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The Impact of Asthma and Chronic Obstructive Pulmonary Disease (COPD) on Patient-Reported Outcomes in Systemic Lupus Erythematosus (SLE)

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Background. Risk of asthma and chronic obstructive pulmonary disease (COPD) may be elevated in systemic lupus erythematosus (SLE), but little research has studied the impact of these conditions on SLE outcomes. We examined prevalence, incidence, and impact of self-reported asthma and COPD in two US-based SLE cohorts (FORWARD and Lupus Outcomes Study [LOS]).

Methods. Prevalence of asthma and COPD were defined as presence of conditions at individuals' first interviews; incidence was defined as new reports over the next 3 years. Cross-sectional associations of asthma/COPD with patient-reported outcomes (PROs) and longitudinal analyses associations with asthma/COPD at entry with PROs 3 years later were examined.

Results. In FORWARD, 19.8% and 8.3% participants reported asthma and COPD, respectively, at entry. In LOS, 36.0% reported the presence of either (US population comparisons: asthma, 9.7%; COPD, 6.1%). Cross-sectionally, asthma/COPD was associated with worse PROs, including disease activity. In FORWARD, individuals with asthma experienced greater worsening of fatigue, pain, and global health ratings longitudinally; individuals with COPD experienced greater increases in self-reported SLE activity. However, no such patterns were noted in the LOS.

Conclusion. Asthma and COPD appeared to be more common in SLE than in the general US population and were associated with worse status on PROs cross-sectionally. Asthma was linked to decrements in PROs longitudinally.

INTRODUCTION

Cigarette smoking is a demonstrated risk factor for onset of systemic lupus erythematosus (SLE), with smokers having approximately 50% increased risk of SLE onset (1–3). Smoking has also been linked with greater cumulative organ damage and greater disease activity among individuals with SLE (4–6). A recent study found current and more than 10 years of smoking associated with onset of double-strand DNA–positive SLE (7).

Smoking is one of the most potent risk factors for onset of chronic obstructive pulmonary disease (COPD) (8). One recent study from Taiwan has found an elevated risk of incident COPD (hazard ratio = 1.73, 95% CI: 1.62–1.84) among individuals with SLE (9). The authors hypothesized that COPD in SLE may not be attributable to smoking alone and that SLE may also play a factor. SLE is also linked to 2.5 times increased risk of developing asthma (10).

SLE is associated with significant decrements in patient-reported outcomes (PROs), such as physical function and fatigue as well as overall quality of life (11–14). Asthma and COPD each have also been demonstrated to have significant impacts on PROs (15–20).

Despite the potential increased risk of both asthma and COPD in SLE, and the demonstrated impact of both conditions on PROs, little research has focused on the impact of asthma or COPD on outcomes in SLE. In these analyses, we examined the prevalence and incidence of self-reported asthma and COPD in two cohorts of individuals with SLE as well as the impact of those conditions on PROs.

METHODS

Data sources. Analyses were conducted in two US-based longitudinal cohorts of persons with SLE.

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FORWARD (The National Databank for Rheumatic Diseases). Participants in FORWARD (21) were recruited primarily from rheumatologists, and SLE diagnoses were provided by the rheumatologist. A minority of participants were enrolled from other sources, in which case diagnoses may have been confirmed by participants' physicians or were self-reported. All participants were at least age 18 at study entry. Data were collected at 6-month intervals by questionnaires. All participants had the option of completing the semiannual questionnaire online, as a mailed paper questionnaire, or by telephone interview. Respondents provided comprehensive sociodemographic and health status measures (eg, age, sex, education, race, household income, comorbidities, physical function, pain, patient global, 36-Item Short Form Survey [SF-36]) as well as smoking history. All FORWARD procedures were approved by Via Christi Institutional Review Board, and all participants provided consent to participate. Data shown in these analyses are from 1998 through 2016.

University of California San Francisco Lupus Outcomes Study. The Lupus Outcomes Study (LOS) was a longitudinal observational cohort, for which participants completed annual structured telephone interviews (22). All SLE diagnoses were physician-confirmed. Respondents were from throughout the United States, with 41 states represented, but approximately 70% were from California. Approximately one-third of LOS participants were from racial/ethnic minorities. Interviews covered comprehensive sociodemographic and health status measures (eg, age, sex, education, race, household income, comorbidities, physical function, pain, SF-36) as well as smoking history. The study was approved by the University of California San Francisco Committee on Human Research, and all participants provided written informed consent. LOS enrollment began in 2003; data shown in these analyses are from 2003 through 2006.

Variables. *Asthma and COPD.* Asthma and COPD were identified in each cohort with the questions below. In each case, prevalent conditions were defined as presence of conditions at the individual's first interview. Incidence was defined as new reports of conditions over the next three years. The self-report items were available in the LOS only for Waves 1 to 4, so a 3-year incidence period was selected in order to have equivalent follow-up periods between cohorts. Specific assessment questions are shown below:

1. FORWARD
   a Asthma: Self-report of asthma as a current health problem
   b COPD: Self-report of any of the following as current health problems: chronic bronchitis, emphysema, or COPD
   c Availability: Every questionnaire

Table 1. PROs available in each data set

Generic measures	FORWARD	LOS
Physical function	• Physical Function subscale of SF-36 (23,24): Higher scores = better function (score range 0-100) • HAQ-II: Higher scores = worse function (0-3)	• Physical Function subscale of SF-36 (23,24): Higher scores = better function (0-100)
Fatigue	• Vitality subscale of SF-36 (23,25): Higher scores = less fatigue. (0-100) • Single-item validated numeric rating scale (26): Rated on a scale of 0 (fatigue is no problem) to 100 (fatigue is a major problem) in 5-point increments.	• Vitality subscale of SF-36 (23,25): reversed so that higher scores reflect more fatigue (0-100)
Cognitive	• Self-report of trouble thinking or remembering (yes/no) (27)	• MOS Cognitive Functioning scale (28): 6-item scale, higher scores = better function (0-24)
Pain	• Single-item numeric rating scale (29): "How much pain have you had because of your illness in the past week?" Rated on a scale of 0 (no pain) to 100 (severe pain) in 5-point increments. • Bodily Pain subscale of SF-36 (23,29): Higher scores = less pain (0-100)	...
Sleep	• Single-item validated numeric rating scale (30): "How much of a problem has sleep been for you in the past week?" Rated on a scale of 0 (sleep is no problem) to 100 (sleep is a major problem) in 5-point increments.	...
Global health rating	• Single-item validated numeric rating scale (31): "Considering all the ways in which your illness affects you, rate how you are doing." Rated on a scale of 0 (very well) to 100 (very poorly) in 5-point increments	...
Depressive symptoms	...	• Center for Epidemiologic Studies Depression scale (CESD) (32): Higher scores = more symptoms • (0-60)
Lupus-specific		
Lupus activity	• Validated one-item numeric rating scale of lupus activity: "How active has your lupus been over the past 6 months?" (0, no activity to 10, extremely active) (33,34)	
Flare	• Self-report of a flare in the past 3 months (yes/no) (33,34)	

Note. In the LOS, only the Physical Function and Vitality domains of the SF-36 were administered.
Abbreviations: HAQ-II, Health Assessment Questionnaire II; LOS, Lupus Outcomes Study; MOS, Medical Outcomes Study; SF-36, 36-item Short Form Survey.

2. LOS
   a Self-report of physician diagnosis of: "lung problems, such as asthma, emphysema, or chronic bronchitis"
   b Availability: Interviews for Waves 1 to 4

PROs. A wide range of PROs were available for each cohort; PROs available in each data set are shown in Table 1.

Other variables. Sociodemographic and other health characteristics were self-reported and included:

- Sociodemographic: age, education, income, race/ethnicity
- General health: smoking status (current, former, never), body mass index (obesity calculated as BMI ≥ 30), and other comorbid conditions
- SLE-related: duration of disease (years), specific manifestations (renal involvement; presence of any clot, including pulmonary embolism, deep vein thrombosis, or other; or history of seizures).

Analysis. Analyses of prevalence were based on an individual's first observation (ie, entry questionnaire or interview). Frequencies of the presence of each condition were tabulated. In FORWARD, individuals with COPD at baseline (n = 179) were excluded from the no-asthma group; likewise, those with asthma (n = 487) were excluded from the no-COPD group.

Incidence was defined as new reports of conditions during the 3 years following an individual's entry questionnaire/interview. Characteristics of individuals with asthma and COPD at entry, incident asthma and COPD, and no asthma and COPD were conducted using bivariate methods (ie, analyses of variance, χ^2 analyses).

To determine the association of asthma and COPD with PROs, univariate cross-sectional analyses were first conducted using *t* tests or χ^2 analyses to compare individuals with and without conditions at entry. Multivariate cross-sectional linear and logistic regression analyses were then conducted. The first multivariate model adjusted for age, sex, race, disease duration, education, income, obesity, and smoking. The second model added adjustment for other comorbid conditions and lupus manifestations at baseline (renal involvement, presence of clots, and history of seizures). In FORWARD, the Rheumatic Disease Comorbidity Index (RDCI) was used to summarize comorbid conditions (35). The RDCI includes heart attack, other cardiovascular conditions, stroke, hypertension, fracture, depression, diabetes, cancer, ulcer or other stomach problem, and lung disease; the latter was removed for this analysis. In the LOS, a sum of the following comorbid conditions was used in the analysis: hypertension, heart disease, myocardial infarction, stroke, cancer, ulcer, and back problems.

Finally, longitudinal analyses were conducted to determine the association of asthma and COPD at entry with PROs collected at the last observation in the 3-year follow-up. Two models were constructed: Model 1 adjusted for baseline age, sex, race, disease duration, education, income, obesity, smoking, and baseline number of other comorbid conditions and lupus manifestations, whereas Model 2 added the baseline value of the dependent variable (PRO) to Model 1 to approximate change.

All regression analyses were conducted separately for asthma and COPD in FORWARD and were combined for the LOS because of differences in the way asthma and COPD were ascertained. Because of differences between FORWARD and the LOS in PRO measures, all analyses were conducted separately for each cohort.

RESULTS

Characteristics of the two cohorts. Table 2 shows the sociodemographic and health characteristics of the two cohorts at first observation. FORWARD cohort members had mean (SD) age of 50.5 (±14.1) years, were 87.2% white non-Hispanic with mean SLE duration of 15.8 (±12.3) years, 6.3% had low education (≤12 years), and 36.1% had obesity. LOS cohort members had mean age of 46.7 (±12.7) years, were 68.5% white with mean SLE duration of 12.6 (±8.5) years, 19.6% had low education, and 25.7% had obesity. Over 90% of each cohort was female, and about 40% of each cohort had a history of ever smoking.

Differences between individuals who were and were not available for the longitudinal analyses are shown in Supplementary

Table 2. Characteristics of the FORWARD and LOS cohorts at baseline

	FORWARD (n = 2804)	LOS (n = 881)
Sociodemographic		
Age, years	50.5 ±14.1	46.7 ± 12.7
Female	93.7%	92.4%
White race	87.2%	68.5%
Total income (×$1000)	49 ± 34	…
Below poverty income	…	10.9%
Education, years	13.8 ±2.4	…
Low education	6.3%	19.6%
Health, general		
Smoking status		
Current	13.9%	9.8%
Former	24.1%	30.8%
Never	61.9%	59.4%
Obese (BMI ≥ 30)	36.1%	25.7%
Comorbid conditions[a]	2.0 ± 1.4	1.6 ± 1.3
Lupus-specific		
Lupus duration (y)	15.8 ± 12.3	12.6 ± 8.5
SLE activity rating (0-10)	3.8 ± 3.0	4.3 ± 3.1

Abbrevations: BMI, body mass index, LOS, Lupus Outcomes Study; SLE, systemic lupus erythematosus.
[a] Comorbid conditions are represented by the Rheumatic Disease Comorbidity Index (excluding lung disease; Index score range 0-7) for the FORWARD cohort, and in the LOS by the number of conditions from the following list: hypertension, heart disease, myocardial infarction, stroke, diabetes, cancer, ulcer, and back problems.

Table 3. FORWARD: Characteristics at study entry of individuals with asthma or COPD compared to those without

	Asthma					COPD				
	No-respiratory condition[a] (n = 1883)	Asthma at study entry (n = 487)	Newly reported asthma[b] (n = 87)	*p*, 3-way	*p*, none vs. any	No-respiratory condition[c] (n = 1869)	COPD at study entry (n = 179)	Newly reported COPD[b] (n = 101)	*p*, 3-way	*p*, none vs. any
Sociodemographic										
Age	50.3 ±14.7	49.3 ±13.2	50.5 ± 12.8	0.31	0.18	50.2 ±14.6	53.4 ±12.5	54.1 ± 12.1	<0.0001	<0.0001
Female	93.0%	96.5%	96.6%	0.01	0.003	93.3%	91.6%	92.1%	0.66	0.97
White race	87.5%	86.2%	85.1%	0.63	0.40	87.6%	87.7%	85.2%	0.78	0.83
Total income ($1000)	51 ± 33	51 ± 35	48 ± 34	0.57	0.80	52 ± 33	37 ± 31	40 ± 30	<0.0001	0.0001
Education years	13.8 ± 2.4	13.8 ± 2.5	13.9 ± 2.5	0.98	0.90	13.8 ± 2.4	13.4 ± 2.2	13.8 ± 2.4	0.12	0.03
Low education	5.5%	7.8%	5.8%	0.15	0.65	5.5%	8.9%	5.0%	0.16	0.10
Health										
Smoking status				0.45	0.37				<0.0001	<0.0001
Current	12.7%	10.3%	11.5%			12.0%	29.6%	23.8%		
Former	23.3%	26.1%	24.4%			23.0%	29.6%	23.0%		
Never	64.6%	57.0%	57.7%			65.0%	40.8%	46.5%		
Smoke, ever	36.3%	34.7%	29.9%	0.41	0.33	35.0%	59.2%	53.5%	<0.0001	<0.0001
Obese (BMI ≥30)	32.5%	41.9%	39.1%	<0.0001	<0.0001	32.5%	43.0%	39.6%	0.008	0.002
Lupus duration (y)	15.6 ± 12.3	15.8 ± 12.1	15.3 ± 11.3	0.92	0.82	15.4 ± 12.2	18.3 ± 13.6	18.2 ± 13.2	0.002	0.012
SLE activity rating (0-10)	3.3 ± 2.9	4.2 ± 3.1	4.1 ± 3.1	<0.0001	<0.0001	3.3 ± 2.9	5.0 ± 3.2	4.5 ± 3.3	<0.0001	0.012

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus.

[a] Those who had new reports of asthma over the 3 years of follow-up are not included in the no-respiratory condition group in this analysis. Individuals who reported COPD at study entry were excluded.

[b] Newly reported cases over three years of follow-up.

[c] Those who had new reports of COPD over the 3 years of follow-up are not included in the no-respiratory condition group in this analysis. Individuals who reported asthma at study entry were excluded.

Table 4. LOS: Characteristics of individuals with and without respiratory comorbidities (asthma and COPD combined)

	No-respiratory condition[a] (n = 503)	Respiratory condition at baseline (n = 314)	Newly developed respiratory condition[b] (n = 64)	*p*, 3-way comparison	*p*, none vs. any
Sociodemographic					
Age	45.4 ± 13.0	49.2 ± 12.8	50.8 ± 12.6	<0.0001	<0.0001
Female	90.5%	91.7	98.4%	0.10	0.21
Race, white	67.9%	74.8%	73.4%	0.09	0.03
Below poverty	9.8%	15.7%	15.6%	0.03	0.01
Low education	17.3%	25.8%	23.4%	0.01	0.003
Health					
Smoking status				0.11	0.03
Current	8.3%	10.8%	12.5%		
Former	29.5%	36.0%	34.4%		
Never	62.2%	53.2%	53.3%		
Smoke, ever	37.8%	46.8%	46.9%	<0.0001	<0.0001
Obese (BMI ≥30)	17.4%	35.7%	34.9%	<0.0001	<0.0001
Duration of lupus	12.8 ± 8.6	12.7 ± 8.5	13.1 ± 8.5	0.93	0.97
SLE activity rating	3.7 ± 3.1	5.2 ± 3.0	4.8 ± 2.6	<0.0001	<0.0001

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; LOS, Lupus Outcomes Study; SLE, systemic lupus erythematosus.
[a] Those who had new reports of respiratory conditions over the 3 years of follow-up are not included in the no-respiratory condition group in this analysis.
[b] Newly reported cases over 3 years of follow-up.

Tables 1 (FORWARD) and 2 (LOS). In FORWARD, those who were not included in follow-up were more likely to be white, had lower income and less education, were more likely to be current smokers, and generally had worse status on the PROs. In the LOS, those not included in follow-up were less likely to be female or white, and more likely to have low income and low education. No significant differences in PROs or in the frequency of asthma and COPD between those who were and were not lost to follow-up were noted.

Prevalence and incidence. At baseline, 487 (487/2457, 19.8%) of the FORWARD cohort reported asthma and 179 (179/2149, 8.3%) reported COPD. Of those with neither condition at baseline, 87 had new reports of asthma (87/1970, 4.4%) and 101 had new reports of COPD (82/1970, 4.2%) over the next 3 years.

At baseline, 36.0% of the LOS participants reported having asthma or COPD (using the combined question; 314/881, 35.6%). Sixty-four individuals newly reported asthma/COPD over the next 3 years (64/567, 11.3%).

Characteristics of those with and without asthma or COPD. *FORWARD.* Individuals with asthma at baseline were more frequently female and more frequently had obesity and had higher SLE activity ratings (Table 3). Those who developed asthma over the follow-up period were similar to those with asthma at baseline.

Individuals with COPD at baseline and who developed COPD during follow-up were older at baseline, had lower incomes, were more likely to be or have been smokers, were more likely to have obesity, had lupus of longer duration, and rated their lupus as more active. Those who newly developed COPD were similar to those with COPD at baseline.

LOS. Individuals with asthma/COPD were older at baseline, had lower incomes and lower education, were more likely to be or have been smokers, were more likely to have obesity, and rated their lupus as more active (Table 4). Those who newly developed asthma/COPD were similar to those with those conditions at baseline.

PROs: cross-sectional analyses. *FORWARD.* In bivariate analyses, asthma was cross-sectionally associated with greater self-reported SLE activity and with worse status on all generic PROs (Table 5). There was, however, no difference in the frequency of self-reported SLE flares between individuals with and without asthma. Findings were unchanged in multivariate models adjusting for socioeconomic and general health variables, including other comorbidities and smoking (Table 6, Asthma Model 1), except for sleep disturbance. In multivariate models also adjusting for SLE manifestations, significant differences remain for SLE activity, Health Assessment Questionnaire II (HAQ-II), fatigue rating, pain, global severity, and cognitive symptoms (Table 6, Asthma Model 2); in each case, individuals with asthma had worse status.

Similar results were noted for COPD. In bivariate analyses, COPD was cross-sectionally associated with greater self-reported SLE activity and with worse status on all generic PROs (Table 5), with no difference in the frequency of self-reported SLE flares between individuals with and without COPD. Findings were unchanged in multivariate models adjusting for socioeconomic and general health variates, including smoking (Table 6, COPD Model 1). Like asthma, after adjusting for SLE manifestations,

Table 5. Bivariate differences in patient-reported outcomes at study entry for individuals with and without respiratory conditions

	FORWARD: Asthma			FORWARD: COPD			LOS (asthma and COPD combined)		
	No-respiratory condition (n = 1893)	Asthma at study entry (n = 487)	*p*	No-respiratory condition (n = 1802)	COPD at study entry (n = 834)	*p*	No-respiratory condition (n = 560)	Respiratory condition at study entry (n = 314)	*p*
Lupus-specific									
SLE Activity (0-10)	3.4 ± 2.9	4.2 ± 3.1	<0.0001	3.4 ± 2.9	5.0 ± 3.2	<0.0001	3.8 ± 3.0	5.2 ± 3.0	<0.0001
Flare in past 3 mo	59.6%	70.5% (n = 204)	0.139	59.9%	75.0% (n = 170)	0.54	42.0%	59.5%	<0.0001
Generic									
SF-36 Physical Function	57.2 ± 29.4	46.6 ± 28.5	<0.0001	57.9 ± 29.3	34.6 ± 25.6	<0.0001	64.6 ± 28.7	46.0 ± 30.6	<0.0001
HAQ-II (0-3)	0.83 ± 0.66	1.08 ± 0.68	<0.0001	0.82 ± 0.66	1.37 ± 0.66	<0.0001			
SF-36 Vitality	37.4 ± 23.0	30.7 ± 21.4	<0.0001	37.6 ± 22.9	26.6 ± 21.6	<0.0001	52.0 ± 23.0	64.4 ± 21.4	<0.0001
Fatigue (0-10)	4.5 ± 3.1	5.3 ± 3.1	<0.0001	4.5 ± 3.1	5.7 ± 2.9	<0.0001	…	…	…
SF-36 Pain	50.5 ± 23.9	41.7 ± 21.7	<0.0001	50.8 ± 24.0	36.3 ± 20.4	<0.0001	…	…	…
Pain (0-10)	3.9 ± 2.9	5.1± 2.9	<0.0001	3.9 ± 2.9	5.6 ± 2.7	<0.0001	…	…	…
Global severity (0-10)	3.6 ± 2.6	4.2 ± 2.5	<0.0001	3.6 ± 2.6	4.8 ± 2.4	<0.0001	…	…	…
Sleep disturbance (0-10)	3.7 ± 3.1	4.2 ± 3.2	<0.0001	3.7 ± 3.1	4.8 ± 3.2	<0.0001	…	…	…
Trouble thinking or remembering (symptoms)	48.6%	63.8%	<0.0001	48.5%	66.7%	<0.0001	…	…	…
Cognitive function	…	…	…	…	…	…	73.8 ± 21.7	63.0 ± 23.8	<0.0001
CESD	…	…	…	…	…	…	14.9 ± 12.4	18.9 ± 12.9	<0.0001

Note. In the LOS, the SF-36 Vitality scale was reverse-scored so that higher scores reflect greater fatigue.
Abbreviations: CESD, Center for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; HAQ-II, Health Assessment Questionnaire II; LOS, Lupus Outcomes Study; SF-26, 36-item Short Form Survey; SLE, systemic lupus erythematosus.

Table 6. Patient-reported outcomes at study entry for individuals with respiratory conditions (from multivariate regression analyses)

	FORWARD: Asthma		FORWARD: COPD		LOS: (asthma and COPD combined)	
	Model 1[a]	Model 2[b]	Model 1	Model 2	Model 1	Model 2
Lupus-specific						
SLE activity (0-10)	0.8*** (0.4, 1.3)	0.6** (0.1, 1.0)	1.1*** (0.5, 1.7)	0.7* (0.1, 1.3)	1.1*** (06, 1.5)	0.8** (0.4, 1.3)
Flare in past 3 mo	1.6 (0.7, 3.8)	1.5 (0.6, 4.0)	1.6 (0.4, 5.4)	1.3 (0.3, 4.9)	1.8** (1.3, 2.4)	1.7** (1.2, 2.3)
Generic						
SF-36 Physical Function	−8.5*** (−11.8, −5.3)	−3.4 (−6.9, 0.1)	−11.7*** (−16.2, −7.2)	−7.9** (−12.6, −3.2)	−11.7*** (−15.8, −7.7)	−8.7*** (−12.7, 4.7)
HAQ-II (0-3)	0.26*** (0.19, 0.33)	0.16*** (0.09, 0.24)	0.33*** (0.23, 0.43)	0.25*** (0.15, 0.35)	...	...
SF-36 Vitality	−5.0*** (−7.7, −2.3)	−2.4 (−5.3, 0.6)	−4.9* (−8.7, −1.0)	−3.0 (−7.1, 1.0)	8.8*** (5.6, 12.0)	6.6*** (3.3, 9.8)
Fatigue (0-10)	0.8*** (0.4, 1.1)	0.6** (0.2, 1.0)	0.9*** (0.4, 1.3)	0.9** (0.4, 1.4)	...	...
SF-36 Pain	−8.2*** (−11.0, −5.5)	−4.9** (−7.8, −1.9)	−7.4*** (−11.3, −3.5)	−4.2* (−8.2, −0.2)	...	...
Pain (0-10)	1.2*** (0.9, 1.5)	0.8*** (0.4, 1.1)	1.2*** (0.7, 1.6)	0.9*** (0.4, 1.3)	...	...
Global severity (0-10)	0.6*** (0.3, 0.9)	0.4* (0.1, 0.7)	0.8*** (0.4, 1.2)	0.7** (0.3, 1.1)	...	...
Sleep disturbance (0-10)	0.3 (−0.0, 0.7)	0.2 (−0.2, 0.6)	0.5* (0.04, 1.0)	0.5 (−0.04, 1.0)	...	...
Trouble thinking or remembering (symptoms)	2.0*** (1.6, 2.6)	1.9*** (1.4, 2.6)	1.7** (1.2, 2.4)	1.5* (1.0, 2.2)	...	...
Cognitive function	...	...	...	...	−8.4*** (−11.6, −5.1)	−6.5** (−9.8, −3.2)
CESD	...	...	...	...	2.7** (0.9, 4.5)	1.8 (−0.1, 3.6)

Note. Tabled values are β (95% confidence interval) from multivariate linear regression or odds ratio (95% confidence interval) from multivariate logistic regression. In the LOS, the SF-36 Vitality scale was reverse-scored so that higher scores reflect greater fatigue.
Abbreviations: CESD, Center for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; HAQ-II, Health Assessment Questionnaire II; LOS, Lupus Outcomes Study; SF-26, 36-item Short Form Survey; SLE, systemic lupus erythematosus.
[a] Model 1 adjusted for age, sex, race, disease duration, education, income, obesity, and smoking.
[b] Model 2 adjusted for age, sex, race, disease duration, education, income, obesity, smoking, comorbid conditions (FORWARD: Rheumatic Disease Comorbidity Index; LOS: number of comorbid conditions), renal involvement, presence of any clot (pulmonary embolism, deep vein thrombosis, other), and presence of seizure.
*** $p < 0.0001$, ** $p < 0.01$, * $p < 0.05$.

significant differences remained for most generic PROs (Table 6, COPD Model 2), with individuals with COPD having worse status than those without.

LOS. In bivariate cross-sectional analyses, asthma/COPD was associated with worse status on both lupus-specific and generic PROs (Table 5). After adjusting for sociodemographic and general health factors, including smoking, significant differences remained for all PROs (Table 6, LOS Model 1). After adjusting for SLE manifestations, differences in depressive symptoms were no longer statistically significant, although differences in the other PROs remained (Table 6, LOS Model 2).

PROs: longitudinal analyses. *FORWARD.* Longitudinally, asthma at baseline was associated with worse status on all PROs at 3-year follow-up except for occurrence of flares and presence of cognitive symptoms (Table 7, Asthma Model 1), even after adjusting for SLE manifestations. However, when the baseline value of the PRO was added to the model (to approximate change), fewer significant differences remained between individuals with and without asthma at baseline (Table 7, Asthma Model 2). Differences remained for fatigue and pain variables and for global severity. In each case, individuals with asthma had greater decrements in these PROs over time.

At 3-year follow-up for those with COPD, when adjusting for baseline sociodemographics, health, and SLE manifestations, differences in SLE activity rating, SF-36 Physical Function, HAQ-II, fatigue rating, SF-Pain, pain, and global severity ratings were significantly worse for those with pulmonary comorbidities (Table 7, COPD Model 1). Further adjustment for baseline values of the PROs left no significant differences between the groups except for self-reported SLE activity, which was significantly worse for those with COPD (Table 7, COPD Model 2).

LOS. SLE activity rating, both measures of physical functioning, and cognitive functioning were significantly worse at 3-year follow-up for individuals with asthma/COPD (Table 7, LOS Model 1). After adjusting for baseline values of the PROs, no significant differences remained between those with and without asthma/COPD (Table 7, LOS Model 2).

Table 7. Longitudinal: effect of baseline asthma/COPD on outcomes 3 years later (from multivariate regression analyses)

	FORWARD: Asthma		FORWARD: COPD		LOS (asthma and COPD combined)	
	Model 1[a]	Model 2[b]	Model 1	Model 2	Model 1	Model 2
Lupus-specific						
SLE activity (0-10)	0.7** (0.2, 1.1)	0.1 (−0.2, 0.4)	1.1*** (0.5, 1.6)	0.4 (−0.04, 0.8	0.7** (0.3, 1.2)	0.4 (−0.01, 0.8)
Flare in past 3 mo	1.9 (0.7, 5.0)	2.7 (0.4, 16.0)	2.3 (0.8, 6.7)	2.5 (0.1, 45.4)	1.6* (1.1, 2.2)	1.4 (0.9, 2.0)
Generic						
SF-36 Physical Function	−4.2* (−8.1, −0.4)	−0.3 (−2.6, 2.0)	−7.6** (−12.5, −2.6)	−1.1 (−4.1, 1.9)	−5.3** (−9.3, −1.3)	−1.0 (−4.3, 2.3)
HAQ-II (0-3)	0.14** (0.06, 0.22)	0.00 (−0.04, 0.05)	0.27*** (0.16, 0.37)	0.05 (−0.01, 0.1)	...	...
SF-36 Vitality	−4.5** (−7.8, −1.1)	−1.4 (−3.5, 0.8)	−4.9* (−9.3, −0.5)	−2.6 (−5.4, 0.2)	5.7** (2.1, 9.3)	1.7 (−1.3, 4.8)
Fatigue (0-10)	0.5* (0.1, 0.9)	0.5 (−0.3, 0.4)	0.5 (−0.1, 1.0)	0.1 (−0.4, 0.6)	...	...
SF-36 Pain	−6.2*** (−9.6, −2.8)	−1.6 (−3.9, 0.6)	−5.4* (−9.7, −1.1)	−1.9 (−4.8, 1.0)	...	...
Pain (0-10)	0.6** (0.3, 1.0)	0.2 (−0.03, 0.5)	0.8** (0.3, 1.3)	0.2 (−0.2, 0.5)	...	...
Global severity (0-10)	0.3* (0.001, 0.6)	0.03 (−0.3, 0.3)	0.5* (0.03, 0.9)	0.2 (−0.2, 0.6)	...	...
Sleep disturbance (0-10)	0.3 (−0.1, 0.7)	0.1 (−0.3, 0.5)	0.5 (−0.1, 1.0)	0.3 (−0.2, 0.8)	...	...
Trouble thinking or remembering	1.4* (1.0, 1.8)	1.2 (0.8, 1.8)	1.4 (0.9, 2.1)	1.1 (0.6, 1.8)	...	...
Cognitive function	...	...	...	...	−6.2** (−9.7, −2.7)	−2.4 (−5.3, 0.4)
CESD	...	...	...	...	2.0* (0.1, 4.0)	1.0 (−0.6, 2.7)

Note. Tabled values are β (95% confidence interval) from multivariate linear regression or odds ratio (95% confidence interval) from multivariate logistic regression. In the LOS, the SF-36 Vitality scale was reverse-scored, so that higher scores reflect greater fatigue.
Abbreviations: CESD, Center for Epidemiologic Studies Depression scale; COPD, chronic obstructive pulmonary disease; HAQ-II, Health Assessment Questionnaire II; LOS, Lupus Outcomes Study; SF-26, 36-item Short Form Survey; SLE, systemic lupus erythematosus.
[a] Model 1 adjusted for age, sex, race, disease duration, education, income, obesity, smoking, comorbid conditions (FORWARD: Rheumatic Disease Comorbidity Index; LOS: number of comorbid conditions), renal involvement, presence of any clot (pulmonary embolism, deep vein thrombosis, other), presence of seizure.
[b] Model 2 = Model 1 + baseline value of patient-reported outcome.
*** $p < 0.0001$, ** $p < 0.01$, * $p < 0.05$.

DISCUSSION

We found that, at baseline, almost 20% of the FORWARD cohort reported asthma and approximately 8% reported COPD. The LOS interview did not separate these two conditions, but 36% of that cohort reported having one of these conditions. For comparison, the prevalence of asthma is approximately 9.7% in the US adult female population at age 18 years or older (36), and the prevalence of COPD in the US adult female population age 18 years or older is approximately 6.1% (37), suggesting an increased prevalence of both conditions, particularly asthma, in these SLE cohorts. The increased prevalence of COPD may be linked to smoking, which has been robustly associated with increased risk of SLE and is the cause of the majority of COPD cases. Some researchers have proposed a mechanism for increases in the risk of asthma in SLE (38), but this hypothesis needs further study.

A clear pattern of worse status on PROs was noted when comparing individuals with asthma or COPD and those without in both cohorts. Even after adjusting for socioeconomic and general health factors, including smoking, and SLE manifestations, individuals with asthma/COPD had worse physical functioning, greater fatigue, worse perceived cognitive functioning, and, in the FORWARD cohort, higher levels of pain. Self-reported SLE disease activity was also greater in those with these comorbidities. Whether these differences in self-reported disease activity are reflected in physician assessments remains for future research. However, symptoms from asthma and COPD may lead patients to perceive worsening in their SLE that would not be recognized in clinical assessments of SLE activity, potentially leading to discordance in patient and provider assessments. The discordance driven by asthma/COPD symptoms may lead to unmet treatment expectations or inaccurately targeted treatments due to misattribution of symptom etiology. The potential for discordance may be particularly pronounced in the PROs we examined. All fall into the Type 2 SLE symptom category (ie, symptoms such as fatigue, depression, or sleep disturbance) (39), with the possible exception of flare reports, although perceptions of flares may also be driven by these Type 2 symptoms. Pisetsky and colleagues note

that acknowledging these symptoms, which are not included in clinical assessments of SLE, may improve patient-physician communication and patient understanding of their disease. Likewise, being able to appropriately attribute respiratory symptoms may lead to both better patient outcomes as well as improved patient-physician communication.

Longitudinal analyses were conducted to determine whether individuals with asthma or COPD experienced greater worsening of symptoms over time in addition to worse symptoms cross-sectionally. We found that in the FORWARD cohort, independent of smoking, obesity, and other covariates, individuals with asthma did experience greater worsening of fatigue, pain, and global health ratings over time, and individuals with COPD experienced greater increases in self-reported SLE activity. However, no such patterns were noted in the LOS. Whether this difference is due to differences in the cohort or the way the conditions were assessed (individual questions for asthma and COPD in FORWARD versus a combined question in LOS) is unknown. It is also possible that the predominant condition in LOS was COPD, where fewer longitudinal differences were seen in FORWARD, as well. The underlying reason for differences in changes of PROs for asthma and not COPD could not be determined in these analyses and needs further study.

This study does have limitations. With the exception of SLE diagnoses, all data were self-reported, including presence of asthma and COPD. It is possible that these diagnoses were inaccurately reported. Studies assessing the accuracy of self-reported asthma and COPD have tended to show underreporting. For example, one study comparing self-reports of physician-diagnosed asthma and COPD to diagnoses derived from administrative data showed moderate agreement for both conditions, with high specificity (0.96 and 0.97, respectively) but moderate to low sensitivity (0.55 and 0.26, respectively) (40). The prevalence of asthma from administrative data was about 15% higher than from self-report (9.8% vs. 8.6%), but the prevalence of COPD from administrative data was almost double that obtained from self-report (11.1% vs. 5.6%). Assuming that the individuals in these cohorts similarly underreported, our estimates of both prevalence and incidence may be conservative. Current smokers and individuals with low education were more likely to be lost to follow-up, which may also contribute to an underestimate of COPD incidence, given the associations noted at baseline. Another consideration is that SLE has disease-specific pulmonary manifestations such as pleurisy, plural effusion, or interstitial lung disease, so it is possible that individuals with those conditions were confused about the origin of pulmonary symptoms. However, we specifically asked about physician's diagnoses of asthma and COPD, which may mitigate this potential confusion. In addition, the LOS question combined asthma and COPD and so has less specificity.

Although all PROs were validated scales or items and all data collection measures were well tested, some measurement error always exists. For example, it is possible that participants may inaccurately report the presence of symptoms or exposures. We assume that such misreporting is not biased in a certain direction (ie, will include inaccurate positive and negative responses). Loss to follow-up may have affected results, particularly in FORWARD, where those who were lost to follow-up had worse status on all PROs. However, presence of asthma or COPD was not associated with differences in follow-up status (Supplemental Tables 1 and 2). Study participants may not represent the spectrum of individuals with SLE. Individuals who are from minority racial/ethnic groups or who are younger may be underrepresented, particularly in the FORWARD cohort, and minority patients often have more severe disease. Individuals with severe disease may be underrepresented because they are too ill to complete surveys/interviews. In addition, individuals with low income and low education were less likely to be included in the longitudinal follow-ups in both cohorts, and in FORWARD, those not in the longitudinal follow-up tended to have worse scores on PROs at the baseline assessment. It is also possible that we did not account for covariates that may impact PRO assessments, such as stress or the presence of fibromyalgia or other comorbidities.

At the same time, the study also has strengths. Both cohorts were based on large national longitudinal cohorts and included a spectrum of validated PROs not commonly measured in studies of SLE. The two data sources are complementary in terms of study duration, variables included, and characteristics of the participants (age, race/ethnicity). Although both FORWARD and the LOS rely on patient-reported data, participants in both cohorts have physician-confirmed SLE diagnoses.

In summary, we found evidence of increased prevalence of asthma and COPD in these cohorts of individuals with SLE. We also found that the presence of these conditions was associated with worse status on physical function, fatigue, perceived cognitive function, and pain, all of which are important PROs in SLE, in both cohorts. These findings suggest that health care providers should routinely screen individuals with SLE for asthma and COPD and ensure that they are receiving adequate treatment for those conditions. In addition, counseling for smoking cessation and screening for occupational exposures that are linked to the development of pulmonary conditions is also advisable. Future analyses of PROs in SLE should also include asthma and COPD as important comorbid conditions.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version. Dr. Katz had full access to all of the data of the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design and conception: Katz, Alemao; Acquisition of data: Katz, Trupin, Yelin, Michaud; Analysis and interpretation of data: Katz, Pedro.

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