluded due to insufficient numbers of underweight SLE cases, thus the model was unstable if an underweight category were included the main exposure (n=3268 women in NHS, of whom 1 developed SLE; n=3949 women in NHSII, of whom 2 developed SLE). We did not include underweight women in the reference group due to concerns about different effects of underweight and normal body mass index on SLE risk. In the sensitivity analyses testing the relationship of BMI at age 18 and SLE risk we were able to include an underweight category (BMI <18.5 kg/m²), as there were a sufficient number of underweight cases at age 18 to stabilize the model. In an analysis of weight change from age 18 to baseline, we included women with BMI <18.5 kg/m² at age 18 or at baseline, as the primary exposure was continuous weight change. In secondary analyses, simple time-varying BMI updated at each questionnaire cycle in WHO categories was the primary exposure. We also assessed SLE risk associated with simple time-varying and cumulative average BMI as continuous measures.

Covariates—Race was dichotomized as White vs. non-White, given that ~90% of NHS and NHSII participants self-report White race. We adjusted for time-varying covariates, updated at each biennial questionnaire, which have previously been associated either with SLE risk, obesity, or both. Age was treated as a continuous variable. U.S. Census-tract household median income was employed as a marker of socioeconomic status (< vs. sample median \$60,000). Cigarette smoking was categorized as never, past, or current.⁵ Cumulative average alcohol intake was categorized as none, >0 to <5 grams/day, or ≥5 grams/day.⁷ Oral contraceptive use was dichotomized as ever vs. never, and age at menarche was dichotomized as ≤10 vs. >10 years old.³ Menopausal status and post-menopausal hormone (PMH) use were categorized in three groups: pre-menopausal, post-menopausal/never used PMH, and post-menopausal/ever used PMH. We tested whether physical activity or husband's educational level were confounders of the relationship between BMI and SLE, and found that neither of these variables changed the effect estimate of BMI category by >10%; thus we did not include them in multivariate models.

Statistical methods—Characteristics of NHS and NHSII participants at cohort entry were analyzed according to baseline BMI category. Among incident SLE cases, features of SLE were examined separately in each cohort according to cumulative average BMI category at date of SLE diagnosis. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for SLE risk by cumulative average BMI category; models were performed separately in each cohort. The proportional hazards assumption was tested using the Wald Chi square test for cumulative average BMI over the duration of

follow-up in NHS and NHSII, and was met in each cohort. Models were initially adjusted only for age and questionnaire cycle, followed by multivariable models adjusted for time-varying covariates. Meta-analysis of NHS and NHSII HRs was performed using a DerSimonian-Laird random effects model.²⁷

In sensitivity analyses, Cox proportional hazards models were re-run using modified exposures and modified windows of follow-up time. We first assessed the effect of shorter-term BMI elevations on SLE risk in “simple time-varying BMI” models. We also evaluated for reverse causation, that is, SLE symptoms resulting in weight change prior to clinical diagnosis, in separate models lagging the exposure time window for >4 years before SLE diagnosis.

We conducted four secondary analyses. Given secular changes in diet and obesity in the U.S., with a sharp rise in obesity prevalence in the general U.S. population in the late 1980s,⁸ we restricted the calendar years of follow-up in NHS to more closely match the calendar years of follow-up in NHSII. In this model NHS follow-up began in 1988, to parallel the 1989 cohort start date of NHSII; follow-up ended on the same dates described in the primary analysis. Of note, women in NHS were ages 42–67 in 1988. Second, in order to test whether age at SLE diagnosis modified the effect of obesity on SLE risk, we performed stratified analyses in each cohort to assess risk of SLE onset at age <50 years vs. ≥50 years, as several studies have investigated differences in SLE manifestations using this age cutoff for early- versus late-onset SLE.^{28–30} Third, we performed an analysis using BMI at age 18 as the exposure, as early life obesity could be related to risk of autoimmune disease in later life.^{16,20} Last, we evaluated weight change between age 18 and cohort enrollment as a risk factor for SLE, as weight gain during young adulthood could be related to increased risk for later development of autoimmune disease. Weight change was calculated as change in pounds divided by 10, in order to present results in 10 pound increments for ease of interpretation. We excluded women reporting pregnancy at age 18 or at cohort enrollment from this secondary analysis, as it was not possible to impute weight from prior cycles. For all analyses, we tested for a linear trend in SLE risk with increasing BMI, using BMI as a continuous variable.

All aspects of this study were approved by the Partners’ HealthCare Institutional Review Board.

RESULTS

We identified 153 incident SLE cases among 114,527 women in NHS, and 115 SLE cases among 109,033 women in NHSII; greater than 90% of women in both cohorts were White. At enrollment, compared to the NHS cohort, NHSII cohort participants were younger, consumed less alcohol, smoked less, were more often pre-menopausal, and had higher oral contraceptive use (Table 1). Mean BMI was also higher in NHSII than NHS participants at cohort entry, with 11.8% obese in NHSII vs. 8.4% in NHS reflecting secular changes in obesity rates in the U.S. Within each cohort, obese women had lower income, lower mean alcohol intake, and menarche at age >10 less frequently than did women with normal BMI.

Among the 268 SLE cases in both cohorts, >95% had a positive ANA and >50% had a positive anti-dsDNA antibody at the time of diagnosis (Table 2). The presence of renal involvement at diagnosis as defined by ACR 1997 SLE Classification Criteria³¹ was similar between cohorts. Cytopenias were more frequent in NHSII, and arthritis was more frequent in NHS. There were no clear differences in these SLE manifestations across cumulative average BMI categories in the two cohorts.

Cumulative average BMI and SLE risk (Table 3)—Mean BMI was higher among obese NHSII participants (35.2 [4.8] kg/m²) compared to obese NHS participants (33.8 [3.6] kg/m²). Among women with normal BMI and overweight women, the mean BMI was similar in NHS and NHSII. In the primary analysis, NHS women who were overweight (HR 1.28 [0.89–1.84]) and obese (HR 1.11 [0.65–1.87]) did not have a significantly increased SLE risk compared to women with normal BMI (Table 3). In NHSII, obesity was associated with a significantly increased risk of SLE [HR 1.85 (1.17–2.92)], while overweight was not associated with increased SLE risk [HR 0.70 [0.41–1.18]]. In NHSII, but not NHS, we observed increased SLE risk as continuous cumulative average BMI increased (p=0.02). Meta-analysis of both cohorts indicated a statistically non-significant increased SLE risk among obese women [HR 1.46 (0.88–2.41)], and SLE risk was not related to continuous BMI (p=0.60).

Simple time-varying BMI and SLE risk—When we used simple time-varying BMI as the exposure, our results were similar although possibly slightly attenuated compared to the models using cumulative average BMI (Table 4a). In NHS, neither overweight (HR 1.15 [0.80–1.67]) nor obesity (HR 1.00 [0.62–1.60]) were associated with elevated SLE risk. In NHSII, we observed a 77% increased risk of SLE among obese women (HR 1.77 [1.12–2.80]) and a non-significantly elevated SLE risk among overweight women (HR 1.11 [0.69–1.79]). As a continuous variable, simple time-varying BMI was associated with increased SLE risk in NHSII (p=0.03). In meta-analysis of NHS and NHSII employing simple time-varying BMI, we observed a statistically non-significant increased SLE risk among overweight and obese women (HR 1.33 [0.76–2.34]) and SLE risk was not related to continuous BMI (p=0.76).

Lagged analyses using cumulative average BMI—To assess for reverse causation (e.g. SLE symptoms affecting BMI immediately prior to clinical diagnosis), we performed models requiring a two-cycle (>4 year) lag between cumulative average BMI assessment and SLE diagnosis. In NHS, we observed a non-significantly increased SLE risk for overweight and obese women (Table 4b). In NHSII, obesity was again associated with significantly increased SLE risk (HR 1.95 [1.20–3.15]) compared to normal BMI, while there was no association between overweight and SLE. Meta-analysis of the cohorts revealed a statistically non-significant elevated SLE risk among obese women (HR 1.48 [0.84–2.60]).

Following both cohorts over similar calendar years—Because the prevalence of obesity in the U.S. steeply rose during the late 1980s, coinciding with the start of NHSII enrollment, we performed an analysis in which we delayed the start of NHS follow-up to more closely match the follow-up period for NHSII, using cumulative average BMI as the

exposure (Table 4c). Thus, we restricted follow-up in NHS women to 1988–2012, while NHSII women were followed 1989–2013 as in the primary analysis. (In 1988, 13.9% of NHS participants were obese compared to 8.4% at cohort baseline in 1976.) Among NHS participants, we observed increased SLE risk among overweight (HR 1.77 [1.03–3.04]) and obese (HR 1.67 [0.81–3.45]) women. We did not observe a linear trend for increasing SLE risk associated with continuous cumulative average BMI ($p=0.45$). The analysis for NHSII was identical to the primary analysis. Meta-analysis showed a significant 80% increased SLE risk for obese women (HR 1.80 [1.22–2.65]) compared to normal BMI and an increased SLE risk associated with continuous cumulative average BMI ($p=0.01$).

Age-stratified analyses—Among 162 women in NHS and NHSII with incident SLE at age <50 years, the HR for cumulative average obesity was 1.07 (0.41–2.80) in a meta-analysis. There were 106 women aged ≥50 at SLE diagnosis in NHS and NHSII; cumulative average obesity was associated with a non-significant increased risk of late-onset SLE (meta-analyzed HR 2.21 [0.87–5.67]). In meta-analysis, continuous cumulative average BMI did not increase SLE risk in either age stratum ($p=0.97$ for SLE diagnosis at age <50, $p=0.29$ for SLE diagnosis at age ≥50).

BMI at age 18—Among women with data available for BMI at age 18, there were a total of 256 SLE cases in NHS and NHSII. Of these, only four were obese; 38 were underweight (BMI <18.5 kg/m²), 200 had normal BMI, and 16 were overweight. Continuous BMI at age 18 was not associated with increased SLE risk (meta-analyzed $p=0.47$). Obesity at age 18 was not associated with elevated SLE risk (meta-analyzed HR 0.73 [0.27–1.99]).

Weight change from age 18 to cohort enrollment—This analysis included a total of 256 SLE cases in NHS and NHSII. In NHS, a gain of 10 pounds between age 18 and cohort entry was not associated with increased SLE risk (HR 1.01 [0.94–1.10]). However, in NHSII, a 10 pound gain between age 18 and enrollment slightly increased SLE risk (HR 1.09 [1.02–1.18]). Notably, among women who gained ≥20 pounds between age 18 and cohort entry, the amount of weight gain was higher in NHSII compared to NHS (mean 39.2 [SD 21.4] pound gain in NHSII vs. mean 35.9 [SD 17.0] pound gain in NHS). Meta-analysis of NHS and NHSII did not reveal increased SLE risk associated with a 10 pound weight gain (meta-analyzed HR 1.06 [0.98–1.14]).

DISCUSSION

In this prospective analysis of two very large cohorts of female nurses with detailed covariate data, obese women in the more recent NHSII cohort had an 85% increased risk for developing SLE compared to women with normal BMI. By contrast, we detected no significant increased SLE risk among obese women in the earlier NHS cohort in the primary analysis. In NHSII, both cumulative average obesity and simple time-varying obesity were associated with increased SLE risk, though the point estimate for obesity was higher in the cumulative average BMI analysis. This is the first prospective cohort study, to our knowledge, to investigate the relationship between obesity and SLE risk. We were able to assess this relationship in two large, nationwide cohorts of female nurses with detailed,

updated covariate data from biennial questionnaires and over 5.6 million person-years of follow-up.

Elevated cumulative average BMI is a long-term measure of adiposity, associated with chronic exposure to inflammatory adipokines and circulating estrogens produced by adipose tissue.^{32,33} Given the importance of systemic inflammation and reproductive factors in the pathogenesis of SLE, there is therefore strong biologic rationale for obesity increasing SLE risk. Obese individuals have higher levels of C-reactive protein and soluble TNF-alpha receptor 2 than non-obese individuals.³³ Obesity has been identified as a risk factor for several other autoimmune diseases, including rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease, and sarcoidosis.^{16,17,34–39} Murine models of SLE-prone mice (NZB/WF1 females) also support the hypothesis that obesity may be associated with increased SLE risk, as these mice have higher body weight and greater visceral fat compared to control mice.⁴⁰

Given that SLE pathogenesis is likely to develop slowly over years due to interactions between environmental exposures and genetic factors that lead to autoimmunity, we hypothesized that long-term exposure to excessive adipose tissue would be associated with increased SLE risk. After controlling for potential hormonal confounders including menopausal status, post-menopausal hormone use, and oral contraceptive use, both cumulative average obesity and simple time-varying obesity remained significant risk factors for SLE in the more recent NHSII cohort. In lagged analyses, we also detected a significant relationship between cumulative average obesity and SLE risk in the NHSII cohort, suggesting that this association was not an artifact of reverse causation. Since we found similar results in NHSII through a variety of different methods, the positive results are less likely related to chance.

There are a number of possible explanations for the disparate results in NHS and NHSII. Compared to NHSII women, NHS women enrolled at an earlier calendar year, participants were older at enrollment and born in the 1920s-1940s, were followed throughout middle and older ages up to age 91, obesity prevalence was lower throughout their most susceptible years, and mean BMI was lower among obese women. The peak incidence of SLE is among women of reproductive age;⁴¹ thus one possibility is that we observed a greater number of younger-onset SLE cases in NHSII due to cohort demographics at enrollment, and that age at diagnosis modifies the effect of obesity on SLE risk. Neither obesity at age 18 nor BMI at age 18 as a continuous measure was associated with increased SLE risk; however, this secondary analysis had limited power to detect an association due to the very small number of obese women at age 18 who later developed SLE after NHS or NHSII enrollment. Additionally, in a stratified analysis (age <50 vs. ≥50 years at SLE diagnosis), obesity did not significantly increase SLE risk among younger women.

Secular trends in obesity are a more likely explanation for the differing results in the NHS and NHSII cohorts. In 1976, when NHS women enrolled, U.S. obesity prevalence was lower, and mean BMI among obese women was lower, compared to 1989, the year of NHSII enrollment.⁸ Therefore, we may have lacked power to detect a relationship between obesity and SLE in NHS due to the lower prevalence of obesity among cases. In a secondary

analysis, the follow-up periods were more closely matched (1988–2012 for NHS, 1989–2013 for NHSII). During these years of follow-up, obesity prevalence in NHS was more closely matched to obesity prevalence in NHSII. Additionally, the point estimate for obesity in NHS (HR 1.67 [0.81–3.45]) was closer in magnitude to the NHSII point estimate (HR 1.85 [1.17–2.92]), and after meta-analysis, obesity was significantly associated with risk of SLE (HR 1.80 [1.22–2.65]) compared to normal BMI. In our secondary analysis examining weight change between age 18 and cohort enrollment as a risk factor for SLE, we observed a significant risk in NHSII but not in NHS. This may be due to the greater weight gain among the NHSII participants, consistent with secular trends in obesity during the calendar years of NHSII enrollment.

Our study has some limitations, including that we cannot infer causation in this observational study. We do not have information on incident SLE at age <30 in NHS or age <25 in NHSII, to study the role of BMI in early-onset SLE. Our definition of SLE was stringent and required confirmation of at least four of 11 ACR 1997 SLE Classification Criteria. We were also not able to control for all potential confounders of the relationship between obesity and SLE. However, we were able to control for known risk factors for SLE and other potential confounders such as age, race, smoking, alcohol use, income as a marker of socioeconomic status, and reproductive and hormonal factors. We measured obesity using BMI rather than body composition measures, the latter of which may be more sensitive for capturing the risks of obesity in SLE patients.⁴² However, our study focused on SLE risk among women without SLE at the time of exposure assessment. We included U.S. Census-tract household median income as an indicator of socioeconomic status, though other socioeconomic factors may be important in the pathogenesis of SLE. Our analysis included female nurses who were older, employed and mostly White, and therefore our results may not apply to more diverse populations.

CONCLUSION

We identified an 85% increased risk of SLE among obese women in NHSII, which started enrollment in 1989, and a non-significant increase in SLE risk among obese women in NHS, which enrolled women in 1976. Overweight (BMI 25 to <30 kg/m²) compared to normal BMI (18.5 to <25 kg/m²) was not associated with increased SLE risk in either cohort, although significant linear relationships with increasing BMI were observed in NHSII. When the NHS cohort was delayed to start follow-up in the late 1980s, when U.S. obesity prevalence started increasing dramatically, meta-analysis of the two cohorts suggested an 80% increased risk of SLE among obese women. Further investigation into secular trends in both obesity and dietary factors in relation to SLE risk observed in recent years is warranted.

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Age-standardized baseline characteristics of 114,527 women in the Nurses' Health Study (NHS, enrolled 1976) and 109,033 women in the Nurses Health Study II (NHSII, enrolled 1989)

Characteristics	NHS				NHSII			
	18.5 to <25	25 to <30	30	Baseline BMI, kg/m ²	18.5 to <25	25 to <30	30	Baseline BMI, kg/m ²
Number (%)	81,201 (70.9)	23,691 (20.7)	9,635 (8.4)		75,435 (69.2)	20,746 (19.0)	12,852 (11.8)	
Mean age, years (SD) *	41.9 (7.2)	44.1 (7.0)	44.0 (6.9)		34.1 (4.7)	35.0 (4.6)	35.4 (4.5)	
White (%)	93.5	91.8	91.3		92.1	90.8	90.9	
Census-tract annual household median income \$60,000 (%)	51.4	43.5	38.0		47.5	39.2	32.3	
Smoking status (%)								
Never	41.8	46.8	50.1		65.0	64.4	65.6	
Past	23.6	23.6	25.3		21.9	21.5	20.9	
Current	34.6	29.6	24.6		13.1	14.1	13.5	
Mean alcohol intake, g/day (SD)	7.1 (11.0)	5.0 (9.6)	3.1 (7.8)		3.3 (5.8)	2.6 (5.8)	1.9 (4.9)	
Menarche age 10 (%)	4.8	8.4	11.7		6.0	10.8	16.0	
OC use, ever (%)	48.6	43.6	42.3		84.3	83.2	80.1	
Menopausal status and PMH use (%)								
Pre-menopausal	68.7	67.3	67.7		94.5	92.8	91.8	
Post-menopausal, never used PMH	16.0	18.1	19.5		2.7	3.6	3.5	
Post-menopausal, ever used PMH	14.3	13.6	11.9		2.7	3.5	4.5	

OC: oral contraceptive PMH: post-menopausal hormone

* Not age-adjusted

Abbreviations: g/day=grams/day

Table 2
Characteristics of 268 SLE cases at diagnosis by cumulative average BMI at diagnosis

Characteristics	NHS (n=153)			NHSII (n=115)		
	Cumulative Average BMI, kg/m ²			Cumulative Average BMI, kg/m ²		
	18.5 to <25	25 to <30	30	18.5 to <25	25 to <30	30
N (% of cases)	88 (57.5)	47 (30.7)	18 (11.8)	67 (58.3)	18 (15.6)	30 (26.1)
Age in years, mean (SD)	51.7 (8.4)	56.0 (9.3)	56.2 (10.1)	41.6 (7.4)	46.9 (9.2)	45.1 (7.5)
White (%)	90.9	91.5	83.3	95.5	77.8	96.7
ANA positive (%)	95.5	95.7	94.4	98.5	100.0	100.0
Anti-dsDNA positive (%)	31.8	42.6	50.0	47.8	77.8	40.0
Renal involvement (%)	18.2	21.3	16.7	13.4	16.7	10.0
Cytopenia (%)	56.8	51.1	33.3	67.2	66.7	60.0
Arthritis (%)	76.1	80.9	77.8	62.7	77.8	73.3

Table 3

SLE risk by cumulative average BMI category among 114,527 women in the Nurses' Health Study (NHS, 1976–2012) and 109,033 women in the Nurses' Health Study II (NHSII, 1989–2013)

	Cumulative Average BMI, kg/m ²			p trend ⁺
	18.5 to <25	25 to <30	30	
	Normal	Overweight	Obese	
NHS <i>n</i> =153 cases				
Mean BMI, kg/m ² (SD)	22.2 (1.6)	27.0 (1.4)	33.8 (3.6)	
Cases/person-years	88/1,989,754	47/897,130	18/380,805	
Adjusted HR (95% CI) [*]	1.00	1.28 (0.89–1.84)	1.11 (0.65–1.87)	0.49
NHSII <i>n</i> =115 cases				
Mean BMI, kg/m ² (SD)	22.1 (1.6)	27.1 (1.4)	35.2 (4.8)	
Cases/person-years	67/1,375,334	18/569,188	30/390,442	
Adjusted HR (95% CI) [*]	1.00	0.70 (0.41–1.18)	1.85 (1.17–2.91)	0.02
NHS+NHSII meta-analysis				
Cases/person-years	155/3,365,088	65/1,466,318	48/771,247	
Adjusted HR (95% CI) [*]	1.00	0.97 (0.54–1.76)	1.46 (0.88–2.40)	0.60

* HRs adjusted for age in months, questionnaire cycle, pregnancy during the questionnaire cycle (yes/no), race (White/non-White), census-tract household median income (<\$60,000 vs. \$60,000), smoking (never/past/current), alcohol intake (none, >0 to <5, 5 grams/day), oral contraceptive use (ever/never), age at menarche (<10 vs. >10 years), menopausal status and post-menopause hormone (PMH) use (pre-menopausal, post-menopausal/never used PMH, post-menopausal/ever used PMH)

⁺ p value for cumulative average BMI (continuous kg/m²) in multivariable Cox models

Table 4a

Sensitivity analysis: simple time-varying BMI SLE risk by simple time-varying BMI category among 114,527 women in the Nurses' Health Study (NHS, 1976–2012) and 109,033 women in the Nurses' Health Study II (NHSII, 1989–2013)

	Simple Updated BMI, kg/m ²			
	18.5 to <25	25 to <30	30	
	<i>Normal</i>	<i>Overweight</i>	<i>Obese</i>	p trend ⁺
NHS <i>n</i> =153 cases				
Mean BMI, kg/m ² (SD)	22.3 (1.6)	27.2 (1.4)	34.3 (4.2)	
Cases/person-years	78/1,640,173	48/953,596	25/546,064	
Adjusted HR (95% CI) *	1.00	1.15 (0.80–1.67)	1.00 (0.62–1.60)	0.30
NHSII <i>n</i> =115 cases				
Mean BMI, kg/m ² (SD)	22.1 (1.6)	27.2 (1.4)	35.7 (5.3)	
Cases/person-years	52/1,166,432	27/610,195	34/515,742	
Adjusted HR (95% CI) *	1.00	1.11 (0.69–1.79)	1.77 (1.12–2.80)	0.03
NHS+NHSII meta-analysis				
Cases/person-years	130/2,806,605	75/1,563,791	59/1,061,806	
Adjusted HR (95% CI) *	1.00	1.14 (0.85–1.52)	1.33 (0.76–2.34)	0.76

4 cases out of 170,454 person-years are missing simple time-varying BMI and are accounted for by a missing indicator, but are not presented in the table

* HRs adjusted for age in months, questionnaire cycle, race (White/non-White), census-tract household median income (<\$60,000 vs. \$60,000), smoking (never/past/current), alcohol intake (none, >0 to <5, 5 grams/day), oral contraceptive use (ever/never), age at menarche (<10 vs. >10 years), menopausal status and post-menopause hormone (PMH) use (pre-menopausal, post-menopausal/never used PMH, post-menopausal/ever used PMH)

⁺ p value for simple time-varying BMI (continuous kg/m²) in multivariate Cox models

Table 4b

Sensitivity analysis: two-cycle lag between cumulative average BMI assessment and SLE diagnosis

	Cumulative Average BMI, kg/m ²			
	18.5 to <25	25 to <30	30	
	<i>Normal</i>	<i>Overweight</i>	<i>Obese</i>	p trend ⁺
<hr/>				
NHS <i>n=143 cases</i>				
Mean BMI, kg/m ² (SD)	22.2 (1.6)	27.0 (1.4)	33.8 (3.6)	
Cases/person-years	89/1,908,660	37/832,768	17/349,424	
Adjusted HR (95% CI) [*]	1.00	1.05 (0.71–1.55)	1.09 (0.64–1.87)	0.59
<hr/>				
NHSII <i>n=103 cases</i>				
Mean BMI, kg/m ² (SD)	22.0 (1.6)	27.1 (1.4)	35.2 (4.8)	
Cases/person-years	59/1,286,026	17/512,544	27/347,356	
Adjusted HR (95% CI) [*]	1.00	0.76 (0.44–1.31)	1.95 (1.20–3.15)	0.01
<hr/>				
NHS+NHSII meta-analysis				
Cases/person-years	148/3,194,686	54/1,345,312	44/696,780	
Adjusted HR (95% CI) [*]	1.00	0.94 (0.68–1.29)	1.48 (0.84–2.60)	0.53

* HRs adjusted for age in months, questionnaire cycle, race (White/non-White), census-tract household median income (<\$60,000 vs. \$60,000), smoking (never/past/current), alcohol intake (none, >0 to <5, 5 grams/day), oral contraceptive use (ever/never), age at menarche (<10 vs. >10 years), menopausal status and post-menopause hormone (PMH) use (pre-menopausal, post-menopausal/never used PMH, post-menopausal/ever used PMH)

⁺ p value for cumulative average BMI (continuous kg/m²) in multivariable Cox models

Table 4c

Sensitivity analysis: similar calendar-years of follow-up for NHS and NHSII SLE risk by cumulative average BMI category among 99,336 women in the Nurses' Health Study (NHS) followed 1988–2012, and 109,033 women in the Nurses' Health Study II (NHSII) followed 1989–2013

	Cumulative Average BMI, kg/m ²			p trend ⁺
	18.5 to <25	25 to <30	30	
	<i>Normal</i>	<i>Overweight</i>	<i>Obese</i>	
NHS <i>n</i> =66 cases				
Mean BMI, kg/m ² (SD)	22.4 (1.5)	27.1 (1.4)	33.8 (3.6)	
Cases/person-years	29/1,100,360	26/593,310	11/255,032	
Adjusted HR (95% CI) [*]	1.00	1.77 (1.03–3.04)	1.67 (0.81–3.45)	0.45
NHSII <i>n</i> =115 cases				
Mean BMI, kg/m ² (SD)	22.1 (1.6)	27.1 (1.4)	35.2 (4.8)	
Cases/person-years	67/1,375,334	18/569,188	30/390,442	
Adjusted HR (95% CI) [*]	1.00	0.70 (0.41–1.18)	1.85 (1.17–2.92)	0.02
NHS+NHSII meta-analysis				
Cases/person-years	96/2,475,694	44/1,162,498	41/645,474	
Adjusted HR (95% CI) [*]	1.00	1.11 (0.44–2.76)	1.80 (1.22–2.65)	0.01

^{*} HRs adjusted for age in months, questionnaire cycle, race (White/non-White), census-tract household median income (<\$60,000 vs. \$60,000), smoking (never/past/current), alcohol intake (none, >0 to <5, 5 grams/day), oral contraceptive use (ever/never), age at menarche (<10 vs. >10 years), menopausal status and post-menopause hormone (PMH) use (pre-menopausal, post-menopausal/never used PMH, post-menopausal/ever used PMH)

⁺ p value for cumulative average BMI (continuous kg/m²) in multivariable Cox models