

ORIGINAL RESEARCH

Distinct pattern of comorbidities hinders treatment target attainment in SLE through persistent disease activity and delayed glucocorticoid tapering: longitudinal data from a multicentre cohort study

Myrto Nikoloudaki,¹ Georgios D Barmparis,² Sofia Pitsigavdaki,¹ Spyridon Katechis,^{3,4} Ettore Silvagni ,⁵ Argyro Repa,¹ Antonio Marangoni,⁵ Nestor Avgoustidis,¹ Irini Flouri ,¹ Ioannis Saridakis,¹ Marcello Govoni,⁵ Prodromos Sidiropoulos ,^{1,6} Antonis Fanouriakis ,^{3,4} Alessandra Bortoluzzi ,⁵ Dimitrios Boumpas ,^{3,4} George Bertsias ,^{1,6}

To cite: Nikoloudaki M, Barmparis GD, Pitsigavdaki S, *et al.* Distinct pattern of comorbidities hinders treatment target attainment in SLE through persistent disease activity and delayed glucocorticoid tapering: longitudinal data from a multicentre cohort study. *RMD Open* 2026;**12**:e006424. doi:10.1136/rmdopen-2025-006424

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/rmdopen-2025-006424>).

Received 8 October 2025
Accepted 3 February 2026



© Author(s) (or their employer(s)) 2026. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

For numbered affiliations see end of article.

Correspondence to

Dr George Bertsias;
gbertsias@uoc.gr

ABSTRACT

Background Remission and low-disease activity are recommended targets in systemic lupus erythematosus (SLE), yet many patients fail to achieve them, underscoring the need to identify contributing barriers. We explored whether comorbidities—some of which share genetic risk with lupus—and their specific patterns influence target accomplishment.

Methods Retrospective cohort of 347 patients with active SLE receiving treatment intensification at inclusion. Comorbidities (n=140), disease activity, treatments and organ damage were monitored (median follow-up 5 years). Mixed-effects assessed relationships between comorbidities and definitions of remission in SLE/lupus low disease activity state (DORIS/LLDAS). Random forests ranked comorbidities according to the strength of associations.

Results Despite the relatively young age (median 46 years) and short disease duration (median 9 months), patients with SLE exhibited high comorbidity burden (comorbidities count, Rheumatic Disease Comorbidity Index, Elixhauser, Charlson), which increased longitudinally and was associated with reduced attainment of DORIS (ORs: 0.77–0.87, $p<0.05$) and LLDAS (ORs: 0.74–0.91, $p<0.01$). Obesity, dyslipidaemia, hypertension, stroke, depression, fibromyalgia and thyroid disorders emerged as the most influential. Presence of ≥ 1 of these conditions (n=238 [68.6%]) was linked to 55–60% lower likelihood of durable DORIS/LLDAS ($\geq 50\%$ time). Marginal structural models (MSMs) confirmed an independent comorbidities-targets association, regardless of prior achievement, explained by smouldering activity and delayed glucocorticoid tapering. While immunosuppressant/biologic use was comparable, comorbid patients received lower glucocorticoid doses during high disease activity. Comorbidities were also

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Comorbidities that share genetic risk with autoimmunity are emerging as plausible modifiers of disease activity in chronic rheumatic disorders, but supporting evidence is lacking in systemic lupus erythematosus (SLE).

WHAT THIS STUDY ADDS

⇒ In patients with SLE, increasing comorbidity burden is associated with reduced likelihood of achieving DORIS remission and LLDAS.
⇒ Machine learning identifies seven conditions—obesity, hypertension, stroke, dyslipidaemia, thyroid disorders, fibromyalgia and depression—as most strongly associated with failure to reach the targets.
⇒ This key cluster of comorbidities was linked to ongoing disease activity and slower glucocorticoid tapering, while overall treatment patterns were largely comparable.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients with SLE might benefit from a comprehensive management approach that addresses comorbid conditions while optimising therapy to achieve and sustain treat-to-target.

associated with greater damage accrual (IRR: 1.38, 95% CI 1.11 to 1.71), attenuated in patients with sustained DORIS/LLDAS.

Conclusions Patients with SLE manifest high comorbidity burden, with distinct patterns linked to reduced target attainment. In these patients, vigilant monitoring and treatment adjustments are essential to sustain disease control and prevent damage.

INTRODUCTION

Suppressing disease activity is a central goal in the management of systemic lupus erythematosus (SLE), and achieving validated endpoints, such as definitions of remission in SLE (DORIS)¹ and the lupus low disease activity state (LLDAS),² results in improved long-term outcomes, including reduced flares, organ damage and mortality.³ In addition to requiring absent or low activity, both definitions permit stable use of immunosuppressive or biologic agents but impose glucocorticoid (GC) limits— ≤ 5 mg/day for DORIS and ≤ 7.5 mg/day for LLDAS.^{1,2} Despite this, these targets are not universally achieved in real-world cohorts, with sustained LLDAS and DORIS typically experienced by fewer than 60–70% and 30–40% of patients, respectively.^{3–6} Rates are even lower in randomised trials,⁷ possibly reflecting the inclusion of more severe or long-standing disease, as well as the impact of more stringent protocols.

Identifying barriers to attaining the treat-to-target goals is essential for bridging the gap between guideline-based recommendations and real-world practice, and for informing tailored interventions to improve prognosis in SLE. Comorbidities are increasingly recognised as plausible modifiers of autoimmune disorders, potentially through shared genetic susceptibility and pathogenic pathways, or their impact on immune regulation and treatment responsiveness. In chronic arthritis, comorbid conditions—whether examined individually, through composite scores or grouped into clusters—may contribute to reduced rates of therapeutic targets.^{8–11} In SLE, case-control^{12–14} and population-based¹⁵ studies have shown that a wide range of coexisting physical and psychiatric conditions are common, with a multifactorial aetiology involving perpetuated inflammation, prolonged glucocorticoid exposure and shared risk factors.^{16–18} However, much of this research relies on administrative databases or focuses on selected conditions, while comprehensive assessments of the overall comorbidity profile in contemporary lupus cohorts remain limited. Furthermore, the extent to which comorbidities—and their specific profiles—influence disease activity and treatment target attainment in patients with SLE has not been explored.

To address these questions, we analysed a real-life, multicentre cohort of patients with active SLE at inclusion who underwent treatment intensification and were followed for a median of 5 years.

Our primary objective was to assess the impact of comorbidity burden on achieving the treatment targets of DORIS remission and LLDAS, evaluated both cross-sectionally and longitudinally. We applied machine learning approaches to prioritise the individual conditions most strongly associated with reduced target attainment. In addition, we examined potential drivers of these associations, focusing on the contributions of persistent disease activity and GC tapering. Finally, we evaluated the impact of comorbidities on long-term outcomes, such as damage accrual, showing that these effects are attenuated

in patients with sustained disease control, therefore informing comorbidity-aware strategies to improve SLE prognosis.

PATIENTS AND METHODS

Analytic framework

The main exposure was comorbidity burden (assessed through comorbidity indices and a cluster of identified comorbidities), and the primary outcomes were DORIS remission and LLDAS, assessed at both the patient-level and visit-level. Covariates included baseline demographic and disease characteristics as well as time-varying prior attainment of DORIS/LLDAS. A directed acyclic graph (figure 1A) illustrates the hypothesised relationships among these variables.

Details on the methodology are provided in the online supplemental file 1.

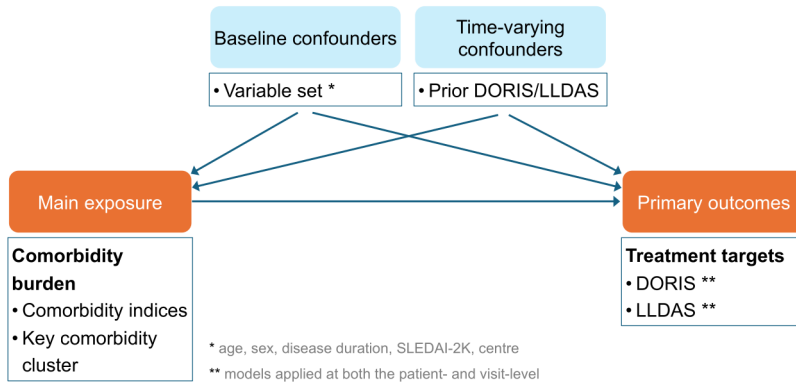
Study design and eligibility criteria

This retrospective study was performed in two lupus clinics and included patients aged ≥ 16 years with SLE, fulfilling the 2012 Systemic Lupus International Collaborating Clinics (SLICC)¹⁹ and/or 2019 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria.²⁰ Eligible patients were identified if they had an inclusion (index) visit between 01/2008 and 06/2018. The index visit was the earliest visit during this period with active disease, defined as systemic lupus erythematosus disease activity index (SLEDAI)-2K ≥ 6 and/or physician global assessment (PGA) ≥ 1.5 (scale: 0 (no activity) to 3 (maximum activity)), requiring treatment initiation or intensification with any of the following: (1) initiation of oral GC (≥ 20 mg/day prednisone-equivalent) and/or intravenous methylprednisolone, (2) at least doubling of oral GC dosage or (3) initiation or switching of immunosuppressive or biological agent (including IVIg). Exclusion criteria included coexisting systemic autoimmune/inflammatory diseases, insufficient data or inadequate follow-up. The minimum visit frequency was every 3–6 months during the first year and every 4–12 months thereafter.

Clinical assessment, variables collection and treatment targets

At inclusion visit, demographics, date of diagnosis, pre-existing comorbidities and previous treatments were registered. At each visit, we recorded the following: (1) SLE treatments and their dosage, (2) SLEDAI-2K, PGA, Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-SLEDAI flare index,²¹ modified to include mycophenolate, belimumab and rituximab under the definition of severe flare, (3) SLICC/ACR damage index (SDI),²² (4) comorbidities, hospitalisations or deaths attributable to any cause and (5) attainment of targets (DORIS,¹ LLDAS⁵) with their detailed definitions provided in online supplemental table S1. PGA was scored before immunological tests were available, and

A



B

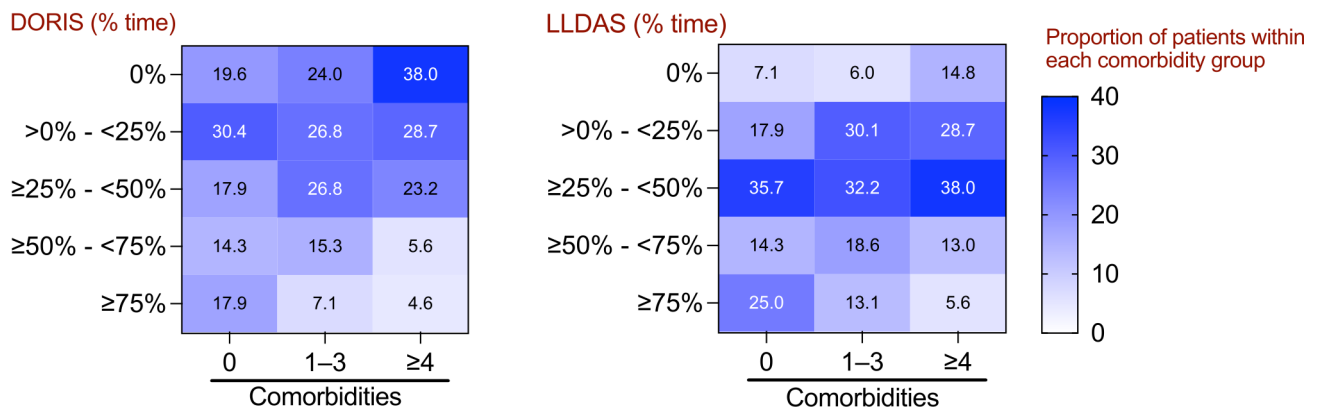


Figure 1 Total comorbidity burden is associated with reduced duration of DORIS remission and LLDAS in patients with SLE. (A) Directed acyclic graph (DAG) illustrating hypothesised relationships among comorbidities and target attainment in SLE. The main exposure is comorbidity burden, evaluated through comorbidity indices and the identified cluster of key comorbidities. The primary outcomes are DORIS remission and LLDAS. Baseline demographic and disease characteristics (age, sex, disease duration, baseline disease activity and study centre) are included as covariates. Prior attainment of DORIS/LLDAS is modelled as a time-varying confounder of subsequent outcomes. (B) Heatmap showing the distribution of patients with SLE across increasing durations of DORIS (left panel) and LLDAS (right panel)—categorised as 0%, <25%, 25–50%, 50–75% and >75% of follow-up time—within groups with 0, 1–3 and ≥4 comorbidities. Columns sum to 100%. When stratified by comorbidity burden (measured at inclusion), patients without comorbidities were more evenly distributed across remission duration categories, whereas those with 1–3, and especially ≥4 comorbidities, were disproportionately represented in the shorter-duration groups ($\chi^2=22.06$, $df=8$, $p=0.006$ for DORIS; $\chi^2=21.69$, $df=8$, $p=0.006$ for LLDAS). DORIS, definitions of remission in SLE; LLDAS, lupus low disease activity state; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.

laboratory results obtained within 30 days of each visit were considered for completing the SLEDAI-2K.

Assessment and ascertainment of comorbidities

A list of 140 comorbidities was compiled using the Rheumatic Disease Comorbidity Index (RDCI) and its modified version,²³ the Elixhauser Comorbidity Index (ECI),²⁴ the Charlson Comorbidity Index (CCI)²⁵ (excluding connective tissue diseases) and relevant items from the Common Terminology Criteria for Adverse Events (CTCAE); https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (online supplemental table S2). A combination of sources was used to detect and confirm comorbidities, including medical charts, electronic hospital records, laboratory and imaging tests, patient reports and the national electronic prescription

systems (ICD-10 classification). The latter became available in Greece and Italy in 2011, enabling physicians to track all prescribed medications. Additionally, both clinics (Heraklion, Ferrara) maintain a comprehensive SLE patient record system. Each patient has a dedicated file that includes laboratory results since diagnosis, reports from other specialists and findings from imaging tests. Within the healthcare setting of both centres, hospital-based rheumatologists also provide primary care-level management, resulting in routine assessment of blood pressure, body weight and body mass index and regular laboratory evaluation of blood lipids, fasting glucose and HbA1c. The long-term patient follow-up facilitates the detection of comorbid disorders and their complications. Therefore, incident comorbidities, symptoms, adverse

events, infections and newly initiated medications were systematically documented at each visit.

Random forests

To prioritise comorbidities associated with the likelihood of DORIS and LLDAS in a high-dimensional and correlated setting, we employed a random forest classifier (Python package Scikit-Learn). This approach was selected because it can flexibly model non-linear effects and interactions among a large number of potentially correlated conditions without requiring strong parametric assumptions. To enhance model interpretability, we assessed feature importance using permutation importance, which quantifies the impact of each feature on predictive performance by measuring the drop in F1-score of 20 repeats when the feature values are randomly shuffled. The resulting rankings were used to identify comorbidities most strongly associated with targets and inform subsequent regression analyses. Details on feature selection and measures to limit overfitting are provided in the online supplemental methods.

Statistical analysis

Longitudinal changes in comorbidities were examined by the Wilcoxon signed-rank or the McNemar test for paired data. For each patient, we calculated the percentage of time spent in each target (including the SLEDAI, PGA and GC dose subcriteria of DORIS and LLDAS) by summing all intervals meeting the target and dividing by the total observation period, and then multiplying by 100. To assess the relationship between comorbidities and target attainment, mixed-effects logistic regression models were applied, treating DORIS/LLDAS as binary outcomes. Baseline covariates were included as fixed effects, and a random intercept for each patient accounted for repeated visits. Patient-level generalised linear models, adjusted for baseline covariates, were used to evaluate the association between comorbidities and the duration of individual DORIS/LLDAS subcriteria. A mixed-effects framework was also used to analyse treatment use, with separate models fitted for visits with PGA ≤ 1 and PGA > 1 , as drug prescriptions and GC dosing may vary with disease activity and organ involvement. All analyses were performed using STATA V.19.5.

Marginal structural models

To estimate the total effect of comorbid disease burden on reaching DORIS/LLDAS excluding reverse causation due to prior target attainment, we employed MSMs with inverse probability of treatment weighting (IPTW), adjusting for time-varying confounding by prior outcome status (lagged DORIS/LLDAS) and baseline covariates. Covariate balance between exposure groups was achieved (standardised mean differences ≤ 0.1 for all variables).

Cox regression

To evaluate whether comorbidities influence GC tapering in patients who achieved clinical disease control, we performed multiple-failures survival analysis using the

Andersen-Gill extended Cox model. The time origin was defined as the visit at which patients fulfilled the clinical DORIS or LLDAS criteria but continued receiving GC at doses > 5 and > 7.5 mg/day, respectively. Episodes began at such visits, and patients could re-enter the risk set if these conditions were met again during follow-up. Failure was defined as attainment of complete DORIS or LLDAS definitions. Robust standard errors were used to account for within-subject correlation.

RESULTS

Patients with SLE exhibit a substantial and accumulating burden of comorbidities

We included 347 patients (92.5% female) with a median (IQR) age of 45.7 (21.3) years and disease duration of 8.7 (66.4) months (table 1). At baseline, all patients had active disease with median (IQR) PGA, SLEDAI-2K and clinical SLEDAI-2K of 2.0 (0.5), 8 (4) and 6 (4), respectively. The average ($\pm$ SD) comorbidities count was 2.5 ± 2.0 at inclusion, increasing to 3.6 ± 2.5 ($p < 0.001$) at last observation (median (IQR) follow-up: 60²⁴ months) (table 2). The proportion of patients without comorbidities declined from 17.1% to 10.1%, while those with ≥ 4 conditions rose from 31.1% to 47.3% ($p < 0.001$). RDCI increased from 1.1 ± 1.1 to 1.5 ± 1.3 ($p < 0.001$), with similar patterns observed for ECI and CCI. Most frequently involved organs/domains were cardiovascular, endocrine, metabolic, musculoskeletal and psychiatric (table 2), all demonstrating increasing trends during follow-up. Collectively, and despite the relatively young age and short disease duration, these data suggest a high prevalence of comorbidities in patients with SLE with accumulating trends over time.

Comorbidity burden is associated with reduced attainment of the treatment targets in SLE

Comorbidities are increasingly recognised as potential disease modifiers in chronic inflammatory disorders, associated with suboptimal disease control.^{11 26} To explore whether such a relationship exists in SLE, we first calculated for each patient the proportion of follow-up time under DORIS and LLDAS. When stratified by comorbidity burden at inclusion, patients without comorbidities were more evenly distributed across remission and low disease activity duration categories, whereas those with 1–3 and especially ≥ 4 comorbidities were disproportionately represented in the shorter-duration groups ($p = 0.006$ for DORIS, $p = 0.006$ for LLDAS) (figure 1B).

As a more robust approach, we used mixed-effects regression to assess the likelihood of achieving the targets over consecutive visits. All comorbidity scores were linked to decreased probability of reaching DORIS or LLDAS, with the strongest reductions observed with the modified RDCI (OR per 1-unit: 0.76; 95% CI 0.63 to 0.91 for DORIS at next visit; 0.76; 95% CI 0.66 to 0.88 for LLDAS at next visit) and the ECI (OR per 1-unit increase: 0.78; 95% CI 0.67 to 0.91 and 0.77; 95% CI 0.68 to 0.88,

Table 1 Demographic and clinical characteristics of patients with SLE at inclusion visit and during follow-up

	N (%) or median (IQR)
Inclusion visit data	
No of patients	347
Gender (female)	321 (92.5%)
Ethnicity (White)	330 (95.4%)
Age (years)	45.7 (21.3)
Disease duration (months)	8.7 (66.4)
Organ damage (SDI>0)	94 (27.1%)
PGA (0–3)	2.0 (0.5)
SLEDAI-2K	8 (4)
Clinical SLEDAI-2K	6 (4)
Follow-up data	
No of visits	2460
No of visits per patient	7 (4)
Follow-up (patient-months)	19356
Follow-up, per patient (months)	60 (24)
Remission (DORIS) attainment	
At least once	250 (72.1%)
No of visits (excluding inclusion visit)	1038 (50.2%)
No of visits in target per patient	4 (4)
Cumulative target duration per patient (months)	10.5 (24.0)
Cumulative target duration per patient (% time)	18.2 (44.4)
Duration ≥50% time (no of patients)	77 (22.2%)
Low disease activity (LLDAS) attainment	
At least once	315 (90.8%)
No of visits (excluding inclusion visit)	1405 (68.0%)
No of visits in target per patient	4 (4)
Cumulative target duration per patient (months)	18.0 (25.5)
Cumulative target duration per patient (% time)	33.3 (43.8)
Duration ≥60% time (no of patients)	81 (23.3%)
DORIS, definition of remission in SLE; LLDAS, lupus low disease activity state; PGA, physician global assessment; SDI, SLICC/ACR damage index; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE disease activity index 2000.	

respectively) (table 3). Comorbidity scores were not associated with excessive flares, suggesting that patients with comorbid SLE tend to experience predominantly smouldering disease activity.

Random forests identify key comorbidities with the strongest associations with target achievement

Since our analysis included several comorbidities across multiple organs/systems, we sought to identify those

Table 2 Burden of comorbidities in patients with SLE at inclusion and during follow-up

	Baseline	Last follow-up	P value*
Comorbidities count	2.5±2.0	3.6±2.5	<0.001
0	56 (17.1%)	35 (10.1%)	<0.001
1–3	183 (52.7%)	148 (42.7%)	
≥4	108 (31.1%)	164 (47.3%)	
Modified RDCI	1.1±1.1	1.5±1.3	<0.001
0	120 (34.6%)	94 (27.1%)	<0.001
1	122 (35.2%)	107 (30.8%)	
≥2	105 (30.3%)	146 (42.1%)	
Elixhauser CI	1.3±1.2	1.7±1.4	<0.001
0	109 (31.4%)	88 (25.4%)	<0.001
1	110 (31.7%)	94 (27.1%)	
≥2	128 (36.9%)	165 (47.6%)	
Charlson CI	0.5±0.9	0.7±1.1	<0.001
0	248 (71.5%)	214 (61.7%)	<0.001
1	58 (16.7%)	74 (21.3%)	
≥2	41 (11.8%)	59 (17.0%)	
Organ/domains of comorbidities			
Cardiovascular	0.41±0.65	0.53±0.79	<0.0001
Cerebrovascular	0.05±0.22	0.07±0.25	0.0253
Endocrine	0.38±0.53	0.46±0.61	<0.0001
Eye	0.04±0.20	0.07±0.27	0.0027
Gastrointestinal	0.10±0.31	0.16±0.41	0.0001
Hepatobiliary	0.08±0.29	0.11±0.35	0.0047
Haematological	0.10±0.30	0.13±0.34	0.0082
Infectious	0.05±0.22	0.14±0.40	<0.0001
Metabolic	0.42±0.60	0.50±0.64	<0.0001
Musculoskeletal	0.29±0.54	0.59±0.77	<0.0001
Malignancies	0.07±0.25	0.10±0.29	0.0047
Benign tumour	0.02±0.15	0.03±0.16	0.3173
Neurological	0.07±0.26	0.15±0.41	<0.0001
Psychiatric	0.22±0.48	0.34±0.63	<0.0001
Renal–urological	0.02±0.15	0.04±0.20	0.0253
Reproductive	0.02±0.14	0.02±0.14	—
Skin	0.01±0.11	0.02±0.13	0.3173
Respiratory	0.10±0.32	0.16±0.40	<0.0001

Comorbidity measures included total comorbidity count (based on 140 conditions; Online supplemental table S2), modified RDCI, Elixhauser CI and Charlson CI. The lower part of the table presents the mean number of comorbidities per patient in each of 18 organ-specific domains, derived by grouping the individual conditions into predefined categories. Values are presented as mean±SD or as number (%) of patients per category.

*Wilcoxon signed ranks paired test or McNemar test comparing follow-up versus baseline comorbidity measures.

CI, Comorbidity Index; RDCI, Rheumatic Disease Comorbidity Index; SLE, systemic lupus erythematosus.

Table 3 Increasing burden of comorbidities is associated with reduced attainment of DORIS remission and LLDAS in patients with SLE

	Comorbidities count	Modified RDCI	Elixhauser CI	Charlson CI
Visit-by-visit analysis	OR (95% CI) per 1-unit increase			
DORIS				
Current visit	0.80 (0.69 to 0.93)*	0.71 (0.56 to 0.89)*	0.74 (0.60 to 0.92)*	0.74 (0.55 to 0.99)†
Next visit	0.84 (0.76 to 0.93)*	0.76 (0.63 to 0.91)*	0.78 (0.67 to 0.91)*	0.79 (0.63 to 0.99)†
≥2 consecutive visits	0.83 (0.72 to 0.95)*	0.78 (0.62 to 0.99)†	0.78 (0.63 to 0.95)†	0.81 (0.61 to 1.07)
LLDAS				
Current visit	0.88 (0.80 to 0.97)†	0.84 (0.71 to 1.00)†	0.87 (0.75 to 1.00)	0.89 (0.75 to 1.06)
Next visit	0.84 (0.78 to 0.91)‡	0.76 (0.66 to 0.88)†	0.77 (0.68 to 0.88)‡	0.87 (0.74 to 1.01)
≥2 consecutive visits	0.83 (0.74 to 0.93)*	0.77 (0.63 to 0.93)*	0.75 (0.63 to 0.90)*	0.94 (0.76 to 1.14)
Flare				
Mild-moderate				
Current visit	1.09 (0.96 to 1.25)	0.98 (0.78 to 1.23)	0.99 (0.83 to 1.20)	0.80 (0.61 to 1.06)
Next visit	1.14 (0.99 to 1.30)	1.10 (0.86 to 1.42)	1.09 (0.89 to 1.35)	0.92 (0.69 to 1.22)
Severe				
Current visit	1.05 (0.94 to 1.18)	1.04 (0.85 to 1.26)	0.99 (0.84 to 1.19)	1.12 (0.95 to 1.32)
Next visit	1.08 (0.95 to 1.23)	1.03 (0.83 to 1.27)	0.96 (0.79 to 1.17)	1.02 (0.82 to 1.27)
Mixed-effects logistic regression assessing target attainment as a binary outcome. Models were adjusted for covariates (fixed effects) and included a random intercept for each patient to account for intra-individual correlation from repeated visits. Values represent the OR (95% CI) per 1-unit increase in each comorbidity measure. Flares were classified according to the SELENA-SLEDAI flare index.				
*p<0.01.				
†p<0.05.				
‡p<0.001.				
CI, Comorbidity Index; DORIS, definition of remission in SLE; LLDAS, lupus low disease activity state; RDCI, Rheumatic Disease Comorbidity Index; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.				

most strongly related to target attainment. We applied a random forest classifier as a well-suited machine learning algorithm to handle possible non-linear effects and complex interactions between comorbidities, while avoiding overfitting (online supplemental figure S1). Following ranking based on permutation-based importance (figure 2A, B), eight comorbidities, namely major depression, fibromyalgia, obesity, dyslipidaemia, hypertension, cerebrovascular disease (stroke), thyroid disorders and osteoporosis, were top-prioritised. In a sensitivity analysis using nested cross-validated LASSO regression, these conditions were consistently retained by LASSO, indicating concordant prioritisation of key features across modelling approaches (online supplemental methods, figure S2).

All comorbidities—except osteoporosis—were negatively associated with both targets (figure 2C, D). When these seven comorbidities were summed, we noted a gradual decline in the likelihood of achieving DORIS or LLDAS, especially among patients with multiple (≥3) conditions (figure 2E, F). The inverse association between comorbidities and targets remained unchanged after adjustment for major organ involvement and disease severity as defined by the EULAR/ACR 2019 classification criteria²⁰ (online supplemental table S3). Similarly, introducing calendar period as a covariate did not influence

the comorbidities-target relationship (online supplemental table S4). Presence of at least one of these comorbidities at baseline (n=238 patients, 68.6%) resulted in 55% (OR 0.45; 95% CI 0.23 to 0.87) and 60% (OR 0.40; 95% CI 0.22 to 0.74) lower rates of durable DORIS and LLDAS (≥50% of time), respectively.

To explore the relative importance of individual conditions within patients bearing ≥3 of the seven key comorbidities, we assessed the impact of excluding each comorbidity from the model. *Obesity* and *fibromyalgia* emerged as the most influential (online supplemental table S5). When examining the full set of seven comorbidities, the negative association with target attainment was present both for conditions existing at baseline and for those accrued subsequently (online supplemental table S6).

Comorbidities influence the likelihood of DORIS and LLDAS without evidence of reverse causation

To estimate the effect of the identified comorbidities on target attainment, while accounting for the possibility that prior DORIS/LLDAS status influences future comorbidity burden, we applied MSMs with inverse probability of treatment weighting (IPTW). Covariate balance was achieved between exposure groups (SMD≤0.1 for all variables) (online supplemental table S7). In weighted models, the negative impact of the seven comorbidities

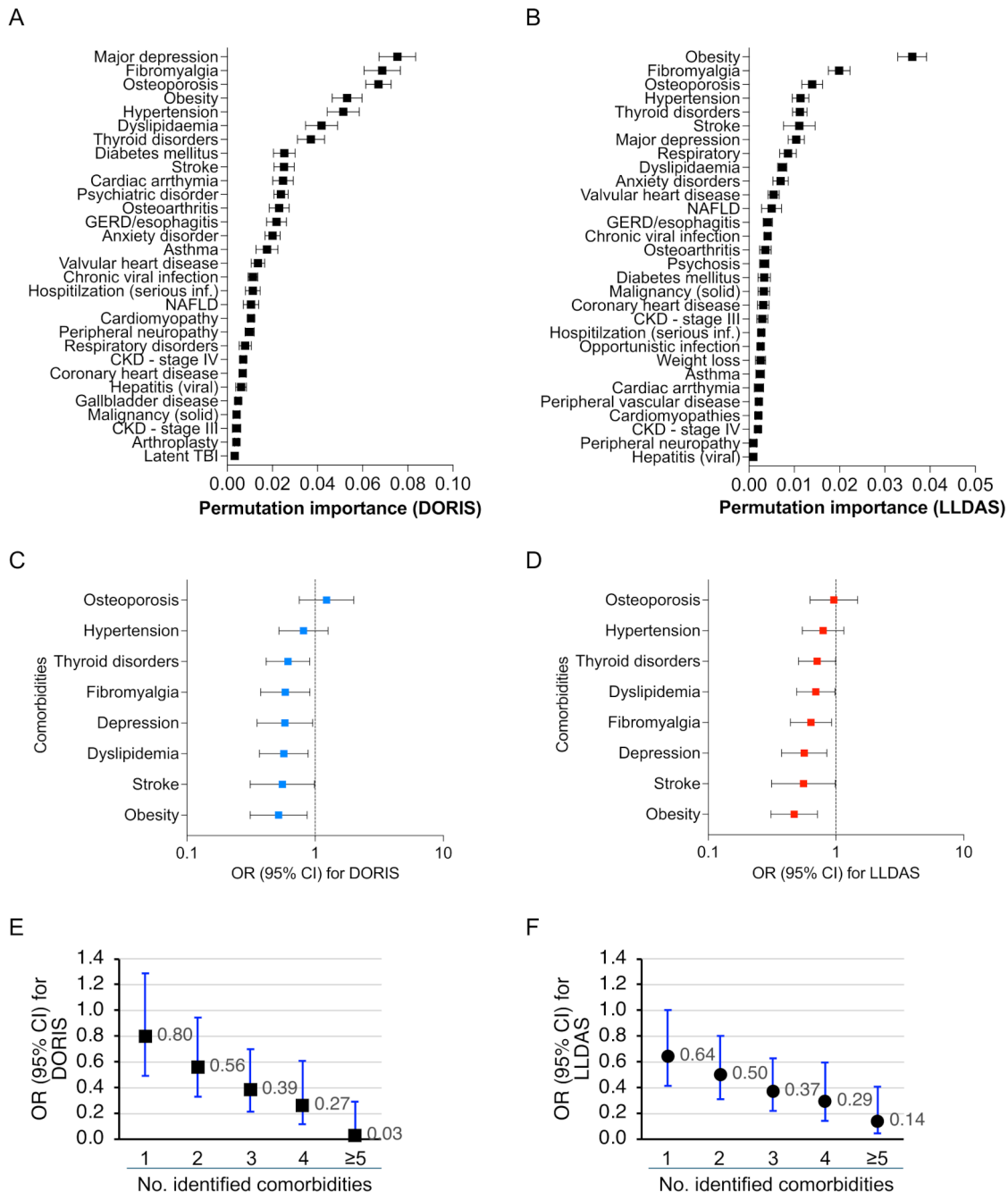


Figure 2 Random forests identify comorbidities most strongly associated with the likelihood of achieving DORIS and LLDAS in patients with SLE (A, B). A random forest classifier was applied to the longitudinal dataset of patients with SLE, as described in the *Methods* and online supplemental methods, to identify conditions with the strongest association with DORIS (A) and LLDAS (B). Comorbidities were ranked using permutation importance, which quantifies how much each feature (condition) contributes to model performance by measuring the decrease in F1-score across 20 repetitions after randomly shuffling the values of that feature. Dots and error bars represent the mean and SE of permutation importance for the top 30 comorbidities. (C, D) Mixed-effects logistic regression was used to estimate the association of each of the top eight comorbidities (identified in panels A and B) with attainment of DORIS (C) and LLDAS (D). Dots represent OR and error bars indicate 95% CIs. (E, F) Mixed-effects logistic regression shows the impact of an increasing number of seven key comorbidities (identified in panels A–B: obesity, hypertension, dyslipidaemia, stroke, fibromyalgia, depression and thyroid disorders) on the likelihood of attaining DORIS (E) and LLDAS (F). Dots represent ORs and error bars indicate 95% CI. CKD, chronic kidney disease; DORIS, definitions of remission in systemic lupus erythematosus; GERD, gastroesophageal reflux disease; LLDAS, lupus low disease activity state; NAFLD, non-alcoholic fatty liver disease; TBI, tuberculosis infection.

cluster on achieving DORIS and LLDAS at the subsequent visit remained robust (OR 0.80 per 1-condition; 95% CI 0.70 to 0.90 and OR 0.83 per 1-condition; 95% CI

0.75 to 0.93, respectively), independent of prior target attainment, thus indicating that the association is not due to reverse causation (online supplemental table S8).

Comorbidities are associated with both increased disease activity and slower glucocorticoid tapering

Since DORIS and LLDAS are composite definitions (online supplemental table S1), we were interested to determine whether their inverse association with comorbidities was driven by the disease activity (PGA, SLEDAI) and/or treatment-related (GC dose) components. Patients with a greater number of target comorbidities

experienced lower duration of all three criteria, namely PGA ($\beta=-0.048$, $p=0.003$ for $\text{PGA}<0.5$; $\beta=-0.046$, $p=0.002$ for $\text{PGA}\leq 1$), SLEDAI ($\beta=-0.050$, $p=0.002$ for clinical SLEDAI-2K ($\text{clinical-S2K}=0$; $\beta=-0.047$, $p=0.001$ for $\text{SLEDAI}\leq 4$), and GC dose ($\beta=-0.034$, $p=0.038$ for ≤ 5 mg/day; $\beta=-0.034$, $p=0.021$ for ≤ 7.5 mg/day) (figure 3A, B). Importantly, higher comorbidity burden was linked to elevated risk of moderate (clinical-S2K 5–9) and high

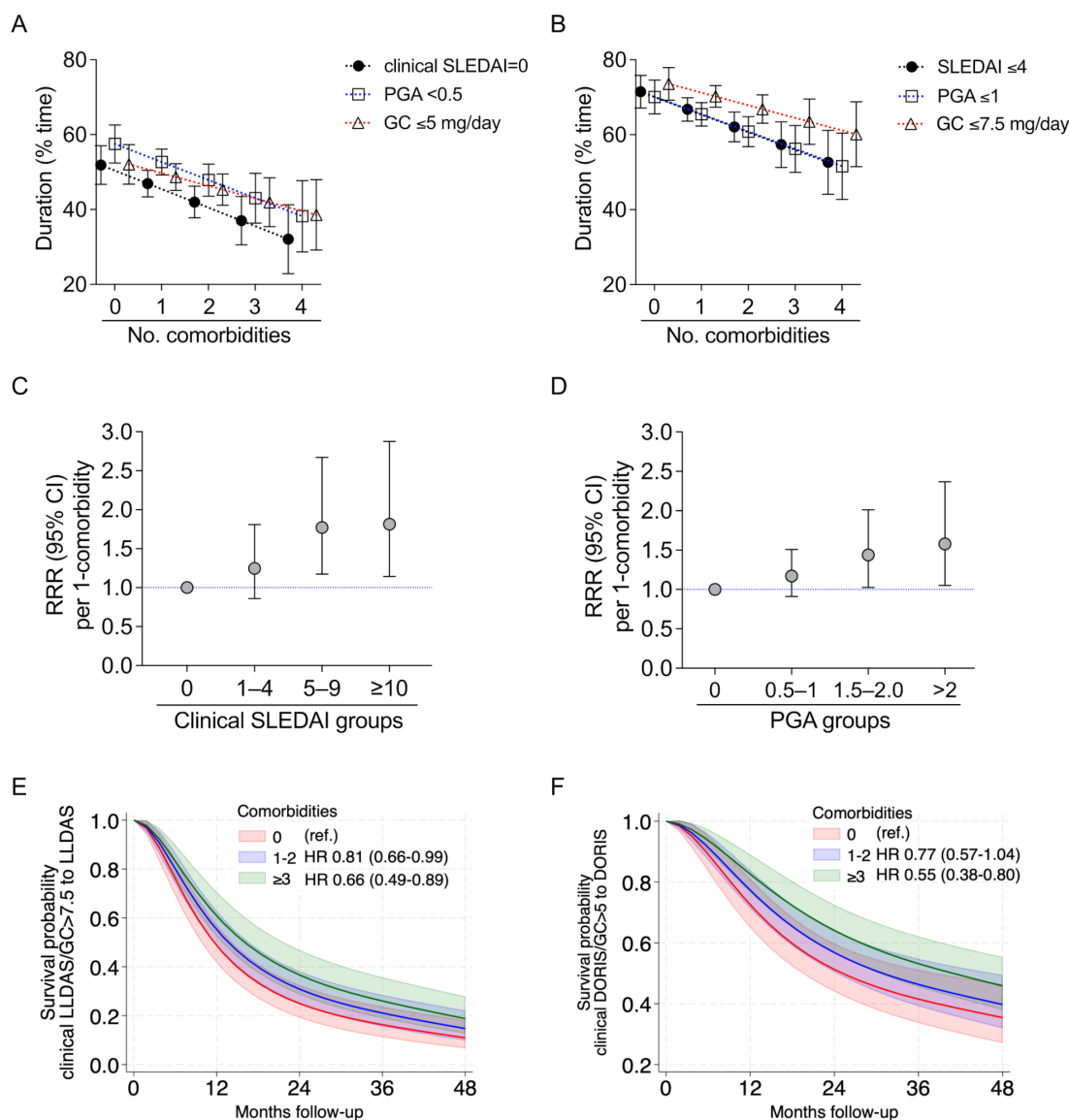


Figure 3 Comorbidity burden is associated with reduced treatment targets through both persistent disease activity and prolonged tapering of glucocorticoids (A, B) Generalised linear models (adjusted for baseline covariates) were used to examine associations between the seven key comorbidities and the duration (% of follow-up time) of each individual component of DORIS (A: cSLEDAI=0, PGA<0.5, GC dose≤5 mg/day) and LLDAS (B: SLEDAI≤4, PGA≤1, GC dose≤7.5 mg/day). Dots, triangles and squares represent the predicted average values, with error bars indicating 95% CIs. (C, D) Logistic regression (multinomial) was performed on consecutive visits, with a random intercept per patient, to assess the impact of the seven key comorbidities on the risk of being in states mild, moderate and high disease activity (C: clinical SLEDAI-2K groups; D: PGA groups), compared with reference states of remission (clinical SLEDAI-2K=0 and PGA=0, respectively). Dots represent the relative risk ratios (RRR) and error bars indicate the 95% CI. (E, F) Cox regression (recurring events) was used to assess the effect of comorbidities on the hazard of reaching GC dose thresholds defined by DORIS (E) and LLDAS (F), with the starting point set as the time when the clinical criteria for these targets were first met. Survival plots show the probability of not reaching the GC dose thresholds, with shaded areas indicating 95% CI. HRs are displayed with 95% CI inside brackets, using the comorbidity-free group as reference. DORIS, definitions of remission in SLE; GC, glucocorticoid; LLDAS, lupus low disease activity state; PGA, physician global assessment; RRR, relative risk ratios; SLEDAI systemic lupus erythematosus disease activity index.

(clinical-S2K ≥ 10) clinical disease activity, with relative risk ratios of 1.77 and 1.81, respectively, compared with clinical-S2K=0; similar trends were observed when activity levels were defined according to PGA (figure 3C, D). Thus, in patients with comorbidities, failure to reach targets coincided with both persistent clinical activity and maintenance of GC dose above the DORIS/LLDAS-defined thresholds.

Notably, during visits where patients met the disease activity criteria for DORIS and LLDAS, the presence of comorbidities was linked to a reduced likelihood of fulfilling the GC dosage criteria (OR 0.73; 95% CI 0.57 to 0.95 for ≤ 5 mg/day; OR 0.83; 95% CI 0.71 to 0.98 for ≤ 7.5 mg/day). To confirm this, we performed Cox regression analysis. The time origin was defined as visits where patients met the clinical criteria for LLDAS or DORIS but had not yet fulfilled the corresponding GC dosage criterion. Comorbid patients had a lower hazard of attaining the ≤ 7.5 mg/day and ≤ 5 mg/day thresholds (figure 3E, F). These findings suggest a tendency for SLE patients with comorbidities to be maintained on low-dose GC even when low or absent disease activity is achieved.

Treatment patterns and glucocorticoid dosing in relation to comorbidity burden among patients with SLE

We wondered whether the identified cluster of comorbidities was associated with variations in the use of lupus medications. Since administered treatments often differ by disease status, we used PGA, which reflects both activity and severity of organ involvement, to stratify our longitudinal dataset into visits with absent/low (PGA ≤ 1) or moderate/high (PGA > 1) SLE activity/severity. Overall, comorbidity burden was not associated with marked changes in treatment patterns after adjustment for baseline covariates (table 4). Nonetheless, during active disease, increasing comorbidity burden tended to correlate with more frequent use of methotrexate ($p=0.044$) and rituximab ($p=0.043$), and with lower use of mycophenolate ($p=0.044$). Of note, the relationship between comorbidity burden and oral GC dose differed by disease activity. Consistent with our above-mentioned data, in visits with PGA ≤ 1 , comorbidities were associated with higher GC doses, whereas in visits with PGA > 1 , increasing comorbidity burden was linked to lower doses. Predicted values of oral GC doses according to PGA score and sum of comorbidities are shown in online supplemental figure S3. To address the possibility that such treatment patterns, potentially influenced by prior disease activity or physician decision-making, might act as time-varying confounders of the comorbidity-target association, we performed additional MSMs incorporating time-varying GC dose and immunosuppressive treatment intensity (online supplemental methods, tables S9, 10). As a complementary sensitivity analysis, conventional regression models, including concurrent treatments (including GC dose) as time-varying covariates, yielded similar results (online supplemental table S11), although

Table 4 Patterns of SLE treatment use according to comorbidity burden, stratified by disease activity status

Treatments	Effect of comorbidity cluster (seven key comorbidities)	
	Visits with PGA ≤ 1	Visits with PGA > 1
	OR/ β -coefficient (SE) per 1-comorbidity	
Hydroxychloroquine (yes/no)	0.98 (0.28)	0.85 (0.20)
Methotrexate (yes/no)	1.29 (0.34)	1.39 (0.22)*
Azathioprine (yes/no)	0.81 (0.18)	0.68 (0.15)
Calcineurin inhibitors (yes/no)	0.85 (0.30)	0.85 (0.20)
Mycophenolate (yes/no)	0.59 (0.18)	0.55 (0.16)*
Belimumab (yes/no)	1.03 (0.26)	1.01 (0.17)
Cyclophosphamide (yes/no)	1.74 (0.53)	1.36 (0.36)
Rituximab (yes/no)	1.03 (0.20)	2.08 (0.76)*
Oral GC (mg/day)	0.27 (0.13)*	-1.15 (0.40)†
IV+other parenteral GC (mg/day; log)	-	-0.013 (0.097)

Mixed-effects regression models (adjusted for baseline covariates) were applied to consecutive visits to estimate the association between increasing comorbidity burden (sum of the seven target-impairing conditions) and the use of SLE treatments, including GC dose. Separate analyses were performed for visits with PGA ≤ 1 (absent/low activity; *maintenance disease phase*) and PGA > 1 (moderate/high activity; *active disease phase*). Values represent the OR or β -coefficient (SE) for the likelihood of treatment use (yes/no) or for GC dose, per 1-unit increase in comorbidity burden. * $p<0.05$. † $p<0.01$. GC, glucocorticoid; PGA, physician global assessment; SLE, systemic lupus erythematosus.

residual confounding or mediation effects cannot be excluded.

Comorbidities are linked to damage accrual, attenuated in patients with sustained disease control

Having identified comorbidities that were negatively associated with the likelihood of DORIS and LLDAS, we also assessed their relationship with organ damage. In Poisson regression adjusting for baseline damage and other covariates, higher comorbidity burden (assessed at last follow-up) was associated with greater SDI increases (incidence rate ratio (IRR) 1.38, 95% CI 1.11 to 1.71). Stratifying patients by increasing duration thresholds of each target, we observed that the association between comorbidities and damage was progressively attenuated, particularly when DORIS was maintained for $\geq 50\%$ of time (figure 4A). For LLDAS, a higher threshold ($\geq 60\%$) was required before a similar attenuation of the comorbidity-damage association was observed (figure 4B). This highlights that sustained

DORIS or LLDAS appears beneficial, even in high-risk groups, consistent with the treat-to-target concept.

DISCUSSION

Using longitudinal data from a multicentre SLE cohort with active disease at inclusion, we demonstrate a high and accumulating burden of comorbidities linked to reduced likelihood of achieving treat-to-target. Seven key conditions—particularly when clustered with obesity and/or fibromyalgia—showed the strongest associations. Their effect was primarily driven by higher disease activity and protracted GC tapering, even when disease control appeared adequate. A plausible influence of these comorbidities on the inflammatory burden was further supported by the comparable use of immunosuppressives and biologics across groups, despite lower GC dosing in comorbid patients during periods of moderate/high SLE activity. Importantly, comorbidities associated with reduced target attainment were also linked to excess damage—a trend not observed when DORIS or LLDAS were achieved for $\geq 50\%$ of the time—underscoring the need to address comorbid conditions together with tight and durable disease control.

Our findings are consistent with prior research, primarily from administrative databases, demonstrating a higher frequency of comorbidities in patients with SLE compared with the general population.^{13 14 27} The high burden, despite relatively short disease duration, aligns with registry data showing that many conditions are already present at SLE onset, diagnosis or even earlier.^{12 28–30} The most prevalent diseases (cardiovascular, endocrine, metabolic, musculoskeletal and psychiatric) also mirror data from previous studies.^{12 28}

At inclusion, 28.5% of patients had CCI ≥ 1 , similar to rates reported in the Denmark National Patient Registry (31.0% at diagnosis),²⁸ yet lower than those in the UK Clinical Practice Research Datalink (38.1% at diagnosis,³⁰ 43.3% after median 2.4 years¹⁴). Estimates of the RDCI—developed from self-reported data in patients with various rheumatic disorders²³—and the generic Elixhauser Index also confirmed the high comorbidity burden in our SLE population. At baseline, 49.0% of patients had an RDCI >0 , increasing to 59.7% at last follow-up (respective modified-RDCI: 68.6% and 74.6%) compared with 47.0% in a Swedish early RA cohort³¹ and 44.0% in the early RA CareRA trial.⁹

Patients with SLE who had a higher comorbidity burden showed lower likelihood of DORIS and LLDAS, echoing findings from other rheumatic diseases¹⁰ where comorbidities have also been associated with reduced treatment response and remission rates.^{9 31} This relationship was most evident in patients with multiple coexisting conditions. In this regard, ‘multimorbidity’ (≥ 2 coexisting conditions) has emerged as a more holistic, patient-centred concept acknowledging the complex interplay between coexisting diseases and their potential amplified impact on disease and patient outcomes.

We identified seven comorbidities as the most strongly associated with targets. Obesity,⁸ dyslipidaemia,³² hypertension,²⁶ thyroid disease,³³ major depression^{9 34} and fibromyalgia²⁶ have been linked to dampened treatment responses and lower remission rates in rheumatoid and psoriatic arthritis. In our cohort, the negative trend was more pronounced in individuals bearing ≥ 3 of these conditions, especially when obesity and fibromyalgia were present. Together with the aforementioned evidence, our work defines a pattern of prevalent comorbidities that

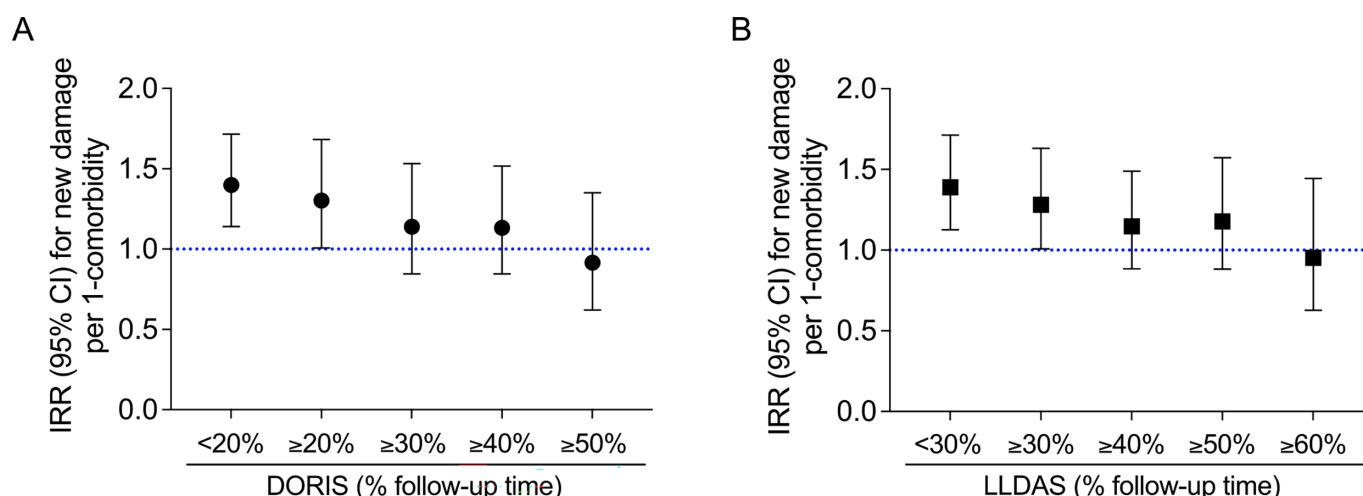


Figure 4 Association of comorbidity burden with organ damage accrual, stratified by treatment target attainment (A, B) Patient-level Poisson regression models (adjusted for baseline damage and other covariates) were used to assess the impact of the seven key comorbidities on the rate of new organ damage during follow-up. Patients were stratified by varying durations (% of follow-up time) of DORIS (A) and LLDAS (B). Dots represent incidence rate ratios (IRRs) per additional comorbidity, with error bars indicating 95% CIs. The adverse effect of comorbidities was not observed among patients who maintained DORIS $\geq 50\%$ or LLDAS $\geq 60\%$ of time. DORIS, definitions of remission in systemic lupus erythematosus; LLDAS, lupus low disease activity state.

may be relevant to treat-to-target in SLE, highlighting the importance of their systematic assessment in clinical practice.

The cluster of identified comorbidities predicted higher trajectories of SLE activity and accordingly, reduced the achievement of both activity-related and GC dose-related components of DORIS and LLDAS. This pattern is consistent with reports from other inflammatory arthritides,^{9 26} although disease activity metrics and underlying biology differ from SLE. Of note, a greater number of comorbidities was associated with higher likelihood of both moderate (SLEDAI 4–9) and high (SLEDAI ≥ 10) activity visits, indicating a meaningful rise in disease activity rather than minor SLEDAI elevations.

A unifying hypothesis linking comorbidities with worse SLE activity-related outcomes likely involves several partly overlapping mechanisms. Symptom-driven conditions, such as fibromyalgia and depression, may amplify pain, fatigue or global assessments, thus complicating the objective evaluation of lupus activity.³⁵ Cardiometabolic comorbidities are characterised by adipokine-driven immune activation, altered lymphocyte phenotypes and heightened innate immune responses.^{36–38} This is consistent with the immunometabolic rewiring and mitochondrial abnormalities in SLE immune cells, resulting in oxidative stress and inflammatory activation.³⁹ In experimental lupus models, high-fat diet-induced obesity exacerbates immune activation, germinal-centre responses and autoantibody production.^{40 41} Moreover, dyslipidaemia and cardiovascular/cerebrovascular disease have been correlated with endothelial dysfunction, TLR7-driven myeloid responses, neutrophil extracellular trap formation and type I interferon pathways.^{42–44} Similarly, shared immune features suggest that thyroid dysfunction may coexist with, or modestly reinforce, immune activation states relevant to lupus.⁴⁵ Finally, depression in patients with SLE has been associated with complement alterations, pro-inflammatory cytokines and thrombo-inflammatory pathways.⁴⁶ Still, most abovementioned evidence is largely correlative and dedicated mechanistic studies remain limited.

Shared genetic architecture between SLE and certain comorbidities, as suggested by Mendelian randomisation studies, may point to overlapping susceptibility potentially contributing to heightened inflammatory burden.^{16 47–49} Moreover, social determinants of health (education, socio-economic status, health literacy, prior trauma or infections), closely linked to development and clustering of comorbidities, may indirectly affect disease outcomes through health behaviours, adherence and healthcare access. Finally, therapeutic inertia, delays in presentation and reluctance by either physicians or patients to escalate immunosuppression when disease is active or to taper glucocorticoids when improving may further perpetuate suboptimal outcomes. While these processes provide a plausible framework for our observation that comorbidities are associated with reduced likelihood of remission and LLDAS in SLE, further research is

needed to disentangle causal pathways from confounding influences.

Patients with comorbidities were offered therapeutic options comparable to those without. Nonetheless, they tended to receive lower GC doses during active/severe disease, possibly due to patient or physician preferences or concerns about worsening coexisting conditions.¹⁷ Although adjustment for GC dosing did not attenuate the comorbidity-target relationship, further studies will be needed to address the extent to which treatment decisions contribute to these associations.

In line with their negative association with target achievement, comorbidities were linked to greater organ damage accrual. Together with evidence linking comorbidities to reduced quality of life, emergency visits, hospitalisations and mortality,^{12 30} our findings reinforce the need for prevention and effective management of comorbid conditions in SLE. Notably, the relationship of comorbidities with damage was less pronounced in patients with sustained DORIS remission or LLDAS, suggesting that prolonged disease control may mitigate their impact. Pending formal validation in prospective studies, these data highlight the importance of treat-to-target adherence in comorbid SLE, including timely use of biologics with potential disease-modifying effects.

Limitations of our study include the lack of a comparator group and the retrospective-based design with possible misclassification/reporting and ascertainment bias in comorbidity recording. Although no formal diagnostic criteria were uniformly applied across all comorbidities, confirmation was supported by multi-source documentation, repeated longitudinal assessment and concordant ICD-anchored clinical or pharmacological evidence, which may have partially reduced classification errors. Given the sample size of our cohort, less frequent comorbidities may have been underrepresented, thus contributing to insufficient statistical power in the associations with treatment targets. Since our cohort included patients with active disease requiring treatment intensification at baseline, it remains uncertain whether the observed effects of comorbidities and GC use extend to other patient groups. We did not evaluate the possible effect of comorbidity treatments on SLE outcomes or the extent to which our results may have been attributed to poor adherence to administered therapies. While adjustment for baseline and time-varying disease activity and treatment intensity did not materially alter the association between comorbidities and treat-to-target outcomes, the possibility of therapeutic inertia cannot be excluded. Next, our cohort consisted exclusively of White European patients, which limits the generalisability of our findings. Racial and ethnic disparities in comorbidity burden are well documented in patients with SLE; for example, non-White populations, particularly African American and Hispanic individuals, exhibit higher prevalences of hypertension, renal disease, cardiovascular disease and stroke.⁵⁰ Consequently, our study population

may underestimate the comorbidity burden observed in more ethnically diverse cohorts.

In conclusion, we identified a distinct comorbidity pattern linked to persistent activity, delayed GC tapering and reduced target attainment in SLE, likely reflecting shared genetic predisposition. Comorbid patients received immunosuppressive and biologic treatments comparable to those without comorbidities, underscoring the need to further examine treatment efficacy, adherence and other contributing factors in this subgroup. The higher risk of damage accrual in patients with greater comorbidity burden highlights the importance of a comprehensive management strategy that addresses coexisting conditions while optimising therapy to achieve and sustain treat-to-target goals.

Author affiliations

¹Rheumatology and Clinical Immunology, University of Crete Medical School, Heraklion, Greece

²Institute of Electronic Structure and Laser, Foundation for Research and Technology-Hellas, Heraklion, Greece

³Joint Rheumatology Program, National and Kapodistrian University of Athens Medical School, Athens, Greece

⁴Rheumatology and Clinical Immunology Unit, 4th Department of Internal Medicine, Attikon University Hospital, Chaidari, Greece

⁵Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria S. Anna, Ferrara, Italy

⁶Division of Immunity, Institute of Molecular Biology and Biotechnology-Foundation for Research and Technology – Hellas (FORTH), Heraklion, Greece

Acknowledgements We are thankful to the staff physicians and nurses of the Rheumatology Departments of the University Hospital of Heraklion and the University of Ferrara for providing care to the patients with SLE. This work has been partially supported by the Special Account for Research Funds of the University of Crete.

Contributors MN collected and curated data and performed data entry; GDB performed machine learning analysis and drafted parts of the methodology; SP evaluated patients, completed data collection forms and performed data entry; SK performed and advised on the statistical analysis; ES, AR, AM and NA evaluated patients and completed data collection forms; IF assisted with the electronic patient registry and data entry process; IS evaluated patients, collected data and performed data entry; MG and PS contributed to results interpretation and evaluated patients; AF contributed to the data analysis plan, interpretation of the results and to manuscript editing; AB evaluated patients and completed data collection forms; DB contributed to interpretation/contextualisation of the results and to manuscript drafting; GB conceived and supervised the study, performed data curation, statistical analysis and drafted the manuscript. All authors had unrestricted access to all study data and assumed final responsibility for the decision to publish. GB acts as guarantor for the current work and presented data.

Funding The study received funding from the Research Account of the University of Crete (KA10210) and the Pancretan Health Association.

Competing interests ES received consulting fees from AstraZeneca out of the present work. AF reports honouraria and/or consulting fees from Lilly, Boehringer, Novartis, Abbvie, AstraZeneca, GSK, MSD, Pfizer, UCB, Amgen, support for attending meetings from UCB. MG has received fees for sponsored lectures from GSK and AstraZeneca. DB reports unrestricted investigational grants from GSK, honouraria and/or consulting fees from GSK, AstraZeneca and Pfizer. AB reports consulting fees from GSK. GB reports grants from AstraZeneca, MSD, honouraria and/or consulting fees from Lilly, Novartis, AstraZeneca, GSK, AbbVie, Otsuka. The remaining authors declare no conflict of interest.

Patient and public involvement statement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and data collection and was approved by the Ethics Committee of the University of Crete (protocol no 13960/10-10-2018) and the Ethics Committee of the Province of Ferrara,

c/o Azienda Ospedaliero-Universitaria S. Anna, Cona, Ferrara, Italy (protocol no 516/2019/Oss/AOUFe). All patients gave informed consent upon inclusion in the respective registries. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data collected for the study are available upon request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Ettore Silvagni <https://orcid.org/0000-0001-7654-8222>

Irini Flouri <https://orcid.org/0000-0002-6966-1304>

Prodromos Sidiropoulos <https://orcid.org/0000-0001-9607-0326>

Antonis Fanouriakis <https://orcid.org/0000-0003-2696-031X>

Alessandra Bortoluzzi <https://orcid.org/0000-0003-2416-8134>

Dimitrios Boumpas <https://orcid.org/0000-0002-9812-4671>

George Bertias <https://orcid.org/0000-0001-5299-1406>

REFERENCES

- van Vollenhoven RF, Bertias G, Doria A, *et al.* 2021 DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med* 2021;8:e000538.
- Franklyn K, Lau CS, Navarra SV, *et al.* Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.
- Pitsigavdaki S, Nikoloudaki M, Garantziotis P, *et al.* Pragmatic targets for moderate/severe SLE and their implications for clinical care and trial design: sustained DORIS or LLDAS for at least 6 months is sufficient while their attainment for at least 24 months ensures high specificity for damage-free progression. *Ann Rheum Dis* 2024;83:464–74.
- Golder V, Kandane-Rathnayake R, Huq M, *et al.* Evaluation of remission definitions for systemic lupus erythematosus: a prospective cohort study. *The Lancet Rheumatology* 2019;1:e103–10.
- Golder V, Kandane-Rathnayake R, Huq M, *et al.* Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study. *The Lancet Rheumatology* 2019;1:e95–102.
- Zen M, Iaccarino L, Gatto M, *et al.* Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018;77:104–10.
- Parodis I, Lindblom J, Levy RA, *et al.* Attainment of remission and low disease activity after treatment with belimumab in patients with systemic lupus erythematosus: a post-hoc analysis of pooled data from five randomised clinical trials. *Lancet Rheumatol* 2024;6:e751–61.
- Ellerby N, Matthey DL, Packham J, *et al.* Obesity and comorbidity are independently associated with a failure to achieve remission in patients with established rheumatoid arthritis. *Ann Rheum Dis* 2014;73:e74.
- Stouten V, Westhovens R, De Cock D, *et al.* Having a co-morbidity predicts worse outcome in early rheumatoid arthritis despite intensive treatment: a post hoc evaluation of the pragmatic randomized controlled CareRA trial. *Rheumatology (Oxford)* 2021;60:3699–708.
- Radner H, Yoshida K, Frits M, *et al.* The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs. *Rheumatology (Oxford)* 2015;54:2076–84.

- 11 Dey M, Nagy G, Nikiforou E. Comorbidities and extra-articular manifestations in difficult-to-treat rheumatoid arthritis: different sides of the same coin? *Rheumatology (Oxford)* 2023;62:1773–9.
- 12 Albrecht K, Redeker I, Aringer M, et al. Comorbidity and healthcare utilisation in persons with incident systemic lupus erythematosus followed for 3 years after diagnosis: analysis of a claims data cohort. *Lupus Sci Med* 2021;8:e000526.
- 13 Kariniemi S, Rantalaiho V, Virta LJ, et al. Multimorbidity among incident Finnish systemic lupus erythematosus patients during 2000–2017. *Lupus (Los Angel)* 2021;30:165–71.
- 14 Rees F, Doherty M, Grainge M, et al. Burden of Comorbidity in Systemic Lupus Erythematosus in the UK, 1999–2012. *Arthritis Care & Research* 2016;68:819–27.
- 15 Gergianaki I, Garantziotis P, Adamichou C, et al. High Comorbidity Burden in Patients with SLE: Data from the Community-Based Lupus Registry of Crete. *J Clin Med* 2021;10:998.
- 16 Kain J, Owen KA, Marion MC, et al. Mendelian randomization and pathway analysis demonstrate shared genetic associations between lupus and coronary artery disease. *Cell Rep Med* 2022;3:100805.
- 17 Frodlund M, Jönsen A, Remkus L, et al. Glucocorticoid treatment in SLE is associated with infections, comorbidities and mortality—a national cohort study. *Rheumatology (Sunnyvale)* 2024;63:1104–12.
- 18 Tselios K, Koumaras C, Gladman DD, et al. Dyslipidemia in systemic lupus erythematosus: just another comorbidity? *Semin Arthritis Rheum* 2016;45:604–10.
- 19 Petri M, Orbai A-M, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
- 20 Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis & Rheumatology* 2019;71:1400–12.
- 21 Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005;353:2550–8.
- 22 Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.
- 23 Dolomisiewicz A, Ali H, Roul P, et al. Updating and Validating the Rheumatic Disease Comorbidity Index to Incorporate ICD-10-CM Diagnostic Codes. *Arthritis Care Res (Hoboken)* 2023;75:2199–206.
- 24 Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
- 25 Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- 26 Bertsias A, Flouri ID, Repa A, et al. Patterns of comorbidities differentially affect long-term functional evolution and disease activity in patients with “difficult to treat” rheumatoid arthritis. *RMD Open* 2024;10:e003808.
- 27 Kósa F, Kunovszki P, Gimesi-Országh J, et al. High risk of depression, anxiety, and an unfavorable complex comorbidity profile is associated with SLE: a nationwide patient-level study. *Arthritis Res Ther* 2022;24:116.
- 28 Hansen RB, Simard JF, Faurschou M, et al. Distinct patterns of comorbidity prior to diagnosis of incident systemic lupus erythematosus in the Danish population. *J Autoimmun* 2021;123:102692.
- 29 Figueroa-Parra G, Meade-Aguilar JA, Hulshizer CA, et al. Multimorbidity in systemic lupus erythematosus in a population-based cohort: the Lupus Midwest Network. *Rheumatology (Oxford)* 2024;63:3056–64.
- 30 Kuo C-F, Chou I-J, Rees F, et al. Temporal relationships between systemic lupus erythematosus and comorbidities. *Rheumatology (Oxford)* 2019;58:840–8.
- 31 Tidblad L, Westerlind H, Delcoigne B, et al. Comorbidities and treatment patterns in early rheumatoid arthritis: a nationwide Swedish study. *RMD Open* 2022;8:e002700.
- 32 Cui K, Movahedi M, Bombardier C, et al. Cardiovascular risk factors are negatively associated with rheumatoid arthritis disease outcomes. *Ther Adv Musculoskelet Dis* 2021;13:1759720X20981217.
- 33 Waldenlind K, Delcoigne B, Saevarsdottir S, et al. Does autoimmune thyroid disease affect rheumatoid arthritis disease activity or response to methotrexate? *RMD Open* 2020;6:e001282.
- 34 Michelsen B, Kristianslund EK, Sexton J, et al. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis* 2017;76:1906–10.
- 35 Corbitt K, Carlucci PM, Cohen B, et al. Clinical and Serologic Phenotyping and Damage Indices in Patients With Systemic Lupus Erythematosus With and Without Fibromyalgia. *ACR Open Rheumatol* 2024;6:172–8.
- 36 Carvalho LM, Carvalho BG, Souza LL, et al. Obesity as an aggravating factor of systemic lupus erythematosus disease: What we already know and what we must explore. A rapid scoping review. *Nutrition* 2024;128:112559.
- 37 Teruya H, Shoda H, Itamiya T, et al. Body weight in systemic lupus erythematosus is associated with disease activity and the adaptive immune system, independent of type I IFN. *Front Immunol* 2025;16:1503559.
- 38 Lai M, Lin K, Chen X, et al. Diverse Cytokines Secreted by Adipocyte in Linking Cardio-Metabolic Disorder and SLE. *Front Biosci (Landmark Ed)* 2024;29.
- 39 Patiño-Martínez E, Kaplan MJ. Immunometabolism in systemic lupus erythematosus. *Nat Rev Rheumatol* 2025;21:377–95.
- 40 Zhang X, Meng J, Shi X, et al. Lupus pathogenesis and autoimmunity are exacerbated by high fat diet-induced obesity in MRL/lpr mice. *Lupus Sci Med* 2023;10:e000898.
- 41 Choi EW, Kim HJ, Jung YC, et al. Effects of high fat diet-induced obesity on pathophysiology, immune cells, and therapeutic efficacy in systemic lupus erythematosus. *Sci Rep* 2022;12:18532.
- 42 Elshikha AS, Teng XY, Kanda N, et al. TLR7 Activation Accelerates Cardiovascular Pathology in a Mouse Model of Lupus. *Front Immunol* 2022;13:914468.
- 43 Guzmán-Martínez G, Marañón C, CYTED RIBLES Network. Immune mechanisms associated with cardiovascular disease in systemic lupus erythematosus: A path to potential biomarkers. *Front Immunol* 2022;13:974826.
- 44 Huang S, Zhang Z, Cui Y, et al. Dyslipidemia is associated with inflammation and organ involvement in systemic lupus erythematosus. *Clin Rheumatol* 2023;42:1565–72.
- 45 Li LL, Li QR, Li L, et al. Commonalities between thyroid disease and systemic lupus erythematosus (SLE). *Lupus (Los Angel)* 2025;34:767–74.
- 46 Duca L, Roman N, Teodorescu A, et al. Association between Inflammation and Thrombotic Pathway Link with Pathogenesis of Depression and Anxiety in SLE Patients. *Biomolecules* 2023;13:567.
- 47 Hu Y, Lin D, Wu D, et al. Systemic lupus erythematosus and epilepsy: A Mendelian randomization study. *Epilepsia Open* 2024;9:2274–82.
- 48 Ren M, Yu H, Xiao B, et al. Causal association between systemic lupus erythematosus and the risk of migraine: A Mendelian randomization study. *Brain Behav* 2024;14:e3417.
- 49 Xue H, Liu S, Zeng L, et al. Causal effect of systemic lupus erythematosus on psychiatric disorders: A two-sample Mendelian randomization study. *J Affect Disord* 2024;347:422–8.
- 50 Garg S, Bartels CM, Bao G, et al. Timing and Predictors of Incident Cardiovascular Disease in Systemic Lupus Erythematosus: Risk Occurs Early and Highlights Racial Disparities. *J Rheumatol* 2023;50:84–92.