SCUOLA DI DOTTORATO
UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

Dipartimento di / Department of Medicine and Surgery

Dottorato di Ricerca in / PhD program Public Health Ciclo / Cycle XXXVIII

Curriculum in (se presente / if it is) Health Services Research and Technology Assessment

TITOLO TESI / THESIS TITLE

Epidemiology and treatment patterns of Systemic Lupus Erythematous: real-world evidence from primary care databases in UK, Italy, Belgium, Germany, Spain, and Romania

Cognome / Surname Zamparini Nome / Name Manuel

Matricola / Registration number 835108

Tutore / Tutor: Prof. Giampiero Mazzaglia

Cotutore / Co-tutor: .....
(se presente / if there is one)

Supervisor: Prof. Giampiero Mazzaglia
(se presente / if there is one)

Coordinatore / Coordinator: Prof. Luigi Badano

ANNO ACCADEMICO / ACADEMIC YEAR 2024/2025

Contents

Acronyms

ANA Antinuclear antibodies

aPL Antiphospholipid Antibodies

APS Antiphospholipid Syndrome

ATC Anatomical Therapeutic Chemical

AZA Azathioprine

BAFF B cell activating factor

BE Belgium

BMI Body Mass Index

CI Confidence Interval

COPD Chronic Obstructive Pulmonary Disease

CPRD Clinical Practice Research Datalink

EHRs Electronic Health Records

ES Spain

EULAR / ACR European League Against Rheumatism / American College of Rheumatology

GDPR General Data Protection Regulation

GE Germany

GP General Practitioner

HCQ Hydroxychloroquine

ICD-10-CM International Classification of Diseases Tenth Revision Clinical Modification

ICD-9-CM International Classification of Disease Ninth Revision Clinical Modification classification

ID Index Date

IT Italy

LE Lupus Erythematosus

MAR Missing At Random

MMF Mycophenolate mofetil

NE Not Estimable

NMDA N-methyl-D-aspartate

NSAIDs Nonsteroidal Anti-Inflammatory Drugs

ORs Odds Ratios

pDCs Plasmacytoid Dendritic Cells

PY Person-Years

RCTs Randomized Controlled Trials

RO Romania

RWD Real-World Data

RWE Real-World Evidence

SD Standard Deviation

SLE Systemic Lupus Erythematosus

SLICC Systemic Lupus Erythematosus International Collaborating Clinics

THIN® The Health Improvement Network

UK United Kingdom

US United States

List of Figures

List of Tables

Abstract

Introduction Systemic Lupus Erythematosus (SLE) is a relapsing–remitting autoimmune disease with heterogeneous organ involvement and substantial long-term burden. Contemporary, population-based estimates for Europe remain variable, and real-world treatment uptake may lag behind guideline recommendations. This dissertation quantified adult SLE incidence and prevalence in multiple European countries, characterized incident cases against matched controls, and described post-diagnosis treatment patterns.

Methods We conducted observational cohort analyses using The Health Improvement Network (THIN®) general practice electronic health records (2017–2022). Adults (≥18 years) contributed person-time while active in participating practices. The main case definition required either a diagnostic code for SLE (excluding cutaneous-only lupus) or ≥2 adapted EULAR / ACR items plus laboratory or pharmacologic confirmation around the Index Date (ID). For epidemiology, we estimated the annual rates of crude and standardized incidence and prevalence by country, sex, and age. For characterization, incident cases were matched 4:1 with controls on sex, age and country, and baseline covariates were compared. For treatment, we followed incident cases with ≥24 months post-ID observation, classifying exposure in 6-month windows to Hydroxychloroquine (HCQ), glucocorticoids, NSAIDs, conventional immunomodulators / immunosuppressants, biologic agents, and cyclophosphamide / rituximab. The determinants of any treatment by 24 months were examined with logistic regression.

Results By 2022, the standardized incidence was the highest in Spain (≈9–10 per 100,000 Person-Years (PY)) and Italy (8.20), intermediate in the UK (5.05) and Romania (4.16), and lowest in Belgium (1.30); Germany solely contributed prevalence estimates due to a limited look-back period. The standardized prevalence was highest in the UK (96.37 per 100,000), intermediate in Italy (58.91) and Spain (57.95), and lower in Germany (44.04), Belgium (29.87), and Romania (20.28). Incidence was largely stable within countries and prevalence rose steadily everywhere. Compared to matched controls, incident cases showed greater multimorbidity and polypharmacy, with consistent excesses in cardiovascular disease, hypertension, mood / anxiety disorders, osteoporosis, malignancy and concomitant autoimmune diagnoses. During the semester immediately after diagnosis, in the pooled cohort near 40% of subjects were treated (≈60% in Italy); HCQ was most common at diagnosis (≈20–35% by country) and persisted for 24 months, while conventional immunosuppressants remained ≈10% and chronic glucocorticoids / NSAIDs ≈5–10%. Treatment flows were concentrated in the first 6 months, with high initiation and persistence of HCQ. Female sex and concomitant rheumatoid arthritis (and, in Spain, Sjögren's syndrome) were associated with treatment received in the first 24 months after diagnosis, while baseline neuropsychiatric symptoms were inversely associated.

Conclusions The burden of adult SLE in European primary care is substantial and is increasing in prevalence, with incidence and prevalence patterns across countries broadly consistent with previous literature but shaped by the maturity of the data-source and the evolving classification. Patients present with significant comorbidity at diagnosis. Routine care remains anchored in HCQ with comparatively restricted chronic steroid signals, but untreated patients and modest escalation in steroid-sparing agents persist. These findings underscore opportunities for earlier, guideline-concordant immunomodulation and pathway optimization, particularly for neuropsychiatric presentations, to reduce flares, damage accrual, and downstream healthcare burden.

Part I

Narrative review of Systemic Lupus Erythematosus

Chapter 1

Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with a relapsing and remitting course that features a wide spectrum of clinical manifestations, from mild to life-threatening conditions[1–3].

SLE is characterized by the production of pathogenic autoantibodies directed against nucleic acids and their binding proteins, reflecting a global loss of self-tolerance. The interplay between demographic, socioeconomic and environmental factors with genetic disposition may contribute to the loss of tolerance with the subsequent immune dysregulation observed in patients with SLE[1, 4–7].

Common symptoms include joint pain, skin rashes, fatigue, and fever, but SLE can also manifest with more serious complications such as kidney inflammation, heart and lung involvement, neurological problems, and hematologic abnormalities. The unpredictable nature of SLE means that its symptoms can vary cyclically and patients experience periods of remission followed by episodes of increased disease activity. The heterogeneity and severity of clinical manifestations may also vary between different ethnic groups, making the diagnosis of SLE particularly challenging[6, 8, 9].

The availability of General Practitioner (GP)-based longitudinal information (demographics, diagnoses, specialist referrals, laboratory investigations, where available, and drug therapies) enables operational definitions of SLE that range from simple diagnostic codes to adapted European League Against Rheumatism / American College of Rheumatology (EULAR / ACR)-based algorithms, making primary care databases a reliable source to study SLE in a population-based setting[8, 9].

In recent decades, several treatments have been considered for the management of symptoms. Glucocorticoids and HCQ are used for a rapid symptoms' relief, but their use is limited due to the potential organ damage associated with their long-term use[10–14]. For patients with poor control of symptoms, the use of immunosuppressive drugs[15], such as Mycophenolate mofetil (MMF), Azathioprine (AZA), and methotrexate, is suggested. In addition, cyclophosphamide can be used as a rescue drug in organ-threatening diseases[16–18]. Biological agents showed promising results in patients with SLE. Specifically, belimumab can be considered in patients with extrarenal disease and inadequate control of symptoms, and in those with persistent disease (high disease activity)[19–21]. Finally, for patients who do not benefit from previous treatment options, the off-label use of rituximab can be considered. It should be noted that the aforementioned therapies could be used alone or in combination according to the characteristics of the patients and the severity of the disease as recommended by the guidelines issued by the main scientific societies[9].

Several studies were conducted to assess treatment patterns in patients with SLE. In particular, data from cross-sectional, real-world studies from United States (US) insurance claims databases have reported

antimalarial use ranging from 43% to 59%, corticosteroids 48% to 69%, immunosuppressants 18% to 26%, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) 35% to 38%, and biologics at approximately 3%[22–25]. Another study conducted in Canada indicated that the use of corticosteroids occurred in approximately half of new-onset SLE, usually in combination with antimalarials and / or immunosuppressants[26]. In contrast, very few studies have been conducted in Europe that evaluated SLE treatment patterns over long follow-up periods.

1.1 Epidemiology

The most recent studies that estimated the incidence and prevalence of SLE have shown considerable variation between different geographical areas.

In a recent systematic review, the incidence ranged from 0.3 to 8.7 per 100,000 PY and the prevalence from 3.2 to 159 per 100,000 people[27]. In Europe, the overall incidence of SLE varies from 1.5 to 7.4 per 100,000 PY[28–30], whereas the estimated prevalence of SLE between 29 and 210 per 100,000 people[28, 31].

Recently, a study conducted in United Kingdom (UK) using the Clinical Practice Research Datalink (CPRD) estimated an incidence of SLE of 4.9 per 100,000 PY and a prevalence of 97 per 100,000 subjects[32].

In Spain (ES), the EPISER2016 survey estimated a point prevalence in adults (≥20 years) of 210 per 100,000 people[31].

In Germany (GE), a nationwide claim analysis (2012–2019) reported a stable incidence of approximately 8.8 per 100,000 PY and an increase in prevalence from roughly 40.5 to 59.9 per 100,000 people by 2019[33].

In Italy (IT), studies conducted in limited geographical contexts observed that the incidence and prevalence of SLE are among the lowest identified in Europe, ranging between 2.0 and 2.6 per 100,000 PY and 39.2 and 81 per 100,000 people, respectively[34–38]. More recently, a large population-based study from the Veneto region (2012–2020) estimated an incidence of 2.8 per 100,000 PY and a standardized point prevalence of 70.6 per 100,000 people[36].

In Belgium (BE), adult incidence was estimated to be approximately 3–4 per 100,000 PY and prevalence 60–70 per 100,000, while in Romania (RO) adult incidence was around 3–5 per 100,000 PY and prevalence 50–60 per 100,000[39].

This variability is likely to be attributed to differences in population structure, ethnicity, and environmental factor distribution. However, they can also be explained by differences in study design, sample size, and difficulties in developing valid case definitions, particularly when cases are selected from electronic claims databases.

The use of claim databases in the identification of SLE cases has in fact some limitations, in particular the completeness of the registration of the disease exemption and the fact that not all subjects with SLE are admitted to a hospital. In fact, a recent review[40] indicates that the identification of SLE based mainly on the disease code alone has a high predictive value, but a sensitivity that varies from 50% to 80% according to the definition of the algorithm and the available data source.

1.1.1 Risk factors

Genetic risk factors

Genetic factors play an important role in predisposing individuals to the development of SLE.

In rare cases, the disease can be linked to deficiencies in individual genes, such as the complement components C1q and C4, but more commonly it arises from the combined effect of multiple genetic variants[41, 42].

Each allele contributes only modestly and the cumulative interaction of several genes substantially increases the risk of disease. Many of the identified genetic variants are located in noncoding regions of immune-related genes, some of which are shared with other autoimmune conditions (e.g. STAT4 and PTPN22 with rheumatoid arthritis and diabetes), while others appear to be more specific for SLE[43].

Recent studies have also highlighted additional risk loci and alterations in gene copy number that can contribute to disease expression; however, although these findings are promising, the loci identified so far can account for only about 15% of the heritability of SLE, suggesting that further genetic and environmental factors must be clarified[44, 45].

Environmental risk factors

Epigenetic and environmental factors have also been implicated in the development of SLE.

Epigenetic changes, such as DNA hypomethylation, have been associated with the use of certain medications known to induce the disease[46].

Lifestyle and environmental exposures, including smoking and exposure to ultraviolet light, have been linked to increased risk in epidemiological studies[47]. Ultraviolet radiation can precipitate cutaneous lesions and amplify the activity of systemic disease, likely by increasing the apoptotic load and the availability of nuclear antigens[4].

Viral infections have also been considered as potential triggers. In particular, patients with SLE become seropositive for Epstein-Barr virus (EBV) faster, with higher viral loads compared to healthy individuals, and reduced ability of CD8+ T cells to control EBV-infected B cells[48, 49].

Furthermore, molecular similarities between EBV nuclear antigen 1 and the common lupus autoantigen Ro suggest a possible role for EBV in driving disease expression. Together, these observations support a model in which environmental exposures lower the threshold for loss of tolerance in genetically predisposed individuals[45].

Female hormones and sex

The marked female predominance observed in SLE suggests an important role for sex hormones and sex chromosomes in the susceptibility of the disease[50].

Although the underlying mechanisms are still incompletely understood, experimental models have shown that the presence of two X chromosomes can independently contribute to the increased severity of the disease, regardless of hormonal status[51]. This effect of X-chromosome dose aligns with clinical observations of increased risk in conditions with supernumerary X chromosomes and highlights X-linked immune genes (e.g., CD40) as plausible contributors. Among the genes located on the X chromosome and involved in the pathogenesis of SLE is CD40, which is involved in immune regulation.

Pregnancy represents a particular challenge for women with SLE. It is well established that disease activity at the time of conception influences pregnancy outcomes, while the precise contribution of hormonal fluctuations, such as estradiol and progesterone, remains less clear. Some studies have reported lower levels of these hormones in patients with SLE during the second and third trimesters compared to healthy pregnant women[52].

Treatment with dehydroepiandrosterone has shown modest clinical benefit in certain cases[53]. In general, optimal outcomes depend on the achievement of stable low disease activity before conception and the maintenance of close monitoring throughout gestation, to balance maternal health and fetal outcomes[45].

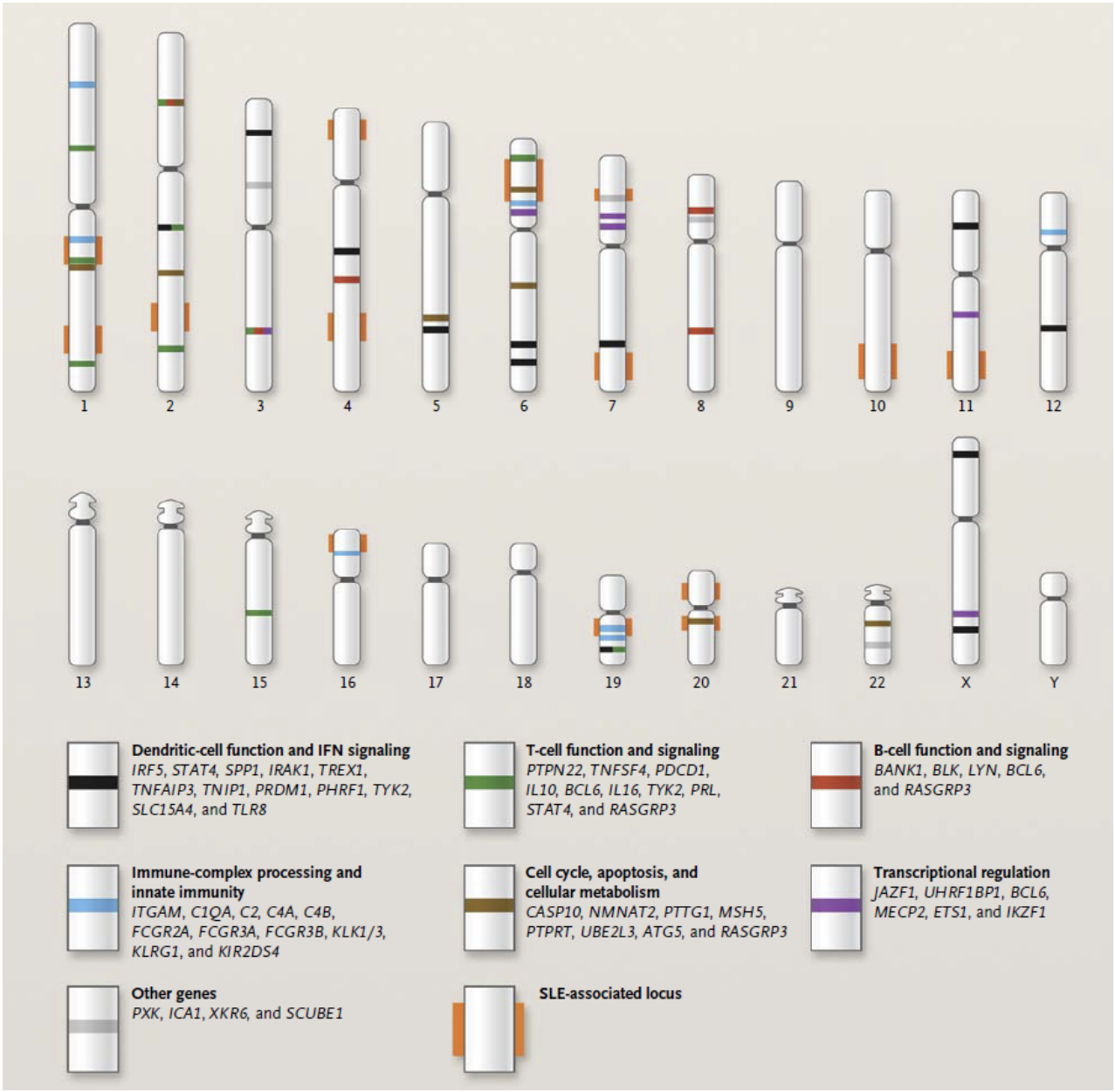

Figure 1. Chromosome loci and genes associated with SLE. Approximate positions of SLE-associated loci across the 22 autosomes and the sex chromosomes. Source: Tsokos, George C. "Systemic Lupus Erythematosus." The New England journal of medicine vol. 365,22 (2011): 2110-21. doi:10.1056/NEJMra1100359

1.2 Burden and healthcare costs

SLE is a complex chronic disease that generates a significant burden on patients and healthcare systems.

The course of the disease is characterized by relapses and remissions, and patients often present with multiple comorbidities such as hypertension, asthma, hyperlipidemia, or chronic obstructive pulmonary disease, which further increases the use of healthcare resources[54, 55].

In a primary care cohort in UK of newly diagnosed adults (CPRD-HES; n=936), incident organ damage after diagnosis was common ($\approx$ 59% over a median 4.3-year follow-up) and was associated with markedly higher visits, admissions, prescriptions and costs before and after the onset of damage; adjusted mean all-cause costs were $\approx$ £4,442 higher per patient year overall, ranging from +£2,709 to +£7,150 varying depending on the affected organ[56].

These cost differentials are directionally consistent with the broader European and North American literature showing that damage accrual (eg, ocular, musculoskeletal, renal, cardiovascular) is a dominant driver of long-term utilization and expenses and is closely linked to cumulative glucocorticoid exposure[10, 57].

Inpatient and outpatient care contribute substantially to the economic impact of SLE. Hospitalizations are frequent and often urgent, with average stays of about a week, and are associated with considerable direct medical costs. Procedures, diagnostic imaging, and drug use represent the main cost components[54, 58].

In a US cohort of commercially insured and Medicare Advantage members with newly confirmed lupus nephritis and continuous 5-year enrollment (Optum; n=335), utilization and costs spiked in the first post-diagnosis year (mean total $\approx$$44,205, largely inpatient-driven), with more than 50% experiencing $\geq$1 emergency department visit and 51% $\geq$1 inpatient admission; high ambulatory care and pharmacy use ($\approx$58-63 prescriptions/year) persisted through years 2-5[59].

Renal involvement is repeatedly associated with disproportionate utilization and costs in different settings, reflecting admissions for episodes of increased disease activity, procedures (eg biopsies), and intensified immunosuppression[57, 59].

Outpatient care also has a heavy burden, as patients with SLE consistently make more use of physician visits, emergency services, and specialist consultations than individuals without SLE[55].

In a large US incident SLE claims cohort (n=2,476), healthcare utilization and SLE-related costs increased as patients advanced to subsequent therapy sequences (from $\approx$$5.0k per patient-year in the first sequence to $\approx$$23.2k in the third), together with substantial concomitant use of corticosteroids and overall suboptimal adherence[60].

From a health system perspective, quality of care gaps (eg delayed referral, inconsistent use of HCQ, prolonged mid- to high-dose steroids) contribute to avoidable utilization; steroid-sparing strategies and adherence to the background therapy recommended by the guidelines (eg, HCQ) are associated with fewer relapses and can attenuate subsequent costs[9, 14, 61].

In general, studies show that SLE patients face substantially higher annual healthcare expenses than matched controls. Inpatient care is typically the main driver, but outpatient visits and pharmacological management also account for a significant share. Indirect costs (work disability, absenteeism / presenteeism, caregiver time) are substantial but not measured in routine databases and are likely to increase with disease activity and organ damage[57, 62].

Taken together, this evidence highlights that SLE is not only a challenging clinical condition but also a significant economic problem, which calls for integrated strategies such as early disease control and steroid-limiting approaches to optimize outcomes and resource allocation[56, 59, 60].

In practical terms, population-based primary care data sets (as used in our study) are well suited to track these trends longitudinally and evaluate whether early diagnosis and consistent care with guidelines result in measurable reductions in utilization and costs[63].

1.3 History

SLE was initially recognized as a predominantly cutaneous disorder before its multisystemic nature was fully understood.

During the twentieth century, advances in clinical observation and immunology redefined lupus from a dermatologic entity to a classic systemic autoimmune disease. The discovery of the Lupus Erythematosus (LE) cell and the subsequent identification of Antinuclear antibodies (ANA) established the centrality of autoimmunity in SLE and enabled immunofluorescence-based ANA testing and the characterization of disease-specific autoantibodies, including anti-double-stranded DNA and anti-Sm, which remain the pillars of diagnosis and disease monitoring today[3, 6, 8, 45].

As evidence accumulated that lupus could inflame virtually any organ system (skin, joints, kidneys, serosa, lungs, heart, and nervous system), the need for common case definitions became clear.

The EULAR / ACR introduced its first widely adopted classification criteria in 1982 (revised in 1997), standardizing clinical research and supporting a more consistent diagnosis in practice[64]. A decade later, the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) group proposed criteria that broadened clinical and immunological entry points (2012), anticipating the current classification criteria of the EULAR / ACR for 2019, which introduced a weighted ANA-positive entry framework to classify SLE earlier and more consistently across phenotypes[3, 6, 8].

Therapeutics evolved in parallel: corticosteroids helped with short-term outcomes but at the cost of cumulative organ damage when used chronically, focusing attention on steroid-sparing regimens[3, 10]. Antimalarials, especially HCQ, have moved from adjuncts to foundational therapy due to their broad benefits on flares, survival, thrombosis, and metabolic profiles, with favorable safety under appropriate ophthalmologic surveillance[14, 64].

For severe organ-threatening diseases such as proliferative lupus nephritis, cyclophosphamide induction became standard in the late twentieth century; subsequent Randomized Controlled Trials (RCTs) demonstrated that lower-dose regimens of cyclophosphamide could achieve comparable efficacy with improved safety in selected populations, helping to reduce gonadotoxic and hematologic harm[18, 64].

The MMF then emerged as an effective alternative for induction and a preferred option for maintenance in many patients, including those with membranous nephritis and specific ancestry, shifting practice away from prolonged exposure to alkylators[64].

The biologic era brought belimumab, approved for antibody-positive SLE with persistent activity despite standard care, as the first targeted agent to demonstrate benefit in multiple organ domains in phase III trials,while using rituximab for off-label B cell reduction, although supported by open-label series, did not meet primary endpoints in two pivotal randomized studies (EXPLORER, LUNAR), leading to selective use in refractory disease[20, 64].

Current EULAR / ACR recommendations emphasize HCQ for virtually all patients, early use of immunosuppressives to minimize glucocorticoids, and rational escalation, including biologics, in persistently active disease, reflecting a decades-long transition from steroid-centric to steroid-sparing strategies[9, 64].

During this time, our understanding of SLE pathogenesis matured, from descriptive autoantibody catalogs

Figure 2. Lupus representation. A historical drawing of Lupus Erythematosus as it was once considered as a non-fatal disfiguring skin disease. Source: Justiz Vaillant, Angel A., et al. "Systemic Lupus Erythematosus." StatPearls, StatPearls Publishing, 4 August 2023.

to integrated models of genetic risk, environmental triggers, innate / adaptive immune dysregulation, and ineffective disposal of apoptotic material. These conceptual changes informed both classification refinements and therapeutic targeting (e.g. B cell activating factor (BAFF) / BlyS inhibition with belimumab)[3, 6, 45]. They also catalyzed an epidemiologic transition: from single-center or hospital-based cohorts to population-based surveillance that employed primary care electronic records.

1.4 Clinical manifestations

SLE is a chronic, relapsing-remitting multisystem autoimmune disease whose clinical expression spans from mild organ-limited disease to life-threatening inflammation affecting the kidneys, lungs, heart, or central nervous system.

Its mutable nature reflects the interplay between autoantibody production and tissue injury mediated by immune complexes, coupled with dysregulated innate and adaptive immunity, and results in heterogeneous patterns between individuals and over time[3, 6].

1.4.1 SLE manifestations

General / constitutional Fatigue, low-grade fever, weight loss, and malaise are common presenting characteristics that often precede the involvement of a specific organ for weeks or months.

Because these symptoms are nonspecific, ongoing careful observation is essential to distinguish early SLE from intercurrent infection or other inflammatory conditions[3, 64].

Mucocutaneous Cutaneous involvement ranges from lupus-specific lesions (acute, subacute, and chronic) to nonspecific rashes.

The classic acute eruption is bilateral malar rash (butterfly) that spare the nasolabial folds; subacute cutaneous lupus can present with papulosquamous or annular lesions in photoexposed areas; and discoid LE (DLE) has adhering erythematous plaques that can scar and cause dyspigmentation.

Photosensitivity, vasculitic lesions, alopecia, and livedo reticularis are frequent nonspecific findings. Reported prevalence rates from clinical cohorts highlight this burden (eg butterfly rash 40%, maculopapular eruption 35%, DLE 20%, alopecia 70%)[64].

Musculoskeletal Symmetrical non-erosive inflammatory arthritis and arthralgia are the most frequent musculoskeletal manifestations (arthralgia / arthritis reported in up to 90% of patients).

Although classically nondeforming and non-erosive, some patients develop reducible subluxations (Jaccoud arthropathy). A minority (≈3-5%) manifest true erosive disease that is sometimes called 'rhupus'. Myalgia and tendinitis are also common, while inflammatory myositis is less frequent[3, 64].

Renal Lupus nephritis is the most consequential determinant of the prognosis. It can involve all renal compartments and typically corresponds to ISN / RPS classes III-V, the most concerning forms of lupus nephritis.

Clinically, proteinuria, microscopic hematuria, and cellular casts are typical findings. Monitoring is centered on urinalysis and a spot protein-creatinine ratio, now generally preferred over 24-hour collections for practicality.

When indicated, a kidney biopsy, performed under ultrasound guidance, defines the class and activity / chronology indices, consequently improving the prognosis and treatment. Hypertension should be aggressively treated to optimize both renal and cardiovascular outcomes.[64].

Cardiopulmonary Serositis commonly presents as pleuritis or pericarditis, with associated effusions that are typically minor but can sometimes become significant.

Less common but clinically serious are lung complications such as interstitial disease, shrinking lung syndrome, pulmonary hypertension, diffuse alveolar hemorrhage, and thromboembolism.

Cardiovascular disease is a parallel concern: in women aged 35-44, the risk of myocardial infarction is markedly higher than in peers without SLE, not fully accounted for by traditional risk factors, and is amplified by active disease, autoantibodies, and exposure to corticosteroids.[3, 64].

Neuropsychiatric The spectrum includes seizures, psychosis, cerebrovascular disease, cognitive dysfunction, peripheral neuropathies, and, rarely, aseptic meningitis.

The hypothesized mechanisms range from microvascular damage and thrombosis due to Antiphospholipid Antibodies (aPL) to antibody-mediated neuronal injury, such as the cross-reactivity of anti-DNA antibodies with N-methyl-D-aspartate (NMDA) receptors, which will likely require an alteration of the blood-brain barrier to become clinically relevant[3, 6, 64].

Hematologic and immunologic Autoimmune hemolytic anemia, leukopenia / lymphopenia, and thrombocytopenia are common hematologic cytopenias and are included in the classic classification criteria.

Immunologically, ANA positivity is near-universal; anti-dsDNA and anti-Sm are highly specific (though variably sensitive), while anti-SSA / Ro and anti-SSB / La are associated with photosensitive rashes and selected overlap features. Hypocomplementemia (low C3 / C4) often accompany active disease, especially nephritis. aPL antibodies identify patients at increased risk for thrombosis and pregnancy morbidity.[3, 64].

Gastrointestinal and other systems The manifestation of symptoms such as anorexia, abdominal discomfort, enlarged liver, nausea, vomiting, and diarrhea can vary.

Chronic liver disorders might be indicative of autoimmune responses, metabolic dysfunction, or adverse drug reactions, which require a thorough evaluation.

Progressive accumulation of damage, including cataracts, fractures due to osteoporosis, arthritic deformities, and early gonadal failure, often results from both the inherent activity of the disease and prolonged exposure to glucocorticoids. This highlights again the critical need for steroid-free treatment strategies.[64].

Beyond organ-specific manifestations, patients often have a substantial burden of comorbidity at diagnosis.

1.4.2 Diagnosis and classification in practice

The diagnosis remains clinical, supported by serology and organ-specific investigations, while classification criteria provide standardized entry for research and can aid clinical reasoning.

The 1982 (revised 1997) EULAR / ACR criteria codified cardinal characteristics, including malar / discoid rash, photosensitivity, oral ulcers, nonerosive arthritis, serositis, renal, neurologic and hematologic disorders, immunological markers (LE cell, anti-dsDNA, anti-Sm, false positive syphilis), and ANA, requiring at least four for classification[64].

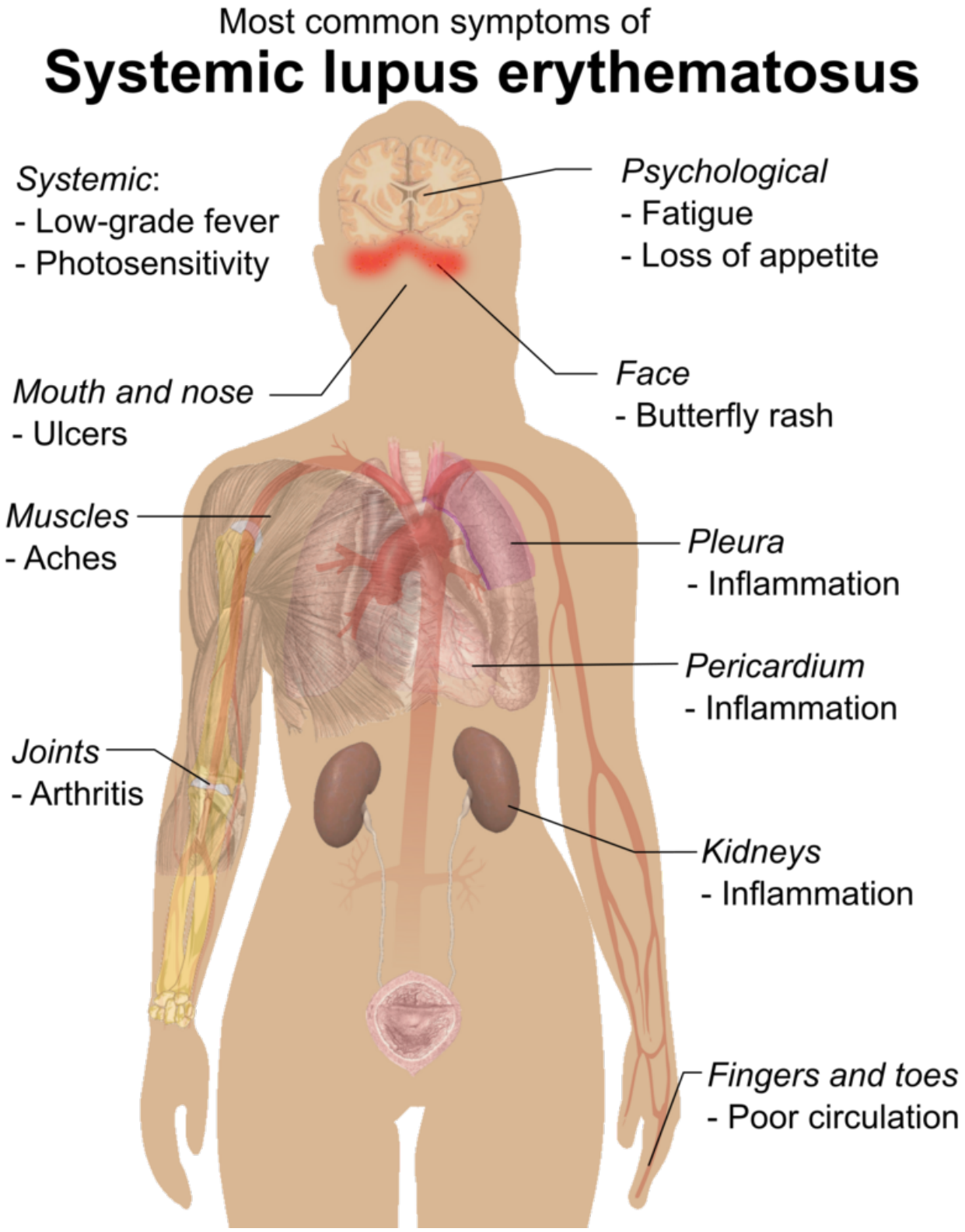

Figure 3. Common signs and symptoms of SLE. Source: Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.

The 2012 SLICC criteria broadened mucocutaneous and immunologic elements, and the 2019 EULAR / ACR criteria introduced a positive ANA (≥1:80) as an entry criterion followed by weighted clinical and immunologic domains to allow for earlier classification by phenotype[8].

In day-to-day care, evaluation combines: (i) a careful history and examination for multisystem features; (ii) laboratory tests (ANA by immunofluorescence, anti-dsDNA, ENA panel including anti-Sm and anti-SSA / SBB, complement C3 / C4, aPL); (iii) urine examination with sediment review and protein / creatinine ratio; and (iv) tissue biopsy when indicated (eg renal) to guide therapy. General practice data sets highlight how structured algorithms that combine diagnostic codes with laboratory evidence and SLE-relevant prescriptions can improve epidemiology case capture while mirroring clinical pathways[65].

SLE emulates infection, malignancy, and other autoimmune disorders, differential diagnoses include viral diseases, drug-induced lupus, mixed connective tissue disease, rheumatoid arthritis, ANCA-related vasculitides, IgA nephropathy, and primary antiphospholipid syndrome. Integration of serology (pattern and specificity), complement levels, organ histology, and longitudinal evolution helps resolve these distinctions[3, 64].

1.4.3 Practical implications

Across organ systems, several themes recur: (1) photosensitivity and ultraviolet exposure can precipitate cutaneous flares and amplify systemic activity, likely by increasing apoptotic load and nuclear antigen availability; (2) atherosclerotic risk is elevated beyond traditional factors, mandating intensive risk-factor management; (3) glucocorticoid toxicity accumulates with dose and duration, arguing for early use of antimalarials and immunosuppressives to minimize steroid exposure; and (4) structured, primary-care-enabled surveillance improves early recognition of organ involvement and comorbidity at diagnosis, an approach increasingly feasible in IT through national GP databases[10, 14, 63, 64].

1.5 Pathophysiology

SLE arises from the failure of immunological self-tolerance, which allows nucleic acid containing self-antigens to maintain coupled innate and adaptive immune activation.

Inefficient clearance of apoptotic material increases extracellular nuclear antigens (DNA, RNA, chromatin), which assemble into immune complexes that are internalized through Fc receptors and engage endosomal TLR7 / TLR9 in B cells and Plasmacytoid Dendritic Cells (pDCs).

pDCs activation fuels a type I interferon (IFN-I) signature, one of the best validated molecular hallmarks of SLE, which in turn primes myeloid and lymphoid compartments, promotes further autoantibody production, and lowers the threshold for flares.

Complement participates at two levels: early component genetic deficiencies (notably C1q and C4) significantly increase susceptibility, while acquired consumption during active disease amplifies inflammation at sites of immune complex deposition. Together, these defects establish the chronic relapsing-remitting pattern typical of SLE.[3, 4, 6, 45]

At the innate immune interface, neutrophils, particularly a low-density pro-inflammatory subset, undergo exaggerated NETosis, releasing neutrophil extracellular traps rich in DNA, histones, and antimicrobial peptides; these structures act as both autoantigen and adjuvant, strengthening TLR signaling and pDC-derived IFN-α production.

Monocytes and tissue macrophages display altered phagocytic clearance of apoptotic bodies, sustaining the antigenic load. Robust exposure to IFN-I reprograms antigen-presenting cells, upregulates BAFF and imprints

the transcriptional IFN signature measured in peripheral blood and target tissues.[6]

Adaptive immunity is characterized by B-cell hyperreactivity and disordered T-cell help. Excess BAFF supports the survival of autoreactive naïve and transitional B cells, while extrafollicular and germinal center reactions generate plasmablasts and long-lived plasma cells that secrete pathogenic autoantibodies (for example, anti-dsDNA, anti-Sm, anti-SSA / SRB).

On the T-cell side, follicular helper T cells expand and provide increased help to B cells; the regulatory number / function of T cells is often diminished; Th17 skew and altered CD3ζ signaling with increased Ca^{2+}/calcineurin-NFAT activation further lower activation thresholds. These abnormalities are reinforced by epigenetic changes, most prominently T-cell DNA hypomethylation, shaped by environmental factors, medications, and sex chromosome dosage.

The marked female predominance probably reflects both estrogenic modulation of B-cell selection and X-chromosome biology (including gene dosage and escape from X-inactivation), which together facilitate autoreactivity in genetically predisposed individuals.[3, 6]

Organ damage in SLE reflects where immune complexes form and fix complement, how vascular beds respond, and whether additional effectors (antiphospholipid antibodies, cytokines) are present. In the kidney, the glomerular deposition of chromatin-rich immune complexes triggers complement activation, inflammatory cell recruitment, and proliferative or membranous patterns of injury; resident mesangial and endothelial cells amplify the response through cytokine and chemokine networks, and chronicity emerges when repair is maladaptive.

In the skin, ultraviolet radiation increases keratinocyte apoptosis and the display of Ro / La antigens, which explains photosensitive rashes and the tendency of UV exposure to precipitate systemic flares.

Neuropsychiatric manifestations are heterogeneous: microvascular injury, blood-brain barrier disruption, aPL-mediated thrombosis, neuronal antibody cross-reactivity, and cytokine effects contribute in variable combinations. Hematologic cytopenias arise from peripheral destruction of opsonized blood cells and, less often, marrow suppression.

Beyond acute inflammation, accelerated atherosclerosis is driven by chronic immune activation, endothelial dysfunction, steroid exposure, and traditional risk factors, producing cardiovascular risk much greater than predicted by age and lipids alone.[3, 6]

These mechanistic insights align with and, in part, explain the therapeutic logic now embedded in contemporary care: HCQ interferes with endosomal TLR signaling and suppresses IFN-I pathways; glucocorticoids broadly reduce inflammatory gene expression but at the cost of cumulative damage; conventional immunosuppressants (MMF, AZA, methotrexate, cyclophosphamide) restrict lymphocyte proliferation and effector function; and BAFF inhibition (belimumab) targets a pivotal survival signal for autoreactive B cells that is up-regulated in the IFN-rich environment of SLE.

The 2019 EULAR / ACR recommendations reflect this mechanistic framework by focusing on universal antimalarial use, steroid-sparing strategies, and selective escalation with biologics when extrarenal or renal disease remains active despite standard therapy.[6, 9]

1.6 Treatment

The therapeutic goals in SLE are to induce and maintain remission or low disease activity, prevent relapses, minimize cumulative organ damage (especially related to glucocorticoids) and preserve quality of life.

Contemporary management follows a steroid-sparing, outcome-focused philosophy anchored in universal

antimalarial use, time-limited glucocorticoids, and progressive immunomodulation according to organ involvement and severity, as codified in the 2019 EULAR / ACR recommendations[9] .

Antimalarials HCQ is recommended for virtually all patients unless contraindicated. HCQ reduces flare risk, thrombotic events, and damage accrual; it should be continued long-term with weight-based dosing and ophthalmologic monitoring.

Mechanically, HCQ reduces endosomal TLR signaling and the IFN-I axis, aligning with current pathophysiology.[6, 9]

Glucocorticoids Glucocorticoids remain effective for rapid control of active disease, but are a major driver of long-term harm (osteoporosis, cardiovascular disease, diabetes, and infections).

The guidelines emphasize the lowest effective dose for the shortest possible time, early absorption, and avoidance of chronic prednisone greater than 5 mg/day whenever possible. Observational cohorts link cumulative exposure with damage accrual, underscoring the urgency of steroid-sparing strategies.[9–11]

Conventional immunosuppressants For persistent extrarenal activity or to avoid steroids, AZA, methotrexate, and MMF are commonly used; drug selection is individualized by phenotype (e.g., MTX for musculoskeletal / skin, AZA or MMF for systemic or hematologic disease).

In organ-threatening scenarios, especially proliferative lupus nephritis, induction with cyclophosphamide or MMF followed by maintenance (AZA or MMF) is standard evidence-based care.[9, 15, 17, 18]

Biologic therapy Belimumab, a BAFF inhibitor, is recommended for patients with active extrarenal disease or lupus nephritis who have inadequate control on standard therapy.

Off-label rituximab may be considered in refractory cases (e.g., severe hematologic disease). These choices reflect the centrality of B-cell survival signals in the pathogenesis of SLE.[9, 19–21]

Coexistence Antiphospholipid Syndrome (APS) is managed according to dedicated guidance (e.g. anticoagulation for thrombotic APS; aspirin in selected high-risk obstetric APS).

Universal cardiovascular risk reduction, osteoporosis prevention, dermatologic photoprotection, and vaccination strategies are integral to limiting non-inflammatory damage.[9]

Pre-pregnancy planning targets sustained low disease activity in pregnancy-compatible regimens (HCQ continuation; AZA as needed; avoidance of MMF, methotrexate and cyclophosphamide). Disease activity at conception is the strongest determinant of maternal-fetal outcomes, necessitating close multidisciplinary monitoring.[3, 9]

Patterns of use and economic implications Real-world analyses highlight persistent reliance on glucocorticoids and underuse or late use of steroid-sparing agents in routine care: the US claims cohorts report antimalarial use 43-59%, corticosteroids 48-69%, immunosuppressants 18-26%, NSAIDs 35-38%, and biologics 3%, with higher resource utilization and costs of resources among patients requiring later-line therapies. Canadian inception data similarly show frequent early corticosteroids exposure, typically combined with HCQ and / or immunosuppressants.

These utilization patterns reinforce the need to implement guideline-concordant, steroid-minimizing regimens in practice.[22–26]

Part II

Real-World Evidence of Systemic Lupus Erythematosus

Chapter 2

Methodology

2.1 Objectives

This dissertation project is based on the study *Epidemiology of SLE in Italy: an observational study using a primary care database*, and the multinational THIN®-based protocol, *Epidemiology of Systemic Lupus Erythematosus in UK, Italy, Belgium, Germany, Spain, and Romania: a population-based study*, approved by the THIN® EuroBoard on 28 May 2025 (Protocol no. 2023-07). Within this framework, the dissertation pursues two primary aims that mirror the Italian study and the multinational protocol:

1. Estimate the annual incidence (per 100,000 PY) and prevalence (per 100,000 people) of SLE, first in IT and then in European countries.

2. Characterize newly diagnosed SLE in terms of demographics, geography, clinical profile (including adapted EULAR / ACR criteria items), comorbidities, and concomitant therapies, using 4:1 matched controls drawn from the same data source.

3. Describe treatment patterns and their determinants in European countries.

2.2 Healthcare databases

Regularly collected healthcare information used for observational research is commonly described as Real-World Data (RWD), with the inferences drawn from it labeled Real-World Evidence (RWE)[66].

Population-based studies that use Electronic Health Records (EHRs) have expanded rapidly alongside the growth in data availability, but since EHRs are generated for clinical, administrative, or reimbursement purposes rather than research purposes, they are considered secondary data. Consequently, many countries have invested in transforming operational databases into research-ready resources, such as preparing documentation, defining data flows, and instituting quality standards, to support robust analyses[67].

EHR-based studies are often faster and less costly to initiate, with data that are immediately analyzable, but these advantages come with trade-offs: limited control over cohort retention and exposure / outcome capture, potential coding errors, and biases intrinsic to secondary use[68].

To address these issues, validation work and a suite of epidemiologic / statistical methods have matured, ranging from outcome / algorithm validation to modern causal inference approaches such as propensity score weighting, matching and target-trial emulation, so as to better balance confounding and approximate randomized allocation where feasible[69–72].

During recent decades, the research value of EHRs has been increasingly recognized, particularly for questions requiring population representativeness, large and diverse samples, and inclusion of patients typically excluded from RCTs (such as older adults, subjects with multiple chronic conditions or those on complex medication regimens). These features enable granular subgroup analyses and risk adjustment using commonly collected variables[66, 71, 73–75].

The quality gap with traditional designs progressively decreases as the detail, structure, and completeness of the EHRs improve. Longitudinal follow-up is another strength: repeated measures of exposures and time-varying confounders facilitate the study of uncommon outcomes and complex causal pathways without the expense of prospective cohorts[68].

The main challenges are about selection processes inherent to healthcare utilization that can bias cohorts towards more severe or persistent conditions, while transient, mild, or self-limited illnesses are under-represented. Careful definition of the source-population and eligibility criteria are critical to support external validity. Intermittent care can produce fragmented observation windows, and person-time at risk must be constructed with design rules that minimize immortal time and other timeline biases. In settings without strong gatekeeping, linking to hospital / secondary care data can be essential for complete case capture.

Of course, traditional cohorts and case-control studies are also not bias-free: participation incentives, recall, and social desirability can distort exposure reporting (e.g., smoking), and some populations are harder to enroll or follow[76].

In EHR studies, selection can be mitigated in design (eligibility windows, activity thresholds) and analysis (right-censoring methods such as Kaplan-Meier / Cox). Missing data require explicit handling: when plausibly Missing At Random (MAR), principled imputation / weighting that conditions on observed covariates and external factors (e.g., policy shifts) can recover unbiased estimates under correct model specification; otherwise, limitations should be transparently reported[77].

Specific to SLE in THIN®, it was noted that several EULAR / ACR classification items, especially some immunological assays, are not consistently captured in Italian (and European) primary care, motivating an adapted case-finding algorithm that requires laboratory or pharmacological confirmation around the ID; furthermore, pediatric cases (under 18 years) are not included in Italian GP data, implying under-ascertainment of pediatric-onset SLE in this source[63].

2.3 Source population

2.3.1 THIN Databases

In our study, we used the primary care databases of THIN® as the main data source. THIN® contains fully anonymized longitudinal GP EHRs with demographics, coded diagnoses, prescriptions, referrals / discharge summaries, selected laboratory tests and vital signs[63, 69, 78, 79].

Data are anonymized at source through a standardized process; patients are informed and may opt out, in which case no records are transmitted to THIN®. Governance follows the protocol's General Data Protection Regulation (GDPR)-compliant framework: analyses run in certified secure environments on anonymized datasets and only aggregated outputs leave the environment. The study received THIN® EuroBoard approval (Protocol 2023-07), and country-specific ethics submissions are pursued where required.

Currently, THIN® collects data from seven European countries (UK, FR, GE, IT, ES, BE, RO), with 70-72 million fully anonymized EHRs extracts. These data originate from GP participating in THIN® and

are specifically used to generate RWE from longitudinal observational studies[66, 69, 80].

Representativeness at the country level has been documented for demographic data (See Figure 4), prevalence of chronic diseases and mortality, supporting generalizability of population-based estimates[69, 81–83].

Primary care organization affects longitudinal capture: in UK, ES, RO, and IT, patients typically register with a single GP (gatekeeping), whereas in GE and BE they may consult multiple GPs or access secondary care directly.

Italy For IT, data collection started in 2000 and the THIN® primary care database includes 1 million active patients with 7 years of clinical history across more than 550 GP distributed nationwide, from which 500,000 are currently actively followed.

UK In UK, data collection started in 1994, collecting data from more than 13 million subjects. Patients are registered with a single GP (gatekeeping model), contributing person-time from registration until death, transfer or end of follow-up[32, 69, 83].

Romania For RO, data collection started in 2012 and THIN® RO is a primary care healthcare database, including 574 GP.

Spain In ES, THIN® ES is mainly a primary care healthcare database, including GP, specialists and pediatricians & nurses. It contains data from approximately 2,000 GP and 2,400 specialists (cardiology, pulmonology, urology, etc.) since 2014. THIN® ES also includes partial activities related to the hospital.

Belgium In BE, THIN® BE collects electronic health records from general practitioners using the HealthOne medical software, distributed by Cegedim Health Data since 2005. Data collection started in 2005, and the database currently includes longitudinal information for approximately 2 million patients from more than 300 participating GP.

Germany In GE, THIN® GE was officially launched in 2023, expanding the THIN® European network to include GE primary and secondary care data sources. The database integrates EHR data from general practitioners and specialists using Cegedim's local software platforms and affiliated networks. At present, THIN® GE contains anonymized EHRs from approximately 4 million patients across more than 600 practices, with continuous recruitment ongoing[84].

2.3.2 Cohort entry / exit and activity windows

The source population will include all active patients (i.e., at least one contact with the GP for any medical or administrative reason in the study period 2017-2022) who are recorded in the databases and with an available follow-back of at least three years from the date of the first contact with the GP (patients' entry) between 1st January 2017 to 31st December 2022. The $\geq$ 3 year look-back prior to ID was required to classify incident versus prevalent status and to capture baseline covariates.

Exits occurred at death (UK, IT, GE, ES, RO), leaving practice (IT, UK, GE, ES, RO), date of last contact within the study period (IT, UK, BE, GE, ES, RO) end of follow-up (31 December 2022), whichever came first.

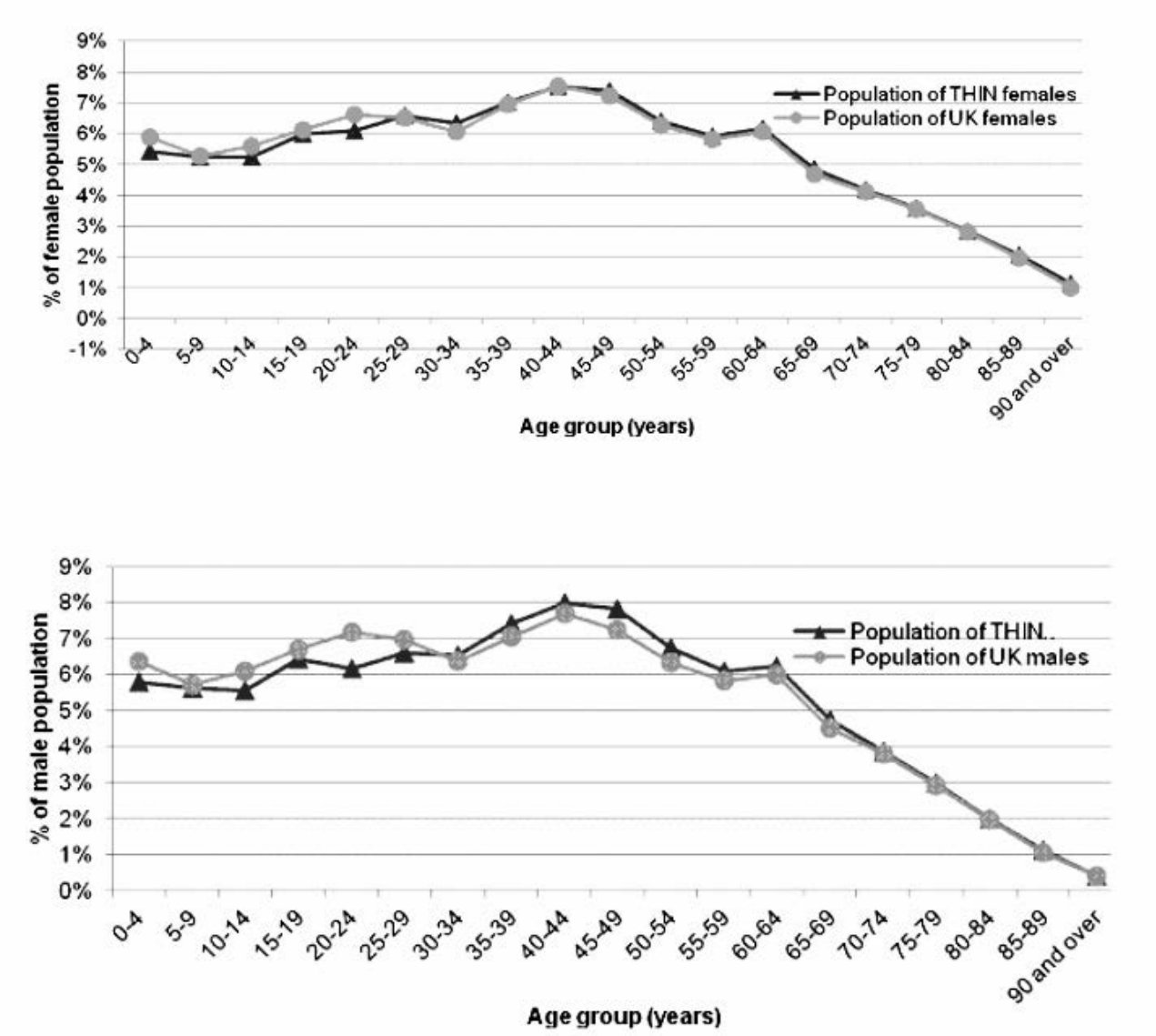

Figure 4. Population trends stratified by sex (females in top chart) and age groups in THIN databases. Source: Blak, Betina et al. (2011). Generalisability of The Health Improvement Network (THIN®) database: demographics, chronic disease prevalence and mortality rates. Informatics in primary care. 19. 251-5. 10.14236/jhi.v19i4.820.

2.3.3 Covariates

Covariates (measured on the ID):

- Demographics: age, sex, geographic area (macroregions, where applicable);
- EULAR / ACR clinical items: symptoms recorded before ID;[8]
- Comorbidities recorded before ID: diabetes, chronic kidney disease, cardiovascular disease, cerebrovascular disease (stroke / TIA), hypertension, dementia / Alzheimer's, Parkinson's disease, mood / anxiety disorders, chronic hepatic disease, osteoporosis, malignancy, Chronic Obstructive Pulmonary Disease (COPD), and autoimmune diseases (multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, myasthenia gravis, ankylosing spondylitis, Sjögren's syndrome);[34]
- Vital signs: Body Mass Index (BMI);
- Concomitant medications: number and type of distinct therapies (Anatomical Therapeutic Chemical (ATC) level V) in the 6 months prior to ID.[63]

2.3.4 Treatment-patterns dataset

For post-ID analyses such as prevalence of treatment use and treatment status at 6 / 12 / 18 / 24 months, we constructed long-format exposure histories for HCQ, glucocorticoids, NSAIDs, immunomodulating / immunosuppressant agents, biologic agents, and other therapies for severe or refractory SLE, and only patients with at least 24 months of observation were considered.

2.3.5 Country-specific considerations

In UK, ES, RO, and IT, subjects register and cared within a single general practice, while in GE they are not required but are likely to develop a long-term relationship with a single GP. It also acts as a gatekeeper to secondary and tertiary care, meaning that longitudinal data can be retrieved for each specific patient from the date of registration until resignation due to change of practice or death.

In BE, subjects can seek care from multiple GP. They are registered at the time of access to care with a central information system that allows GP to retrieve patient' history. Based on these considerations, we will include the whole population recruited in UK, ES, RO, GE, and IT and only those patients referred to representative GP in BE.

2.3.6 Notes on coding systems

THIN®-IT uses International Classification of Disease Ninth Revision Clinical Modification classification (ICD-9-CM) for medical events and national formulary codes for prescriptions; THIN®-UK historically used Read codes for diagnoses. THIN®-ES,THIN®-BE ,THIN®-GE ,THIN®-RO use International Classification of Diseases Tenth Revision Clinical Modification (ICD-10-CM) for medical events. The heterogeneity in the coding in countries (ICD-9-CM, ICD-10-CM, Read / SNOMED) is addressed through the protocol's common data model and harmonized concept lists for diagnoses, drugs (ATC) and laboratories.[63, 69, 78, 79].

All codes that have been used and their correspondences between the coding systems are shown in Table S39.

2.4 Case definition

Identification of SLE in primary care EHRs requires attention to the implementation of case definition. Claims / EHR algorithms based only on diagnosis codes can have a high PPV but variable sensitivity (≈50-80%) depending on the algorithm and source. To mitigate this, recent work uses combined diagnostic, laboratory, and pharmacologic information[32, 40, 85].

As said above, code-based SLE identification can vary in sensitivity; combining diagnoses with labs and SLE-specific treatments improves validity. GP databases can underestimate the diagnosis of pediatric-onset SLE and some secondary-care-only manifestations; regional differences in data capture and healthcare pathways can influence observed gradients. In particular, in our analysis of Italian general practice data, the 2019 EULAR / ACR criteria coincided with a visible increase in incident case capture, underscoring how classification updates can influence epidemiological determination in real-world settings[40, 63, 85].

To gain a deeper understanding of the characteristics of SLE, the Italian study considered three different definitions (Figure 5):

First Definition Our first definition (considered the main one) included diagnosis for SLE (excluding cutaneous-only lupus) or individuals who met two or more criteria of an adapted version of the EULAR / ACR classification, but only if they had at least one prescription for the commonly used medication for SLE or positive results on laboratory tests within 6 months after ID diagnosis. The rationale for using an adapted version of the EULAR / ACR classification is due to the fact that, considering how the databases of GP in IT are constructed, it should be noted that certain criteria items of the EULAR / ACR (eg, some laboratory test results) may not be recorded in primary care databases.

Second Definition The second definition was more conservative, only including diagnostic codes that represent SLE or a subtype of SLE while excluding cutaneous-only lupus.

Third Definition The third definition was less restrictive, including subjects selected under the first definition, without excluding cutaneous-only lupus.

The ID was considered the first date of registration of codes related to inclusion criteria. Exclusion criteria were applied for patients identified using the diagnostic code for SLE or cutaneous-only lupus if the following diseases were retrieved prior to the ID: primary vasculitis, myositis, polymyositis, dermatomyositis, psoriatic arthritis, CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia) or scleroderma, to reduce misclassification of overlapped autoimmune / connective tissue diseases.

In the multicountry analysis, we applied only the main definition, and not the other two alternative definitions (considered as sensitivity scenarios, implemented to balance sensitivity and specificity), and the Italian incident cases were updated.

2.5 Study size

Based on recent reviews, SLE prevalence in Europe ranges between 29-210 per 100,000 (0.029-0.21%) and incidence 1.5-7.4 per 100,000 PY (with a wider global range of 0.3-8.7)[27–31]. Using the standard precision formulas[86], the required denominators are:

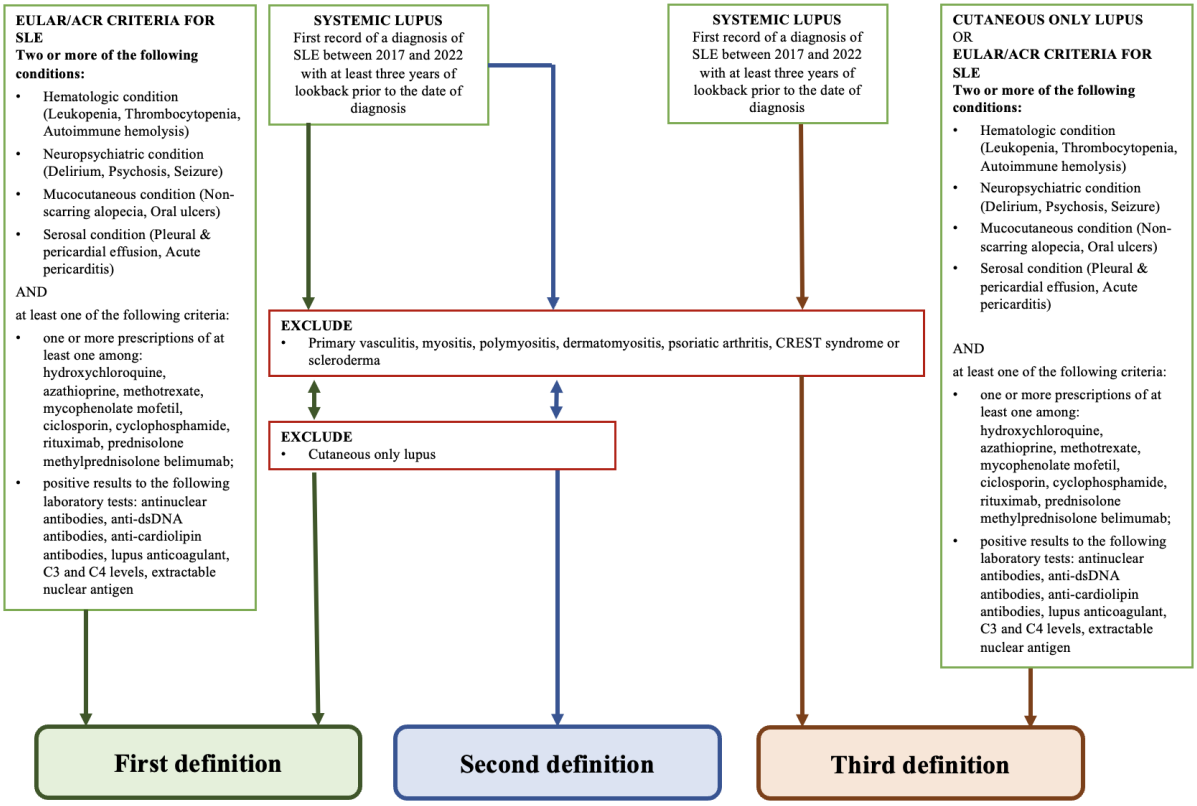

Figure 5. Graphical algorithm illustrating the three different SLE definitions.

$$n \;=\; \frac{Z_{1-\alpha/2}^{2}\,P(1-P)}{d^{2}},$$

with $Z_{0.975} = 1.96$, prevalence P expressed as a proportion and absolute precision d.

Target precision $d = 0.0002$ (i.e., 0.02%).

$$\begin{aligned} P = 0.029\%\ (= 0.00029) \quad &\Rightarrow \quad n \approx 27{,}843, \\ P = 0.10\%\ (= 0.001) \quad &\Rightarrow \quad n \approx 96{,}040, \\ P = 0.21\%\ (= 0.0021) \quad &\Rightarrow \quad n \approx 201{,}260. \end{aligned}$$

Target precision $d = 0.0001$ (i.e., 0.01%).

$$\begin{aligned} P = 0.029\%\ (= 0.00029) \quad &\Rightarrow \quad n \approx 111{,}372, \\ P = 0.10\%\ (= 0.001) \quad &\Rightarrow \quad n \approx 384{,}160, \\ P = 0.21\%\ (= 0.0021) \quad &\Rightarrow \quad n \approx 805{,}040. \end{aligned}$$

These figures indicate that the country-year denominators in THIN® (millions of active adults) are sufficient to achieve absolute precision $\leq 0.02\%$ for the SLE prevalence estimates in each country-year.

Incidence. For a Poisson rate λ (for 100,000 PY) and desired absolute precision d (for 100,000),[86] we have

$$\varepsilon \;=\; \frac{d}{\lambda}, \qquad \text{required events } r \;=\; \left(\frac{Z_{1-\alpha/2}}{\varepsilon}\right)^{2}, \qquad \text{PY PY} \;=\; \frac{r \cdot 100{,}000}{\lambda}.$$

Illustrative scenarios (95% CI):

- $\lambda = 5.0/100{,}000$, $d = 1.0/100{,}000$: events ≈ 96; PY ≈ 1.92 million
- $\lambda = 7.4/100{,}000$, $d = 1.0/100{,}000$: events ≈ 210; PY ≈ 2.84 million
- $\lambda = 1.5/100{,}000$, $d = 1.0/100{,}000$: events ≈ 9; PY ≈ 0.58 million

Relaxing the precision to $d = 2/100{,}000$ reduces the required PY approximately fourfold. Given multi-country pooling for 10 years, the protocol's "descriptive-no formal power" is appropriate; still, the available PY in THIN® should comfortably support country-year incidence with $d \approx 1$–$2/100{,}000$ in most settings.

2.6 Prevalence and incidence rates

Prevalent SLE cases were those alive and who met the definition on 31 December each year; incidence was the number of first-ever SLE cases per 100,000 PY among the eligible population. The rates were estimated both as crude and standardized for age and sex using the European 2022 population.

2.6.1 Rates and Standardization

Point prevalence for year$_x$ was defined as the ratio between all living SLE cases that met the study case definition by December 31 of year$_{x-1}$ and were still active on January 1 of year$_x$ (see 2.3.2), and the active

source population on January 1 of year$_x$, and 95% Confidence Interval (CI) were obtained using the exact binomial method. Incidence for year$_x$ was calculated as the number of first-ever SLE diagnoses during year$_x$ (per the algorithm in 2.4) divided by the average person-time at risk accrued that year (entry at January 1 or cohort entry; exit at the earliest of SLE diagnosis, death, transfer-out / last contact, or December 31), expressed in person-years, and 95% CI were derived using the exact Poisson method. For standardization, age–sex–specific rates were directly standardized to the 2022 Italian population for Italy-specific estimates and to the 2022 European Standard Population for multi-country results, with 95% CIs by normal approximation using the usual weighted-sum variance:

$$\mathrm{SE}\Big(\hat{\lambda}_{\mathrm{std}}\Big) = \sqrt{\sum_i d_i \left(\frac{w_i}{y_i}\right)^2},$$

where d_i is the incident count, y_i the stratum PY, and w_i the weight of the standard population.

2.7 Characterization of the incident cohort

We characterized incident SLE cases at baseline (pre-ID) and compared them with a cohort of healthy controls selected from the same source population and matched 4:1 to cases on sex, age, and geographic area. For continuous variables we reported means and Standard Deviation (SD), while for categorical variables we reported counts and percentages.

Differences Between-groups were assessed using hypothesis tests appropriate to scale and distribution: chi-square for categorical variables and Student's t-test for continuous variables. Effects' magnitude were represented through Odds Ratios (ORs) and CI. ORs were computed only under minimal cell-frequency conditions. In univariable 2x2 comparisons we estimated ORs only when no cell count was zero. In multivariable logistic models we required that all observed and expected cell counts were greater than 5; when this condition was not met, ORs were Not Estimable (NE)[87–89].

Global variables (composite) were excluded from multivariable models due to linear dependence with their component variables (granular) (e.g., "concomitant autoimmune disease" vs specific diagnoses such as multiple sclerosis). BMI was not included because it was recorded only for a subset of the cohort. "Concomitant therapies" was also excluded from the European study, as it acts as a proxy for the overall burden of comorbidities and therefore is highly collinear with individual comorbidities.

2.8 Treatment patterns

We described pharmacological management from 12 months before to 24 months after SLE ID. Only incident cases with at least 24 months of post-ID observation were eligible for these analyses.

2.8.1 Drug classes and exposure rules

Treatments were grouped into six mutually exclusive classes, ordered by increasing the intensity / complexity of the treatment (hierarchy used to break the tie when a patient met criteria for multiple classes within the same 6-month window):

1. **Antimalarials**: hydroxychloroquine (HCQ).

2. **Glucocorticoids**.

3. **NSAIDs**.

4. **Immunomodulating / immunosuppressive agents**: methotrexate, azathioprine, mycophenolate.

5. **Biologic agents**: belimumab, anifrolumab.

6. **Therapies for severe or refractory SLE**: cyclophosphamide and / or rituximab.

Exposure was assessed in consecutive 6-month intervals (semesters): $[-12, -6]$, $[-6, 0]$ before ID, and $[0, 6]$, $[6, 12]$, $[12, 18]$, $[18, 24]$ months after ID. The Class-specific exposure criteria were:

- **Glucocorticoids**: counted only if chronic use was observed, defined as prescriptions dispensed in at least three distinct months within the semester.
- **NSAIDs**: counted only if chronic use was observed, defined as prescriptions dispensed in at least two distinct months within the semester.
- **Antimalarials, immunosuppressants, biologics, cyclophosphamide / rituximab**: exposure defined by $\geq$1 prescription within the semester.

When a patient met the exposure criteria for more than one class in the same semester, we assign the patient to the highest class according to the hierarchy above (from 1=least intensive to 6=most intensive). Patients who did not have qualifying exposure in a given semester were classified as untreated for that window.

2.8.2 Prevalence of use and treatment dynamics

For each semester, we estimated the prevalence of use by class as the proportion of the SLE cohort meeting exposure criteria in that window. To visualize treatment dynamics over time, we plotted Sankey diagrams showing transitions between classes from the ID semester to each post-ID semester.

2.8.3 Characterization of treated patients

We defined two cumulative groups over the first 24 months after ID:

- **Treated**: any qualifying exposure to *any* class in $[0, 24]$ months.
- **Untreated**: no qualifying exposure to any class in $[0, 24]$ months.

We compared baseline covariates (pre-ID) between treated and untreated using standard descriptive statistics, for continuous variables we reported means and SD; for categorical variables we reported counts and percentages. Differences Between-groups were assessed using hypothesis tests appropriate to scale and distribution: chi-square for categorical variables and Student's t-test for continuous variables.

2.8.4 Determinants of treatment

To explore factors associated with receiving pharmacotherapy in the first two years after diagnosis, we fitted logistic regression models with outcome *any treatment in* $[0, 24]$ *months* (yes / no), reporting ORs with 95% CI.

Candidate covariates (measured prior to ID unless stated) included: sex, age, country (in pooled analyses), SLE symptoms, comorbidities, concomitant autoimmune diseases, and vital signs (BMI). We present estimates for the pooled cohort (including a country indicator) and stratified by country.

The magnitude of the effects was represented through ORs and CI. ORs were computed only under minimal cell-frequency conditions. In univariable 2x2 comparisons we estimated ORs only when no cell count was zero. In multivariable logistic models we required that all observed and expected cell counts be greater than 5; when this condition was not met, ORs were NE[87–89].

Global variables (composite) were excluded from multivariable models due to linear dependence with their component variables (granular) (e.g., "concomitant autoimmune disease" vs specific diagnoses such as multiple sclerosis). BMI was not included because it was recorded only for a subset of the cohort (substantial missingness). "Concomitant therapies" was also excluded, as it acts as a proxy for the overall burden of comorbidity and is therefore highly collinear with individual comorbidities, and is by design greater in treated patients and could absorb the effects of other variables.

Chapter 3

Results: the Italian study

3.1 Incidence and Prevalence

During the study period, a total of 191 incident cases were identified in the study population using the first definition. Tables 1,S1,S4 report data on incident and prevalent cases of SLE during the years 2017–2022, in general and stratified by age and sex, while the results of the alternative definitions are shown in tables S2,S5,S3,S6.

SLE cases showed a gradual increase in the standardised incidence rates from 4.99 (95% CI 4.79 to 5.18) per 100,000 PY in 2017 to 6.51 (95% CI 6.29 to 6.74) in 2022. It peaked significantly in 2021, reaching a level two times higher than that of the previous year, and then returned to the previous trend.

Prevalence reported a steadier linear increase, rising from 36.04 (95% CI 35.51 to 36.57) per 100,000 individuals in 2017 to 60.57 (95% CI 59.89 to 61.25) in 2022. Both estimates were higher than those under the second definition, which reported an incidence of 6.16 (95% CI 5.94 to 6.38) and a prevalence of 54.94 (95% CI 54.29 to 55.59) in the year 2022, but lower than the third definition, which estimated incidence and prevalence in 2022 at 9.67 (95% CI 9.40 to 9.95) and 74.20 (95% CI 73.44 to 74.96).

All the alternative definitions reported similar trends in terms of year, age, sex and geographical location. In 2022, the incidence was highest among women in the 40–49 age group, while in men, the peak occurred at a later age. Additionally, it was greater in women compared with men for all ages (Figure 6). Throughout all study years, prevalence was higher in women than men, with a ratio of approximately 5 to 1.

Table 1. SLE incidence rate (per 100,000 PYs) and prevalence (per 100,000 people) by year, 2017–2022 (first definition).

Year	Incident cases	Person-years	Incidence crude (95%CI)	Incidence standardised* (95%CI)	Prevalent cases	Prevalence crude (95%CI)	Prevalence standardised* (95%CI)
2017	25	472,862	5.29 (3.21–7.36)	4.99 (4.79–5.18)	176	37.22 (31.72–42.72)	36.04 (35.51–36.57)
2018	28	482,920	5.80 (3.65–7.95)	5.46 (5.25–5.66)	198	41.00 (35.29–46.71)	39.75 (39.20–40.30)
2019	23	491,726	4.68 (2.77–6.59)	4.46 (4.27–4.65)	216	43.93 (38.07–49.78)	42.73 (42.15–43.30)
2020	26	495,645	5.25 (3.23–7.26)	5.07 (4.87–5.27)	233	47.01 (40.97–53.04)	46.13 (45.53–46.73)
2021	58	497,692	11.65 (8.65–14.65)	11.19 (10.89–11.48)	281	56.46 (49.86–63.06)	55.60 (54.95–56.26)
2022	31	458,820	6.76 (4.38–9.13)	6.51 (6.29–6.74)	281	61.24 (54.09–68.40)	60.57 (59.89–61.25)

* Standardised by age and sex; year 2022 Italian population as reference.

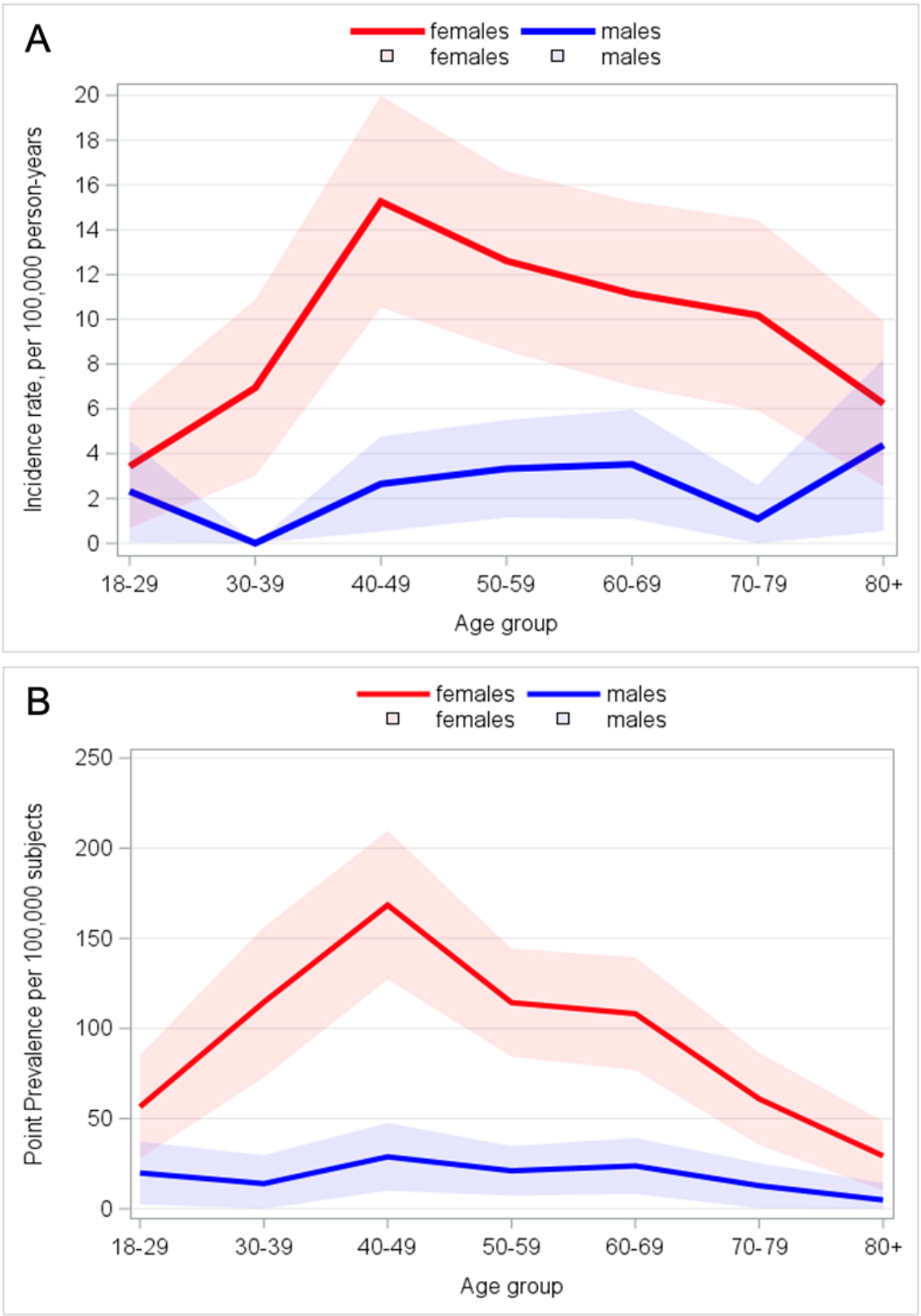

Figure 6. Line chart of incidence and prevalence. Line chart of sex- and age-specific incidence rate (2017–2022; Panel A) and point prevalence (2022; Panel B) for SLE. The lines represent the estimates, and the bands indicate the 95% confidence intervals.

3.2 Characterization of the incident cohort

Table 2 describes clinical and demographic characteristics of incident cases of SLE compared with age- and sex-matched controls.

Mean age at diagnosis was 55.9 years and women accounted for 82.1% of SLE cases. Incidence exhibited geographical variation, being highest in Northern IT (44.74%) and lowest in Southern IT and the Islands (20.53%). Overall, at the time of diagnosis, 6.84% of cases had already registered at least one SLE symptom according to EULAR / ACR criteria, compared with only 0.13% (one patient) in the control group.

Compared with controls, subjects with SLE had a higher prevalence of certain comorbidities, such as CKD (5.79% vs 1.45%), chronic hepatic disease (6.32% vs 1.97%) and osteoporosis (16.32% vs 9.47%), as well as concomitant autoimmune diseases, including rheumatoid arthritis (5.79% vs 1.97%) and Sjogren's syndrome (3.68% vs 0.39%).

The results of the adjusted multivariate analyses confirmed that, at the time of SLE diagnosis, patients had higher significant odds of being previously diagnosed with CKD (OR 3.88; 95% CI 1.62 to 9.26), chronic hepatic disease (OR 2.93; 95% CI 1.31 to 6.59), rheumatoid arthritis (OR 2.55; 95% CI 1.09 to 5.95), Sjogren's syndrome (OR 6.66; 95% CI 1.63 to 27.29), as well as a higher odds of being prescribed with five or more concomitant therapies (OR 1.47; 95% CI 1.05 to 2.05) (Table 3).

Table 2. Demographic and clinical characteristics of incident SLE cases.

	SLE CASES N (%)	CONTROLS N (%)	P-value
Overall	190	760	–
Sex[a]			
Male	34 (17.9)	136 (17.9)	–
Female	156 (82.1)	624 (82.1)	–
Age, mean (SD)[a]			
Mean (SD)	55.94 (±15.66)	55.94 (±15.63)	–
Age class[a]			
18–29	10 (5.26)	40 (5.26)	–
30–39	12 (6.32)	48 (6.32)	–
40–49	46 (24.21)	184 (24.21)	–
50–59	46 (24.21)	184 (24.21)	–
60–69	36 (18.95)	144 (18.95)	–
70–79	24 (12.63)	96 (12.63)	–
80+	16 (8.42)	64 (8.42)	–
Geographical area			
Northern IT	85 (44.74)	294 (38.68)	.0318
Central IT	66 (34.74)	233 (30.66)	–
Southern IT and the Islands	39 (20.53)	227 (29.87)	–
SLE symptoms (EULAR / ACR criteria)			
Present	13 (6.84)	1 (0.13)	< .0001
Comorbidities			
Diabetes	11 (5.79)	75 (9.87)	.0797
Chronic kidney disease	11 (5.79)	11 (1.45)	.0004
Cardiovascular disease	12 (6.32)	56 (7.37)	.6147
Cerebrovascular accident	10 (5.26)	26 (3.42)	.2343
Hypertension	82 (43.16)	286 (37.63)	.1619
Dementia / Alzheimer's disease	4 (2.11)	7 (0.92)	.1723
Parkinson disease	2 (1.05)	6 (0.79)	.7226
Mood and anxiety disorders	35 (18.42)	117 (15.39)	.3088
Chronic hepatic disease	12 (6.32)	15 (1.97)	.0013
Osteoporosis	31 (16.32)	72 (9.47)	.0067
Malignancy	33 (17.37)	106 (13.95)	.2327
Chronic obstructive pulmonary disease	15 (7.89)	38 (5.00)	.1200
Concomitant autoimmune disease	27 (14.21)	38 (5.00)	< .0001
Multiple sclerosis	2 (1.05)	2 (0.26)	.1328
Rheumatoid arthritis	11 (5.79)	15 (1.97)	.0039
Inflammatory bowel disease	4 (2.11)	14 (1.84)	.8119
Ankylosing spondylitis	3 (1.58)	4 (0.53)	.1292
Myasthenia gravis	2 (1.05)	1 (0.13)	.1037
Sjogren's syndrome	7 (3.68)	3 (0.39)	< .0001
Body mass index (BMI)			
Mean (SD)	27.26 (±5.01)	27.12 (±6.41)	.9057
>30	10 (5.26)	41 (5.39)	.9974
Concomitant therapies			
N. of different V ATC level (mean ± SD)	6.31 (±5.25)	4.84 (±4.10)	< .0001

[a] Sex and age were matching variables.

Table 3. Crude and multivariable logistic regression analyses of the association between SLE and selected characteristics.

	Crude OR (95% CI)	**Adjusted OR[^] (95% CI)**
Geographical area		
Northern IT	1.68 (1.11–2.55)	1.73 (1.21–2.67)
Central IT	1.65 (1.07–2.55)	1.62 (1.03–2.54)
Southern IT & Islands	1 (Ref)	1 (Ref)
Comorbidities[#]		
Chronic kidney disease	4.18 (1.79–9.81)	3.88 (1.62–9.26)
Chronic hepatic disease	3.35 (1.54–7.27)	2.93 (1.31–6.59)
Osteoporosis	1.86 (1.18–2.94)	1.44 (0.89–2.33)
Concomitant autoimmune diseases		
Rheumatoid arthritis	3.05 (1.38–6.76)	2.55 (1.09–5.95)
Sjogren's syndrome	9.65 (2.47–37.68)	6.66 (1.63–27.29)
Concomitant therapies[§]		
Five or more distinct medications	1.65 (1.19–2.27)	1.47 (1.05–2.05)

[^] Adjusted by geographical area, chronic kidney disease, chronic hepatic disease, osteoporosis, rheumatoid arthritis, Sjogren's syndrome, concomitant therapies.

[#] Reference category: absence of disease.

[§] Reference category: 0–4 distinct medications.

Chapter 4

Results: the European study

4.1 Incidence and Prevalence

During 2017–2022, the incidence of SLE was largely stable within each country, with a few country-specific deviations, while the absolute incidence levels differed between countries (Figure 7).

The UK showed a flat incidence rate of around 5 per 100,000 PY during the study period and the highest prevalence by 2022, reaching 96.37 (96.14–96.59), up from 80.76 (80.56–80.97) in 2017 (Table 4).

BE consistently reported the lowest incidence (range 1.30–3.83 per 100,000) with a nearly flat prevalence of around 30 per 100,000 (Table 5).

In GE no incidence was estimated because the database was very new in the observation window, resulting in insufficient look-back to robustly identify first cases and so contributed prevalence only. Prevalence rose from 13.26 (13.17–13.34) in 2021 to 44.04 (43.89–44.20) in 2022 (Table 6).

RO showed low-to-moderate incidence without a clear temporal trend (range 2.49–6.62 per 100,000) and prevalence increased from 13.95 (13.87–14.04) to 20.28 (20.17–20.38) (Table 7).

ES showed the highest incidence at the beginning of the observation, which likely reflects a very young database in 2017 with a small eligible denominator at cohort entry; then rates declined and stabilized around 9 per 100,000 from 2020 onward, along with a steady increase in prevalence to 57.95 (57.77 58.12) in 2022 (Table 8).

By 2022, standardized incidence ranked highest in ES (9.36 per 100,000 PY), intermediate in the UK (5.05) and RO (4.16), and lowest in BE (1.30); standardized prevalence was highest in the UK (96.37 per 100,000) and similar in IT (58.91) and ES (57.95), with GE (44.04), BE (29.87) and RO (20.28) lower.

Table 4. SLE incidence rate (per 100,000 PYs) and prevalence (per 100,000 people) by year — UK.

Year	Incident cases	Person-years	Incidence crude (95% CI)	Incidence standardised (95% CI)	Prevalent cases	Prevalence crude (95% CI)	Prevalence standardised (95% CI)
2017	218	3,947,197	5.52 (4.81–6.31)	5.41 (5.36–5.46)	3,194	80.92 (78.14–83.77)	80.76 (80.56–80.97)
2018	188	3,751,694	5.01 (4.32–5.78)	4.90 (4.85–4.95)	3,088	82.31 (79.43–85.26)	81.79 (81.58–82.00)
2019	180	3,496,745	5.15 (4.42–5.96)	5.05 (5.00–5.10)	2,988	85.45 (82.42–88.57)	84.23 (84.02–84.44)
2020	160	3,098,007	5.16 (4.40–6.03)	5.07 (5.02–5.13)	2,806	90.57 (87.26–93.99)	88.95 (88.73–89.16)
2021	147	2,830,263	5.19 (4.39–6.10)	5.09 (5.03–5.14)	2,723	96.21 (92.63–99.89)	94.16 (93.94–94.38)
2022	133	2,540,349	5.24 (4.38–6.20)	5.05 (4.99–5.10)	2,551	100.42 (96.56–104.39)	96.37 (96.14–96.59)

Table 5. SLE incidence rate (per 100,000 PYs) and prevalence (per 100,000 people) by year — BE.

Year	Incident cases	Person-years	Incidence crude (95% CI)	Incidence standardised (95% CI)	Prevalent cases	Prevalence crude (95% CI)	Prevalence standardised (95% CI)
2017	8	457,460	1.75 (0.76–3.45)	1.67 (1.64–1.70)	140	30.60 (25.75–36.11)	29.50 (29.37–29.62)
2018	17	458,245	3.71 (2.16–5.94)	3.83 (3.79–3.88)	143	31.21 (26.30–36.76)	30.31 (30.18–30.44)
2019	12	454,284	2.64 (1.36–4.61)	2.54 (2.51–2.58)	144	31.70 (26.73–37.32)	30.57 (30.44–30.70)
2020	12	445,739	2.69 (1.39–4.70)	2.64 (2.60–2.68)	144	32.31 (27.25–38.03)	31.22 (31.09–31.35)
2021	13	444,472	2.92 (1.56–5.00)	2.89 (2.86–2.93)	146	32.85 (27.74–38.63)	31.83 (31.70–31.96)
2022	5	388,665	1.29 (0.42–3.00)	1.30 (1.27–1.33)	121	31.13 (25.83–37.20)	29.87 (29.74–29.99)

Table 6. SLE incidence rate (per 100,000 PYs) and prevalence (per 100,000 people) by year — GE.

Year	Incident cases	Person-years	Incidence crude (95% CI)	Incidence standardised (95% CI)	Prevalent cases	Prevalence crude (95% CI)	Prevalence standardised (95% CI)
2017	–	–	–	–	–	–	–
2018	–	–	–	–	–	–	–
2019	–	–	–	–	–	–	–
2020	–	–	–	–	–	–	–
2021	395,367	NE	NE	NE	55	13.91 (10.48–18.11)	13.26 (13.17–13.34)
2022	431,709	NE	NE	NE	202	46.79 (40.56–53.71)	44.04 (43.89–44.20)

Table 7. SLE incidence rate (per 100,000 PYs) and prevalence (per 100,000 people) by year — RO.

Year	Incident cases	Person-years	Incidence crude (95% CI)	Incidence standardised (95% CI)	Prevalent cases	Prevalence crude (95% CI)	Prevalence standardised (95% CI)
2017	21	305,693	6.87 (4.25–10.50)	6.62 (6.56–6.68)	44	14.39 (10.46–19.32)	13.95 (13.87–14.04)
2018	12	348,449	3.44 (1.78–6.02)	3.38 (3.34–3.42)	55	15.78 (11.89–20.54)	15.23 (15.14–15.32)
2019	12	369,359	3.25 (1.68–5.68)	3.30 (3.25–3.34)	61	16.52 (12.63–21.21)	15.80 (15.71–15.89)
2020	17	372,223	4.57 (2.66–7.31)	4.04 (4.00–4.09)	77	20.69 (16.33–25.85)	19.24 (19.14–19.34)
2021	10	367,943	2.72 (1.30–5.00)	2.49 (2.45–2.52)	77	20.93 (16.52–26.15)	18.96 (18.86–19.06)
2022	16	371,384	4.31 (2.46–7.00)	4.16 (4.11–4.21)	84	22.62 (18.04–28.00)	20.28 (20.17–20.38)

Table 8. SLE incidence rate (per 100,000 PYs) and prevalence (per 100,000 people) by year — ES.

Year	Incident cases	Person-years	Incidence crude (95% CI)	Incidence standardised (95% CI)	Prevalent cases	Prevalence crude (95% CI)	Prevalence standardised (95% CI)
2017	53	223,202	23.75 (17.79–31.06)	32.30 (32.17–32.44)	75	33.60 (26.43–42.12)	41.01 (40.86–41.16)
2018	80	544,453	14.69 (11.65–18.29)	14.14 (14.05–14.23)	154	28.29 (23.99–33.12)	27.20 (27.08–27.32)
2019	74	611,519	12.10 (9.50–15.19)	11.58 (11.51–11.66)	227	37.12 (32.45–42.28)	35.83 (35.69–35.97)
2020	66	648,094	10.18 (7.88–12.96)	9.71 (9.64–9.78)	291	44.90 (39.89–50.37)	43.33 (43.18–43.48)
2021	66	678,045	9.73 (7.53–12.38)	9.41 (9.34–9.48)	357	52.65 (47.33–58.40)	51.04 (50.87–51.20)
2022	67	687,807	9.74 (7.55–12.37)	9.36 (9.29–9.43)	414	60.19 (54.53–66.28)	57.95 (57.77–58.12)

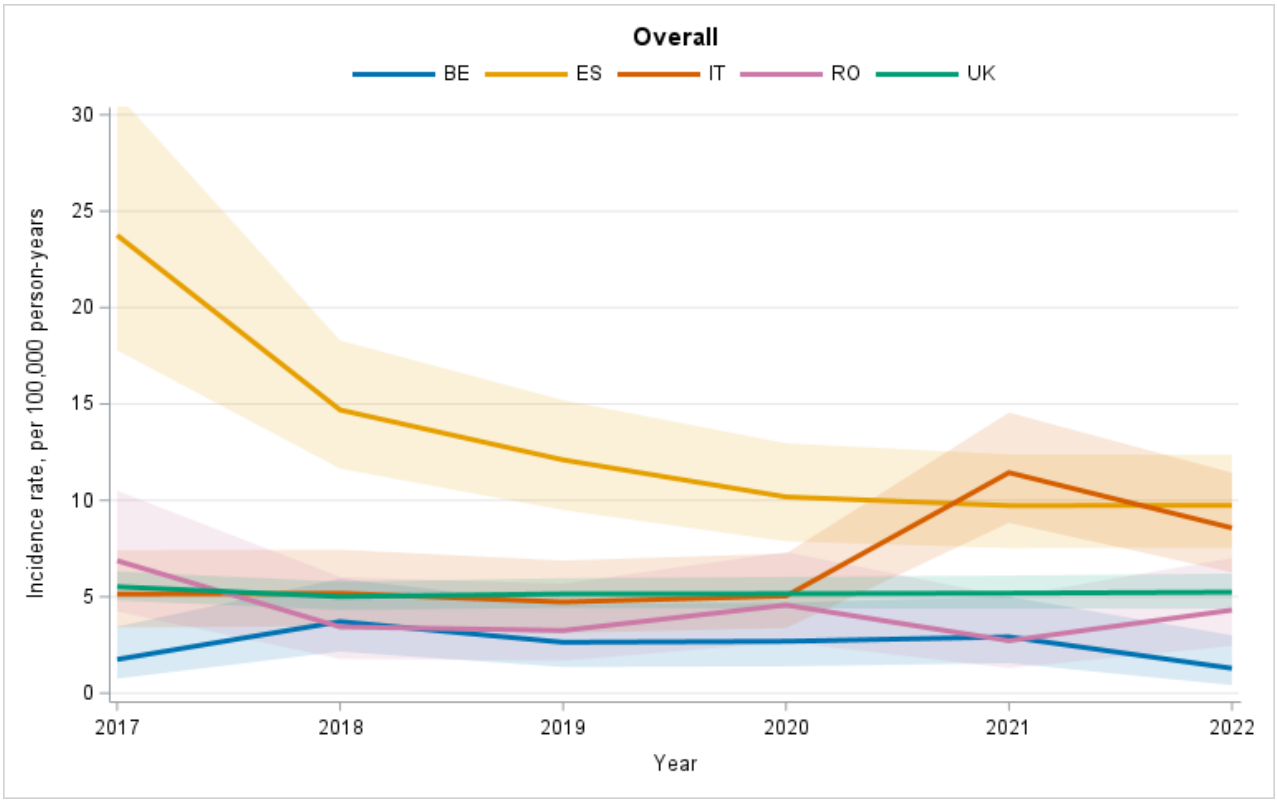

Figure 7. Line chart of annual incidence rate Line chart of country-specific incidence rate (2017–2022) for SLE. The lines represent the estimates, and the bands indicate the 95% confidence intervals.

In countries and years, the standardized incidence was consistently higher in women than in men, with female–to–male contrasts evident in all settings (Tables S7–S12).

Age-specific patterns were also broadly similar: the rates tended to peak in mid-life, typically in the 40–59 bands for women and slightly older in men, with lower values in the youngest (18–29) and oldest ($\geq$ 80) groups.

As country-specific anomalies, ES showed inflated early-year rates across several age strata in 2017 that subsequently stabilized, the's very low counts of BE yielded wide CI and occasional zeros in the finer strata, RO showed small-number variability, and GE had no estimable incidence by sex / age due to immaturity of the database in the observation window. In general, the sex and age gradients are summarized and confirmed in Figures 8–11.

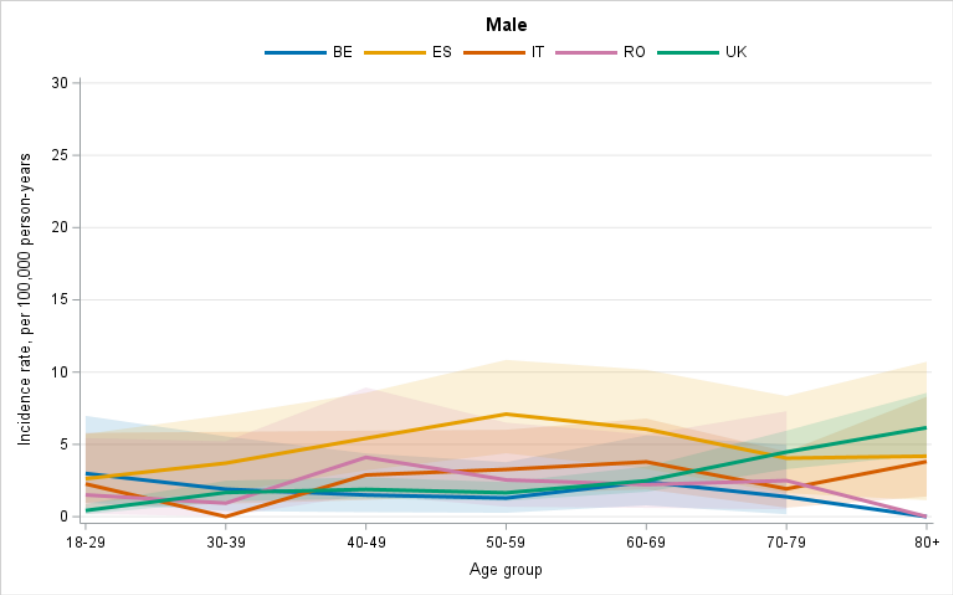

Figure 8. Line chart of incidence - Male Line chart of country- and age-specific incidence rate (2017–2022) for SLE in males. The lines represent the estimates, and the bands indicate the 95% confidence intervals.

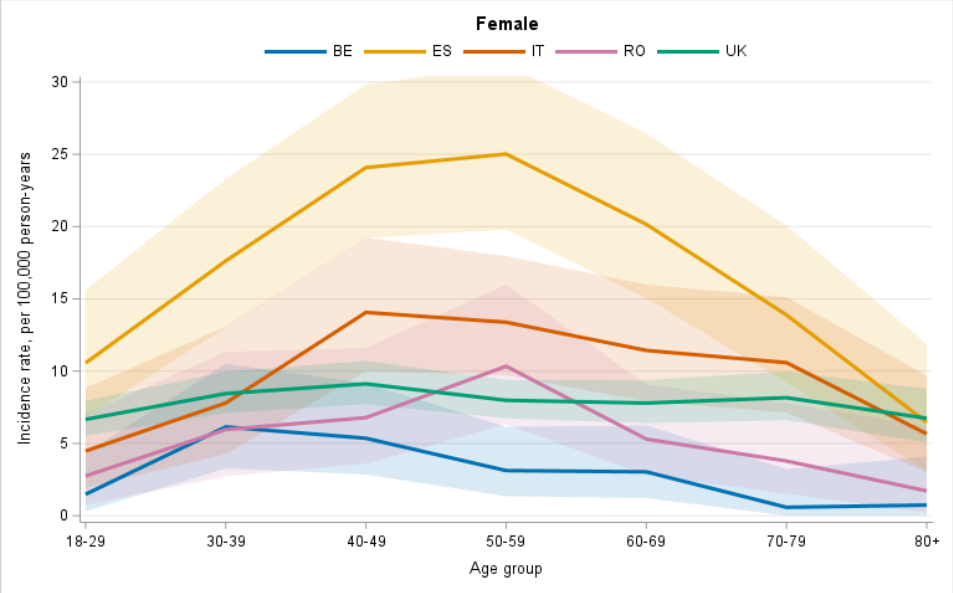

Figure 9. Line chart of incidence - Female Line chart of country- and age-specific incidence rate (2017–2022) for SLE in females. The lines represent the estimates, and the bands indicate the 95% confidence intervals.

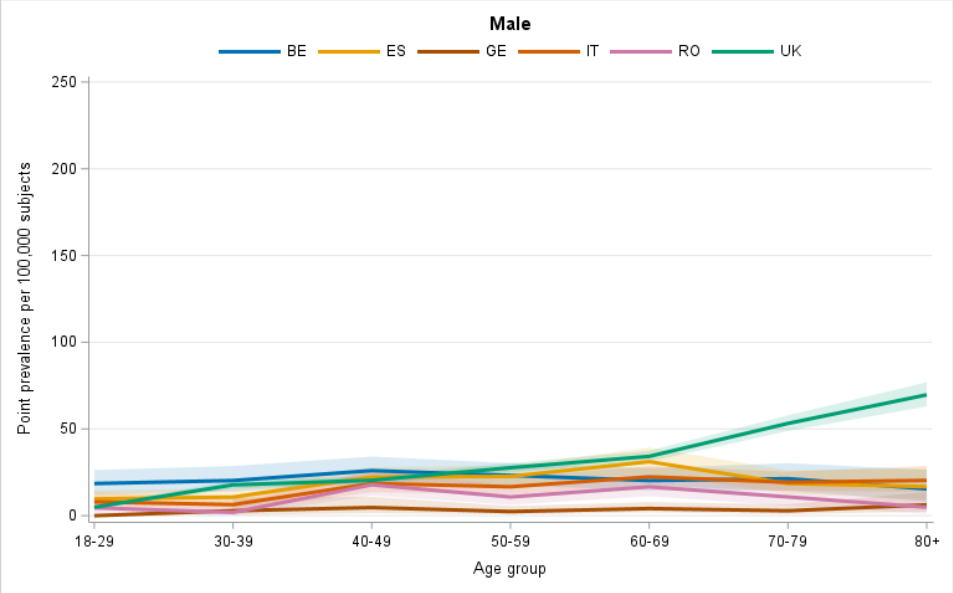

Figure 10. Line chart of prevalence - Male Line chart of country- and age-specific prevalence rate (2017–2022) for SLE in males. The lines represent the estimates, and the bands indicate the 95% confidence intervals.

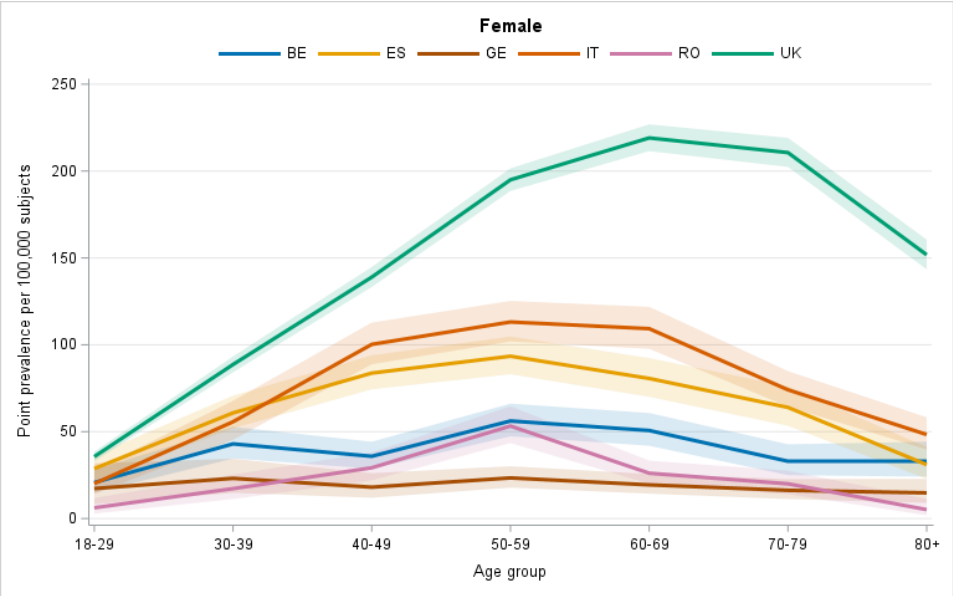

Figure 11. Line chart of prevalence - Female Line chart of country- and age-specific prevalence rate (2017–2022) for SLE in females. The lines represent the estimates, and the bands indicate the 95% confidence intervals.

4.2 Characterization of the incident cohort

As per study design, cases and controls were matched on sex and age: women were about 80% in both groups and the mean age was identical (52.6 years overall), with overlapping age-class distributions (Table 9).

At the time of diagnosis, EULAR / ACR SLE symptoms were already documented in a substantial proportion of cases (28.9%), whereas they were rare among controls (1.6%), highlighting a clear clinical distinction between the two populations at index.

In the pooled cohort, incident SLE cases exhibited a substantially higher burden of comorbidities than controls. Several differences were large in magnitude and remained evident after multivariable adjustment. Chronic kidney disease was observed in 1.6% of cases versus 0.1% of controls, cardiovascular disease in 19.5% versus 2.1%, and hypertension in 27.0% versus 3.6%. Mood and anxiety disorders were present in over one third of cases (36.0%) compared with fewer than 5% of controls. Osteoporosis (7.9% vs 0.7%), malignancy (21.9% vs 2.2%), chronic hepatic disease (2.7% vs 0.2%), and chronic obstructive pulmonary disease (7.8% vs 0.8%) were also significantly more common among cases.

Other conditions, such as diabetes (9.5% vs 1.6%) and cerebrovascular disease (2.2% vs 0.2%), showed pronounced crude differences but were substantially attenuated after adjustment, suggesting that these associations were partly explained by correlated comorbidity patterns rather than representing independent distinguishing features of SLE status.

Body mass index was comparable between groups, both in terms of mean values (27.6 vs 28.1) and prevalence of obesity (31.4% vs 35.1%), indicating no relevant difference in overall adiposity.

Concomitant autoimmune diseases were substantially more frequent among cases (17.6%) than controls (0.7%). In particular, rheumatoid arthritis (7.3% vs 0.2%) and inflammatory bowel disease (7.7% vs 0.5%) displayed large absolute differences that remained stable after adjustment, supporting the presence of a broader autoimmune background among individuals with incident SLE.

Medication burden differed significantly between groups. Cases were exposed, on average, to 7.0 distinct ATC classes, compared with only 0.3 among controls, reflecting both disease severity and markedly higher healthcare utilization in the SLE population.

The country-specific results were directionally consistent with the pooled findings, although the magnitude of differences varied and some estimates were unstable in smaller datasets.

In the UK (Table S20), EULAR / ACR SLE symptoms were recorded in 38.5% of cases compared with 2.5% of controls. Several comorbidities were markedly more frequent among cases, including cardiovascular disease (23.0% vs 1.3%), hypertension (26.1% vs 2.0%), and mood and anxiety disorders (38.5% vs 3.6%); these contrasts remained evident in the multivariable model. Malignancy was also substantially more common in cases (27.4% vs 2.3%), as were rheumatoid arthritis (7.8% vs 0.1%) and inflammatory bowel disease (10.5% vs 0.6%), with the corresponding associations persisting after adjustment. Osteoporosis (5.7% vs 0.5%) and COPD (9.0% vs 0.7%) were also higher in cases, with associations that remained apparent after multivariable adjustment.

In BE (Table S21), small sample size resulted in sparse cells and several non-estimable (NE) adjusted comparisons. SLE symptoms were recorded in 20.9% of cases and in none of the controls. Large crude differences were observed for several comorbidities (e.g., hypertension 32.8% vs 2.6%; mood and anxiety disorders 55.2% vs 2.2%), and these two contrasts remained evident in the adjusted model. The baseline medication burden also differed markedly, with a higher mean number of distinct ATC classes among cases than controls (5.9 vs 0.1).

In RO (Table S22), SLE symptoms were recorded in 4.5% of cases and in none of the controls. The Romanian cohort showed the highest overall comorbidity burden among cases, particularly cardiovascular disease (51.1% in cases vs 7.7% in controls) and hypertension (52.3% vs 15.1%). Diabetes was also more frequent in cases (17.0% vs 3.4%). In the multivariable model, the contrasts that remained most clearly apparent were for diabetes and cardiovascular disease, while the difference for hypertension was attenuated after adjustment. Medication burden was again higher in cases than controls (mean 4.0 vs 0.5 distinct ATC classes).

In ES (Table S23), SLE symptoms were recorded in 13.5% of cases versus 0.6% of controls. Several conditions were more frequent among cases, including cardiovascular disease (9.4% vs 1.9%), mood and anxiety disorders (41.4% vs 10.4%), osteoporosis (7.1% vs 1.0%), and malignancy (13.3% vs 3.2%); these associations remained evident after multivariable adjustment. Hypertension was also more common among cases (21.9% vs 6.6%), although the adjusted contrast was attenuated. As in all countries, the mean number of distinct ATC classes was substantially higher among cases than controls (5.4 vs 0.7).

In summary, despite matching in age and sex, incident SLE cases showed substantially higher comorbidity and treatment burden than controls in all countries, with the clearest and most consistent adjusted signals for cardiovascular disease, hypertension, mood and anxiety disorders, osteoporosis, malignancy, and concomitant autoimmune diagnoses (notably rheumatoid arthritis and inflammatory bowel disease). A summary of demographic and clinical characteristics of incident cases of SLE and controls by country is shown in Tables 10 and 11.

The demographic profile of cases and controls was broadly comparable across countries, with women accounting for approximately 80% of subjects in IT, UK and ES, and a slightly lower proportion in BE (68.7%) and RO (77.2%). Mean age varied modestly across countries, ranging from 46.4 years in BE to 57.2 years in IT, with intermediate values in the UK, RO and ES.

Across countries, incident SLE cases showed some heterogeneity both in terms of comorbidity burden and autoimmune co-diagnoses.

Cardiovascular disease showed substantial variation, ranging from 9–13% in IT, BE and ES to 23.0% in the UK, and reaching 51.1% in RO, where cardiovascular conditions represented the most prevalent comorbidity. A similar pattern was observed for hypertension, which affected over half of cases in RO (52.3%) compared with approximately one quarter in IT and the UK, and 21.9% in ES.

Chronic hepatic disease was one of the most heterogeneous comorbidity: it was uncommon in IT (4.0%), the UK (2.2%), BE (0.0%) and ES (0.7%), but affected 15.9% of cases in RO.

Mood and anxiety disorders were reported in over half of cases in BE (55.2%) and were frequent in the UK (38.5%) and ES (41.4%), whereas substantially lower proportions were observed in IT (15.1%) and RO (21.6%).

The prevalence of concomitant autoimmune disease followed a similarly heterogeneous pattern. Any autoimmune diagnosis was most common in RO (28.4%) and the UK (21.0%), intermediate in BE (16.4%) and IT (12.4%), and lowest in ES (9.9%). In particular, rheumatoid arthritis ranged from 4.4–7.8% in IT, UK and ES, but reached 18.2% in RO. Inflammatory bowel disease was especially frequent in the UK (10.5%) and RO (11.4%), compared with lower proportions in IT (2.2%) and ES (2.5%).

Differences were also evident in metabolic profiles. Mean BMI was broadly similar across IT, UK and ES (approximately 27), lower in BE (24.4), and markedly higher in RO (34.9), where the only two patients with available BMI data were classified as obese.

Finally, treatment complexity at baseline varied across countries, with the highest mean number of distinct

ATC classes observed in the UK (8.0), intermediate in IT (6.6), BE (5.9), and ES (5.4) and lower values in RO (4.0), reflecting differences in healthcare utilization and comorbidity management at diagnosis.

Relevant heterogeneity in comorbidity burden was observed also between controls across countries. Cardiovascular disease was rare among controls in IT (0.7%), UK (0.8%), BE (1.1%) and ES (1.9%), but markedly more frequent in RO (7.7%). A similar pattern was observed for hypertension, which affected 15.1% of controls in RO compared with 1–3% in IT, UK and BE, and 6.6% in ES.

Chronic hepatic disease again emerged as a distinctive feature of the Romanian cohort, affecting 3.1% of controls in RO, while remaining rare (0.1% in ES) or absent in all other countries. Chronic obstructive pulmonary disease followed a comparable pattern, being uncommon in IT (0.1%), UK (0.4%), BE (0.4%), and ES (0.8%) but more frequent in RO (4.0%).

Neuropsychiatric conditions showed substantial between-country variability. Mood and anxiety disorders were infrequent among controls in IT (0.9%) and the UK (2.0%), intermediate in BE (2.2%) and RO (5.7%), and most prevalent in ES (10.4%), mirroring patterns observed among cases.

Table 9. Demographic and clinical characteristics of incident SLE cases — Pooled.

	SLE CASES N (%)	CONTROLS N (%)	P-value	Adjusted P-value^
Overall	1,812	7,242	–	–
Sex				
Male	366 (20.2)	1,464 (20.2)	–	–
Female	1,446 (79.8)	5,778 (79.8)	–	–
Age, mean (SD)				
Mean (SD)	52.6 (17.3)	52.6 (17.3)	–	–
Age class				
18–29	188 (10.4)	752 (10.4)	–	–
30–39	264 (14.6)	1,056 (14.6)	–	–
40–49	361 (19.9)	1,441 (19.9)	–	–
50–59	361 (19.9)	1,444 (19.9)	–	–
60–69	286 (15.8)	1,142 (15.8)	–	–
70–79	226 (12.5)	904 (12.5)	–	–
80+	126 (7.0)	503 (6.9)	–	–
Geographical area				
IT	225 (12.4)	899 (12.4)	–	–
UK	1,026 (56.6)	4,104 (56.7)	–	–
BE	67 (3.7)	268 (3.7)	–	–
GE	Not included	Not included	–	–
RO	88 (4.9)	351 (4.8)	–	–
ES	406 (22.4)	1,620 (22.4)	–	–
SLE symptoms (EULAR / ACR criteria)				
Present	523 (28.9)	115 (1.6)	< .0001	
Comorbidities				
Diabetes	173 (9.5)	114 (1.6)	< .0001	0.9297
Chronic kidney disease	29 (1.6)	10 (0.1)	< .0001	0.0121
Cardiovascular disease	354 (19.5)	119 (2.1)	< .0001	< .0001
Cerebrovascular accident	39 (2.2)	16 (0.2)	< .0001	0.2854
Hypertension	489 (27.0)	264 (3.6)	< .0001	< .0001
Dementia / Alzheimer's disease	17 (0.9)	24 (0.3)	0.0006	0.1066
Parkinson disease	11 (0.6)	3 (0.0)	< .0001	NE
Mood and anxiety disorders	653 (36.0)	350 (4.8)	< .0001	< .0001
Chronic hepatic disease	49 (2.7)	15 (0.2)	< .0001	< .0001
Osteoporosis	143 (7.9)	52 (0.7)	< .0001	< .0001
Malignancy	397 (21.9)	157 (2.2)	< .0001	< .0001
Chronic obstructive pulmonary disease	141 (7.8)	57 (0.8)	< .0001	0.0001
Concomitant autoimmune disease	319 (17.6)	51 (0.7)	< .0001	
Multiple sclerosis	9 (0.5)	0 (0.0)	< .0001	NE
Rheumatoid arthritis	133 (7.3)	11 (0.2)	< .0001	< .0001
Inflammatory bowel disease	139 (7.7)	37 (0.5)	< .0001	< .0001
Ankylosing spondylitis	8 (0.4)	0 (0.0)	< .0001	NE
Myasthenia gravis	8 (0.4)	0 (0.0)	< .0001	NE
Sjogren's syndrome	63 (3.5)	3 (0.0)	< .0001	NE
Body mass index (BMI)				
Mean (SD)	27.6 (6.1)	28.1 (6.2)	0.1438	
>30	390 (31.4)	130 (35.1)	0.1714	
Concomitant therapies				
N. of different V ATC level (mean ± SD)	7.0 (6.2)	0.3 (1.5)	< .0001	

^ Adjusted by diabetes, chronic kidney disease, cardiovascular disease, cerebrovascular disease, hypertension, dementia / alzheimer's disease, mood and anxiety disorders, chronic hepatic disease, osteoporosis, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease.

Table 10. Demographic and clinical characteristics of incident SLE cases by country.

	IT CASES N (%)	UK CASES N (%)	BE CASES N (%)	RO CASES N (%)	ES CASES N (%)
Overall	225	1,026	67	88	406
Sex					
Male	43 (19.1)	203 (19.8)	21 (31.3)	20 (22.7)	79 (19.5)
Female	182 (80.9)	823 (80.2)	46 (68.7)	68 (77.3)	327 (80.5)
Age, mean (SD)					
Mean (SD)	57.2 (15.8)	52.5 (18.6)	46.4 (15.1)	52.8 (14.5)	51.2 (15.1)
Age class					
18–29	12 (5.3)	131 (12.8)	8 (11.9)	6 (6.8)	31 (7.6)
30–39	14 (6.2)	166 (16.2)	16 (23.9)	10 (11.4)	58 (14.3)
40–49	46 (20.4)	178 (17.4)	16 (23.9)	19 (21.6)	102 (25.1)
50–59	54 (24.0)	172 (16.8)	11 (16.4)	24 (27.3)	100 (24.6)
60–69	45 (20.0)	146 (14.1)	12 (17.9)	17 (19.3)	66 (16.3)
70–79	35 (15.6)	143 (14.0)	3 (4.5)	10 (11.4)	35 (8.6)
80+	19 (8.4)	90 (8.8)	1 (1.5)	2 (2.3)	14 (3.4)
SLE symptoms (EULAR / ACR criteria)					
Present	55 (24.4)	395 (38.5)	14 (20.9)	4 (4.5)	55 (13.5)
Comorbidities					
Diabetes	16 (7.1)	103 (10.0)	10 (14.9)	15 (17.0)	29 (7.1)
Chronic kidney disease	10 (4.4)	11 (1.1)	0 (0.0)	0 (0.0)	8 (2.0)
Cardiovascular disease	26 (11.6)	236 (23.0)	9 (13.4)	45 (51.1)	38 (9.4)
Cerebrovascular accident	8 (3.6)	24 (2.3)	2 (3.0)	1 (1.1)	4 (1.0)
Hypertension	64 (28.4)	268 (26.1)	22 (32.8)	46 (52.3)	89 (21.9)
Dementia / Alzheimer's disease	5 (2.2)	6 (0.6)	0 (0.0)	0 (0.0)	6 (1.5)
Parkinson disease	2 (0.9)	6 (0.6)	0 (0.0)	1 (1.1)	2 (0.5)
Mood and anxiety disorders	34 (15.1)	395 (38.5)	37 (55.2)	19 (21.6)	168 (41.4)
Chronic hepatic disease	9 (4.0)	23 (2.2)	0 (0.0)	14 (15.9)	3 (0.7)
Osteoporosis	32 (14.2)	58 (5.7)	8 (11.9)	16 (18.2)	29 (7.1)
Malignancy	36 (16.0)	281 (27.4)	11 (16.4)	15 (17.0)	54 (13.3)
Chronic obstructive pulmonary disease	13 (5.8)	92 (9.0)	13 (19.4)	10 (11.4)	13 (3.2)
Concomitant autoimmune disease					
Any autoimmune disease	28 (12.4)	215 (21.0)	11 (16.4)	25 (28.4)	40 (9.9)
Multiple sclerosis	2 (0.9)	6 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Rheumatoid arthritis	13 (5.8)	80 (7.8)	6 (9.0)	16 (18.2)	18 (4.4)
Inflammatory bowel disease	5 (2.2)	108 (10.5)	6 (9.0)	10 (11.4)	10 (2.5)
Ankylosing spondylitis	3 (1.3)	4 (0.4)	0 (0.0)	1 (1.1)	0 (0.0)
Myasthenia gravis	2 (0.9)	5 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Sjögren's syndrome	7 (3.1)	40 (3.9)	0 (0.0)	0 (0.0)	16 (3.9)
Body mass index (BMI)					
Mean (SD)	26.8 (5.0)	27.7 (6.2)	24.4 (7.4)	34.9 (0.4)	27.4 (5.7)
>30	13 (22.8)	310 (32.1)	2 (16.7)	2 (100.0)	63 (30.6)
Concomitant therapies					
N. of different V ATC level (mean ± SD)	6.6 (5.3)	8.0 (6.8)	5.9 (5.4)	4.0 (3.7)	5.4 (4.7)

Table 11. Demographic and clinical characteristics of controls by country.

	IT CONTROLS N (%)	UK CONTROLS N (%)	BE CONTROLS N (%)	RO CONTROLS N (%)	ES CONTROLS N (%)
Overall	899	4,104	268	351	1,620
Sex					
Male	172 (19.1)	812 (19.8)	84 (31.3)	80 (22.8)	316 (19.5)
Female	727 (80.9)	3,292 (80.2)	184 (68.7)	271 (77.2)	1,304 (80.5)
Age, mean (SD)					
Mean (SD)	57.2 (15.8)	52.6 (18.6)	46.4 (15.0)	52.8 (14.5)	51.2 (15.1)
Age class					
18–29	48 (5.3)	524 (12.8)	32 (11.9)	24 (6.8)	124 (7.7)
30–39	56 (6.2)	664 (16.2)	64 (23.9)	40 (11.4)	232 (14.3)
40–49	184 (20.5)	712 (17.3)	64 (23.9)	75 (21.4)	406 (25.1)
50–59	216 (24.0)	688 (16.8)	44 (16.4)	96 (27.4)	400 (24.7)
60–69	180 (20.0)	584 (14.2)	48 (17.9)	68 (19.4)	262 (16.2)
70–79	140 (15.6)	572 (13.9)	12 (4.5)	40 (11.4)	140 (8.6)
80+	75 (8.3)	360 (8.8)	4 (1.5)	8 (2.3)	56 (3.5)
SLE symptoms (EULAR / ACR criteria)					
Present	4 (0.4)	8 (0.2)	0 (0.0)	0 (0.0)	9 (0.6)
Comorbidities					
Diabetes	10 (1.1)	32 (0.8)	2 (0.7)	12 (3.4)	43 (2.7)
Chronic kidney disease	0 (0.0)	3 (0.1)	0 (0.0)	1 (0.3)	5 (0.3)
Cardiovascular disease	6 (0.7)	31 (0.8)	3 (1.1)	27 (7.7)	30 (1.9)
Cerebrovascular accident	1 (0.1)	8 (0.2)	0 (0.0)	2 (0.6)	2 (0.1)
Hypertension	15 (1.7)	51 (1.2)	7 (2.6)	53 (15.1)	107 (6.6)
Dementia / Alzheimer's disease	1 (0.1)	12 (0.3)	0 (0.0)	1 (0.3)	7 (0.4)
Parkinson disease	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Mood and anxiety disorders	8 (0.9)	82 (2.0)	6 (2.2)	20 (5.7)	169 (10.4)
Chronic hepatic disease	0 (0.0)	1 (0.0)	0 (0.0)	11 (3.1)	2 (0.1)
Osteoporosis	5 (0.6)	17 (0.4)	1 (0.4)	8 (2.3)	17 (1.0)
Malignancy	4 (0.4)	64 (1.6)	0 (0.0)	5 (1.4)	52 (3.2)
Chronic obstructive pulmonary disease	1 (0.1)	15 (0.4)	1 (0.4)	14 (4.0)	13 (0.8)
Concomitant autoimmune disease					
Any autoimmune disease	1 (0.1)	23 (0.6)	0 (0.0)	5 (1.4)	13 (0.8)
Multiple sclerosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid arthritis	1 (0.1)	3 (0.1)	0 (0.0)	1 (0.3)	3 (0.2)
Inflammatory bowel disease	0 (0.0)	20 (0.5)	0 (0.0)	4 (1.1)	7 (0.4)
Ankylosing spondylitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myasthenia gravis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sjögren's syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)
Body mass index (BMI)					
Mean (SD)	27.1 (5.0)	28.6 (6.9)	25.0 (5.8)	28.9 (9.1)	28.0 (5.8)
>30	7 (26.9)	49 (40.8)	0 (0.0)	3 (42.9)	71 (33.5)
Concomitant therapies					
N. of different V ATC level, mean (SD)	0.3 (1.4)	0.2 (1.2)	0.1 (0.9)	0.5 (1.6)	0.7 (2.1)

In multivariable models, the largest adjusted associations varied by country, but were generally consistent with the descriptive patterns.

In UK (Table S25), rheumatoid arthritis showed the largest effect (OR = 29.00, 95% CI 11.68–71.97), with additional strong associations for cardiovascular disease (OR = 8.87, 95% CI 6.08–12.95) and mood and anxiety disorders (OR = 8.00, 95% CI 6.25–10.25), and moderate associations for inflammatory bowel disease (OR = 6.02, 95% CI 3.57–10.14), malignancy (OR = 5.52, 95% CI 4.09–7.45), and hypertension (OR = 5.30, 95% CI 3.77–7.46).

In RO (Table S26), the main significant associations were cardiovascular disease (OR = 6.78, 95% CI 3.41–13.49) and diabetes (OR = 3.10, 95% CI 1.17–8.22), while other estimates were small or not statistically significant.

In ES (Table S27), the largest adjusted effects were mood and anxiety disorders (OR = 4.55, 95% CI 3.47–5.98) and osteoporosis (OR = 3.95, 95% CI 1.98–7.86), with smaller but significant associations for malignancy (OR = 2.61, 95% CI 1.66–4.08) and cardiovascular disease (OR = 2.55, 95% CI 1.41–4.60).

In BE (Table S28), despite the small number, mood and anxiety disorders showed a very strong association (OR = 38.88, 95% CI 14.68–102.98), and hypertension remained strong (OR = 8.83, 95% CI 2.88–27.04).

A summary of multivariable logistic regression analyses by country is shown in Table 12.

Table 12. Summary of multivariable logistic regression analyses of the association between SLE (the comparators are the non-SLE patients) and selected characteristics by country.

Country	Characteristic	Adjusted OR (95% CI)
IT		
	Diabetes	1.41 (0.42–4.77)
	Cardiovascular disease	8.13 (2.83–23.32)
	Hypertension	12.22 (6.39–23.38)
	Mood and anxiety disorders	6.30 (2.44–16.31)
	Osteoporosis	17.96 (6.41–50.29)
	Chronic obstructive pulmonary disease	1.41 (0.42–4.77)
UK		
	Diabetes	0.78 (0.47–1.29)
	Cardiovascular disease	8.87 (6.08–12.95)
	Cerebrovascular accident	1.13 (0.44–2.87)
	Hypertension	5.30 (3.77–7.46)
	Mood and anxiety disorders	8.00 (6.25–10.25)
	Osteoporosis	2.30 (1.18–4.48)
	Malignancy	5.52 (4.09–7.45)
	Chronic obstructive pulmonary disease	3.07 (1.77–5.31)
	Rheumatoid arthritis	29.00 (11.68–71.97)
	Inflammatory bowel disease	6.02 (3.57–10.14)
BE		
	Hypertension	8.83 (2.88–27.04)
	Mood and anxiety disorders	38.88 (14.68–102.98)
RO		
	Diabetes	3.10 (1.17–8.22)
	Cardiovascular disease	6.78 (3.41–13.49)
	Hypertension	1.94 (1.00–3.76)
	Mood and anxiety disorders	1.63 (0.71–3.78)
	Chronic hepatic disease	2.22 (0.82–6.02)
ES		
	Diabetes	1.14 (0.63–2.06)
	Cardiovascular disease	2.55 (1.41–4.60)
	Hypertension	1.54 (1.05–2.25)
	Mood and anxiety disorders	4.55 (3.47–5.98)
	Osteoporosis	3.95 (1.98–7.86)
	Malignancy	2.61 (1.66–4.08)
	Chronic obstructive pulmonary disease	1.61 (0.65–3.96)

4.3 Treatment patterns

To assess whether restricting the analyses to patients with at least 24 months of follow-up could have introduced selection bias, we compared demographic and clinical characteristics of all incident SLE cases with those of patients retained after the follow-up restriction. This comparison showed that the two populations were largely comparable across sociodemographic and clinical variables (Table 13).

In the pooled cohort, the use of treatment increased markedly in ID, with "any treatment" reaching approximately 50% and then settling around 40%; HCQ was the most common class in index (approximately 30%) and remained the leading therapy through follow-up, immunomodulators / immunosuppressants were around 10% with a mild post-index increase, glucocorticoids and NSAIDs stayed lower at approximately 5% (Figure 12).

IT showed the same hierarchy with slightly higher levels, as "any treatment" remained around 60% at ID and HCQ consistently was the top class near 35%, followed by immunomodulators, glucocorticoids and NSAIDs around 10% (Figure S1).

The UK mirrored the pooled pattern: a rise at ID and stabilization around 40% overall during the two-year period, HCQ as the leading drug class near 25%, immunomodulators around 10%, and limited use of glucocorticoids and NSAIDs (Figure S2).

BE was the outlier, with very volatile curves driven by small numbers, a sharp increase for "any treatment" and HCQ at ID and a marked drop at six months (Figure S3).

ES also aligned with the pooled profile, with "any treatment" stabilizing around 35–40% during the period, HCQ the most used class near 20–25%, immunomodulators and NSAIDs next around 10% (Figure S4).

RO followed the same overall order: "any treatment" reached about 40% in ID, HCQ was the leading class around 25%, followed by NSAIDs and immunomodulators, around 5 and 12% at the end of the period (Figure S5).

Table 13. Demographic and clinical characteristics of all incident SLE cases versus those with ≥24 months of follow-up.

Characteristic	All SLE cases N (%)	SLE cases ≥24m FU N (%)	Crude *P*-value
Overall, *n*	1,812	1,463	
Sex			
Male	366 (20.2)	267 (18.3)	< 0.0001
Female	1,446 (79.8)	1,196 (81.7)	
Age, mean (SD)	52.6 (17.3)	51.6 (16.7)	< 0.0001
Age class			
18–29	188 (10.4)	152 (10.4)	< 0.0001
30–39	264 (14.6)	230 (15.7)	
40–49	361 (19.9)	300 (20.5)	
50–59	361 (19.9)	299 (20.4)	
60–69	286 (15.8)	237 (16.2)	
70–79	226 (12.5)	166 (11.3)	
80+	126 (7.0)	79 (5.4)	
Geographical area			
BE	67 (3.7)	44 (3.0)	< 0.0001
ES	406 (22.4)	391 (26.7)	
IT	225 (12.4)	127 (8.7)	
RO	88 (4.9)	69 (4.7)	
UK	1,026 (56.6)	832 (56.9)	
SLE symptoms (EULAR / ACR criteria)			
Any symptom	523 (28.9)	407 (27.8)	0.0447
Comorbidities			
Diabetes	173 (9.5)	136 (9.3)	0.4557
Chronic kidney disease	29 (1.6)	16 (1.1)	0.0004
Cardiovascular disease	354 (19.5)	266 (18.2)	0.0029
Cerebrovascular accident	39 (2.2)	27 (1.8)	0.0654
Hypertension	489 (27.0)	375 (25.6)	0.0078
Dementia / Alzheimer's disease	17 (0.9)	9 (0.6)	0.0084
Parkinson disease	11 (0.6)	5 (0.3)	0.0094
Mood and anxiety disorders	653 (36.0)	542 (37.0)	0.0668
Chronic hepatic disease	49 (2.7)	37 (2.5)	0.3467
Osteoporosis	143 (7.9)	112 (7.7)	0.4449
Malignancy	397 (21.9)	326 (22.3)	0.4313
COPD	141 (7.8)	103 (7.0)	0.0159
Concomitant autoimmune disease	319 (17.6)	260 (17.8)	0.7026
Multiple sclerosis	9 (0.5)	9 (0.6)	0.2208
Rheumatoid arthritis	133 (7.3)	106 (7.2)	0.7520
Inflammatory bowel disease	139 (7.7)	115 (7.9)	0.5349
Ankylosing spondylitis	8 (0.4)	3 (0.2)	0.0087
Myasthenia gravis	8 (0.4)	5 (0.3)	0.1866
Sjogren's syndrome	63 (3.5)	52 (3.6)	0.7123
Body mass index, mean (SD)	27.6 (6.1)	27.7 (6.1)	0.1282
>30	390 (31.4)	334 (32.2)	0.1315
Concomitant therapies			
N. of different ATC level, mean (SD)	7.0 (6.2)	6.8 (6.0)	0.0133

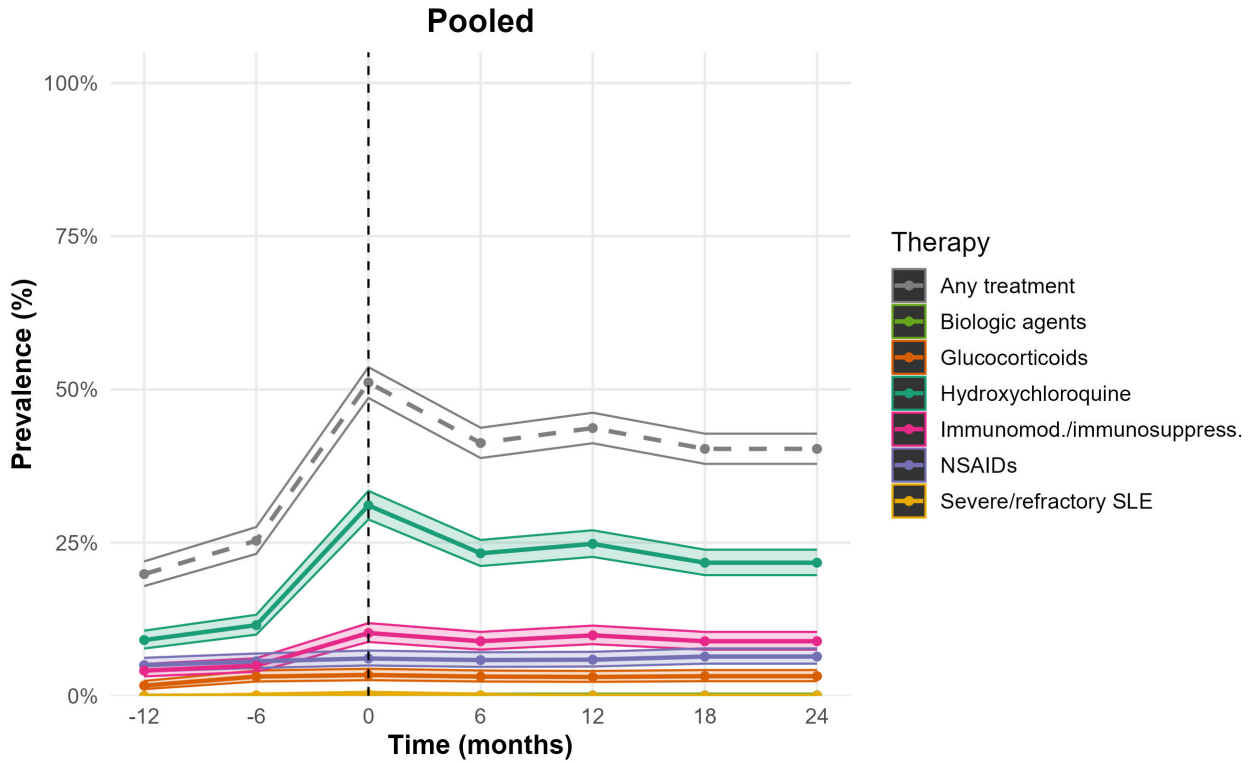

Figure 12. Prevalence of treatment classes - Pooled Prevalence of treatment classes from 12 months before and 24 months after ID in the Pooled cohort. The lines represent the estimates, and the bands indicate the 95% confidence intervals; the vertical dashed line marks ID.

In the pooled cohort, flows confirmed that treatment use was concentrated in a few classes: a large share remained untreated throughout, while HCQ formed the dominant treated stream from the index onward and showed high persistence; most switching occurred between the index and 6 months, mainly from HCQ into untreated and, to a lesser extent, into immunomodulators or NSAIDs; after 6 months, the ribbons narrowed and the trajectories stabilized, glucocorticoids persisted at low levels with limited inflow and outflow (Figure 13).

IT mirrored this structure, but with a higher prevalence of general treatments and a visible increase in the use of glucocorticoids that remained present over time (Figure S6).

The UK looked very close to the pooled patterns, with early movement from untreated to HCQ and modest flows to immunomodulators, then a broadly stable class membership for 24 months (Figure S7).

BE departed the most: the untreated band dominated, and after the first 6 months there was a huge flow from HCQ to untreated. In addition, the NSAIDs class completely disappeared after the first semester, and the immunomoulators users were half-full. At the end of the period, almost all HCQ users have become untreated (Figure S8).

ES aligned with the pooled figure, with clear early initiation in HCQ and steady persistence after a drop in the second semester (Figure S9).

RO showed the same hierarchy, but with a noticeable late drift from untreated to NSAIDs (Figure S10).

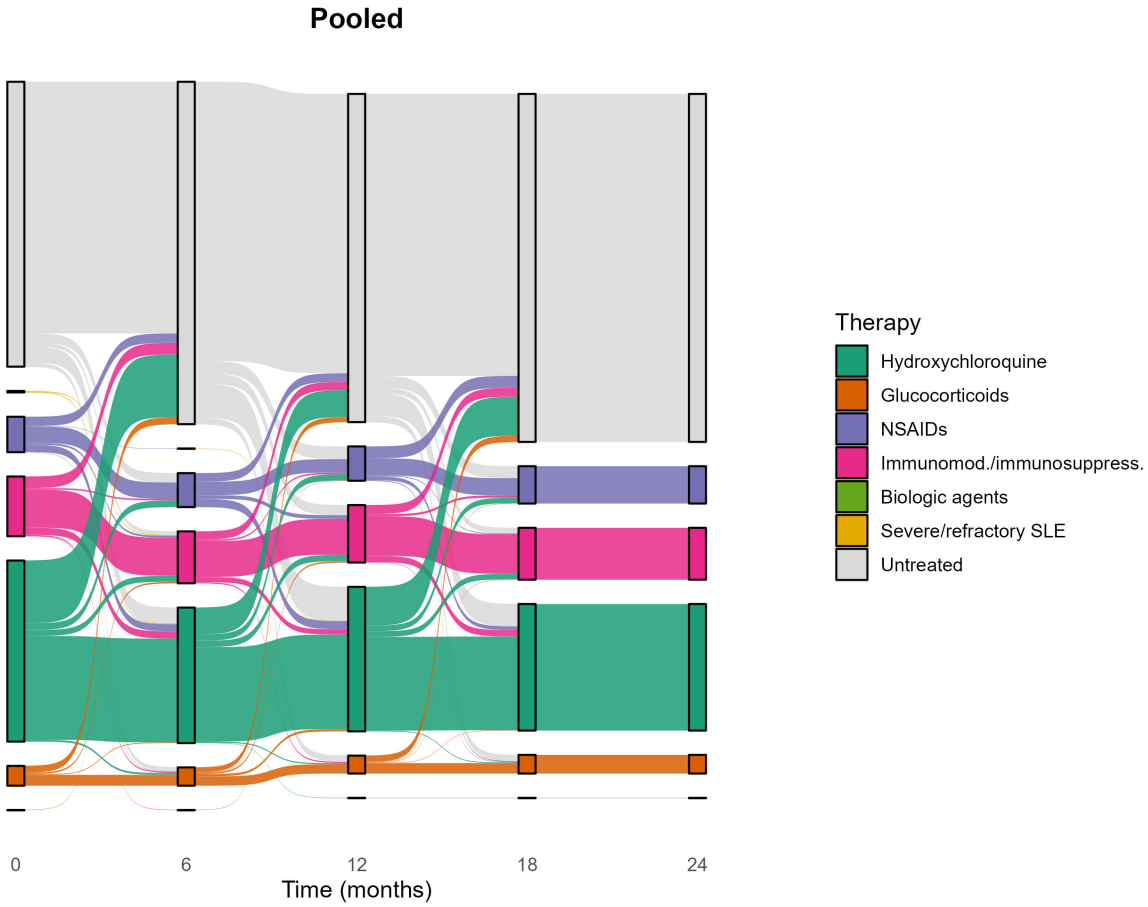

Figure 13. Sankey plot of treatment classes utilization - Pooled Sankey diagram of treatment class utilization in the Pooled cohort from index to 24 months. Each node represents a time point (0, 6, 12, 18, 24 months); link widths are proportional to the number of patients transitioning between classes, including 'Untreated.

4.3.1 Characterization of treated patients

Treated patients were more frequently women, accounting for 84.7% of the treated group compared with 76.7% among untreated patients, and were slightly younger on average (mean age 50.8 vs 52.9 years). Age-class distributions were broadly similar, although untreated patients were relatively more represented in the oldest age strata.

Baseline clinical presentation differed between the two groups. Untreated patients more often displayed EULAR / ACR SLE manifestations at diagnosis, with any symptom recorded in 34.8% compared with 23.7% of treated patients. Neuropsychiatric involvement was particularly more common among untreated individuals (16.3% vs 8.6%), driven mainly by seizures, which occurred in 10.7% of untreated patients versus 5.4% of those treated. These differences remained evident after accounting for demographic and clinical covariates, suggesting a clinically meaningful imbalance in baseline neurological severity between groups.

In contrast, most non-neurological comorbidities were similarly distributed between treated and untreated patients after adjustment. A notable exception was rheumatoid arthritis, which was more prevalent among treated patients (8.6%) than among untreated patients (5.0%), and this difference that persisted after multivariable adjustment. Other autoimmune conditions showed smaller absolute differences that were largely attenuated after adjustment.

As expected, pharmacological complexity was substantially greater among treated patients. The mean number of distinct ATC classes was 7.5 in treated individuals compared with 5.5 among untreated patients, reflecting both treatment indication and a higher overall disease and healthcare burden.

Geographical patterns were broadly consistent across countries. Treatment at 24 months was relatively more frequent in Italy (9.9% of treated vs 6.7% of untreated cases), a difference that remained after adjustment, while no marked imbalance in treatment prevalence was observed for the UK, Romania, or Spain once covariates were taken into account (Table 14).

When examining country-specific results, these patterns were largely consistent, with some heterogeneity driven by sample size and local clinical profiles.

In Italy (Table S29), treated and untreated patients had comparable age and sex distributions. Untreated patients more frequently presented SLE manifestations at baseline, particularly mucocutaneous involvement (22.2% vs 3.3%) and any recorded SLE symptom (36.1% vs 15.4%). Treated patients, instead, had a higher baseline medication burden (mean 6.7 vs 3.9 ATC classes).

In the UK (Table S30), untreated patients again showed a greater baseline disease burden, especially neuropsychiatric manifestations (21.8% vs 10.5%) and seizures (14.2% vs 7.2%). Treated patients more frequently had rheumatoid arthritis (9.3% vs 5.7%), slightly higher body mass index (mean 28.2 vs 27.3), and a higher number of concomitant medications (8.4 vs 6.8 ATC classes).

In Belgium (Table S31), the small number of patients limited the identification of clear differences between groups. Overall, treated and untreated patients showed broadly similar demographic and clinical profiles, with no consistent pattern emerging across disease manifestations or comorbidities.

In Romania (Table S32), treated and untreated patients were generally comparable in terms of demographic characteristics and SLE manifestations. However, rheumatoid arthritis was more common among treated patients (26.3% vs 6.5%), and treated patients also had a higher medication burden (mean 5.4 vs 3.0 ATC classes).

In Spain (Table S33), treated patients more frequently had concomitant autoimmune disease overall (13.2% vs 3.7%), with Sjögren's syndrome notably more common among treated patients (5.8% vs 0.7%). As observed in other countries, treated patients also received more concomitant therapies (mean 6.3 vs 3.4 ATC classes).

Overall, two years after diagnosis, treatment was more common among women and patients with a higher baseline medication burden and concomitant autoimmune disease, particularly rheumatoid arthritis. Conversely, untreated patients more often presented neuropsychiatric manifestations at baseline, suggesting that early disease severity and clinical presentation may influence long-term treatment patterns. These findings were broadly consistent across countries, with minor variations largely attributable to differences in sample size and local clinical profiles.

Among treated patients at 24 months after diagnosis, relevant heterogeneity emerged across countries in terms of demographic profile, baseline disease manifestations, and comorbidity burden (Table 15).

Treated patients were predominantly female in all countries, with proportions ranging from approximately 83–88% in IT, UK, RO, and ES, while BE showed a comparatively lower female predominance (71%). Mean age differed across countries, with treated patients being youngest in BE (mean 43.8 years), while IT, UK, RO, and ES showed largely comparable age distributions.

Baseline SLE manifestations varied markedly by country. The proportion of treated patients with any recorded SLE symptom ranged from 0% in RO to over 30% in the UK, with intermediate values observed in BE (23.8%), IT (15.4%), and ES (15.2%). Neuropsychiatric involvement was particularly frequent among treated patients in BE (19.0%) and the UK (10.5%), whereas it was absent in RO and less common in IT and ES (5–6%). Similarly, mucocutaneous manifestations were most prevalent in the UK (11.8%), absent in RO, and less common in IT, BE and ES (3–6%).

Substantial between-country differences were also observed in comorbidity profiles. Cardiovascular disease was especially frequent among treated patients in RO, affecting more than half of patients (60.5%), compared with much lower proportions in IT (8.8%), ES (8.2%), and BE (4.8%). Hypertension followed a similar pattern, with the highest prevalence in RO (57.9%) and BE (28.6%), compared with approximately 20–23% in IT, UK, and ES. Mood and anxiety disorders showed wide variability, ranging from 5.5% in IT to over 40% in the UK and ES, and reaching 66.7% in BE.

Concomitant autoimmune diseases were common among treated patients across all countries but with notable heterogeneity. Overall prevalence ranged from 13.2% in IT and ES to 36.8% in RO. Rheumatoid arthritis was particularly frequent among treated patients in RO (26.3%) and BE (19.0%), compared with lower proportions in IT (4.4%) and ES (5.1%). Sjögren's syndrome was most frequently observed in ES (5.8%) and the UK (4.5%), while it was absent in BE and RO.

Table 14. Demographic and clinical characteristics of incident SLE cases treated and untreated at 24 months after ID — Pooled.

Characteristic	Treated N (%)	Untreated N (%)	Crude *P*-value	Adjusted *P*-value^
Overall, *n*	923	540		
Sex				
Male	141 (15.3)	126 (23.3)		
Female	782 (84.7)	414 (76.7)	0.0001	0.0029
Age, mean (SD)	50.8 (16.2)	52.9 (17.4)	0.0218	
Age class				
18–29	96 (10.4)	56 (10.4)	0.0007	
30–39	149 (16.1)	81 (15.0)		
40–49	199 (21.6)	101 (18.7)		
50–59	181 (19.6)	118 (21.9)		
60–69	167 (18.1)	70 (13.0)		
70–79	97 (10.5)	69 (12.8)		
80+	34 (3.7)	45 (8.3)		
Geographical area				
IT	91 (9.9)	36 (6.7)	0.0047	0.0242
UK	516 (55.9)	316 (58.5)	0.0609	0.1223
BE	21 (2.3)	23 (4.3)		
GE	–	–		
RO	38 (4.1)	31 (5.7)	0.4464	0.7588
ES	257 (27.8)	134 (24.8)	0.0204	0.0899
SLE symptoms (EULAR / ACR criteria)				
Any symptom	219 (23.7)	188 (34.8)	< 0.0001	
Hematologic	51 (5.5)	38 (7.0)	0.2431	
Leukopenia	19 (2.1)	11 (2.0)	0.9777	
Thrombocytopenia	30 (3.3)	26 (4.8)	0.1323	
Autoimmune hemolysis	2 (0.2)	3 (0.6)	0.3648	
Neuropsychiatric	79 (8.6)	88 (16.3)	< 0.0001	
Delirium	7 (0.8)	5 (0.9)	0.7685	
Psychosis	29 (3.1)	28 (5.2)	0.0513	0.3287
Seizure	50 (5.4)	58 (10.7)	0.0002	0.0032
Mucocutaneous	81 (8.8)	66 (12.2)	0.0343	
Non-scarring alopecia	78 (8.5)	62 (11.5)	0.0572	0.1244
Oral ulcers	3 (0.3)	4 (0.7)	0.4341	
Serosal	59 (6.4)	43 (8.0)	0.2549	
Pleural & pericardial effusion	46 (5.0)	36 (6.7)	0.1769	
Acute pericarditis	15 (1.6)	8 (1.5)	0.8312	
Comorbidities				
Diabetes	75 (8.1)	61 (11.3)	0.0439	0.5736
Chronic kidney disease	13 (1.4)	3 (0.6)	0.1301	
Cardiovascular disease	153 (16.6)	113 (20.9)	0.0374	0.3901
Cerebrovascular accident	13 (1.4)	14 (2.6)	0.1044	
Hypertension	221 (23.9)	154 (28.5)	0.0531	0.5361
Dementia / Alzheimer's disease	4 (0.4)	5 (0.9)	0.3034	
Parkinson disease	2 (0.2)	3 (0.6)	0.3648	
Mood and anxiety disorders	350 (37.9)	192 (35.6)	0.3662	
Chronic hepatic disease	23 (2.5)	14 (2.6)	0.9057	
Osteoporosis	72 (7.8)	40 (7.4)	0.7849	
Malignancy	192 (20.8)	134 (24.8)	0.0751	0.2025
COPD	54 (5.9)	49 (9.1)	0.0200	0.6878
Concomitant autoimmune disease	189 (20.5)	71 (13.1)	0.0004	
Multiple sclerosis	8 (0.9)	1 (0.2)	0.1667	
Rheumatoid arthritis	79 (8.6)	27 (5.0)	0.0113	0.0037
Inflammatory bowel disease	79 (8.6)	36 (6.7)	0.1943	
Ankylosing spondylitis	0 (0.0)	3 (0.6)	0.0501	
Myasthenia gravis	3 (0.3)	2 (0.4)	0.8860	
Sjogren's syndrome	41 (4.4)	11 (2.0)	0.0165	0.0652
Body mass index, mean (SD)	28.0 (6.1)	27.2 (5.9)	0.0211	
>30	181 (34.8)	94 (29.5)	0.0590	
Concomitant therapies				
N. of different ATC level, mean (SD)	7.5 (5.9)	5.5 (5.9)	< 0.0001	

^ Adjusted by sex, geographical area, psychosis, seizure, non-scarring alopecia, diabetes, cardiovascular disease, hypertension, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis, Sjogren's syndrome.

Table 15. Demographic and clinical characteristics of incident SLE cases treated at 24 months after ID by country.

	IT Treated N (%)	UK Treated N (%)	BE Treated N (%)	RO Treated N (%)	ES Treated N (%)
Overall, *n*	91	516	21	38	257
Sex					
Male	11 (12.1)	76 (14.7)	6 (28.6)	5 (13.2)	43 (16.7)
Female	80 (87.9)	440 (85.3)	15 (71.4)	33 (86.8)	214 (83.3)
Age					
Mean (SD)	53.9 (14.6)	50.3 (17.3)	43.8 (14.7)	52.7 (13.8)	51.0 (14.6)
18–29	4 (4.4)	66 (12.8)	3 (14.3)	3 (7.9)	20 (7.8)
30–39	8 (8.8)	94 (18.2)	7 (33.3)	4 (10.5)	36 (14.0)
40–49	26 (28.6)	98 (19.0)	3 (14.3)	5 (13.2)	67 (26.1)
50–59	18 (19.8)	89 (17.2)	4 (19.0)	14 (36.8)	56 (21.8)
60–69	23 (25.3)	82 (15.9)	3 (14.3)	8 (21.1)	51 (19.8)
70–79	8 (8.8)	64 (12.4)	1 (4.8)	3 (7.9)	21 (8.2)
80+	4 (4.4)	23 (4.5)	0 (0.0)	1 (2.6)	6 (2.3)
SLE symptoms (EULAR / ACR)					
Any symptom	14 (15.4)	161 (31.2)	5 (23.8)	0 (0.0)	39 (15.2)
Hematologic	8 (8.8)	33 (6.4)	0 (0.0)	0 (0.0)	10 (3.9)
Leukopenia	2 (2.2)	12 (2.3)	0 (0.0)	0 (0.0)	5 (1.9)
Thrombocytopenia	6 (6.6)	19 (3.7)	0 (0.0)	0 (0.0)	5 (1.9)
Autoimmune hemolysis	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropsychiatric	5 (5.5)	54 (10.5)	4 (19.0)	0 (0.0)	16 (6.2)
Delirium	0 (0.0)	7 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychosis	3 (3.3)	16 (3.1)	3 (14.3)	0 (0.0)	7 (2.7)
Seizure	2 (2.2)	37 (7.2)	2 (9.5)	0 (0.0)	9 (3.5)
Mucocutaneous	3 (3.3)	61 (11.8)	1 (4.8)	0 (0.0)	16 (6.2)
Non-scarring alopecia	2 (2.2)	61 (11.8)	1 (4.8)	0 (0.0)	14 (5.4)
Oral ulcers	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Serosal	2 (2.2)	50 (9.7)	3 (14.3)	0 (0.0)	4 (1.6)
Pleural & pericardial effusion	2 (2.2)	44 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)
Acute pericarditis	0 (0.0)	8 (1.6)	3 (14.3)	0 (0.0)	4 (1.6)
Comorbidities					
Diabetes	3 (3.3)	47 (9.1)	3 (14.3)	5 (13.2)	17 (6.6)
Chronic kidney disease	1 (1.1)	6 (1.2)	0 (0.0)	0 (0.0)	6 (2.3)
Cardiovascular disease	8 (8.8)	100 (19.4)	1 (4.8)	23 (60.5)	21 (8.2)
Cerebrovascular accident	3 (3.3)	7 (1.4)	0 (0.0)	1 (2.6)	2 (0.8)
Hypertension	18 (19.8)	119 (23.1)	6 (28.6)	22 (57.9)	56 (21.8)
Dementia / Alzheimer's disease	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	3 (1.2)
Parkinson disease	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)
Mood and anxiety disorders	5 (5.5)	210 (40.7)	14 (66.7)	10 (26.3)	111 (43.2)
Chronic hepatic disease	1 (1.1)	12 (2.3)	0 (0.0)	7 (18.4)	3 (1.2)
Osteoporosis	10 (11.0)	29 (5.6)	3 (14.3)	10 (26.3)	20 (7.8)
Malignancy	15 (16.5)	129 (25.0)	4 (19.0)	8 (21.1)	36 (14.0)
COPD	3 (3.3)	34 (6.6)	3 (14.3)	7 (18.4)	7 (2.7)
Concomitant autoimmune disease					
Any	12 (13.2)	124 (24.0)	5 (23.8)	14 (36.8)	34 (13.2)
Multiple sclerosis	2 (2.2)	5 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)
Rheumatoid arthritis	4 (4.4)	48 (9.3)	4 (19.0)	10 (26.3)	13 (5.1)
Inflammatory bowel disease	3 (3.3)	60 (11.6)	2 (9.5)	5 (13.2)	9 (3.5)
Ankylosing spondylitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myasthenia gravis	1 (1.1)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)
Sjögren's syndrome	3 (3.3)	23 (4.5)	0 (0.0)	0 (0.0)	15 (5.8)
Body mass index					
Mean (SD)	27.6 (5.1)	28.2 (6.3)	22.6 (3.9)	NA	27.6 (5.7)
>30	8 (27.6)	172 (35.2)	0 (0.0)	NA	40 (29.9)
Concomitant therapies					
N. of different ATC level, mean (SD)	6.7 (4.7)	8.4 (6.6)	7.5 (5.6)	5.4 (3.1)	6.3 (4.7)

4.3.2 Determinants of treatment

In the pooled analysis (Table 16), being treated at 24 months was more likely in females than in males (adjusted OR = 1.53, 95% CI 1.16–2.03) and in IT compared to BE (OR = 2.31, 95% CI 1.12–4.78), while other regions did not differ clearly after adjustment. Baseline neuropsychiatric involvement was linked to a lower probability of treatment, with seizures showing a robust inverse association (OR = 0.54, 95% CI 0.36–0.81) and psychosis not clearly significant (OR = 0.76, 95% CI 0.43–1.32). Among comorbidities, rheumatoid arthritis remained significantly associated with treatment (OR = 2.02, 95% CI 1.26–3.24) in the adjusted model, while diabetes, hypertension, malignancy, COPD and BMI over 30 did not.

By country, IT (Table S34) did not show adjusted associations that reached significance, with wide intervals. In UK (Table S35), rheumatoid arthritis predicted treatment (OR = 1.84, 95% CI 1.03–3.29) and seizures were again inversely associated (OR = 0.52, 95% CI 0.32–0.83), while sex, age and major comorbidities were not significant in the adjusted model. BE (Table S36) did not yield significant or estimable adjusted effects, probably due to the small number. In RO (Table S37), rheumatoid arthritis strongly predicted treatment (OR = 5.18, 95% CI 1.04–25.77), without other clear associations. In ES (Table S38), Sjogren's syndrome was the only significant predictor (OR = 8.24, 95% CI 1.08–63.10). A summary of multivariable logistic regression analyses of the association between SLE treatment and selected characteristics by country is shown in Table 17.

Table 16. Crude and multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics — Pooled.

Characteristic	Crude OR (95% CI)	Adjusted OR[a](95% CI)
Sex		
Female (Ref.: Male)	1.69 (1.29–2.21)	1.53 (1.16–2.03)
Age class		
>50 (Ref.: <50)	0.85 (0.69–1.05)	
Geographical area		
IT	2.77 (1.37–5.61)	2.31 (1.12–4.78)
UK	1.79 (0.97–3.28)	1.64 (0.88–3.08)
BE	Ref	Ref
RO	1.34 (0.63–2.87)	1.13 (0.51–2.49)
ES	2.10 (1.12–3.93)	1.75 (0.92–3.35)
SLE symptoms (EULAR / ACR criteria)		
Any symptom	0.58 (0.46–0.74)	
Hematologic	0.77 (0.50–1.19)	
Leukopenia	1.01 (0.48–2.14)	
Thrombocytopenia	0.66 (0.39–1.14)	
Autoimmune hemolysis	0.39 (0.06–2.33)	
Neuropsychiatric	0.48 (0.35–0.67)	
Delirium	0.82 (0.26–2.59)	
Psychosis	0.59 (0.35–1.01)	0.76 (0.43–1.32)
Seizure	0.48 (0.32–0.71)	0.54 (0.36–0.81)
Mucocutaneous	0.69 (0.49–0.97)	
Non-scarring alopecia	0.71 (0.50–1.01)	0.75 (0.52–1.08)
Oral ulcers	0.44 (0.10–1.96)	
Serosal	0.79 (0.52–1.19)	
Pleural & pericardial effusion	0.73 (0.47–1.15)	
Acute pericarditis	1.10 (0.46–2.61)	
Comorbidities		
Diabetes	0.69 (0.49–0.99)	0.89 (0.60–1.32)
Chronic kidney disease	2.56 (0.73–9.01)	
Cardiovascular disease	0.75 (0.57–0.98)	0.88 (0.65-1.18)
Cerebrovascular accident	0.54 (0.25–1.15)	
Hypertension	0.79 (0.62–1.00)	0.92 (0.70–1.20)
Dementia / Alzheimer's disease	0.47 (0.12–1.74)	
Parkinson disease	0.39 (0.06–2.33)	
Mood and anxiety disorders	1.11 (0.89–1.38)	
Chronic hepatic disease	0.96 (0.49–1.88)	
Osteoporosis	1.06 (0.71–1.58)	
Malignancy	0.80 (0.62–1.02)	0.84 (0.65–1.10)
COPD	0.62 (0.42–0.93)	0.91 (0.59–1.42)
Concomitant autoimmune disease		
Multiple sclerosis	4.71 (0.59–37.78)	
Rheumatoid arthritis	1.78 (1.13–2.79)	2.02 (1.26–3.24)
Inflammatory bowel disease	1.31 (0.87–1.97)	
Ankylosing spondylitis	NE	
Myasthenia gravis	0.88 (0.15–5.27)	
Sjögren's syndrome	2.24 (1.14–4.39)	1.91 (0.96–3.82)
Body mass index >30	1.22 (0.92–1.60)	

[a] Adjusted by sex, geographical area, psychosis, seizure, non-scarring alopecia, diabetes, cardiovascular disease, hypertension, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis, Sjögren's syndrome.

Table 17. Summary of multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics by country.

Characteristic	Adjusted OR (95% CI)
IT	
Non-scarring alopecia	0.20 (0.03–1.23)
Oral ulcers	0.18 (0.01–2.20)
Mood and anxiety disorders	0.49 (0.11–2.10)
Malignancy	0.54 (0.21–1.42)
UK	
Female (Ref.: Male)	1.40 (0.96–2.05)
Thrombocytopenia	0.62 (0.32–1.23)
Psychosis	0.51 (0.26–1.01)
Seizure	0.52 (0.32–0.83)
Cardiovascular disease	0.85 (0.59–1.22)
Cerebrovascular accident	0.51 (0.19–1.38)
Hypertension	0.85 (0.60–1.19)
Malignancy	0.79 (0.57–1.08)
COPD	0.91 (0.53–1.57)
Rheumatoid arthritis	1.84 (1.03–3.29)
BE	
None	
RO	
None	
ES	
None	

Chapter 5

Conclusions

5.1 Epidemiology of SLE

Our multi-country analyses provide an updated and internally consistent picture of adult SLE epidemiology in Europe based on primary-care THIN EHRs in 2017-2022.

Standardized incidence and prevalence levels and trends largely reproduce the known contours of SLE epidemiology such as higher rates in women (roughly three to six times men), mid-life peaks with a slightly later peak in men, and clear differences between countries, while also clarifying how the organization of the healthcare-system and the maturity of the data-sources shape what we observe[27–30].

In the UK, our stable incidence near 5 per 100,000 PY and high prevalence align closely with previous CPRD estimates, supporting the validity of primary-care surveillance in a gatekeeping context[32]. In ES, the prevalence by 2022 (≈58 per 100,000) is below the EPISER2016 adult survey (≈210 per 100,000 $\geq$ 20 years), as expected given the youth database and the fact that population surveys and GP EHRs capture different universes and apply different case definitions; after an early artifact consistent with a "young" database, the incidence stabilized around 9–10 per 100,000 PY, well within European ranges[28, 31]. In IT, national THIN® estimates, mid-range for Europe, exceed older regional / administrative figures (e.g., Veneto incidence 2.8 and prevalence 70.6 per 100,000), plausibly reflecting better primary-care capture of non-hospital diagnoses together with our diagnostic-laboratory-pharmacological algorithm[36, 40, 63]. For BE and RO, lower values are compatible with published model-based intervals and with THIN® coverage / coding differences in these settings[39].

Where our series deviates from national reports, the gaps are explainable by data-generation processes rather than biology: database maturity (e.g. ES' inflated early rates), limited historical depth (e.g. GE, which therefore contributed only prevalence), and differential linkage to specialist / hospital data in systems with weaker gatekeeping. The' sharp increase in incidence IT in 2021 and the subsequent partial normalization are directionally consistent with contemporaneous changes in classification and care pathways (2019 EULAR / ACR criteria) and pandemic-related diagnostic perturbations[8, 63].

Against this epidemiological context, newly diagnosed SLE cases exhibited substantial comorbidity and treatment burden at baseline compared to 4:1 matched controls, with consistent excesses in cardiovascular disease, hypertension, mood and anxiety disorders, osteoporosis, malignancy, and concomitant autoimmune diagnoses (notably rheumatoid arthritis and inflammatory bowel disease).

This cross-country reproducibility indicates that SLE commonly emerges in contexts of multimorbidity and

polypharmacy, reinforcing the need for integrated early treatment, such as modification of cardiovascular risk, systematic evaluation of bone-health, screening for co-autoimmunity, and medication reconciliation to limit interactions and cumulative corticosteroid exposure, along with disease-directed therapy[9, 63].

The concordance of sex / age gradients with prior literature, the alignment of UK rates with CPRD benchmarks[32], and the expected positioning of Spanish and Italian estimates relative to survey-based and administrative studies collectively support the external credibility of THIN-based surveillance[28, 31, 36].

Methodologically, strengths include the multinational scope, harmonized case definition across countries, and the advantages of GP-based EHRs for population-based inference: capture of non-hospital diagnoses and prescriptions, referral / discharge information, and (where available) laboratory and vital-signs data[66, 69].

These features enable both robust rate estimation and pre-diagnostic characterization that are difficult to achieve with claims alone. Limitations are those intrinsic to real-world data: cross-country heterogeneity in coding and lab availability; residual misclassification given the absence of a broad external gold standard; database immaturity in some settings and, in IT, the lack of pediatric cases (hence the under-ascertainment of pediatric-onset SLE in this source); and the sensitivity / PPV trade-offs in EHR algorithms[40, 63]. Together, these imply that our prevalence is likely more conservative than survey-based estimates but more complete for non-hospital diagnoses than purely administrative sources, a pattern consistent with the literature[28, 31, 36].

Overall, THIN multi-country analyses place adult SLE incidence within the expected European range and document rising prevalence across health systems, likely reflecting improved survival and accumulation of recognized cases.

In this context, the operational priorities are to sustain longitudinal surveillance with shared definitions and adequate look-back, validate algorithms specifics for RWD to quantify sensitivity / PPV and, where gatekeeping is weak, strengthen linkage to hospital and laboratory networks. Clinically, earlier recognition and consistent background therapy (e.g. HCQ) remain plausible levers to reduce flares, damage accrual, and downstream use[32, 63].

5.2 Treatment patterns in SLE

In sum, our multi-country analyses portray a contemporary treatment landscape that is broadly aligned with guideline priorities, yet still marked by undertreatment and delayed uptake of steroid-sparing agents.

In all settings, pharmacotherapy increased sharply in ID and then stabilized, with "any treatment" settling around 40% in the pooled cohort and near 60% in IT; HCQ was the dominant class at diagnosis (≈20–35% by country) and remained the agent most widely used for 24 months, consistent with the universal use of antimalarial recommended by the 2019 EULAR / ACR guide[9].

The use of conventional immunomodulating / immunosuppressive agents hovered around 10% with only a modest post-ID improvement, while chronic glucocorticoid and NSAIDs exposure (defined strictly as prescriptions in ≥ 3 and ≥ 2 distinct months per semester, respectively) persisted at relatively low levels (5–10%), a pattern compatible with the practice of minimizing steroids but also with incomplete capture of short bursts in primary care.

The treatment flows visualized by the Sankey diagrams showed that most of the class changes occurred in the first six months after ID: a large stream started HCQ and persisted or returned to "untreated," with smaller transitions to immunosuppressants; after month six, the trajectories narrowed and stabilized, again highlighting HCQ persistence and limited long-term use of glucocorticoids.

The country contrasts were directionally consistent with these pooled features. The UK closely mirrored

the pooled series, while IT showed a higher overall exposure, including a visible larger and more sustained glucocorticoid component; ES converged rapidly to the pooled profile after an early, database-maturity phase; RO preserved the same hierarchy with a late drift from untreated to NSAIDs; BE was the notable outlier, with small denominators producing volatile curves and a marked early fall-off from HCQ to untreated.

The clinical correlates of treatment at 24 months reinforce the impression that uptake follows recognizable needs, but is also shaped by phenotype. The treated patients were more often women and slightly younger, and, after adjustment, co-diagnosed rheumatoid arthritis was strongly associated with treatment in the pooled cohort and in several countries, as did Sjögren's syndrome in ES; on the contrary, baseline neuropsychiatric features, especially seizures, were associated with lower odds of treatment, a finding that may reflect referral pathways to neurology, concern for drug interactions. The burden of medication at baseline was higher in those subsequently treated, consistent with the larger multimorbidity and polypharmacy profile observed in incident SLE[63].

These patterns are consistent with the 2019 EULAR / ACR steroid-sparing philosophy, with HCQ as a foundation, time-limited glucocorticoids and escalation to AZA, methotrexate or MMF and, where appropriate, biologics such as belimumab[9].

In claims-based studies from US, antimalarials are used in roughly half of patients, corticosteroids in approximately half to two-thirds, immunosuppressants in one-fifth to one-quarter, and biologics in a small minority, with Canadian inception data likewise documenting frequent early steroid exposure, typically alongside HCQ and / or immunosuppressants[22–26]. Against that benchmark, our primary-care estimates suggest better alignment with antimalarial anchoring and a comparatively restrained signal for chronic steroids, yet they also reveal sizeable untreated fractions and limited movement into immunosuppressive or biologic classes over two years.

Methodologically, two design choices help interpret these results. First, our hierarchy assigned patients exposed to multiple classes within a semester to the highest-intensity class, preventing double counting but biasing class shares toward the top of the ladder; second, chronic-use thresholds for glucocorticoids and NSAIDs likely filtered out short tapers and intermittent analgesia, lowering apparent exposure. Both choices are conservative with respect to steroid minimization and analgesic use and should be taken into account when comparing to claims studies that count any dispensing.

However, the core messages are robust: real-world care in European primary care settings remains anchored in HCQ, the escalation to steroid-sparing agents is measurable but modest, and a nontrivial share of incident patients does not receive qualifying pharmacotherapy over two years. These observations support the rationale for earlier, guideline-concordant treatment, particularly in patients with systemic or hematologic involvement, ensuring timely HCQ initiation, minimizing cumulative glucocorticoid dose, and deploying immunosuppressants or biologics where indicated.

Bibliography

[1] Muhammad Atif Ameer et al. "An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management". In: *Cureus* 14.10 (2022).

[2] G. K. Bertsias et al. "Diagnostic criteria for systemic lupus erythematosus: has the time come?" In: *Nature Reviews Rheumatology* 9.11 (2013), pp. 687–694. DOI: 10.1038/nrrheum.2013.103.

[3] Anisur Rahman and David A. Isenberg. "Systemic lupus erythematosus". In: *The New England Journal of Medicine* 358.9 (2008), pp. 929–939. DOI: 10.1056/NEJMra071297.

[4] Antonietta Fava and Michelle Petri. "Systemic lupus erythematosus: Diagnosis and clinical management". In: *Journal of Autoimmunity* 96 (2019), pp. 1–13. DOI: 10.1016/j.jaut.2018.11.001.

[5] J. Blomberg et al. "Increased antiretroviral antibody reactivity in sera from patients with SLE". In: *Arthritis and Rheumatism* 37.1 (1994), pp. 57–66. DOI: 10.1002/art.1780370109.

[6] George C. Tsokos et al. "New insights into the immunopathogenesis of systemic lupus erythematosus". In: *Nature Reviews Rheumatology* 12.12 (2016), pp. 716–730. DOI: 10.1038/nrrheum.2016.186.

[7] E. Generali et al. "Lessons learned from twins in autoimmune and chronic inflammatory diseases". In: *Journal of Autoimmunity* 83 (2017), pp. 51–61. DOI: 10.1016/j.jaut.2017.04.005.

[8] Martin Aringer et al. "2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus". In: *Arthritis & rheumatology* 71.9 (2019), pp. 1400–1412.

[9] Antonis Fanouriakis et al. "2019 update of the EULAR recommendations for the management of systemic lupus erythematosus". In: *Annals of the rheumatic diseases* 78.6 (2019), pp. 736–745.

[10] I. N. Bruce et al. "Factors associated with damage accrual in SLE: SLICC inception cohort". In: *Annals of the Rheumatic Diseases* 74.9 (2015), pp. 1706–1713. DOI: 10.1136/annrheumdis-2013-205171.

[11] H.-L. Chen et al. "Cumulative burden of glucocorticoid-related adverse events in SLE". In: *The Journal of Rheumatology* 45.1 (2018), pp. 83–89. DOI: 10.3899/jrheum.160214.

[12] L. S. H. Lim et al. "From Childhood to Adulthood: The Trajectory of Damage in Juvenile-Onset SLE". In: *Arthritis Care & Research* 69.11 (2017), pp. 1627–1635. DOI: 10.1002/acr.23199.

[13] C. S. Yee et al. "Birmingham SLE cohort: outcomes of a large inception cohort". In: *Rheumatology (Oxford)* 54.5 (2015), pp. 836–843. DOI: 10.1093/rheumatology/keu412.

[14] G. Ruiz-Irastorza et al. "Clinical efficacy and side effects of antimalarials in SLE: a systematic review". In: *Annals of the Rheumatic Diseases* 69.1 (2010), pp. 20–28. DOI: 10.1136/ard.2008.101766.

[15] J. M. Pego-Reigosa et al. "Efficacy and safety of nonbiologic immunosuppressants in nonrenal SLE: a systematic review". In: *Arthritis Care & Research* 65.11 (2013), pp. 1775–1785. DOI: 10.1002/acr.22035.

[16] J. H. Knight et al. “Reproductive characteristics in women with SLE: GOAL study”. In: *Lupus Science & Medicine* 3.1 (2016), e000139. DOI: 10.1136/lupus-2015-000139.

[17] C. C. Mok, P. T. Chan, and C. H. To. “Anti-müllerian hormone and ovarian reserve in SLE”. In: *Arthritis & Rheumatism* 65.1 (2013), pp. 206–210. DOI: 10.1002/art.37719.

[18] F. Tamirou et al. “Euro-Lupus low-dose IV cyclophosphamide does not impact ovarian reserve”. In: *Arthritis & Rheumatology* 69.6 (2017), pp. 1267–1271. DOI: 10.1002/art.40079.

[19] L. Iaccarino et al. “Predictors of response and discontinuation of belimumab in SLE: real-life study”. In: *Journal of Autoimmunity* 86 (2018), pp. 1–8. DOI: 10.1016/j.jaut.2017.09.004.

[20] S. Manzi et al. “Belimumab effects across organ domains in SLE: pooled BLISS-52/76”. In: *Annals of the Rheumatic Diseases* 71.11 (2012), pp. 1833–1838. DOI: 10.1136/annrheumdis-2011-200831.

[21] R. F. van Vollenhoven et al. “Belimumab in SLE: high disease activity predictors of response”. In: *Annals of the Rheumatic Diseases* 71.8 (2012), pp. 1343–1349. DOI: 10.1136/annrheumdis-2011-200937.

[22] S. Y. Chen et al. “Glucocorticoid use in SLE: dose and healthcare utilization/costs”. In: *Arthritis Care & Research* 67.8 (2015), pp. 1086–1094. DOI: 10.1002/acr.22551.

[23] F. Kariburyo et al. “Medication use and economic outcomes in incident SLE (USA)”. In: *Journal of Medical Economics* 23.1 (2019), pp. 1–9. DOI: 10.1080/13696998.2019.1674748.

[24] J. A. Birt et al. “Corticosteroid dosing and opioid use remain high after belimumab”. In: *Lupus Science & Medicine* 7 (2020), e000435. DOI: 10.1136/lupus-2020-000435.

[25] C. F. Bell et al. “Treatment patterns, HCRU and costs in SLE patients treated with belimumab (USA claims)”. In: *Lupus Science & Medicine* 7 (2020), e000357. DOI: 10.1136/lupus-2019-000357.

[26] JG Hanly et al. “Treatment pathways in an inception lupus cohort over the first three years”. In: *Lupus* 26.2 (2017), pp. 119–124.

[27] F. Fatoye, T. Gebrye, and L. W. Svenson. “Real-world incidence and prevalence of SLE in Alberta, Canada”. In: *Rheumatology International* 38.9 (2018), pp. 1721–1726. DOI: 10.1007/s00296-018-4091-4.

[28] R. Magro and A. A. Borg. “Characterisation of patients with SLE in Malta: population-based study”. In: *BioMed Research International* 2018 (2018), p. 2385386. DOI: 10.1155/2018/2385386.

[29] K. Otsa et al. “Prevalence and incidence of SLE in the adult population of Estonia”. In: *Lupus* 26.10 (2017), pp. 1115–1120. DOI: 10.1177/0961203316686705.

[30] I. Gergianaki et al. “Epidemiology and burden of SLE in Crete, Greece”. In: *Annals of the Rheumatic Diseases* 76.12 (2017), pp. 1992–2000. DOI: 10.1136/annrheumdis-2017-211206.

[31] R. Cortés Verdú et al. “Prevalence of SLE in Spain: EPISER2016”. In: *Rheumatology (Oxford)* 59.9 (2020), pp. 2556–2562. DOI: 10.1093/rheumatology/kez668.

[32] Frances Rees et al. “The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012”. In: *Annals of the rheumatic diseases* 75.1 (2016), pp. 136–141.

[33] Tobias Alexander et al. “Real-World Prevalence, Incidence and Management of Systemic Lupus Erythematosus in Germany: A Retrospective Claims Data Analysis”. In: *Rheumatology and Therapy* 12.2 (2025), pp. 237–254.

[34] Vasiliki Tsioni et al. “The prevalence and incidence of systemic lupus erythematosus in children and adults: a population-based study in a mountain community in northern Italy”. In: *Clin Exp Rheumatol* 33.5 (2015), pp. 681–687.

[35] Maurizio Benucci et al. “Systemic lupus erythematosus (SLE) in Italy: an Italian prevalence study based on a two-step strategy in an area of Florence (Scandicci-Le Signe).” In: *Medical science monitor: international medical journal of experimental and clinical research* 11.9 (2005), CR420–5.

[36] Margherita Zen et al. “Systemic lupus erythematosus incidence and prevalence in a large population-based study in northeastern Italy”. In: *Rheumatology* 62.8 (2023), pp. 2773–2779.

[37] Claudia Sardu et al. “Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity”. In: *PloS one* 7.3 (2012), e32487.

[38] Marcello Govoni et al. “Incidence and prevalence of systemic lupus erythematosus in a district of north Italy”. In: *Lupus* 15.2 (2006), pp. 110–113.

[39] Jingru Tian et al. “Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study”. In: *Annals of the rheumatic diseases* 82.3 (2023), pp. 351–356.

[40] Kevin G Moores and Nila A Sathe. “A systematic review of validated methods for identifying systemic lupus erythematosus (SLE) using administrative or claims data”. In: *Vaccine* 31 (2013), K62–K73.

[41] Kathy L Moser et al. “Recent insights into the genetic basis of systemic lupus erythematosus”. In: *Genes & Immunity* 10.5 (2009), pp. 373–379.

[42] George C Tsokos and Gary M Kammer. “Molecular aberrations in human systemic lupus erythematosus”. In: *Molecular medicine today* 6.11 (2000), pp. 418–424.

[43] John B Harley et al. “The genetics of human systemic lupus erythematosus”. In: *Current opinion in immunology* 10.6 (1998), pp. 690–696.

[44] Teri A Manolio et al. “Finding the missing heritability of complex diseases”. In: *Nature* 461.7265 (2009), pp. 747–753.

[45] George C. Tsokos. “Systemic lupus erythematosus”. In: *The New England Journal of Medicine* 365.22 (2011), pp. 2110–2121. DOI: 10.1056/NEJMra1100359.

[46] Esteban Ballestar, Manel Esteller, and Bruce C Richardson. “The epigenetic face of systemic lupus erythematosus”. In: *The Journal of Immunology* 176.12 (2006), pp. 7143–7147.

[47] Julia F Simard et al. “Exposure to maternal smoking and incident SLE in a prospective cohort study”. In: *Lupus* 18.5 (2009), pp. 431–435.

[48] GC Tsokos, IT Magrath, and JE Balow. “Epstein-Barr virus induces normal B cell responses but defective suppressor T cell responses in patients with systemic lupus erythematosus.” In: *Journal of immunology (Baltimore, Md.: 1950)* 131.4 (1983), pp. 1797–1801.

[49] Insoo Kang et al. “Defective control of latent Epstein-Barr virus infection in systemic lupus erythematosus”. In: *The Journal of Immunology* 172.2 (2004), pp. 1287–1294.

[50] Catia Duarte et al. “Epidemiology of systemic lupus erythematosus”. In: *Systemic lupus erythematosus*. Elsevier, 2011, pp. 673–696.

[51] Deborah L Smith-Bouvier et al. “A role for sex chromosome complement in the female bias in autoimmune disease”. In: *The Journal of experimental medicine* 205.5 (2008), pp. 1099–1108.

[52] Andrea Doria et al. "Steroid hormones and disease activity during pregnancy in systemic lupus erythematosus". In: *Arthritis Care & Research: Official Journal of the American College of Rheumatology* 47.2 (2002), pp. 202–209.

[53] Deh-Ming Chang et al. "Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus: A multicenter randomized, double-blind, placebo-controlled trial". In: *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology* 46.11 (2002), pp. 2924–2927.

[54] Josep Darba, Meritxell Ascanio, and Ainoa Agüera. "Incidence and medical costs of lupus in Spanish hospitals: a retrospective database analysis". In: *Orphanet Journal of Rare Diseases* 19.1 (2024), p. 74.

[55] Hong J Kan et al. "Healthcare utilization and costs of systemic lupus erythematosus in Medicaid". In: *BioMed research international* 2013.1 (2013), p. 808391.

[56] H. A. Stirnadel-Farrant and et al. "Healthcare Resource Use and Costs Associated with Organ Damage in Newly Diagnosed Adults with SLE in the UK". In: *Rheumatology and Therapy* 10.4 (2023), pp. 1245–1263. DOI: 10.1007/s40744-023-00631-9.

[57] Katinka Albrecht 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". In: *Lupus science & medicine* 8.1 (2021), e000526.

[58] Juan C Pérez-Correa et al. "Cost of hospital care in patients with systemic lupus erythematosus in a high complexity hospital in Colombia". In: *Revista Colombiana de Reumatología (English Edition)* (2025).

[59] C. F. Bell and et al. "Healthcare resource utilization and costs in patients with newly confirmed lupus nephritis in the United States over a 5-year follow-up". In: *BMC Health Services Research* 24 (2024), p. 691. DOI: 10.1186/s12913-024-11060-6.

[60] Prajakta P Masurkar et al. "Real-world treatment patterns, healthcare resource utilisation and costs in patients with SLE in the USA". In: *Lupus Science & Medicine* 11.2 (2024).

[61] Erica F Lawson and Jinoos Yazdany. "Healthcare quality in systemic lupus erythematosus: using Donabedian's conceptual framework to understand what we know". In: *International journal of clinical rheumatology* 7.1 (2012), p. 95.

[62] Megan RW Barber et al. "Global epidemiology of systemic lupus erythematosus". In: *Nature Reviews Rheumatology* 17.9 (2021), pp. 515–532.

[63] Pietro Ferrara et al. "Epidemiology of SLE in Italy: an observational study using a primary care database". In: *Lupus Science & Medicine* 11.1 (2024).

[64] Serena Fasano and David A Isenberg. "Systemic lupus erythematosus and the role of the GP." In: *Prescriber* 26.20 (2015).

[65] Alison L Nightingale et al. "Presentation of SLE in UK primary care using the Clinical Practice Research Datalink". In: *Lupus science & medicine* 4.1 (2017), e000172.

[66] Ana Marta Anes et al. "The European network of centres for pharmacoepidemiology and pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology (revision 1, 2012, revision 2, 2013, revision 3, 2014)". In: (2012).

[67] Kenneth J Rothman, Sander Greenland, Timothy L Lash, et al. *Modern epidemiology*. Vol. 3. Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia, 2008.

[68] Joan A Casey et al. "Using electronic health records for population health research: a review of methods and applications". In: *Annual review of public health* 37.1 (2016), pp. 61–81.

[69] Betina T Blak et al. "Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates." In: *Informatics in primary care* 19.4 (2011), pp. 251–255. DOI: 10.14236/jhi.v19i4.820.

[70] Judea Pearl. "Causal inference in statistics: An overview". In: (2009).

[71] Miguel A Hernán and James M Robins. "Using big data to emulate a target trial when a randomized trial is not available". In: *American journal of epidemiology* 183.8 (2016), pp. 758–764.

[72] Peter C Austin. "An introduction to propensity score methods for reducing the effects of confounding in observational studies". In: *Multivariate behavioral research* 46.3 (2011), pp. 399–424.

[73] Peter M Rothwell. "External validity of randomised controlled trials:"to whom do the results of this trial apply?"" In: *The Lancet* 365.9453 (2005), pp. 82–93.

[74] Kenneth J Rothman, John EJ Gallacher, and Elizabeth E Hatch. "Why representativeness should be avoided". In: *International journal of epidemiology* 42.4 (2013), pp. 1012–1014.

[75] Lorenzo Richiardi, Costanza Pizzi, and Neil Pearce. "Commentary: Representativeness is usually not necessary and often should be avoided". In: *International journal of epidemiology* 42.4 (2013), pp. 1018–1022.

[76] Ellen A Nohr and Zeyan Liew. "How to investigate and adjust for selection bias in cohort studies". In: *Acta obstetricia et gynecologica Scandinavica* 97.4 (2018), pp. 407–416.

[77] Alma B Pedersen et al. "Missing data and multiple imputation in clinical epidemiological research". In: *Clinical epidemiology* (2017), pp. 157–166.

[78] I. C. Antonazzo et al. "Treatment patterns in essential tremor: Real-world evidence from a UK and France primary care database". In: *European Journal of Neurology* 31.1 (2024), e16064. DOI: 10.1111/ene.16064.

[79] Claudio Cricelli et al. "Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases". In: *Journal of Public Health* 25.3 (2003), pp. 254–257.

[80] *The Health Improvement Network (THIN)*. Cegedim Health Data. URL: https://www.the-health-improvement-network.com/ (visited on 10/02/2025).

[81] Ana Ruigómez, Elisa Martín-Merino, and Luis Alberto García Rodríguez. "Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN)". In: *Pharmacoepidemiology and drug safety* 19.6 (2010), pp. 579–585.

[82] James D Lewis et al. "Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research". In: *Pharmacoepidemiology and drug safety* 16.4 (2007), pp. 393–401.

[83] Laurent Eckert et al. "Treatment patterns in UK adult patients with atopic dermatitis treated with systemic immunosuppressants: data from The Health Improvement Network (THIN)". In: *Journal of Dermatological Treatment* 31.8 (2020), pp. 815–820.

[84] Cegedim Health Data. *Cegedim Health Data launches THIN® in Germany*. Press release. Nov. 13, 2023. URL: https://www.cegedim.com/Communique/CegedimHealthData_THIN_Germany_Launch_13112023_EN.pdf (visited on 10/15/2025).

[85] S Bernatsky et al. "A population-based assessment of systemic lupus erythematosus incidence and prevalence—results and implications of using administrative data for epidemiological studies". In: *Rheumatology* 46.12 (2007), pp. 1814–1818.

[86] Stephen K Lwanga and Stanley Lemeshow. "Sample size determination in health studies". In: *Geneva: World Health Organization* 1 (1991).

[87] William G Cochran. "Some methods for strengthening the common χ 2 tests". In: *Biometrics* 10.4 (1954), pp. 417–451.

[88] Mary L McHugh. "The chi-square test of independence". In: *Biochemia medica* 23.2 (2013), pp. 143–149.

[89] Alan Agresti and Maria Kateri. "Categorical data analysis". In: *International Encyclopedia of Statistical Science*. Springer, 2025, pp. 408–411.

Chapter 6

Supplementary Materials

Table S1. Annual (2017–2022) standardised incidence rate (per 100,000 PYs) of SLE, stratified by sex, age, and geographical area — **First definition**.

Variable	2017	2018	2019	2020	2021	2022
Overall	4.99 (4.79–5.18)	5.46 (5.25–5.66)	4.46 (4.27–4.65)	5.07 (4.87–5.27)	11.19 (10.89–11.48)	6.51 (6.29–6.74)
Sex						
Female	9.08 (5.37–12.80)	8.91 (5.27–12.55)	7.61 (4.27–10.94)	7.54 (4.23–10.84)	18.33 (13.20–23.47)	8.87 (5.16–12.57)
Male	0.91 (0–2.17)	2.23 (0.27–4.18)	1.31 (0–2.79)	2.61 (0.52–4.69)	3.91 (1.35–6.46)	4.27 (1.48–7.06)
Age						
18–29	1.73 (0–5.11)	0	1.67 (0–4.93)	3.35 (0–7.99)	6.81 (0.15–13.49)	3.86 (0–9.22)
30–39	1.77 (0–5.23)	3.56 (0–8.48)	5.39 (0–11.49)	1.83 (0–5.43)	7.52 (0.15–14.88)	2.13 (0–6.32)
40–49	9.22 (2.83–15.61)	9.27 (2.85–15.69)	5.89 (0.73–11.06)	12.16 (4.63–19.70)	11.35 (3.94–18.77)	8.66 (1.73–15.60)
50–59	8.78 (2.70–14.86)	5.29 (0.65–9.93)	3.09 (0–6.59)	7.12 (1.85–12.40)	18.15 (9.77–26.54)	6.54 (1.31–11.77)
60–69	2.65 (0–6.32)	7.77 (1.55–13.99)	6.28 (0.78–11.78)	3.68 (0–7.85)	11.89 (4.52–19.27)	12.43 (4.73–20.13)
70–79	3.21 (0–7.67)	4.63 (0–9.87)	7.48 (0.92–14.04)	1.46 (0–4.33)	14.22 (5.41–23.03)	4.45 (0–9.48)
80+	7.02 (0–14.97)	8.94 (0.18–17.70)	2.09 (0–6.20)	3.92 (0–9.36)	5.67 (0–12.08)	5.85 (0–12.47)
Geographical area						
Northern IT	3.28 (3.05–3.52)	5.00 (4.72–5.29)	4.62 (4.35–4.90)	6.33 (6.01–6.66)	12.40 (11.95–12.86)	7.55 (7.19–7.90)
Central IT	7.92 (7.36–8.47)	7.69 (7.14–8.23)	4.86 (4.43–5.30)	3.63 (3.26–4.01)	10.76 (10.12–11.41)	5.03 (4.59–5.47)
Southern IT & Islands	4.04 (3.74–4.35)	3.28 (3.00–3.55)	3.89 (3.59–4.19)	4.80 (4.47–5.13)	9.34 (8.88–9.80)	6.79 (6.40–7.19)

Table S2. Annual (2017–2022) standardised incidence rate (per 100,000 PYs) of SLE, stratified by sex, age, and geographical area — **Second definition**.

Variable	2017	2018	2019	2020	2021	2022
Overall	4.58 (4.40–4.77)	5.08 (4.88–5.27)	4.05 (3.87–4.22)	4.82 (4.63–5.02)	10.48 (10.19–10.76)	6.16 (5.94–6.38)
Sex						
Female	8.69 (5.06–12.32)	8.52 (4.96–12.08)	6.85 (3.68–10.01)	7.54 (4.23–10.84)	16.84 (11.92–21.76)	8.06 (4.53–11.59)
Male	0.46 (0–1.35)	1.78 (0.04–3.52)	1.31 (0–2.79)	2.17 (0.27–4.07)	3.91 (1.35–6.46)	4.27 (1.48–7.06)
Age						
18–29	1.73 (0–5.11)	0	1.67 (0–4.93)	1.68 (0–4.96)	6.81 (0.14–13.49)	3.86 (0–9.22)
30–39	1.77 (0–5.23)	3.56 (0–8.48)	3.59 (0–8.58)	1.83 (0–5.43)	7.52 (0.15–14.88)	2.13 (0–6.32)
40–49	9.22 (2.83–15.61)	9.27 (2.85–15.69)	4.72 (0.09–9.34)	12.16 (4.63–19.70)	11.35 (3.94–18.77)	8.66 (1.73–15.60)
50–59	8.78 (2.70–14.86)	5.29 (0.65–9.93)	3.09 (0–6.59)	7.12 (1.85–12.40)	16.13 (8.23–24.04)	6.54 (1.31–11.77)
60–69	2.65 (0–6.32)	7.77 (1.55–13.99)	6.28 (0.78–11.78)	3.68 (0–7.85)	11.89 (4.52–19.27)	12.43 (4.73–20.13)
70–79	1.61 (0–4.75)	3.09 (0–7.37)	7.48 (0.92–14.04)	1.46 (0–4.33)	14.22 (5.41–23.03)	4.45 (0–9.48)
80+	4.68 (0–11.17)	6.71 (0–14.29)	2.09 (0–6.20)	3.92 (0–9.36)	1.89 (0–5.59)	1.95 (0–5.77)
Geographical area						
Northern IT	2.81 (2.60–3.03)	5.00 (4.72–5.29)	3.65 (3.40–3.89)	5.76 (5.45–6.07)	11.97 (11.52–12.41)	7.55 (7.19–7.90)
Central IT	7.33 (6.80–7.87)	7.12 (6.60–7.65)	4.86 (4.43–5.30)	3.63 (3.26–4.01)	9.10 (8.50–9.69)	4.47 (4.05–4.88)
Southern IT & Islands	4.04 (3.74–4.35)	2.42 (2.18–2.66)	3.89 (3.59–4.19)	4.80 (4.47–5.13)	9.34 (8.88–9.80)	6.07 (5.70–6.45)

Table S3. Annual (2017–2022) standardised incidence rate (per 100,000 PYs) of SLE, stratified by sex, age, and geographical area — **Third definition**.

Variable	2017	2018	2019	2020	2021	2022
Overall	6.23 (6.02–6.45)	6.22 (6.01–6.44)	5.02 (4.82–5.22)	5.90 (5.69–6.12)	14.68 (14.34–15.02)	9.67 (9.40–9.95)
Sex						
Female	10.66 (6.64–14.69)	10.46 (6.51–14.40)	8.75 (5.17–12.32)	9.05 (5.43–12.66)	22.82 (17.10–28.55)	13.30 (8.76–17.84)
Male	1.82 (0.04–3.61)	2.23 (0.27–4.18)	1.31 (0–2.79)	2.61 (0.52–4.69)	6.08 (2.89–9.26)	6.17 (2.82–9.52)
Age						
18–29	3.45 (0–8.24)	0	1.67 (0–4.93)	3.35 (0–7.99)	8.52 (1.05–15.98)	3.86 (0–9.22)
30–39	1.77 (0–5.23)	3.56 (0–8.48)	5.39 (0–11.49)	5.50 (0–11.72)	9.40 (1.16–17.63)	6.40 (0–13.64)
40–49	10.37 (3.60–17.15)	11.59 (4.41–18.77)	7.07 (1.41–12.73)	12.16 (4.63–19.70)	22.70 (12.21–33.19)	11.55 (3.55–19.56)
50–59	10.98 (4.17–17.78)	7.41 (1.92–12.90)	3.09 (0–6.59)	9.16 (3.17–15.14)	20.17 (11.33–29.01)	10.90 (4.14–17.65)
60–69	3.97 (0–8.47)	7.77 (1.55–13.99)	7.53 (1.51–13.56)	3.68 (0–7.85)	14.27 (6.20–22.35)	17.40 (8.29–26.52)
70–79	4.82 (0–10.27)	4.63 (0–9.87)	8.98 (1.80–16.17)	1.46 (0–4.33)	17.06 (7.41–26.72)	7.42 (0.92–13.92)
80+	7.02 (0–14.97)	8.94 (0.18–17.70)	2.09 (0–6.20)	3.92 (0–9.36)	5.67 (0–12.08)	7.80 (0.16–15.44)
Geographical area						
Northern IT	4.83 (4.54–5.11)	6.34 (6.02–6.67)	5.49 (5.19–5.80)	6.33 (6.01–6.66)	16.60 (16.07–17.12)	11.24 (10.81–11.68)
Central IT	9.11 (8.51–9.70)	8.29 (7.72–8.86)	5.42 (4.96–5.87)	4.92 (4.49–5.36)	14.65 (13.89–15.40)	6.98 (6.46–7.50)
Southern IT & Islands	4.95 (4.61–5.29)	3.28 (3.00–3.55)	3.89 (3.59–4.19)	6.44 (6.05–6.82)	11.12 (10.61–11.62)	10.41 (9.92–10.90)

Table S4. Annual (2017–2022) standardised prevalence (per 100,000 people) of SLE, stratified by sex, age, and geographical area — **First definition**.

Variable	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Overall	36.04 (35.51–36.57)	39.75 (39.20–40.30)	42.73 (42.15–43.30)	46.13 (45.53–46.73)	55.60 (54.95–56.26)	60.57 (59.89–61.25)
Sex						
Female	60.03 (50.49–69.58)	65.84 (55.94–75.73)	70.74 (60.58–80.91)	75.38 (64.94–85.82)	90.54 (79.14–101.90)	97.14 (84.88–109.40)
Male	10.93 (6.55–15.30)	12.46 (7.85–17.08)	13.11 (8.42–17.80)	14.33 (9.44–19.22)	16.93 (11.61–22.24)	18.98 (13.10–24.86)
Age						
18–29	22.45 (10.25–34.65)	21.97 (10.03–33.91)	23.32 (11.11–35.54)	26.80 (13.67–39.94)	34.07 (19.14–49.00)	38.65 (21.71–55.59)
30–39	47.70 (29.71–65.69)	51.56 (32.80–70.32)	55.72 (36.11–75.33)	58.67 (38.34–78.99)	67.65 (45.56–89.74)	68.28 (44.63–91.93)
40–49	48.40 (33.77–63.04)	56.77 (40.88–72.66)	63.66 (46.68–80.63)	77.85 (58.78–96.92)	90.80 (69.84–111.70)	105.41 (81.24–129.60)
50–59	48.29 (34.03–62.56)	51.85 (37.34–66.37)	51.54 (37.26–65.83)	54.94 (40.29–69.59)	69.58 (53.17–85.99)	70.82 (53.61–88.03)
60–69	34.44 (21.20–47.67)	41.46 (27.10–55.83)	45.20 (30.44–59.96)	46.62 (31.80–61.44)	57.09 (40.95–73.24)	68.36 (50.30–86.42)
70–79	25.70 (13.11–38.29)	24.70 (12.60–36.81)	29.94 (16.82–43.06)	29.24 (16.43–42.05)	38.39 (23.91–52.87)	38.56 (23.74–53.38)
80+	18.73 (5.75–31.71)	22.35 (8.50–36.21)	23.03 (9.42–36.63)	17.65 (6.12–29.18)	17.01 (5.90–28.12)	19.50 (7.41–31.58)
Geographical area						
Northern IT	42.93 (42.09–43.78)	45.05 (44.19–45.92)	47.93 (47.03–48.82)	52.74 (51.80–53.67)	63.38 (62.35–64.40)	69.93 (68.85–71.00)
Central IT	36.28 (35.10–37.47)	42.95 (41.66–44.24)	46.49 (45.15–47.83)	48.93 (47.55–50.31)	58.99 (57.47–60.50)	62.75 (61.19–64.31)
Southern IT & Islands	23.72 (22.98–24.46)	26.38 (25.60–27.16)	29.00 (28.19–29.82)	30.92 (30.08–31.76)	37.26 (36.33–38.18)	41.87 (40.89–42.85)

Table S5. Annual (2017–2022) standardised prevalence (per 100,000 people) of SLE, stratified by sex, age, and geographical area — **Second definition**.

Variable	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Overall	31.09 (30.60–31.58)	34.96 (34.44–35.48)	37.85 (37.31–38.39)	41.78 (41.21–42.35)	50.55 (49.93–51.18)	54.94 (54.29–55.59)
Sex						
Female	54.50 (45.41–63.60)	60.42 (50.94–69.89)	64.66 (54.94–74.37)	70.10 (60.03–80.17)	83.81 (72.84–94.78)	89.48 (77.72–101.20)
Male	6.37 (3.03–9.71)	8.01 (4.31–11.71)	9.18 (5.25–13.10)	10.85 (6.60–15.11)	13.45 (8.72–18.19)	15.19 (9.92–20.45)
Age						
18–29	22.45 (10.25–34.65)	21.97 (10.03–33.91)	23.32 (11.11–35.54)	25.13 (12.41–37.84)	32.37 (17.81–46.92)	36.72 (20.21–53.22)
30–39	42.40 (25.44–59.36)	46.22 (28.46–63.99)	48.53 (30.23–66.83)	51.33 (32.32–70.34)	60.13 (39.30–80.96)	59.74 (37.62–81.86)
40–49	47.25 (32.79–61.71)	55.61 (39.88–71.34)	61.30 (44.64–77.96)	75.42 (56.65–94.18)	88.28 (67.61–108.90)	102.52 (78.69–126.30)
50–59	45.00 (31.23–58.77)	48.68 (34.62–62.74)	48.45 (34.60–62.30)	52.91 (38.53–67.28)	64.54 (48.73–80.35)	65.37 (48.84–81.91)
60–69	29.14 (16.96–41.31)	36.28 (22.84–49.72)	40.18 (26.26–54.09)	41.71 (27.70–55.73)	52.34 (36.88–67.80)	63.39 (46.00–80.78)
70–79	12.85 (3.95–21.76)	10.81 (2.80–18.81)	17.96 (7.80–28.13)	17.54 (7.62–27.47)	28.44 (15.98–40.90)	29.66 (16.66–42.66)
80+	7.02 (0–14.97)	13.41 (2.68–24.14)	14.65 (3.80–25.51)	15.69 (4.82–26.56)	11.34 (2.27–20.41)	9.75 (1.20–18.29)
Geographical area						
Northern IT	37.22 (36.43–38.00)	40.41 (39.59–41.23)	42.45 (41.61–43.29)	47.51 (46.62–48.40)	57.63 (56.65–58.61)	63.95 (62.92–64.98)
Central IT	33.74 (32.60–34.88)	39.85 (38.61–41.09)	43.39 (42.10–44.69)	45.83 (44.50–47.17)	54.21 (52.77–55.66)	57.09 (55.60–58.58)
Southern IT & Islands	16.75 (16.13–17.38)	18.91 (18.25–19.56)	22.65 (21.93–23.38)	26.27 (25.50–27.05)	32.79 (31.92–33.66)	36.64 (35.72–37.56)

Table S6. Annual (2017–2022) standardised prevalence (per 100,000 people) of SLE, stratified by sex, age, and geographical area — **Third definition**.

Variable	**2017**	**2018**	**2019**	**2020**	**2021**	**2022**
Overall	42.44 (41.87–43.01)	46.43 (45.83–47.03)	49.90 (49.28–50.52)	53.74 (53.10–54.39)	66.55 (65.83–67.27)	74.20 (73.44–74.96)
Sex						
Female	69.12 (58.88–79.36)	75.52 (64.92–86.12)	81.39 (70.49–92.29)	86.68 (75.49–97.88)	105.88 (93.55–118.20)	115.68 (102.31–129.00)
Male	14.57 (9.52–19.61)	16.02 (10.79–21.25)	16.61 (11.33–21.89)	17.80 (12.35–23.25)	22.57 (16.43–28.70)	26.58 (19.62–33.53)
Age						
18–29	27.63 (14.09–41.16)	27.04 (13.79–40.28)	28.32 (14.86–41.78)	31.83 (17.52–46.14)	40.88 (24.53–57.24)	46.38 (27.83–64.93)
30–39	56.54 (36.95–76.12)	60.44 (40.13–80.76)	64.71 (43.58–85.84)	71.50 (49.07–93.93)	82.68 (58.26–107.10)	83.21 (57.11–109.32)
40–49	56.47 (40.66–72.28)	66.04 (48.90–83.18)	74.27 (55.94–92.60)	87.58 (67.36–107.80)	112.24 (88.94–135.50)	131.40 (104.42–158.40)
50–59	54.88 (39.67–70.08)	60.32 (44.67–75.98)	59.79 (44.41–75.17)	64.10 (48.27–79.92)	79.67 (62.11–97.23)	86.07 (67.10–105.05)
60–69	41.06 (26.61–55.51)	47.94 (32.50–63.39)	52.73 (36.79–68.67)	53.98 (38.04–69.93)	66.61 (49.17–84.05)	82.03 (62.25–101.82)
70–79	32.13 (18.05–46.21)	30.88 (17.35–44.41)	37.42 (22.76–52.09)	36.55 (22.22–50.87)	48.35 (32.10–64.59)	48.94 (32.25–65.64)
80+	21.07 (7.31–34.84)	22.35 (8.50–36.21)	23.03 (9.42–36.63)	17.65 (6.12–29.18)	17.01 (5.90–28.12)	21.45 (8.77–34.12)
Geographical area						
Northern IT	50.23 (49.32–51.15)	53.10 (52.16–54.04)	56.71 (55.74–57.69)	61.04 (60.03–62.05)	75.94 (74.82–77.06)	84.96 (83.78–86.15)
Central IT	42.42 (41.14–43.71)	49.07 (47.69–50.45)	53.18 (51.74–54.61)	56.32 (54.85–57.80)	69.65 (68.00–71.29)	75.11 (73.41–76.82)
Southern IT & Islands	28.76 (27.95–29.57)	31.29 (30.44–32.14)	33.82 (32.94–34.70)	37.40 (36.48–38.33)	45.55 (44.53–46.57)	54.41 (53.29–55.53)

Table S7. Annual (2017–2022) incidence rate (per 100,000 PYs) of SLE, stratified by sex and age — IT.

Variable	2017	2018	2019	2020	2021	2022
Overall	4.69 (4.64–4.74)	4.67 (4.62–4.72)	4.41 (4.36–4.45)	5.16 (5.11–5.21)	10.58 (10.50–10.65)	8.20 (8.13–8.26)
Sex						
Female	8.69 (5.63–12.83)	8.82 (5.76–12.92)	7.32 (4.59–11.09)	7.59 (4.81–11.39)	18.06 (13.60–23.50)	10.89 (7.40–15.46)
Male	1.16 (0.24–3.40)	1.13 (0.23–3.31)	1.85 (0.60–4.32)	2.20 (0.81–4.79)	4.04 (2.01–7.22)	5.94 (3.33–9.80)
Age						
18–29	1.69 (0.04–9.44)	0	3.26 (0.40–11.79)	1.64 (0.04–9.13)	6.63 (1.81–16.99)	7.46 (2.03–19.10)
30–39	1.70 (0.04–9.47)	3.42 (0.41–12.35)	3.45 (0.42–12.48)	7.04 (1.92–18.02)	7.21 (1.96–18.46)	2.03 (0.05–11.33)
40–49	8.68 (3.75–17.10)	7.63 (3.07–15.72)	4.44 (1.21–11.36)	11.44 (5.49–21.04)	10.69 (4.89–20.29)	10.80 (4.66–21.28)
50–59	7.88 (3.40–15.53)	5.71 (2.10–12.43)	2.79 (0.57–8.14)	6.42 (2.58–13.24)	18.22 (11.13–28.14)	9.82 (4.71–18.05)
60–69	4.28 (1.17–10.95)	6.28 (2.31–13.68)	9.16 (4.19–17.38)	3.00 (0.62–8.77)	10.77 (5.37–19.26)	12.22 (6.32–21.35)
70–79	3.54 (0.73–10.36)	5.65 (1.83–13.18)	5.48 (1.78–12.79)	2.15 (0.26–7.78)	12.67 (6.55–22.14)	8.77 (3.79–17.29)
80+	5.42 (1.12–15.84)	5.02 (1.03–14.66)	3.12 (0.38–11.26)	2.93 (0.35–10.58)	8.50 (3.12–18.50)	4.35 (0.90–12.73)

Table S8. Annual (2017–2022) incidence rate (per 100,000 PYs) of SLE, stratified by sex and age — UK.

Variable	2017	2018	2019	2020	2021	2022
Overall	5.41 (5.36–5.46)	4.90 (4.85–4.95)	5.05 (5.00–5.10)	5.07 (5.02–5.13)	5.09 (5.03–5.14)	5.05 (4.99–5.10)
Sex						
Female	8.67 (7.45–10.03)	7.91 (6.72–9.25)	7.87 (6.65–9.26)	7.20 (5.96–8.63)	7.36 (6.05–8.87)	8.16 (6.71–9.82)
Male	1.99 (1.40–2.74)	1.75 (1.19–2.49)	2.07 (1.43–2.89)	2.88 (2.07–3.89)	2.77 (1.95–3.82)	1.87 (1.17–2.82)
Age						
18–29	4.06 (2.74–5.80)	3.64 (2.36–5.38)	3.51 (2.20–5.32)	3.67 (2.24–5.67)	2.87 (1.57–4.82)	4.79 (2.93–7.40)
30–39	5.46 (3.78–7.63)	5.18 (3.52–7.36)	5.04 (3.35–7.29)	5.09 (3.29–7.51)	5.31 (3.40–7.91)	6.03 (3.87–8.98)
40–49	6.44 (4.64–8.71)	5.60 (3.88–7.82)	5.92 (4.08–8.32)	4.94 (3.16–7.35)	4.32 (2.60–6.75)	6.70 (4.38–9.81)
50–59	6.17 (4.47–8.32)	3.92 (2.56–5.74)	4.64 (3.11–6.66)	5.78 (3.95–8.16)	5.34 (3.52–7.77)	3.31 (1.85–5.46)
60–69	6.21 (4.30–8.68)	5.97 (4.06–8.48)	5.48 (3.61–7.98)	4.04 (2.40–6.39)	3.86 (2.20–6.26)	5.15 (3.15–7.96)
70–79	5.20 (3.26–7.87)	6.57 (4.33–9.56)	6.34 (4.10–9.35)	7.53 (4.96–10.95)	9.35 (6.36–13.28)	3.57 (1.78–6.39)
80+	4.85 (2.58–8.30)	5.27 (2.88–8.85)	6.51 (3.72–10.57)	6.41 (3.51–10.76)	8.02 (4.58–13.02)	9.07 (5.28–14.52)

Table S9. Annual (2017–2022) incidence rate (per 100,000 PYs) of SLE, stratified by sex and age — BE.

Variable	2017	2018	2019	2020	2021	2022
Overall	1.67 (1.64–1.70)	3.83 (3.79–3.88)	2.54 (2.51–2.58)	2.64 (2.60–2.68)	2.89 (2.86–2.93)	1.30 (1.27–1.33)
Sex						
Female	1.98 (0.64–4.63)	3.96 (1.90–7.29)	4.01 (1.92–7.37)	3.28 (1.42–6.47)	3.70 (1.69–7.03)	1.88 (0.51–4.81)
Male	1.46 (0.30–4.27)	3.40 (1.37–7.01)	0.98 (0.12–3.53)	1.98 (0.54–5.07)	1.98 (0.54–5.08)	0.57 (0.01–3.17)
Age						
18–29	0	7.82 (2.54–18.24)	3.15 (0.38–11.39)	0	1.60 (0.04–8.93)	0
30–39	4.66 (0.96–13.62)	4.70 (0.97–13.73)	7.92 (2.57–18.48)	1.61 (0.04–8.99)	3.22 (0.39–11.62)	3.69 (0.45–13.34)
40–49	1.29 (0.03–7.20)	3.89 (0.80–11.36)	1.32 (0.03–7.34)	6.70 (2.18–15.64)	6.75 (2.19–15.76)	1.56 (0.04–8.71)
50–59	2.31 (0.28–8.33)	2.32 (0.28–8.37)	1.19 (0.03–6.61)	3.66 (0.76–10.70)	2.49 (0.30–8.98)	1.44 (0.04–8.03)
60–69	2.65 (0.32–9.56)	5.31 (1.45–13.60)	1.33 (0.03–7.41)	2.72 (0.33–9.81)	2.71 (0.33–9.81)	1.54 (0.04–8.57)
70–79	0	0	1.85 (0.05–10.29)	1.86 (0.05–10.35)	1.82 (0.05–10.15)	0
80+	0	0	2.62 (0.07–14.60)	0	0	0

Table S10. Annual (2017–2022) incidence rate (per 100,000 PYs) of SLE, stratified by sex and age — GE.

Variable	2017	2018	2019	2020	2021	2022
Overall	–	–	–	–	NE	NE
Sex						
Female	–	–	–	–	NE	NE
Male	–	–	–	–	NE	NE
Age						
18–29	–	–	–	–	NE	NE
30–39	–	–	–	–	NE	NE
40–49	–	–	–	–	NE	NE
50–59	–	–	–	–	NE	NE
60–69	–	–	–	–	NE	NE
70–79	–	–	–	–	NE	NE
80+	–	–	–	–	NE	NE

NE, not estimable.

Table S11. Annual (2017–2022) incidence rate (per 100,000 PYs) of SLE, stratified by sex and age — ES.

Variable	2017	2018	2019	2020	2021	2022
Overall	32.30 (32.17–32.44)	14.14 (14.05–14.23)	11.58 (11.51–11.66)	9.71 (9.64–9.78)	9.41 (9.34–9.48)	9.36 (9.29–9.43)
Sex						
Female	33.67 (24.36–45.35)	20.40 (15.56–26.25)	18.27 (13.91–23.57)	17.41 (13.26–22.46)	14.48 (10.78–19.03)	15.37 (11.58–20.01)
Male	10.47 (5.02–19.26)	7.99 (4.88–12.34)	5.20 (2.91–8.57)	2.26 (0.91–4.66)	4.60 (2.58–7.59)	3.64 (1.88–6.35)
Age						
18–29	35.74 (7.37–104.45)	9.19 (3.69–18.93)	7.96 (3.20–16.40)	5.33 (1.73–12.43)	7.08 (2.85–14.58)	2 (0.24–7.23)
30–39	91.35 (47.20–159.57)	10.24 (4.68–19.44)	12.01 (6.21–20.98)	6.70 (2.69–13.79)	8.33 (3.81–15.81)	8.38 (3.83–15.90)
40–49	43.82 (21.87–78.40)	21.11 (13.38–31.67)	14.16 (8.39–22.38)	12.49 (7.27–20.00)	12.70 (7.53–20.07)	10.58 (5.92–17.44)
50–59	24.19 (11.60–44.49)	24.25 (15.37–36.39)	15.74 (9.17–25.19)	14.64 (8.53–23.44)	11.32 (6.19–18.99)	14.87 (8.95–23.22)
60–69	21.26 (10.61–38.04)	15.62 (8.07–27.28)	14.37 (7.43–25.10)	12.40 (6.19–22.18)	9.68 (4.43–18.37)	11.53 (5.75–20.63)
70–79	12.76 (4.68–27.78)	5.08 (1.05–14.85)	7.88 (2.56–18.40)	10.66 (4.29–21.97)	10.20 (4.10–21.01)	9.89 (3.97–20.37)
80+	0	7.38 (1.52–21.56)	7.22 (1.49–21.10)	4.64 (0.56–16.77)	4.55 (0.55–16.42)	8.96 (2.44–22.93)

Table S12. Annual (2017–2022) incidence rate (per 100,000 PYs) of SLE, stratified by sex and age — RO.

Variable	2017	2018	2019	2020	2021	2022
Overall	6.62 (6.56–6.68)	3.38 (3.34–3.42)	3.30 (3.25–3.34)	4.04 (4.00–4.09)	2.49 (2.45–2.52)	4.16 (4.11–4.21)
Sex						
Female	8.95 (5.12–14.53)	3.97 (1.71–7.82)	3.78 (1.63–7.45)	6.13 (3.26–10.48)	4.28 (1.96–8.12)	6.53 (3.57–10.96)
Male	3.94 (1.28–9.19)	2.72 (0.74–6.98)	2.54 (0.69–6.50)	2.50 (0.68–6.40)	0.63 (0.02–3.54)	1.27 (0.15–4.60)
Age						
18–29	0	6.48 (1.34–18.94)	2.06 (0.05–11.50)	0	0	4.24 (0.51–15.31)
30–39	5.69 (0.69–20.54)	4.77 (0.58–17.22)	4.40 (0.53–15.90)	4.35 (0.53–15.71)	4.45 (0.54–16.07)	0
40–49	14.56 (5.86–30.01)	1.81 (0.05–10.10)	5.12 (1.06–14.97)	1.69 (0.04–9.40)	3.41 (0.41–12.33)	8.59 (2.79–20.05)
50–59	12.86 (4.72–28.00)	1.82 (0.05–10.14)	5.00 (1.03–14.63)	8.07 (2.62–18.84)	3.19 (0.39–11.52)	10.82 (4.35–22.28)
60–69	6.20 (1.69–15.88)	0	4.02 (0.83–11.74)	8.22 (3.02–17.90)	4.23 (0.87–12.36)	1.42 (0.04–7.91)
70–79	4.48 (0.54–16.17)	8.24 (2.25–21.11)	0	5.73 (1.18–16.76)	1.89 (0.05–10.55)	0
80+	0	3.41 (0.09–18.99)	0	0	0	3.28 (0.08–18.28)

Also for prevalence, over 2017–2022 was consistently higher in women than men, with female rates typically 3–6 times than male rates within the same age band (Tables S13–S18).

Age patterns were broadly similar: prevalence increased from young adulthood to mid- / older-age bands (≈40–69 years), with lower values in the 18–39 and ≥ 70 groups.

Table S13. Annual (2017–2022) prevalence (per 100,000 people) of SLE, stratified by sex and age — IT.

Variable	2017	2018	2019	2020	2021	2022
Overall	38.13 (37.99–38.27)	40.42 (40.28–40.57)	42.82 (42.67–42.97)	45.10 (44.94–45.25)	53.76 (53.59–53.93)	58.91 (58.73–59.09)
Sex						
Female	65.73 (56.69–75.79)	70.23 (60.99–80.47)	74.56 (65.12–84.98)	78.55 (68.89–89.19)	93.89 (83.33–105.42)	101.20 (89.85–113.58)
Male	14.37 (10.12–19.80)	14.73 (10.48–20.14)	15.54 (11.20–21.01)	15.79 (11.42–21.26)	18.71 (13.93–24.60)	21.79 (16.42–28.36)
Age						
18–29	11.86 (4.77–24.42)	9.94 (3.65–21.64)	11.43 (4.59–23.54)	11.47 (4.61–23.64)	18.25 (9.11–32.64)	22.38 (11.57–39.09)
30–39	25.48 (14.26–42.03)	29.06 (16.93–46.53)	29.37 (17.11–47.01)	33.43 (20.13–52.21)	39.66 (24.86–60.05)	40.67 (24.84–62.80)
40–49	53.16 (39.33–70.28)	56.66 (42.32–74.30)	57.68 (43.08–75.63)	61.77 (46.41–80.59)	67.68 (51.26–87.68)	79.65 (60.64–102.74)
50–59	56.16 (42.54–72.76)	55.19 (41.91–71.34)	56.64 (43.33–72.75)	63.33 (49.28–80.14)	82.91 (66.76–101.79)	85.40 (68.41–105.34)
60–69	51.32 (37.84–68.03)	56.56 (42.49–73.79)	66.12 (51.04–84.27)	66.02 (51.06–83.98)	72.42 (56.87–90.91)	84.54 (67.34–104.79)
70–79	36.63 (24.89–51.99)	46.30 (33.23–62.81)	46.05 (33.19–62.24)	46.30 (33.51–62.37)	54.92 (41.02–72.02)	55.94 (41.65–73.54)
80+	34.33 (20.67–53.61)	30.10 (17.84–47.57)	34.29 (21.49–51.92)	33.67 (21.34–50.51)	42.50 (28.68–60.67)	45.00 (30.58–63.87)

Table S14. Annual (2017–2022) prevalence (per 100,000 people) of SLE, stratified by sex and age — UK.

Variable	2017	2018	2019	2020	2021	2022
Overall	80.76 (80.56–80.97)	81.79 (81.58–82.00)	84.23 (84.02–84.44)	88.95 (88.73–89.16)	94.16 (93.94–94.38)	96.37 (96.14–96.59)
Sex						
Female	130.89 (126.03–135.88)	133.16 (128.13–138.33)	137.89 (132.61–143.34)	145.83 (140.05–151.80)	155.13 (148.88–161.57)	160.27 (153.62–167.14)
Male	24.84 (22.63–27.21)	25.19 (22.90–27.64)	26.19 (23.78–28.79)	28.56 (25.89–31.44)	30.25 (27.38–33.35)	31.37 (28.25–34.73)
Age						
18–29	20.72 (17.57–24.27)	20.39 (17.15–24.06)	21.23 (17.78–25.16)	21.68 (17.94–25.96)	21.53 (17.61–26.06)	22.52 (18.20–27.56)
30–39	50.77 (45.33–56.69)	52.82 (47.16–58.98)	54.38 (48.42–60.87)	57.77 (51.25–64.89)	60.88 (53.90–68.51)	63.34 (55.76–71.66)
40–49	77.31 (70.71–84.36)	76.54 (69.74–83.82)	81.15 (73.85–88.99)	83.94 (75.99–92.49)	86.93 (78.44–96.10)	97.12 (87.56–107.43)
50–59	109.42 (101.79–117.46)	109.34 (101.53–117.58)	109.90 (101.84–118.43)	117.96 (109.09–127.36)	120.28 (110.92–130.23)	121.36 (111.44–131.94)
60–69	122.47 (113.38–132.10)	123.15 (113.79–133.08)	124.12 (114.48–134.36)	127.11 (116.86–138.02)	139.30 (128.18–151.12)	142.72 (131.09–155.10)
70–79	127.16 (116.65–138.37)	129.21 (118.46–140.68)	133.29 (122.15–145.17)	139.64 (127.69–152.41)	147.55 (134.77–161.22)	146.36 (133.18–160.51)
80+	93.71 (82.48–106.04)	102.06 (90.28–114.96)	112.65 (99.78–126.72)	126.39 (111.93–142.20)	143.28 (127.16–160.87)	145.66 (128.90–163.98)

Table S15. Annual (2017–2022) prevalence (per 100,000 people) of SLE, stratified by sex and age — BE.

Variable	2017	2018	2019	2020	2021	2022
Overall	29.50 (29.37–29.62)	30.31 (30.18–30.44)	30.57 (30.44–30.70)	31.22 (31.09–31.35)	31.83 (31.70–31.96)	29.87 (29.74–29.99)
Sex						
Female	38.48 (31.20–46.94)	39.22 (31.88–47.75)	40.86 (33.32–49.60)	41.02 (33.37–49.88)	41.98 (34.23–50.96)	39.02 (31.08–48.36)
Male	20.94 (15.15–28.20)	21.38 (15.53–28.69)	20.52 (14.79–27.74)	21.79 (15.83–29.25)	21.83 (15.86–29.31)	21.60 (15.29–29.65)
Age						
18–29	17.16 (8.57–30.70)	21.88 (11.96–36.72)	23.64 (13.23–38.99)	19.30 (9.98–33.72)	19.24 (9.94–33.61)	16.71 (7.64–31.73)
30–39	34.18 (21.42–51.74)	36.01 (22.83–54.03)	36.42 (23.09–54.64)	37.11 (23.53–55.69)	33.77 (20.90–51.61)	20.31 (10.14–36.34)
40–49	33.59 (21.95–49.22)	31.09 (19.92–46.25)	26.34 (16.09–40.68)	29.50 (18.49–44.66)	35.11 (22.93–51.44)	32.84 (20.33–50.19)
50–59	36.90 (25.24–52.09)	37.09 (25.37–52.35)	42.72 (29.92–59.13)	42.72 (29.76–59.41)	42.26 (29.27–59.05)	41.80 (28.00–60.03)
60–69	31.76 (20.35–47.25)	35.85 (23.63–52.16)	33.27 (21.53–49.10)	39.38 (26.38–56.55)	39.37 (26.37–56.53)	38.45 (24.88–56.75)
70–79	30.49 (17.43–49.52)	26.09 (14.26–43.77)	27.70 (15.50–45.68)	24.14 (12.85–41.28)	25.50 (13.94–42.78)	32.52 (18.59–52.80)
80+	24.45 (11.18–46.40)	23.72 (10.85–45.03)	26.21 (12.57–48.19)	26.59 (12.75–48.90)	27.15 (13.02–49.93)	30.20 (14.48–55.53)

Table S16. Annual (2017–2022) prevalence (per 100,000 people) of SLE, stratified by sex and age — GE.

Variable	2017	2018	2019	2020	2021	2022
Overall	–	–	–	–	13.26 (13.17–13.34)	44.04 (43.89–44.20)
Sex						
Female	–	–	–	–	22.79 (16.92–30.05)	73.26 (62.81–84.95)
Male	–	–	–	–	2.84 (0.92–6.63)	14.00 (9.23–20.37)
Age						
18–29	–	–	–	–	10.23 (1.24–36.95)	37.49 (16.19–73.85)
30–39	–	–	–	–	21.52 (8.65–44.34)	54.09 (32.57–84.46)
40–49	–	–	–	–	15.09 (6.07–31.09)	52.68 (34.41–77.17)
50–59	–	–	–	–	17.84 (9.98–29.42)	57.35 (42.57–75.60)
60–69	–	–	–	–	15.79 (8.63–26.49)	45.31 (32.93–60.83)
70–79	–	–	–	–	8.33 (3.06–18.13)	41.62 (28.65–58.44)
80+	–	–	–	–	7.68 (2.09–19.65)	35.31 (22.13–53.46)

Table S17. Annual (2017–2022) prevalence (per 100,000 people) of SLE, stratified by sex and age — RO.

Variable	2017	2018	2019	2020	2021	2022
Overall	13.95 (13.87–14.04)	15.23 (15.14–15.32)	15.80 (15.71–15.89)	19.24 (19.14–19.34)	18.96 (18.86–19.06)	20.28 (20.17–20.38)
Sex						
Female	18.46 (12.71–25.92)	19.84 (14.17–27.01)	21.25 (15.50–28.44)	26.86 (20.34–34.80)	28.04 (21.35–36.17)	31.26 (24.22–39.69)
Male	8.67 (4.33–15.51)	10.22 (5.72–16.85)	10.15 (5.80–16.48)	12.50 (7.64–19.30)	11.43 (6.77–18.06)	10.83 (6.31–17.33)
Age						
18–29	2.50 (0.06–13.92)	8.64 (2.35–22.12)	6.19 (1.28–18.09)	6.15 (1.27–17.96)	2.09 (0.05–11.67)	6.36 (1.31–18.57)
30–39	8.53 (1.76–24.93)	9.53 (2.60–24.40)	11.01 (3.57–25.68)	10.87 (3.53–25.36)	13.35 (4.90–29.05)	11.20 (3.64–26.13)
40–49	27.05 (14.40–46.25)	23.57 (12.55–40.31)	23.91 (13.07–40.11)	23.62 (12.91–39.63)	22.18 (11.81–37.92)	25.77 (14.43–42.51)
50–59	32.16 (18.00–53.03)	30.95 (18.03–49.54)	31.69 (19.08–49.49)	38.75 (24.83–57.66)	35.07 (21.98–53.08)	35.54 (22.53–53.32)
60–69	15.50 (7.43–28.51)	12.46 (5.70–23.65)	14.73 (7.35–26.36)	24.67 (14.62–38.99)	32.44 (20.56–48.67)	32.66 (20.71–49.01)
70–79	4.48 (0.54–16.16)	14.43 (5.80–29.72)	15.58 (6.73–30.70)	21.03 (10.50–37.62)	18.94 (9.08–34.84)	21.53 (11.13–37.61)
80+	0	3.41 (0.09–18.99)	3.23 (0.08–18.00)	6.47 (0.78–23.36)	6.62 (0.80–23.92)	9.84 (2.03–28.76)

Table S18. Annual (2017–2022) prevalence (per 100,000 people) of SLE, stratified by sex and age — ES.

Variable	2017	2018	2019	2020	2021	2022
Overall	41.01 (40.86–41.16)	27.20 (27.08–27.32)	35.83 (35.69–35.97)	43.33 (43.18–43.48)	51.04 (50.87–51.20)	57.95 (57.77–58.12)
Sex						
Female	46.19 (35.17–59.58)	40.11 (33.20–48.03)	54.81 (47.03–63.50)	69.36 (60.78–78.82)	81.19 (72.05–91.16)	93.34 (83.60–103.90)
Male	16.76 (9.58–27.21)	14.38 (10.07–19.91)	17.33 (12.86–22.84)	18.11 (13.68–23.51)	21.79 (17.02–27.49)	24.25 (19.23–30.17)
Age						
18–29	35.74 (7.37–104.41)	13.12 (6.29–24.13)	17.05 (9.54–28.12)	20.25 (12.19–31.62)	23.25 (14.74–34.89)	20.02 (12.23–30.92)
30–39	98.96 (52.70–169.17)	25.03 (15.69–37.89)	32.03 (21.91–45.21)	35.39 (24.92–48.78)	39.78 (28.79–53.59)	44.68 (32.95–59.24)
40–49	63.73 (36.43–103.48)	33.96 (23.91–46.80)	44.05 (33.27–57.19)	52.16 (40.74–65.79)	59.97 (47.90–74.14)	71.22 (58.01–86.53)
50–59	31.45 (16.75–53.78)	37.96 (26.58–52.54)	49.06 (36.75–64.16)	61.15 (47.76–77.12)	70.35 (56.35–86.77)	79.83 (65.09–96.90)
60–69	36.72 (22.11–57.33)	39.04 (26.34–55.73)	46.70 (33.21–63.84)	56.35 (41.83–74.29)	72.05 (55.84–91.49)	78.60 (61.83–98.51)
70–79	21.27 (10.20–39.12)	23.72 (12.97–39.79)	37.84 (24.25–56.30)	45.70 (30.83–65.23)	50.99 (35.52–70.91)	67.79 (49.98–89.86)
80+	2.74 (0.07–15.27)	12.30 (3.99–28.69)	19.26 (8.31–37.94)	30.17 (16.06–51.59)	38.64 (22.51–61.86)	44.79 (27.36–69.16)

Table S19. Demographic and clinical characteristics of incident SLE cases — IT.

	SLE CASES N (%)	CONTROLS N (%)	P-value	Adjusted P-value^
Overall	225	899	–	–
Sex				
Male	43 (19.1)	172 (19.1)	–	–
Female	182 (80.9)	727 (80.9)	–	–
Age, mean (SD)				
Mean (SD)	57.2 (15.8)	57.2 (15.8)	–	–
Age class				
18–29	12 (5.3)	48 (5.3)	–	–
30–39	14 (6.2)	56 (6.2)	–	–
40–49	46 (20.4)	184 (20.5)	–	–
50–59	54 (24.0)	216 (24.0)	–	–
60–69	45 (20.0)	180 (20.0)	–	–
70–79	35 (15.6)	140 (15.6)	–	–
80+	19 (8.4)	75 (8.3)	–	–
SLE symptoms (EULAR / ACR criteria)				
Present	55 (24.4)	4 (0.4)	< .0001	
Comorbidities				
Diabetes	16 (7.1)	10 (1.1)	< .0001	0.5820
Chronic kidney disease	10 (4.4)	0 (0.0)	< .0001	NE
Cardiovascular disease	26 (11.6)	6 (0.7)	< .0001	0.0001
Cerebrovascular accident	8 (3.6)	1 (0.1)	< .0001	NE
Hypertension	64 (28.4)	15 (1.7)	< .0001	< .0001
Dementia / Alzheimer's disease	5 (2.2)	1 (0.1)	0.0016	NE
Parkinson disease	2 (0.9)	1 (0.1)	0.1039	NE
Mood and anxiety disorders	34 (15.1)	8 (0.9)	< .0001	0.0001
Chronic hepatic disease	9 (4.0)	0 (0.0)	< .0001	NE
Osteoporosis	32 (14.2)	5 (0.6)	< .0001	< .0001
Malignancy	36 (16.0)	4 (0.4)	< .0001	NE
Chronic obstructive pulmonary disease	13 (5.8)	1 (0.1)	< .0001	NE
Concomitant autoimmune disease	28 (12.4)	1 (0.1)	< .0001	
Multiple sclerosis	2 (0.9)	0 (0.0)	0.0399	NE
Rheumatoid arthritis	13 (5.8)	1 (0.1)	< .0001	NE
Inflammatory bowel disease	5 (2.2)	0 (0.0)	0.0003	NE
Ankylosing spondylitis	3 (1.3)	0 (0.0)	0.0079	NE
Myasthenia gravis	2 (0.9)	0 (0.0)	0.0399	NE
Sjogren's syndrome	7 (3.1)	0 (0.0)	< .0001	NE
Body mass index (BMI)				
Mean (SD)	26.8 (5.0)	27.1 (5.0)	0.8079	
>30	13 (22.8)	7 (26.9)	0.6842	
Concomitant therapies				
N. of different V ATC level (mean ± SD)	6.6 (5.3)	0.3 (1.4)	< .0001	

^ Adjusted by diabetes, cardiovascular disease, hypertension, mood and anxiety disorders, osteoporosis.

Table S20. Demographic and clinical characteristics of incident SLE cases — UK.

	SLE CASES N (%)	CONTROLS N (%)	P-value	Adjusted P-value^
Overall	1,026	4,104	–	–
Sex				
Male	203 (19.8)	812 (19.8)	–	–
Female	823 (80.2)	3,292 (80.2)	–	–
Age, mean (SD)				
Mean (SD)	52.5 (18.6)	52.5 (18.6)	–	–
Age class				
18–29	131 (12.8)	524 (12.8)	–	–
30–39	166 (16.2)	664 (16.2)	–	–
40–49	178 (17.4)	712 (17.4)	–	–
50–59	172 (16.8)	688 (16.8)	–	–
60–69	146 (14.1)	580 (14.1)	–	–
70–79	143 (14.0)	572 (14.0)	–	–
80+	90 (8.8)	360 (8.8)	–	–
SLE symptoms (EULAR / ACR criteria)				
Present	395 (38.5)	102 (2.5)	< .0001	
Comorbidities				
Diabetes	103 (10.0)	47 (1.1)	< .0001	0.3328
Chronic kidney disease	11 (1.1)	4 (0.1)	< .0001	NE
Cardiovascular disease	236 (23.0)	53 (1.3)	< .0001	< .0001
Cerebrovascular accident	24 (2.3)	11 (0.3)	< .0001	0.8023
Hypertension	268 (26.1)	82 (2.0)	< .0001	< .0001
Dementia / Alzheimer's disease	6 (0.6)	15 (0.4)	0.4085	
Parkinson disease	6 (0.6)	1 (0.0)	0.0004	NE
Mood and anxiety disorders	395 (38.5)	147 (3.6)	< .0001	< .0001
Chronic hepatic disease	23 (2.2)	2 (0.0)	< .0001	NE
Osteoporosis	58 (5.7)	21 (0.5)	< .0001	0.0147
Malignancy	281 (27.4)	96 (2.3)	< .0001	< .0001
Chronic obstructive pulmonary disease	92 (9.0)	28 (0.7)	< .0001	0.0001
Concomitant autoimmune disease	215 (21.0)	32 (0.8)	< .0001	
Multiple sclerosis	6 (0.6)	0 (0.0)	< .0001	
Rheumatoid arthritis	80 (7.8)	6 (0.1)	< .0001	< .0001
Inflammatory bowel disease	108 (10.5)	26 (0.6)	< .0001	< .0001
Ankylosing spondylitis	4 (0.4)	0 (0.0)	0.0016	NE
Myasthenia gravis	5 (0.5)	0 (0.0)	0.0003	NE
Sjogren's syndrome	40 (3.9)	0 (0.0)	< .0001	NE
Body mass index (BMI)				
Mean (SD)	27.7 (6.2)	28.6 (6.9)	0.1634	
>30	310 (32.1)	49 (40.8)	0.0539	
Concomitant therapies				
N. of different ATC level, mean (SD)	8.0 (6.8)	0.2 (1.2)	< .0001	

^ Adjusted by diabetes, cardiovascular disease, cerebrovascular disease, hypertension, mood and anxiety disorders, osteoporosis, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease.

Table S21. Demographic and clinical characteristics of incident SLE cases — BE.

	SLE CASES N (%)	CONTROLS N (%)	P-value	Adjusted P-value^
Overall	67	268	–	–
Sex				
Male	21 (31.3)	84 (31.3)	–	–
Female	46 (68.7)	184 (68.7)	–	–
Age, mean (SD)				
Mean (SD)	46.4 (15.1)	46.4 (15.0)	–	–
Age class				
18–29	8 (11.9)	32 (11.9)	–	–
30–39	16 (23.9)	64 (23.9)	–	–
40–49	16 (23.9)	64 (23.9)	–	–
50–59	11 (16.4)	44 (16.4)	–	–
60–69	12 (17.9)	48 (17.9)	–	–
70–79	3 (4.5)	12 (4.5)	–	–
80+	1 (1.5)	4 (1.5)	–	–
SLE symptoms (EULAR / ACR criteria)				
Present	14 (20.9)	0 (0.0)	< .0001	
Comorbidities				
Diabetes	10 (14.9)	2 (0.7)	< .0001	NE
Chronic kidney disease	0 (0.0)	0 (0.0)	NE	
Cardiovascular disease	9 (13.4)	3 (1.1)	< .0001	NE
Cerebrovascular accident	2 (3.0)	0 (0.0)	0.0395	NE
Hypertension	22 (32.8)	7 (2.6)	< .0001	< .0001
Dementia / Alzheimer's disease	0 (0.0)	0 (0.0)	NE	
Parkinson disease	0 (0.0)	0 (0.0)	NE	
Mood and anxiety disorders	37 (55.2)	6 (2.2)	< .0001	0.0001
Chronic hepatic disease	0 (0.0)	0 (0.0)	NE	
Osteoporosis	8 (11.9)	1 (0.4)	< .0001	NE
Malignancy	11 (16.4)	0 (0.0)	< .0001	NE
Chronic obstructive pulmonary disease	13 (19.4)	1 (0.4)	< .0001	NE
Concomitant autoimmune disease	11 (16.4)	0 (0.0)	< .0001	
Multiple sclerosis	0 (0.0)	0 (0.0)	NE	
Rheumatoid arthritis	6 (9.0)	0 (0.0)	< .0001	NE
Inflammatory bowel disease	6 (9.0)	0 (0.0)	< .0001	NE
Ankylosing spondylitis	0 (0.0)	0 (0.0)	NE	
Myasthenia gravis	0 (0.0)	0 (0.0)	NE	
Sjogren's syndrome	0 (0.0)	0 (0.0)	NE	
Body mass index (BMI)				
Mean (SD)	24.4 (7.4)	25.0 (5.8)	0.8673	
>30	2 (16.7)	0 (0.0)	0.7804	
Concomitant therapies				
N. of different V ATC level (mean ± SD)	5.9 (5.4)	0.1 (0.9)	< .0001	

^ Adjusted by hypertension, mood and anxiety disorders.

Table S22. Demographic and clinical characteristics of incident SLE cases — RO.

	SLE CASES N (%)	CONTROLS N (%)	P-value	Adjusted P-value^
Overall	88	351	–	–
Sex				
Male	20 (22.7)	80 (22.8)	–	–
Female	68 (77.3)	271 (77.2)	–	–
Age, mean (SD)				
Mean (SD)	52.8 (14.5)	52.8 (14.5)	–	–
Age class				
18–29	6 (6.8)	24 (6.8)	–	–
30–39	10 (11.4)	40 (11.4)	–	–
40–49	19 (21.6)	75 (21.4)	–	–
50–59	24 (27.3)	96 (27.4)	–	–
60–69	17 (19.3)	68 (19.4)	–	–
70–79	10 (11.4)	40 (11.4)	–	–
80+	2 (2.3)	8 (2.3)	–	–
SLE symptoms (EULAR / ACR criteria)				
Present	4 (4.5)	0 (0.0)	0.0015	
Comorbidities				
Diabetes	15 (17.0)	12 (3.4)	< .0001	0.0229
Chronic kidney disease	0 (0.0)	1 (0.3)	NE	
Cardiovascular disease	45 (51.1)	27 (7.7)	< .0001	< .0001
Cerebrovascular accident	1 (1.1)	2 (0.6)	0.4898	
Hypertension	46 (52.3)	53 (15.1)	< .0001	0.0502
Dementia / Alzheimer's disease	0 (0.0)	1 (0.3)	NE	
Parkinson disease	1 (1.1)	0 (0.0)	0.2005	
Mood and anxiety disorders	19 (21.6)	20 (5.7)	< .0001	0.2499
Chronic hepatic disease	14 (15.9)	11 (3.1)	< .0001	0.1178
Osteoporosis	16 (18.2)	8 (2.3)	< .0001	NE
Malignancy	15 (17.0)	5 (1.4)	< .0001	NE
Chronic obstructive pulmonary disease	10 (11.4)	14 (4.0)	0.0146	NE
Concomitant autoimmune disease	25 (28.4)	5 (1.4)	< .0001	
Multiple sclerosis	0 (0.0)	0 (0.0)	NE	
Rheumatoid arthritis	16 (18.2)	1 (0.3)	< .0001	NE
Inflammatory bowel disease	10 (11.4)	4 (1.1)	0.0001	NE
Ankylosing spondylitis	1 (1.1)	0 (0.0)	0.2005	
Myasthenia gravis	0 (0.0)	0 (0.0)	NE	
Sjogren's syndrome	0 (0.0)	0 (0.0)	NE	
Body mass index (BMI)				
Mean (SD)	34.9 (0.4)	28.9 (9.1)	0.1320	
>30	2 (100.0)	3 (42.9)	0.4444	
Concomitant therapies				
N. of different V ATC level (mean ± SD)	4.0 (3.7)	0.5 (1.6)	< .0001	

^ Adjusted by diabetes, cardiovascular disease, hypertension, mood and anxiety disorders, chronic hepatic disease.

Table S23. Demographic and clinical characteristics of incident SLE cases — ES.

	SLE CASES N (%)	CONTROLS N (%)	P-value	Adjusted P-value^
Overall	406	1,620	–	–
Sex				
Male	79 (19.5)	316 (19.5)	–	–
Female	327 (80.5)	1,304 (80.5)	–	–
Age, mean (SD)				
Mean (SD)	51.2 (15.1)	51.2 (15.1)	–	–
Age class				
18–29	31 (7.6)	124 (7.7)	–	–
30–39	58 (14.3)	232 (14.3)	–	–
40–49	102 (25.1)	406 (25.1)	–	–
50–59	100 (24.6)	400 (24.7)	–	–
60–69	66 (16.3)	262 (16.2)	–	–
70–79	35 (8.6)	140 (8.6)	–	–
80+	14 (3.4)	56 (3.5)	–	–
SLE symptoms (EULAR / ACR criteria)				
Present	55 (13.5)	9 (0.6)	< .0001	
Comorbidities				
Diabetes	29 (7.1)	43 (2.7)	< .0001	0.8260
Chronic kidney disease	8 (2.0)	5 (0.3)	0.0012	NE
Cardiovascular disease	38 (9.4)	30 (1.9)	< .0001	0.0042
Cerebrovascular accident	4 (1.0)	2 (0.1)	0.0169	NE
Hypertension	89 (21.9)	107 (6.6)	< .0001	0.0558
Dementia / Alzheimer's disease	6 (1.5)	7 (0.4)	0.0299	NE
Parkinson disease	2 (0.5)	1 (0.1)	0.1042	
Mood and anxiety disorders	168 (41.4)	169 (10.4)	< .0001	< .0001
Chronic hepatic disease	3 (0.7)	2 (0.1)	0.0580	NE
Osteoporosis	29 (7.1)	17 (1.0)	< .0001	0.0052
Malignancy	54 (13.3)	52 (3.2)	< .0001	0.0306
Chronic obstructive pulmonary disease	13 (3.2)	13 (0.8)	0.0001	0.8577
Concomitant autoimmune disease	40 (9.9)	13 (0.8)	< .0001	
Multiple sclerosis	1 (0.2)	0 (0.0)	0.2004	
Rheumatoid arthritis	18 (4.4)	3 (0.2)	< .0001	NE
Inflammatory bowel disease	10 (2.5)	7 (0.4)	0.0005	NE
Ankylosing spondylitis	0 (0.0)	0 (0.0)	NE	
Myasthenia gravis	1 (0.2)	0 (0.0)	0.2004	
Sjögren's syndrome	16 (3.9)	3 (0.2)	< .0001	
Body mass index (BMI)				
Mean (SD)	27.4 (5.7)	28.0 (5.8)	0.2449	
>30	63 (30.6)	71 (33.5)	0.5242	
Concomitant therapies				
N. of different V ATC level (mean ± SD)	5.4 (4.7)	0.7 (2.1)	< .0001	

^ Adjusted by diabetes, cardiovascular disease, hypertension, mood and anxiety disorders, osteoporosis, malignancy, chronic obstructive pulmonary disease.

Table S24. Crude and multivariable logistic regression analyses of the association between SLE (the comparators are the non-SLE patients) and selected characteristics — IT.

Characteristic	**Crude OR** (95% CI)	**Adjusted OR** (95% CI)[^]
Comorbidities		
Diabetes	6.81 (3.04–15.21)	1.41 (0.42–4.77)
Chronic kidney disease	NE	
Cardiovascular disease	19.45 (7.90–47.87)	8.13 (2.83–23.32)
Cerebrovascular accident	33.11 (4.12–266.08)	
Hypertension	23.43 (13.03–42.13)	12.22 (6.39–23.38)
Dementia / Alzheimer's disease	20.41 (2.37–175.58)	
Parkinson disease	8.05 (0.73–89.22)	
Mood and anxiety disorders	19.83 (9.04–43.50)	6.30 (2.44–16.31)
Chronic hepatic disease	NE	
Osteoporosis	29.65 (11.40–77.06)	17.96 (6.41–50.29)
Malignancy	42.62 (14.99–121.15)	
Chronic obstructive pulmonary disease	55.07 (7.18–422.23)	NE
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	55.07 (7.18–422.23)	NE
Inflammatory bowel disease	NE	
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjogren's syndrome	NE	
Body mass index >30	0.80 (0.28–2.33)	
Concomitant therapies	57.63 (34.97-94.98)	

[^] Adjusted by diabetes, cardiovascular disease, hypertension, mood and anxiety disorders, osteoporosis.

Table S25. Crude and multivariable logistic regression analyses of the association between SLE (the comparators are the non-SLE patients) and selected characteristics — UK.

Characteristic	**Crude OR** (95% CI)	**Adjusted OR** (95% CI)[^]
Comorbidities		
Diabetes	9.63 (6.77–13.70)	0.78 (0.47–1.29)
Chronic kidney disease	11.11 (3.53–34.96)	
Cardiovascular disease	22.83 (16.79–31.05)	8.87 (6.08–12.95)
Cerebrovascular accident	8.91 (4.35–18.25)	1.13 (0.44–2.87)
Hypertension	17.34 (13.38–22.47)	5.30 (3.77–7.46)
Dementia / Alzheimer's disease	1.60 (0.62–4.14)	
Parkinson disease	24.14 (2.90–200.70)	
Mood and anxiety disorders	16.85 (13.70–20.73)	8.00 (6.25–10.25)
Chronic hepatic disease	47.03 (11.08–199.65)	
Osteoporosis	11.65 (7.04–19.28)	2.30 (1.18–4.48)
Malignancy	15.75 (12.33–20.11)	5.52 (4.09–7.45)
Chronic obstructive pulmonary disease	14.34 (9.34–22.02)	3.07 (1.77–5.31)
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	57.76 (25.12–132.81)	29.00 (11.68–71.97)
Inflammatory bowel disease	18.45 (11.95–28.48)	6.02 (3.57–10.14)
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjogren's syndrome	NE	
Body mass index >30	0.68 (0.46–1.01)	
Concomitant therapies	116.03 (87.28-154.25)	

[^] Adjusted by diabetes, cardiovascular disease, cerebrovascular disease, hypertension, mood and anxiety disorders, osteoporosis, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease.

Table S26. Crude and multivariable logistic regression analyses of the association between SLE (the comparators are the non-SLE patients) and selected characteristics — RO.

Characteristic	**Crude OR** (95% CI)	**Adjusted OR** (95% CI)[^]
Comorbidities		
Diabetes	5.80 (2.61–12.92)	3.10 (1.17–8.22)
Chronic kidney disease	NE	
Cardiovascular disease	12.56 (7.08–22.28)	6.78 (3.41–13.49)
Cerebrovascular accident	2.01 (0.18–22.37)	
Hypertension	6.16 (3.70–10.26)	1.94 (1.00–3.76)
Dementia / Alzheimer's disease	NE	
Parkinson disease	NE	
Mood and anxiety disorders	4.56 (2.31–8.99)	1.63 (0.71–3.78)
Chronic hepatic disease	5.85 (2.55–13.39)	2.22 (0.82–6.02)
Osteoporosis	NE	
Malignancy	14.22 (5.01–40.36)	NE
Chronic obstructive pulmonary disease	3.09 (1.32–7.21)	NE
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	77.78 (10.15–595.84)	NE
Inflammatory bowel disease	11.12 (3.40–36.39)	NE
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjogren's syndrome	NE	
Body mass index >30	NE	
Concomitant therapies	13.42 (7.11-25.34)	

[^] Adjusted by diabetes, cardiovascular disease, hypertension, mood and anxiety disorders, chronic hepatic disease.

Table S27. Crude and multivariable logistic regression analyses of the association between SLE (the comparators are the non-SLE patients) and selected characteristics — ES.

Characteristic	**Crude OR** (95% CI)	**Adjusted OR** (95% CI)[^]
Comorbidities		
Diabetes	2.82 (1.74–4.58)	1.14 (0.63–2.06)
Chronic kidney disease	6.49 (2.11–19.95)	NE
Cardiovascular disease	5.47 (3.35–8.95)	2.55 (1.41–4.60)
Cerebrovascular accident	8.05 (1.47–44.10)	
Hypertension	3.97 (2.92–5.39)	1.54 (1.05–2.25)
Dementia / Alzheimer's disease	3.46 (1.16–10.34)	
Parkinson disease	8.01 (0.72–88.61)	
Mood and anxiety disorders	6.06 (4.70–7.81)	4.55 (3.47–5.98)
Chronic hepatic disease	6.02 (1.00–36.16)	
Osteoporosis	7.25 (3.94–13.34)	3.95 (1.98–7.86)
Malignancy	4.63 (3.11–6.89)	2.61 (1.66–4.08)
Chronic obstructive pulmonary disease	4.09 (1.88–8.89)	1.61 (0.65–3.96)
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	25.01 (7.33–85.31)	NE
Inflammatory bowel disease	5.82 (2.20–15.38)	NE
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjogren's syndrome	22.11 (6.41–76.27)	NE
Body mass index >30	0.87 (0.58–1.32)	
Concomitant therapies	14.77 (11.15-19.57)	

[^] Adjusted by diabetes, cardiovascular disease, hypertension, mood and anxiety disorders, osteoporosis, malignancy, chronic obstructive pulmonary disease.

Table S28. Crude and multivariable logistic regression analyses of the association between SLE (the comparators are the non-SLE patients) and selected characteristics — BE.

Characteristic	**Crude OR** (95% CI)	**Adjusted OR** (95% CI)[^]
Comorbidities		
Diabetes	23.33 (4.98–109.37)	NE
Chronic kidney disease	NE	
Cardiovascular disease	13.71 (3.60–52.20)	NE
Cerebrovascular accident	NE	
Hypertension	18.23 (7.36–45.17)	8.83 (2.88–27.04)
Dementia / Alzheimer's disease	NE	
Parkinson disease	NE	
Mood and anxiety disorders	53.86 (21.00–138.10)	38.88 (14.68–102.98)
Chronic hepatic disease	NE	
Osteoporosis	NE	
Malignancy	NE	
Chronic obstructive pulmonary disease	64.28 (8.23–501.74)	NE
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	NE	
Inflammatory bowel disease	NE	
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjogren's syndrome	NE	
Body mass index >30	NE	
Concomitant therapies	72.19 (24.09-216.33)	

[^] Adjusted by hypertension, mood and anxiety disorders.

Table S29. Demographic and clinical characteristics of incident SLE cases treated and untreated at 24 months after ID — IT.

Characteristic	Treated N (%)	Untreated N (%)	Crude *P*-value	Adjusted *P*-value^
Overall, *n*	91	36		
Sex				
Male	11 (12.1)	5 (13.9)		
Female	80 (87.9)	31 (86.1)	0.7725	
Age, mean (SD)	53.9 (14.6)	57.5 (13.6)	0.1937	
Age class				
18–29	4 (4.4)	0 (0.0)	0.3938	
30–39	8 (8.8)	4 (11.1)		
40–49	26 (28.6)	6 (16.7)		
50–59	18 (19.8)	11 (30.6)		
60–69	23 (25.3)	7 (19.4)		
70–79	8 (8.8)	6 (16.7)		
80+	4 (4.4)	2 (5.6)		
SLE symptoms (EULAR / ACR criteria)				
Any symptom	14 (15.4)	13 (36.1)	0.0101	
Hematologic	8 (8.8)	3 (8.3)	0.9341	
Leukopenia	2 (2.2)	0 (0.0)	0.9886	
Thrombocytopenia	6 (6.6)	3 (8.3)	0.7123	
Autoimmune hemolysis	0 (0.0)	0 (0.0)	NE	
Neuropsychiatric	5 (5.5)	5 (13.9)	0.1449	
Delirium	0 (0.0)	0 (0.0)	NE	
Psychosis	3 (3.3)	2 (5.6)	0.6215	
Seizure	2 (2.2)	3 (8.3)	0.1376	
Mucocutaneous	3 (3.3)	8 (22.2)	0.0018	
Non-scarring alopecia	2 (2.2)	5 (13.9)	0.0194	0.0826
Oral ulcers	1 (1.1)	3 (8.3)	0.0686	0.1789
Serosal	2 (2.2)	1 (2.8)	0.8465	
Pleural & pericardial effusion	2 (2.2)	1 (2.8)	0.8465	
Acute pericarditis	0 (0.0)	0 (0.0)	NE	
Comorbidities				
Diabetes	3 (3.3)	4 (11.1)	0.0994	
Chronic kidney disease	1 (1.1)	0 (0.0)	0.9920	
Cardiovascular disease	8 (8.8)	1 (2.8)	0.4437	
Cerebrovascular accident	3 (3.3)	0 (0.0)	0.5578	
Hypertension	18 (19.8)	9 (25.0)	0.5170	
Dementia / Alzheimer's disease	0 (0.0)	0 (0.0)	NE	
Parkinson disease	0 (0.0)	0 (0.0)	NE	
Mood and anxiety disorders	5 (5.5)	7 (19.4)	0.0371	0.3337
Chronic hepatic disease	1 (1.1)	2 (5.6)	0.1934	
Osteoporosis	10 (11.0)	5 (13.9)	0.7611	
Malignancy	15 (16.5)	11 (30.6)	0.0765	0.2145
COPD	3 (3.3)	1 (2.8)	0.8802	
Concomitant autoimmune disease	12 (13.2)	2 (5.6)	0.3466	
Multiple sclerosis	2 (2.2)	0 (0.0)	0.9886	
Rheumatoid arthritis	4 (4.4)	2 (5.6)	0.7817	
Inflammatory bowel disease	3 (3.3)	0 (0.0)	0.5578	
Ankylosing spondylitis	0 (0.0)	1 (2.8)	0.9909	
Myasthenia gravis	1 (1.1)	0 (0.0)	0.9920	
Sjögren's syndrome	3 (3.3)	1 (2.8)	0.8802	
Body mass index, mean (SD)	27.6 (5.1)	25.9 (3.8)	0.3364	
>30	8 (27.6)	1 (14.3)	0.6518	
Concomitant therapies				
N. of different ATC level, mean (SD)	6.7 (4.7)	3.9 (4.5)	0.0028	

^ Adjusted by non-scarring alopecia, oral ulcers, mood and anxiety disorders, malignancy.

Table S30. Demographic and clinical characteristics of incident SLE cases treated and untreated at 24 months after ID — UK.

Characteristic	Treated N (%)	Untreated N (%)	Crude *P*-value	Adjusted *P*-value^
Overall, *n*	516	316		
Sex				
Male	76 (14.7)	72 (22.8)		
Female	440 (85.3)	244 (77.2)	0.0032	0.0829
Age, mean (SD)	50.3 (17.3)	53.5 (19.1)	0.0145	
Age class				
18–29	66 (12.8)	43 (13.6)	0.0042	
30–39	94 (18.2)	48 (15.2)		
40–49	98 (19.0)	49 (15.5)		
50–59	89 (17.2)	54 (17.1)		
60–69	82 (15.9)	38 (12.0)		
70–79	64 (12.4)	48 (15.2)		
80+	23 (4.5)	36 (11.4)		
SLE symptoms (EULAR / ACR criteria)				
Any symptom	161 (31.2)	154 (48.7)	< .0001	
Hematologic	33 (6.4)	31 (9.8)	0.0728	
Leukopenia	12 (2.3)	10 (3.2)	0.4642	
Thrombocytopenia	19 (3.7)	20 (6.3)	0.0796	0.1719
Autoimmune hemolysis	2 (0.4)	3 (0.9)	0.3738	
Neuropsychiatric	54 (10.5)	69 (21.8)	< .0001	
Delirium	7 (1.4)	5 (1.6)	0.7732	
Psychosis	16 (3.1)	22 (7.0)	0.0096	0.0545
Seizure	37 (7.2)	45 (14.2)	0.0009	0.0065
Mucocutaneous	61 (11.8)	49 (15.5)	0.1278	
Non-scarring alopecia	61 (11.8)	48 (15.2)	0.1623	
Oral ulcers	0 (0.0)	1 (0.3)	0.3798	
Serosal	50 (9.7)	42 (13.3)	0.1079	
Pleural & pericardial effusion	44 (8.5)	35 (11.1)	0.2235	
Acute pericarditis	8 (1.6)	8 (2.5)	0.3172	
Comorbidities				
Diabetes	47 (9.1)	37 (11.7)	0.2269	
Chronic kidney disease	6 (1.2)	2 (0.6)	0.7171	
Cardiovascular disease	100 (19.4)	80 (25.3)	0.0435	0.3733
Cerebrovascular accident	7 (1.4)	12 (3.8)	0.0222	0.1847
Hypertension	119 (23.1)	93 (29.4)	0.0408	0.3386
Dementia / Alzheimer's disease	1 (0.2)	3 (0.9)	0.1562	
Parkinson disease	1 (0.2)	2 (0.6)	0.5610	
Mood and anxiety disorders	210 (40.7)	115 (36.4)	0.2167	
Chronic hepatic disease	12 (2.3)	7 (2.2)	0.9176	
Osteoporosis	29 (5.6)	18 (5.7)	0.9632	
Malignancy	129 (25.0)	99 (31.3)	0.0470	0.1406
COPD	34 (6.6)	33 (10.4)	0.0474	0.7407
Concomitant autoimmune disease	124 (24.0)	54 (17.1)	0.0178	
Multiple sclerosis	5 (1.0)	1 (0.3)	0.4167	
Rheumatoid arthritis	48 (9.3)	18 (5.7)	0.0618	0.0399
Inflammatory bowel disease	60 (11.6)	28 (8.9)	0.2078	
Ankylosing spondylitis	0 (0.0)	2 (0.6)	0.1440	
Myasthenia gravis	1 (0.2)	2 (0.6)	0.5610	
Sjögren's syndrome	23 (4.5)	9 (2.8)	0.2414	
Body mass index, mean (SD)	28.2 (6.3)	27.3 (5.9)	0.0330	
>30	172 (35.2)	90 (29.5)	0.0947	
Concomitant therapies				
N. of different ATC level, mean (SD)	8.4 (6.6)	6.8 (6.6)	0.0004	

^ Adjusted by sex, thrombocytopenia, psychosis, seizure, cardiovascular disease, cerebrovascular disease, hypertension, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis.

Table S31. Demographic and clinical characteristics of incident SLE cases treated and untreated at 24 months after ID — BE.

Characteristic	Treated N (%)	Untreated N (%)	Crude *P*-value	Adjusted *P*-value[^]
Overall, *n*	21	23		
Sex				
Male	6 (28.6)	10 (43.5)		
Female	15 (71.4)	13 (56.5)	0.3046	
Age, mean (SD)	43.8 (14.7)	50.3 (16.7)	0.1771	
Age class				
18–29	3 (14.3)	3 (13.0)	0.7218	
30–39	7 (33.3)	3 (13.0)		
40–49	3 (14.3)	5 (21.7)		
50–59	4 (19.0)	4 (17.4)		
60–69	3 (14.3)	6 (26.1)		
70–79	1 (4.8)	1 (4.3)		
80+	0 (0.0)	1 (4.3)		
SLE symptoms (EULAR / ACR criteria)				
Any symptom	5 (23.8)	6 (26.1)	0.8617	
Hematologic	0 (0.0)	0 (0.0)	NE	
Leukopenia	0 (0.0)	0 (0.0)	NE	
Thrombocytopenia	0 (0.0)	0 (0.0)	NE	
Autoimmune hemolysis	0 (0.0)	0 (0.0)	NE	
Neuropsychiatric	4 (19.0)	5 (21.7)	0.8251	
Delirium	0 (0.0)	0 (0.0)	NE	
Psychosis	3 (14.3)	2 (8.7)	0.6575	
Seizure	2 (9.5)	3 (13.0)	0.7143	
Mucocutaneous	1 (4.8)	4 (17.4)	0.3477	
Non-scarring alopecia	1 (4.8)	4 (17.4)	0.3477	
Oral ulcers	0 (0.0)	0 (0.0)	NE	
Serosal	3 (14.3)	0 (0.0)	0.1004	
Pleural & pericardial effusion	0 (0.0)	0 (0.0)	NE	
Acute pericarditis	3 (14.3)	0 (0.0)	0.1004	
Comorbidities				
Diabetes	3 (14.3)	6 (26.1)	0.4618	
Chronic kidney disease	0 (0.0)	0 (0.0)	NE	
Cardiovascular disease	1 (4.8)	5 (21.7)	0.1884	
Cerebrovascular accident	0 (0.0)	0 (0.0)	NE	
Hypertension	6 (28.6)	10 (43.5)	0.3046	
Dementia / Alzheimer's disease	0 (0.0)	0 (0.0)	NE	
Parkinson disease	0 (0.0)	0 (0.0)	NE	
Mood and anxiety disorders	14 (66.7)	12 (52.2)	0.3288	
Chronic hepatic disease	0 (0.0)	0 (0.0)	NE	
Osteoporosis	3 (14.3)	4 (17.4)	0.7788	
Malignancy	4 (19.0)	3 (13.0)	0.6927	
COPD	3 (14.3)	8 (34.8)	0.1168	
Concomitant autoimmune disease	5 (23.8)	3 (13.0)	0.4485	
Multiple sclerosis	0 (0.0)	0 (0.0)	NE	
Rheumatoid arthritis	4 (19.0)	1 (4.3)	0.1765	
Inflammatory bowel disease	2 (9.5)	2 (8.7)	0.9240	
Ankylosing spondylitis	0 (0.0)	0 (0.0)	NE	
Myasthenia gravis	0 (0.0)	0 (0.0)	NE	
Sjögren's syndrome	0 (0.0)	0 (0.0)	NE	
Body mass index, mean (SD)	22.6 (3.9)	27.6 (9.4)	0.3315	
>30	0 (0.0)	2 (33.3)	0.9969	
Concomitant therapies				
N. of different ATC level, mean (SD)	7.5 (5.6)	5.6 (4.9)	0.2250	

[^] It was not possible to perform any adjusted model.

Table S32. Demographic and clinical characteristics of incident SLE cases treated and untreated at 24 months after ID — RO.

Characteristic	Treated N (%)	Untreated N (%)	Crude *P*-value	Adjusted *P*-value[^]
Overall, *n*	38	31		
Sex				
Male	5 (13.2)	8 (25.8)		
Female	33 (86.8)	23 (74.2)	0.1814	
Age, mean (SD)	52.7 (13.8)	55.0 (13.6)	0.4971	
Age class				
18–29	3 (7.9)	0 (0.0)	0.3172	
30–39	4 (10.5)	4 (12.9)		
40–49	5 (13.2)	9 (29.0)		
50–59	14 (36.8)	7 (22.6)		
60–69	8 (21.1)	5 (16.1)		
70–79	3 (7.9)	5 (16.1)		
80+	1 (2.6)	1 (3.2)		
SLE symptoms (EULAR / ACR criteria)				
Any symptom	0 (0.0)	1 (3.2)	0.4493	
Hematologic	0 (0.0)	0 (0.0)	NE	
Leukopenia	0 (0.0)	0 (0.0)	NE	
Thrombocytopenia	0 (0.0)	0 (0.0)	NE	
Autoimmune hemolysis	0 (0.0)	0 (0.0)	NE	
Neuropsychiatric	0 (0.0)	1 (3.2)	0.4493	
Delirium	0 (0.0)	0 (0.0)	NE	
Psychosis	0 (0.0)	0 (0.0)	NE	
Seizure	0 (0.0)	1 (3.2)	0.4493	
Mucocutaneous	0 (0.0)	0 (0.0)	NE	
Non-scarring alopecia	0 (0.0)	0 (0.0)	NE	
Oral ulcers	0 (0.0)	0 (0.0)	NE	
Serosal	0 (0.0)	0 (0.0)	NE	
Pleural & pericardial effusion	0 (0.0)	0 (0.0)	NE	
Acute pericarditis	0 (0.0)	0 (0.0)	NE	
Comorbidities				
Diabetes	5 (13.2)	6 (19.4)	0.5251	
Chronic kidney disease	0 (0.0)	0 (0.0)	NE	
Cardiovascular disease	23 (60.5)	15 (48.4)	0.3133	
Cerebrovascular accident	1 (2.6)	0 (0.0)	0.9916	
Hypertension	22 (57.9)	15 (48.4)	0.4308	
Dementia / Alzheimer's disease	0 (0.0)	0 (0.0)	NE	
Parkinson disease	0 (0.0)	1 (3.2)	0.4493	
Mood and anxiety disorders	10 (26.3)	6 (19.4)	0.4956	
Chronic hepatic disease	7 (18.4)	5 (16.1)	0.8027	
Osteoporosis	10 (26.3)	5 (16.1)	0.3075	
Malignancy	8 (21.1)	5 (16.1)	0.6029	
COPD	7 (18.4)	2 (6.5)	0.1714	
Concomitant autoimmune disease	14 (36.8)	7 (22.6)	0.2003	
Multiple sclerosis	0 (0.0)	0 (0.0)	NE	
Rheumatoid arthritis	10 (26.3)	2 (6.5)	0.0304	
Inflammatory bowel disease	5 (13.2)	5 (16.1)	0.7445	
Ankylosing spondylitis	0 (0.0)	0 (0.0)	NE	
Myasthenia gravis	0 (0.0)	0 (0.0)	NE	
Sjögren's syndrome	0 (0.0)	0 (0.0)	NE	
Body mass index, mean (SD)	NA (NA)	NA (NA)	NE	
>30	NA (NA)	NA (NA)	NE	
Concomitant therapies				
N. of different ATC level, mean (SD)	5.4 (3.1)	3.0 (3.6)	0.0047	

[^] It was not possible to perform any adjusted model.

Table S33. Demographic and clinical characteristics of incident SLE cases treated and untreated at 24 months after ID — ES.

Characteristic	Treated N (%)	Untreated N (%)	Crude *P*-value	Adjusted *P*-value[^]
Overall, *n*	257	134		
Sex				
Male	43 (16.7)	31 (23.1)		
Female	214 (83.3)	103 (76.9)	0.1250	
Age, mean (SD)	51.0 (14.6)	50.2 (14.8)	0.6179	
Age class				
18–29	20 (7.8)	10 (7.5)	0.1594	
30–39	36 (14.0)	22 (16.4)		
40–49	67 (26.1)	32 (23.9)		
50–59	56 (21.8)	42 (31.3)		
60–69	51 (19.8)	14 (10.4)		
70–79	21 (8.2)	9 (6.7)		
80+	6 (2.3)	5 (3.7)		
SLE symptoms (EULAR / ACR criteria)				
Any symptom	39 (15.2)	14 (10.4)	0.1950	
Hematologic	10 (3.9)	4 (3.0)	0.7793	
Leukopenia	5 (1.9)	1 (0.7)	0.6687	
Thrombocytopenia	5 (1.9)	3 (2.2)	0.8460	
Autoimmune hemolysis	0 (0.0)	0 (0.0)	NE	
Neuropsychiatric	16 (6.2)	8 (6.0)	0.9204	
Delirium	0 (0.0)	0 (0.0)	NE	
Psychosis	7 (2.7)	2 (1.5)	0.7242	
Seizure	9 (3.5)	6 (4.5)	0.6336	
Mucocutaneous	16 (6.2)	5 (3.7)	0.2991	
Non-scarring alopecia	14 (5.4)	5 (3.7)	0.4538	
Oral ulcers	2 (0.8)	0 (0.0)	0.5483	
Serosal	4 (1.6)	0 (0.0)	0.3036	
Pleural & pericardial effusion	0 (0.0)	0 (0.0)	NE	
Acute pericarditis	4 (1.6)	0 (0.0)	0.3036	
Comorbidities				
Diabetes	17 (6.6)	8 (6.0)	0.8047	
Chronic kidney disease	6 (2.3)	1 (0.7)	0.4301	
Cardiovascular disease	21 (8.2)	12 (9.0)	0.7912	
Cerebrovascular accident	2 (0.8)	2 (1.5)	0.6093	
Hypertension	56 (21.8)	27 (20.1)	0.7065	
Dementia / Alzheimer's disease	3 (1.2)	2 (1.5)	0.7864	
Parkinson disease	1 (0.4)	0 (0.0)	0.9808	
Mood and anxiety disorders	111 (43.2)	52 (38.8)	0.4039	
Chronic hepatic disease	3 (1.2)	0 (0.0)	0.5541	
Osteoporosis	20 (7.8)	8 (6.0)	0.5096	
Malignancy	36 (14.0)	16 (11.9)	0.5677	
COPD	7 (2.7)	5 (3.7)	0.5544	
Concomitant autoimmune disease	34 (13.2)	5 (3.7)	0.0029	
Multiple sclerosis	1 (0.4)	0 (0.0)	0.9808	
Rheumatoid arthritis	13 (5.1)	4 (3.0)	0.3400	
Inflammatory bowel disease	9 (3.5)	1 (0.7)	0.1745	
Ankylosing spondylitis	0 (0.0)	0 (0.0)	NE	
Myasthenia gravis	1 (0.4)	0 (0.0)	0.9808	
Sjögren's syndrome	15 (5.8)	1 (0.7)	0.0159	
Body mass index, mean (SD)	27.6 (5.7)	26.6 (5.8)	0.2704	
>30	40 (29.9)	19 (30.2)	0.9649	
Concomitant therapies				
N. of different ATC level, mean (SD)	6.3 (4.7)	3.4 (3.7)	< .0001	

[^] It was not possible to perform any adjusted model.

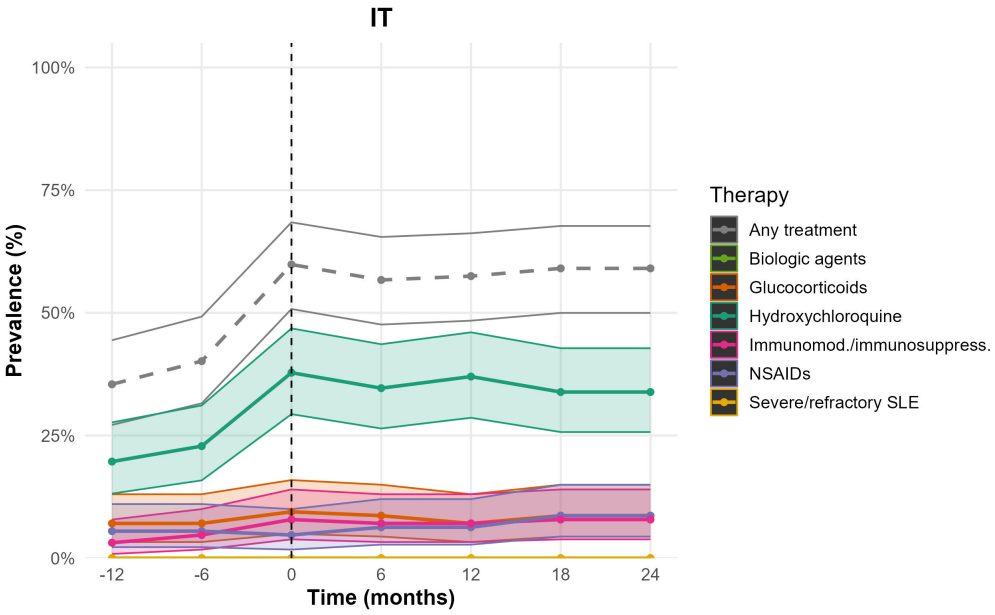

Figure S1. Prevalence of treatment classes - IT Prevalence of treatment classes from 12 months before and 24 months after ID in the Italian cohort. The lines represent the estimates, and the bands indicate the 95% confidence intervals; the vertical dashed line marks ID.

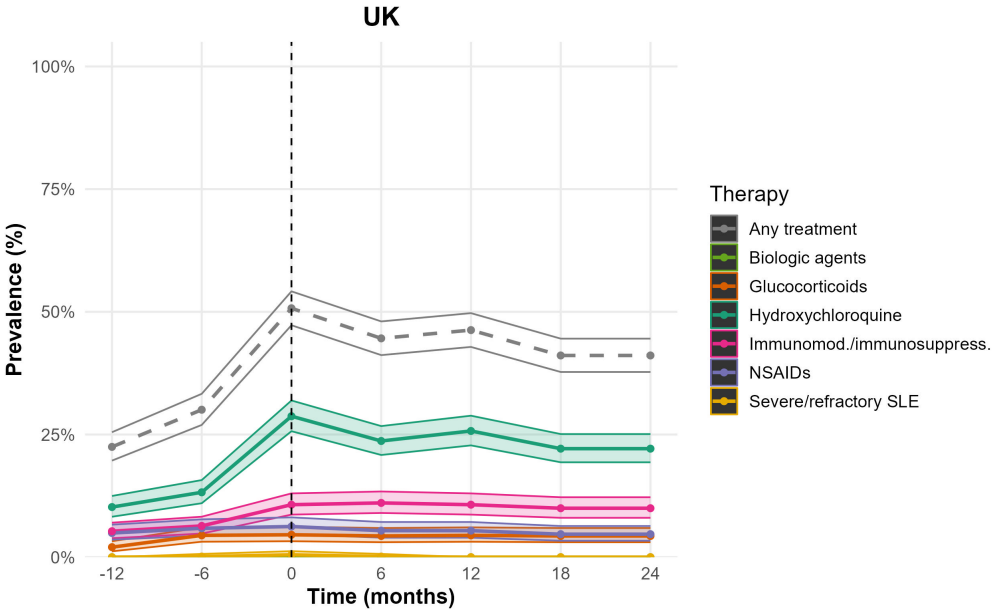

Figure S2. Prevalence of treatment classes - UK Prevalence of treatment classes from 12 months before and 24 months after ID in the UK cohort. The lines represent the estimates, and the bands indicate the 95% confidence intervals; the vertical dashed line marks ID.

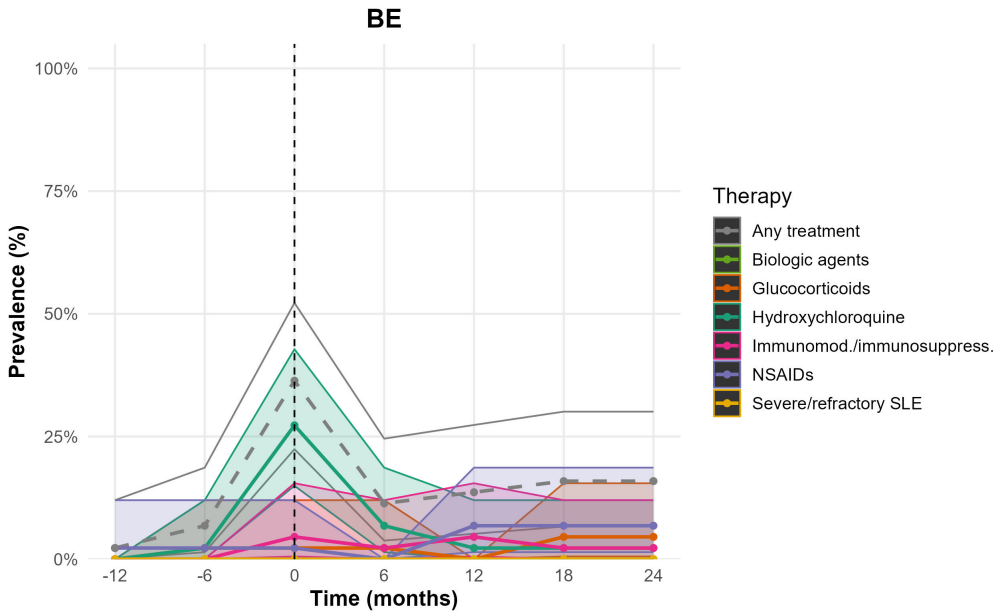

Figure S3. Prevalence of treatment classes - BE Prevalence of treatment classes from 12 months before and 24 months after ID in the Belgium cohort. The lines represent the estimates, and the bands indicate the 95% confidence intervals; the vertical dashed line marks ID.

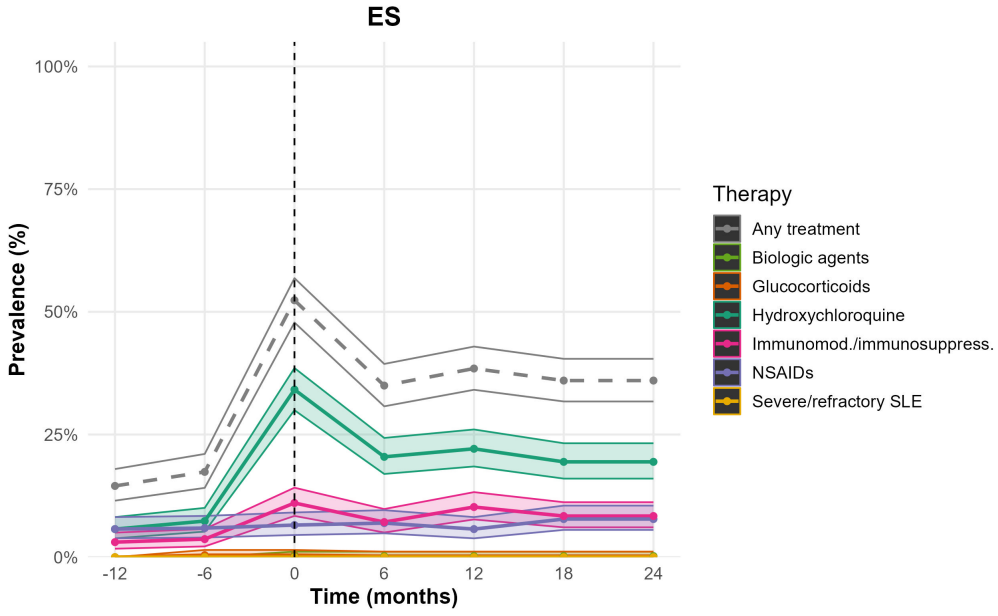

Figure S4. Prevalence of treatment classes - ES Prevalence of treatment classes from 12 months before and 24 months after ID in the Spanish cohort. The lines represent the estimates, and the bands indicate the 95% confidence intervals; the vertical dashed line marks ID.

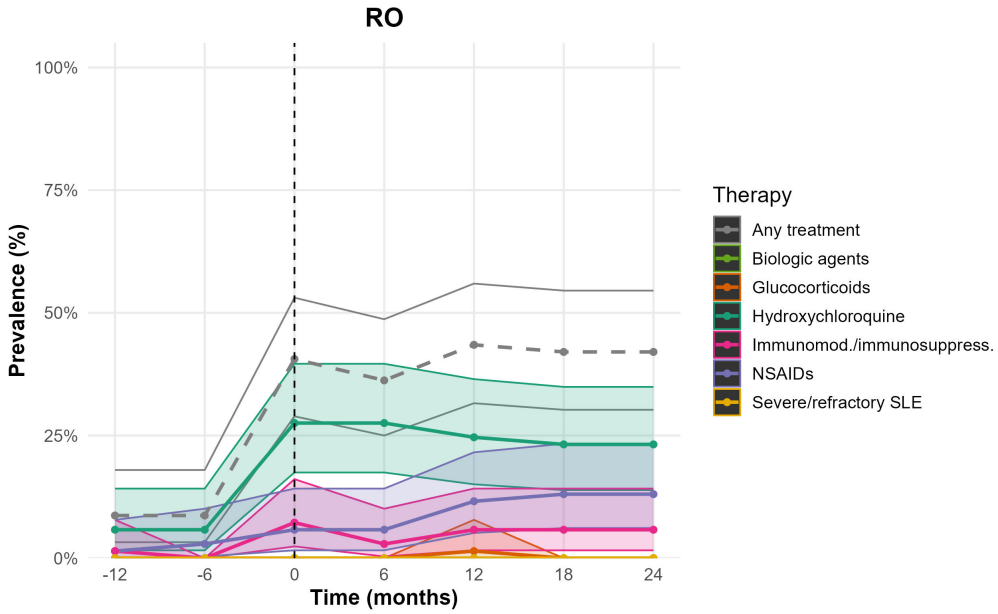

Figure S5. Prevalence of treatment classes - RO Prevalence of treatment classes from 12 months before and 24 months after ID in the Romanian cohort. The lines represent the estimates, and the bands indicate the 95% confidence intervals; the vertical dashed line marks ID.

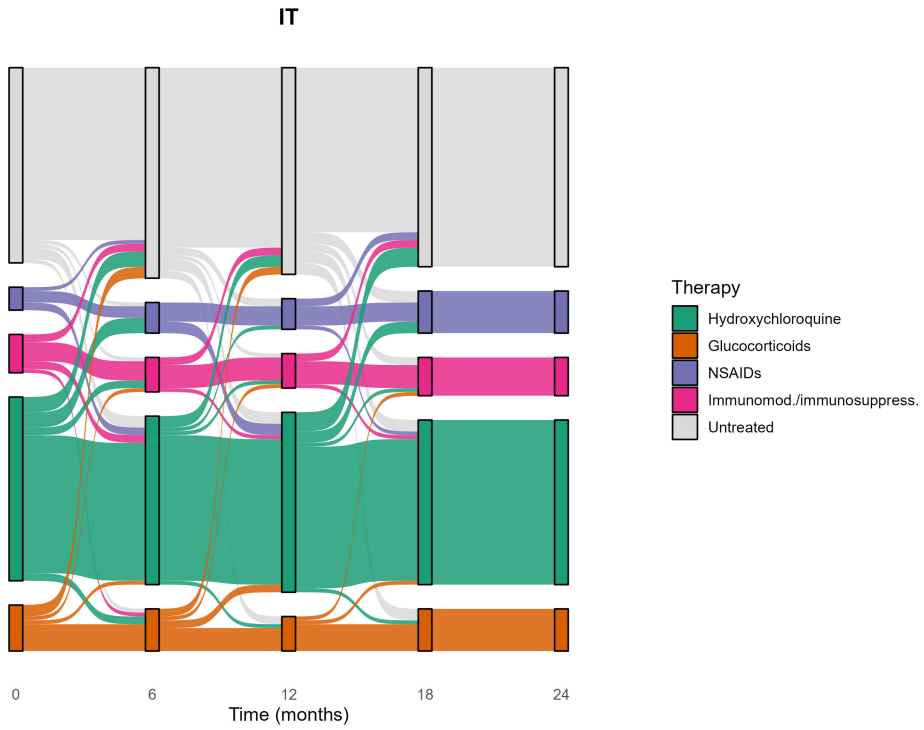

Figure S6. Sankey plot of treatment classes utilization - IT Sankey diagram of treatment class utilization in the Italian cohort from index to 24 months. Each node represents a time point (0, 6, 12, 18, 24 months); link widths are proportional to the number of patients transitioning between classes, including 'Untreated.

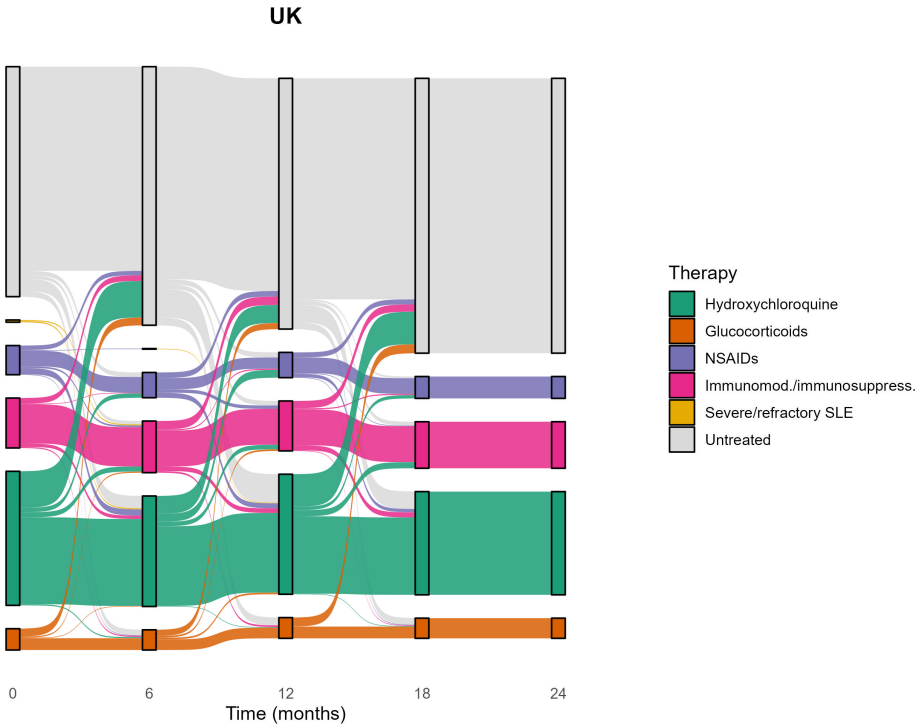

Figure S7. Sankey plot of treatment classes utilization - UK Sankey diagram of treatment class utilization in the UK cohort from index to 24 months. Each node represents a time point (0, 6, 12, 18, 24 months); link widths are proportional to the number of patients transitioning between classes, including 'Untreated.

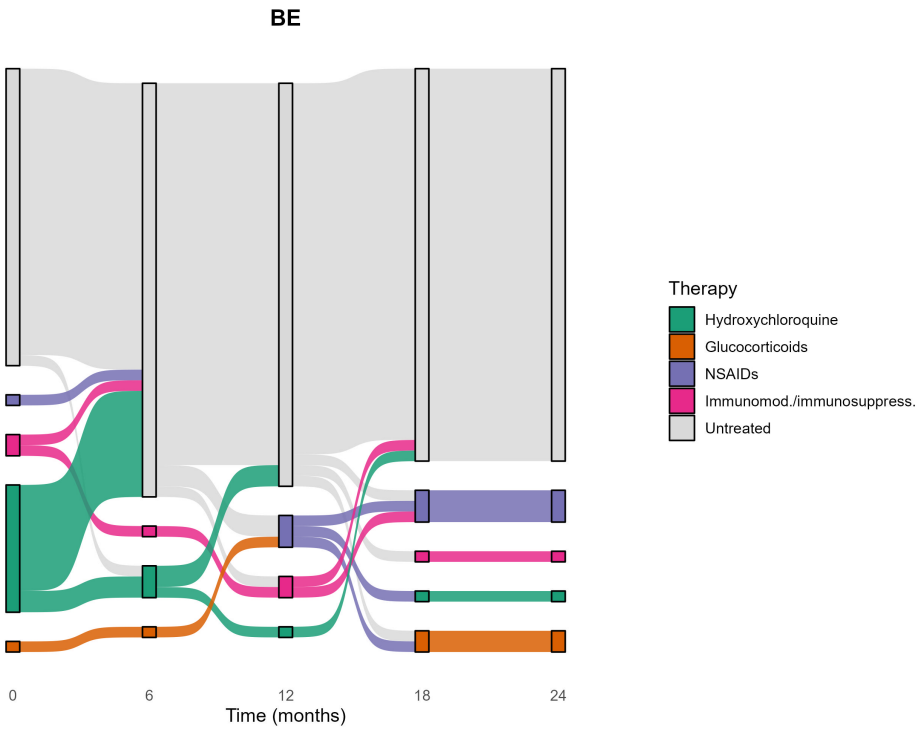

Figure S8. Sankey plot of treatment classes utilization - BE Sankey diagram of treatment class utilization in the Belgium cohort from index to 24 months. Each node represents a time point (0, 6, 12, 18, 24 months); link widths are proportional to the number of patients transitioning between classes, including 'Untreated.

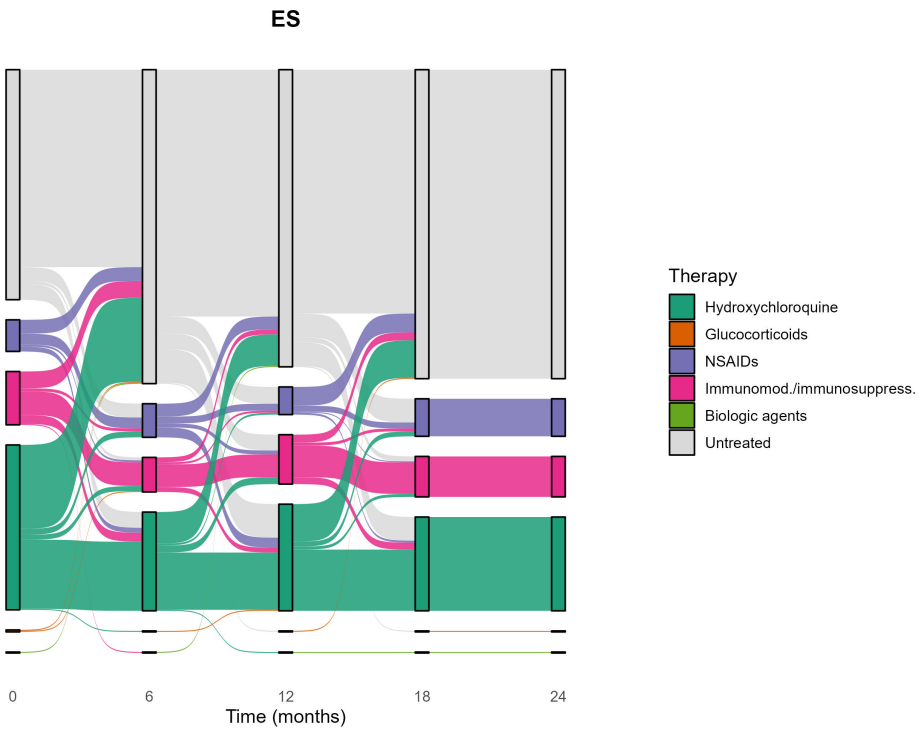

Figure S9. Sankey plot of treatment classes utilization - ES Sankey diagram of treatment class utilization in the Spanish cohort from index to 24 months. Each node represents a time point (0, 6, 12, 18, 24 months); link widths are proportional to the number of patients transitioning between classes, including 'Untreated.

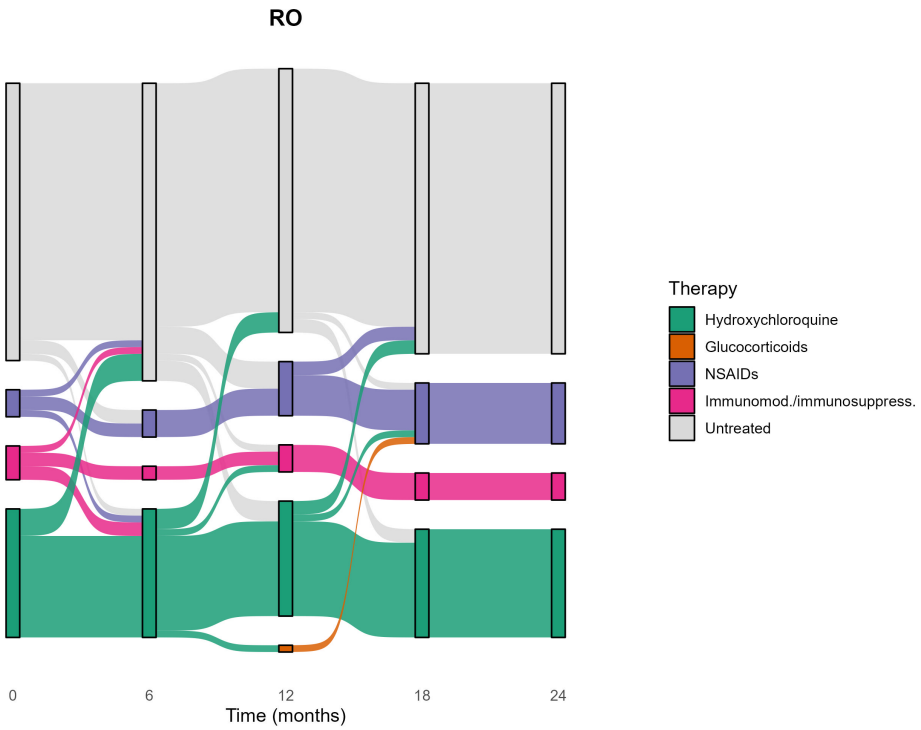

Figure S10. Sankey plot of treatment classes utilization - RO Sankey diagram of treatment class utilization in the Romanian cohort from index to 24 months. Each node represents a time point (0, 6, 12, 18, 24 months); link widths are proportional to the number of patients transitioning between classes, including 'Untreated.

Table S34. Crude and multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics — IT.

Characteristic	Crude OR (95% CI)	Adjusted OR^ (95% CI)
Sex		
Female (Ref.: Male)	1.17 (0.38–3.65)	
Age class		
>50 (Ref.: <50)	0.54 (0.23–1.24)	
SLE symptoms (EULAR / ACR criteria)		
Any symptom	0.32 (0.13–0.78)	
Hematologic	1.06 (0.26–4.24)	
Leukopenia	NE	
Thrombocytopenia	0.78 (0.18–3.29)	
Autoimmune hemolysis	NE	
Neuropsychiatric	0.36 (0.10–1.33)	
Delirium	NE	
Psychosis	0.58 (0.09–3.62)	
Seizure	0.25 (0.04–1.55)	
Mucocutaneous	0.12 (0.03–0.48)	
Non-scarring alopecia	0.14 (0.03–0.76)	0.20 (0.03–1.23)
Oral ulcers	0.12 (0.01–1.22)	0.18 (0.01–2.20)
Serosal	0.79 (0.07–8.95)	
Pleural & pericardial effusion	0.79 (0.07–8.95)	
Acute pericarditis	NE	
Comorbidities		
Diabetes	0.27 (0.06–1.29)	
Chronic kidney disease	NE	
Cardiovascular disease	3.37 (0.41–27.99)	
Cerebrovascular accident	NE	
Hypertension	0.74 (0.30–1.84)	
Dementia / Alzheimer's disease	NE	
Parkinson disease	NE	
Mood and anxiety disorders	0.24 (0.07–0.82)	0.49 (0.11–2.10)
Chronic hepatic disease	0.19 (0.02–2.15)	
Osteoporosis	0.77 (0.24–2.42)	
Malignancy	0.45 (0.18–1.10)	0.54 (0.21–1.42)
COPD	1.19 (0.12–11.86)	
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	0.78 (0.14–4.47)	
Inflammatory bowel disease	NE	
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjögren's syndrome	1.19 (0.12–11.86)	
Body mass index >30	1.28 (0.95–1.73)	

^ Adjusted by non-scarring alopecia, oral ulcers, mood and anxiety disorders, malignancy.

Table S35. Crude and multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics — UK.

Characteristic	Crude OR (95% CI)	Adjusted OR^ (95% CI)
Sex		
Female (Ref.: Male)	1.71 (1.19–2.44)	1.40 (0.96–2.05)
Age class		
>50 (Ref.: <50)	0.80 (0.60–1.05)	
SLE symptoms (EULAR / ACR criteria)		
Any symptom	0.48 (0.36–0.64)	
Hematologic	0.63 (0.38–1.05)	
Leukopenia	0.73 (0.31–1.71)	
Thrombocytopenia	0.57 (0.30–1.08)	0.62 (0.32–1.23)
Autoimmune hemolysis	0.41 (0.07–2.44)	
Neuropsychiatric	0.42 (0.28–0.62)	
Delirium	0.86 (0.27–2.72)	
Psychosis	0.43 (0.22–0.83)	0.51 (0.26–1.01)
Seizure	0.47 (0.29–0.74)	0.52 (0.32–0.83)
Mucocutaneous	0.73 (0.49–1.10)	
Non-scarring alopecia	0.75 (0.50–1.12)	
Oral ulcers	NE	
Serosal	0.70 (0.45–1.08)	
Pleural & pericardial effusion	0.75 (0.47–1.19)	
Acute pericarditis	0.61 (0.23–1.63)	
Comorbidities		
Diabetes	0.76 (0.48–1.19)	
Chronic kidney disease	1.85 (0.37–9.21)	
Cardiovascular disease	0.71 (0.51–0.99)	0.85 (0.59–1.22)
Cerebrovascular accident	0.35 (0.14–0.89)	0.51 (0.19–1.38)
Hypertension	0.72 (0.52–0.99)	0.85 (0.60–1.19)
Dementia / Alzheimer's disease	0.20 (0.02–1.96)	
Parkinson disease	0.30 (0.03–3.38)	
Mood and anxiety disorders	1.20 (0.90–1.60)	
Chronic hepatic disease	1.05 (0.41–2.70)	
Osteoporosis	0.99 (0.54–1.81)	
Malignancy	0.73 (0.54–1.00)	0.79 (0.57–1.08)
COPD	0.60 (0.37–1.00)	0.91 (0.53–1.57)
Concomitant autoimmune disease		
Multiple sclerosis	3.08 (0.36–26.50)	
Rheumatoid arthritis	1.70 (0.97–2.98)	1.84 (1.03–3.29)
Inflammatory bowel disease	1.35 (0.84–2.17)	
Ankylosing spondylitis	NE	
Myasthenia gravis	0.30 (0.03–3.38)	
Sjögren's syndrome	1.59 (0.73–3.48)	
Body mass index >30	1.30 (0.96–1.77)	

^ Adjusted by sex, thrombocytopenia, psychosis, seizure, cardiovascular disease, cerebrovascular disease, hypertension, malignancy, chronic obstructive pulmonary disease, rheumatoid arthritis.

Table S36. Crude and multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics — BE.

Characteristic	Crude OR (95% CI)	Adjusted OR[^] (95% CI)
Sex		
Female (Ref.: Male)	1.92 (0.55–6.75)	
Age class		
>50 (Ref.: <50)	0.56 (0.17–1.88)	
SLE symptoms (EULAR / ACR criteria)		
Any symptom	0.89 (0.23–3.48)	
Hematologic	NE	
Leukopenia	NE	
Thrombocytopenia	NE	
Autoimmune hemolysis	NE	
Neuropsychiatric	0.85 (0.19–3.69)	
Delirium	NE	
Psychosis	1.75 (0.26–11.66)	
Seizure	0.70 (0.11–4.67)	
Mucocutaneous	0.24 (0.02–2.32)	
Non-scarring alopecia	0.24 (0.02–2.32)	
Oral ulcers	NE	
Serosal	NE	
Pleural & pericardial effusion	NE	
Acute pericarditis	NE	
Comorbidities		
Diabetes	0.47 (0.10–2.19)	
Chronic kidney disease	NE	
Cardiovascular disease	0.18 (0.02–1.69)	
Cerebrovascular accident	NE	
Hypertension	0.52 (0.15–1.82)	
Dementia / Alzheimer's disease	NE	
Parkinson disease	NE	
Mood and anxiety disorders	1.83 (0.54–6.22)	
Chronic hepatic disease	NE	
Osteoporosis	0.79 (0.16–4.04)	
Malignancy	1.57 (0.31–8.01)	
COPD	0.31 (0.07–1.39)	
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	5.18 (0.53–50.65)	
Inflammatory bowel disease	1.11 (0.14–8.64)	
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjögren's syndrome	NE	
Body mass index >30	NE	

[^] It was not possible to perform any adjusted model.

Table S37. Crude and multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics — RO.

Characteristic	Crude OR (95% CI)	Adjusted OR[^] (95% CI)
Sex		
Female (Ref.: Male)	2.30 (0.67–7.91)	
Age class		
>50 (Ref.: <50)	1.56 (0.58–4.20)	
SLE symptoms (EULAR / ACR criteria)		
Any symptom	NE	
Hematologic	NE	
Leukopenia	NE	
Thrombocytopenia	NE	
Autoimmune hemolysis	NE	
Neuropsychiatric	NE	
Delirium	NE	
Psychosis	NE	
Seizure	NE	
Mucocutaneous	NE	
Non-scarring alopecia	NE	
Oral ulcers	NE	
Serosal	NE	
Pleural & pericardial effusion	NE	
Acute pericarditis	NE	
Comorbidities		
Diabetes	0.63 (0.17–2.31)	
Chronic kidney disease	NE	
Cardiovascular disease	1.64 (0.63–4.27)	
Cerebrovascular accident	NE	
Hypertension	1.47 (0.56–3.81)	
Dementia / Alzheimer's disease	NE	
Parkinson disease	NE	
Mood and anxiety disorders	1.49 (0.47–4.68)	
Chronic hepatic disease	1.17 (0.33–4.14)	
Osteoporosis	1.86 (0.56–6.16)	
Malignancy	1.39 (0.40–4.77)	
COPD	3.27 (0.63–17.07)	
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	5.18 (1.04–25.77)	
Inflammatory bowel disease	0.79 (0.21–3.01)	
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjögren's syndrome	NE	
Body mass index >30	NE	

[^] It was not possible to perform any adjusted model.

Table S38. Crude and multivariable logistic regression analyses of the association between SLE treatment (comparators are the untreated at 24 months) and selected characteristics — ES.

Characteristic	Crude OR (95% CI)	Adjusted OR(̂95% CI)
Sex		
Female (Ref.: Male)	1.50 (0.89–2.51)	
Age class		
>50 (Ref.: <50)	1.00 (0.66–1.51)	
SLE symptoms (EULAR / ACR criteria)		
Any symptom	1.53 (0.80–2.94)	
Hematologic	1.32 (0.40–4.28)	
Leukopenia	2.64 (0.31–22.82)	
Thrombocytopenia	0.87 (0.20–3.68)	
Autoimmune hemolysis	NE	
Neuropsychiatric	1.05 (0.44–2.51)	
Delirium	NE	
Psychosis	1.85 (0.38–9.02)	
Seizure	0.77 (0.27–2.22)	
Mucocutaneous	1.71 (0.61–4.78)	
Non-scarring alopecia	1.49 (0.52–4.22)	
Oral ulcers	NE	
Serosal	NE	
Pleural & pericardial effusion	NE	
Acute pericarditis	NE	
Comorbidities		
Diabetes	1.12 (0.47–2.66)	
Chronic kidney disease	3.18 (0.38–26.68)	
Cardiovascular disease	0.90 (0.43–1.90)	
Cerebrovascular accident	0.52 (0.07–3.72)	
Hypertension	1.10 (0.66–1.85)	
Dementia / Alzheimer's disease	0.78 (0.13–4.72)	
Parkinson disease	NE	
Mood and anxiety disorders	1.20 (0.78–1.84)	
Chronic hepatic disease	NE	
Osteoporosis	1.33 (0.57–3.10)	
Malignancy	1.20 (0.64–2.26)	
COPD	0.72 (0.22–2.32)	
Concomitant autoimmune disease		
Multiple sclerosis	NE	
Rheumatoid arthritis	1.73 (0.55–5.42)	
Inflammatory bowel disease	4.83 (0.61–38.50)	
Ankylosing spondylitis	NE	
Myasthenia gravis	NE	
Sjögren's syndrome	8.24 (1.08–63.10)	
Body mass index >30	0.99 (0.51–1.89)	

̂ It was not possible to perform any adjusted model.

Table S39. List of coded diagnoses for disease identification and patients' characterization.

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
Main inclusion criteria			
Systemic lupus erythematous	710.0	M32, M32.1*, M32.8*, M32.9*	N000300, M154.00, F371000, N000400, F396100, N000000, K01x400, M154z00, N000.00, H57y400, Nyu4300, N000z00, N000600
Cutaneous only lupus	695.4*, 373.34	L93*	N000500, F4D3300, N000200, M154200, M154600, M154700, M154300, M154400, Myu7800, M154500, AD53000, M154000, M154100
EULAR / ACR criteria			
Leukopenia	288.50, 288.59	D72.81*	D400A00, 42H2.00, 42H2.00
Thrombocytop	287.3, 287.4, 287.5	D69.4, D69.5, D69.6	42P2.00, 42P8., B937500, C3912, D313.00, D313000, D3131, D313200, D313300, D313y00, D313z00, D314.00, D314100, D314200, D314300, D314y00, D314z00, D315.00, Dyu3200, G756100
Autoimmune hemolysis	283.0	D59.1, D59.8, D59.9	D1y..00, D1z..00, D11z.00, D1...00, Dyu1500, D110z00, Dyu1700, D103100, D111400, D11..00, D110.00, D110400, 1453.00, Dyu1.00
Delirium	297	F05.0, F05.8, F05.9	2233.00, E001100, E003.00, E004100, E02y000, E030.00, E030.11, E030000, E030100, E030200, E030300, E030400, E031.00, E031.11, E031000, E031100, E031300, E031400, E031z00, Eu04.00, Eu04.11, Eu04.12, Eu04.13, Eu04.14, Eu04.15, Eu04000, Eu04100, Eu04y00, Eu04z00
Psychosis	290–299	F20–F29*	128A.00, 146H.00, 1BH..00, 1BH..11, 1BH0.00, 1BH1.00, 1BH2.00, 1BH3.00, 212T.00, 212X.00, 8BM0100, 8HHs.00, E0...00, E00..00, E001100, E001200, E002000, E002z00, E003.00, E004100, E004200, E00y.00, E00y.11, E00z.00, E01..00, E010.00, E010.11, E010.12, E011000, E011100, E013.00, E015.00, E01y.00, E01yz00, E01z.00, E02..00, E021.00, E021000, E021100, E021z00, E02y.00, E02y000, E02yz00, E02z.00, E03..00, E030.00, E030.11, E030.12, E030000, E030100, E030200, E030300, E030400, E030z00, E031.00, E031.11, E031000, E031100, E031300, E031400, E031z00, E03y.00, E03y000, E03y100, E03y200, E03y300, E03yz00, E03z.00, E04..00, E04y.00, E04z.00, E0y..00, E0z..00, E10..00, E100.00, E100.11, E100000, E100100, E100200, E100300, E100400, E100500, E100z00, E101.00, E101000, E101400, E101500, E101z00, E102.00, E102000, E102100, E102500, E102z00, E103.00, E103000, E103200, E103300, E103400, E103500, E103z00, E104.00, E104.11, E105.00, E105000, E105200, E105500, E105z00, E106.00, E107.00, E107.11, E107000, E107100, E107200, E107300, E107400, E107500, E107z00, E10y.00, E10y.11, E10y000, E10y100, E10yz00, E10z.00, E110.00, E110.11, E110000, E110100, E110200, E110300, E110400, E110600, E110z00, E111.00, E111000, E111100, E111200, E111300, E111400, E111500, E111600, E111z00, E112400, E113400, E114.00, E114.11, E114000, E114100, E114200, E114300, E114400, E114500, E114600, E114z00, E115.00, E115.11, E115000, E115100, E115200, E115300, E115400, E115500, E115600, E115z00, E116.00, E116000, E116100, E116200, E116300, E116400, E116500, E116600, E116z00, E117.00, E117000, E117100, E117200, E117300, E117400, E117500, E117600, E117z00, E11y.00, E11y000, E11y100, E11y200, E11y300, E11yz00, E11z.00, E11z000, E11zz00, E12..00, E120.00, E121.00, E122.00, E123.00, E123.11, E12y.00, E12y000, E12yz00, E12z.00, E13..00, E130.00, E130.11, E131.00, E133.00, E134.00, E13y.00, E13y000, E13y100, E13yz00, E13z.00, E14..00, E141.00, E141.11, E141000, E141100, E141z00, E14y.00, E14y000, E14y100, E14yz00, E14z.00, E14z.11, E1y..00, E1z..00, Eu04.00, Eu04.11, Eu04.12, Eu04.13, Eu04.14, Eu04.15, Eu04000, Eu04100, Eu04y00, Eu04z00, Eu05000, Eu05200, Eu10400, Eu10411, Eu10500, Eu10511, Eu10512, Eu10513, Eu10514, Eu10700, Eu11400, Eu11500, Eu11700, Eu12500, Eu12700, Eu13400, Eu13500, Eu14500, Eu14700, Eu15500, Eu15700, Eu16500, Eu16711, Eu17500, Eu18400, Eu18500, Eu18700, Eu19400, Eu19500, Eu19700, Eu1A500, Eu20.00, Eu20000, Eu20011, Eu20100, Eu20111, Eu20200, Eu20211, Eu20212, Eu20213, Eu20214, Eu20300, Eu20311, Eu20400, Eu20500, Eu20511, Eu20600, Eu20y00, Eu20y12, Eu20y13, Eu20z00, Eu23.00, Eu23000, Eu23011, Eu23012, Eu23100, Eu23112, Eu23200, Eu23211, Eu23212, Eu23214, Eu23300, Eu23312, Eu23y00, Eu23z00, Eu23z11, Eu23z12, Eu24.00, Eu24.12, Eu24.13, Eu26.00, Eu2y.00, Eu2z.00, Eu30200, Eu31200, Eu32300, Eu32800, Eu62100, R001.00, R001000, R001100, R001200, R001300, R001400, R001z00
Epilepsy and recurrent seizures	333.2, 345*	G25.3, G40*	1473, 2823, 2824, 2825, 2828, 13ZD.00, 1B1W.00, 1B26.00, 1B27.00, 1O30.00, 2824.11, 667B.00, 667N.00, 667Q.00, 667R.00, 667S.00, 667T.00, 667V.00, E201500, Eu05212, Eu05y11, Eu06013, Eu10800, Eu80300, F132100, F132200, F25..00, F25.z.11, F250.00, F250000, F250011, F250100, F250200, F250300, F250400, F250500, F250y00, F250z00, F251.00, F251000, F251011, F251100, F251111, F251200, F251300, F251400, F251500, F251600, F251y00, F251z00, F252.00, F253.00, F253.11, F254.00, F254000, F254100, F254200, F254300, F254400, F254500, F254z00, F255.00, F255000, F255011, F255012, F255100, F255200, F255300, F255311, F255400, F255500, F255600, F255y00, F255z00, F256.00, F256.11, F256.12, F256000, F256100, F256z00, F257.00, F259.00, F259.11, F25A.00, F25B.00, F25C.00, F25D.00, F25E.00, F25F.00, F25G.00, F25H.00, F25X.00, F25y.00, F25y000, F25y100, F25y200, F25y300, F25y400, F25y500, F25yz00, F25z.00, Fyu5000, Fyu5100, Fyu5200, Fyu5900, R003300, R003400, SC20000, ZS82.00, ZS82.11

(Continued on next page)

(Continued from previous page)

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
Non-scarring alopecia	704.0*	L65.9	Myu6500, A918100, Myu6E00, M240600, 22D7.00, M240700, M240z00, M240800, M24X.00, PH40200, M240K00, M240500, PH40z00, M240900, M240300, M240F00, M240000, M240J00, M240400, PH40.00, M240E00, PH40000, M240L00, M240A00, M240100, PH40100, M240B00, 12H3.00, M240H00, M240200, 38V8.00, M240C00, Myu6200, Myu6300, M240V00, M240P00, M240D00, M240.00
Oral ulcers	528.0*	K12.3*	2567.00, J080000, J082000, J082100, J085800, J031100, 2533.00
Acute pericarditis	420*	I30*	G50z300, G50z400, G500.00, G50z500, G50z000, G532.00, G50z100, Gyu5000, G531.00, G500z00, G010.00, G50z.00, G500500, G500300, G532z00, G500000, G50..00, G500400, G531z00, G500100, G500200, G50zz00, G50z200
Pleural & pericardial effusion	391.0, 393, 423.1, 423.2, 510.9, 511	I31.3*, J90*	G534.00, G533.00, 24CA.00, G53z.00, G536000, G536.00, 4D53.00, 4D42.00, S723200, 4D62.00, H51y700, H51zz00, R126.00, H51yz00, 4D52.00, H501000, 4D61.00, H51y.00, 4D23.00, Hyu7000, 4DZ1.00, H51z.00, 4D32.00
Exclusion criteria			
Primary vasculitis	446*, 447.5*	M30*, M31*	C332100, Myu7G00, G758.00, F421E00, M2y0200, M2y0X00, Myu7A00, N040N00, G76B.00
Myositis	729.1*	M60.9*	Nyu8000, N241z00, F4G1200, N231100, N231200, N233200, N241100, N241200, N241.00, N23y000
Polymyositis / Dermatomyositis	710.3, 710.4	M33*	N004.00, 43aA.00, H57y100, N231400, N003X00, Nyu4E00, Nyu4400, N003.00, N003000
Psoriatic arthritis	696.0	L40.5*	M160.11, Nyu1300, M160200, M160.00, M160000, M160100, M160z00
CREST syndrome or scleroderma	710.1	M34*	N001100, 7M2C200, 43aA.00, F396600, M210z00, Q471100, K0H..00, N001.00, M210.00, M210400, 12I3.00, M210000, K0J0.00, H572.00, N001000, N001200, Nyu4500
Comorbidity			
Diabetes	250*	E10*, E11*, E13*	F420.00, 9OL1.00, 66Aa.00, C108z00, C10A000, C108H00, C10EM00, 9N0o.00, C104100, 8CP2.00, C108800, C10E700, 66AU.00, C10M000, 66Ao.00, Cyu2000, 8CE0.00, C10FN00, C106y00, 9OL3.00, 66Ac.00, C10N100, C106100, 66Al.00, 8I6G.00, F420200, C107z00, C108700, 6761, Q441.00, C10A600, F464000, 66An.00, C10N000, C10z.00, C10EN00, 66Az.00, C10E800, 66Ab.00, 9OLJ.00, 66AI.00, C10F900, 2BBK.00, 2BBo.00, 2BBW.00, Cyu2100, C10y.00, C108200, C109900, C105100, C10E300, C10E900, C10A100, M037200, C109300, C103000, C107100, 2G5I.00, C107.00, C10z000, C10A200, 2BBJ.00, C109J00, L180400, C109400, 8HBG.00, C10AX00, C10EJ00, C10E400, 2BBV.00, 2G5H.00, C107200, C135.00, 9Oy0200, 8CR2.00, 2BBL.00, C108300, F372000, Lyu2900, 1I0..00, L180800, 9m0..00, C10EP00, 38Gv.00, C10EK00, C10E500, C109E00, 9Oy0300, 2BBl.00, C10D.00, C108.00, C108400, 14F4.00, 2G5G.00, C10FJ00, C10F400, F345000, C10FP00, C10C.00, 66As.00, C102z00, F372100, 2G5F.00, C108E00, C108500, 2G51000, C10FK00, C10B.00, C10F500, C10FQ00, C10N.00, N030100, C101y00, 66A5.00, C106.00, C135000, R054300, C108F00, C108000, M271100, C10F600, 66AZ.00, C101z00, 9OL6.00, 66AN.00, C109G00, C10F000, C10FL00, C109K00, C10E000, C109500, L180500, C10A.00, C100z00, 9OL5.00, C105.00, C10EF00, C10M.00, C109B00, C10FG00, C10F100, C109200, C10F700, C10EH00, C107000, 2BBP.00, 66AM.00, C10EL00, C10yz00, C10E600, 9OLZ.00, L180000, C109000, L180600, C109600, C10FM00, 66AJz00, 9OL4.00, C109100, L180700, F420z00, C10EG00, C100.00, C10E100, C10FH00, C10F200, C108A00, C108100, C10EB00, C108C00, C10E200, G73y000, 2BBr.00, 2G5d.00, 8I3X.00, C10F300, 68AB.00, 8HBH.00, C10FC00, K081.00, 66At100, 38QW.00, C108B00, C10EC00, L180z00, C10AW00, 9b92000, C109C00, N030000, 2G5L.00, C102000, C10FD00, C10F.00, C10..00, R054200, F420800, C103100, C10E.00, 2G5W.00, 7276, 2G5K.00, C109D00, C109.00, C10ED00, K27y700, C10G.00, Kyu0300, 2BBX.00, 2G5e.00, C103y00, K081000, F420300, C10A700, C105y00, C101000, 66Ak.00, 8A12.00, K01x100, C106z00, F420400, 2G5V.00, K081100, C108D00, C104y00, 2G5J.00, C105z00, 9OLF.00, C10EE00, C101100, 1252, 2BBG.00, F440700, 1M8..00, C108900, C10y000, C100000, M271000, C104z00, F3y0.00, C10FE00, C10zy00, 1JL..00, Cyu2300, C10FR00, 66AS000, C10G000, K08yA00, 66Ai.00, C10y100, C100100, F420500, C102100, 66AJ100, C10FF00, 2BBT.00, C103z00, C10yy00, 1434, 2BBQ.00, C104.00, C10FA00, C10zz00, 2BBk.00, 2BBS.00, C10EQ00, C10z100, 2BBF.00, F372200, C105000, C101.00, C109700, 2G5C.00, C103.00, 66AW.00, F171100, 2G5B.00, C10A400, C109A00, 66b1.00, C10EA00, C102.00, C10FB00, Cyu2.00, F381300, F372.00, F35z000, C108y00, C104000, L180X00, C106000, 66A2.00, C108600, C107y00, F420100

(Continued on next page)

(Continued from previous page)

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
Chronic Kidney Disease	403*, 582, 585 (unspecified), 585.1, 585.2, 585.9	I12*, N03*, N18.1, N18.2, N18.9	1Z10.00, 1Z11.00, 1Z12.00, 1Z13.00, 1Z14.00, 1Z15.00, 1Z16.00, 1Z17.00, 1Z18.00, 1Z19.00, 1Z1A.00, 1Z1a.00, 1Z1B.00, 1Z1b.00, 1Z1C.00, 1Z1c.00, 1Z1D.00, 1Z1d.00, 1Z1E.00, 1Z1e.00, 1Z1F.00, 1Z1f.00, 1Z1G.00, 1Z1H.00, 1Z1J.00, 1Z1K.00, 1Z1L.00, 1Z1M.00, 1Z1N.00, 1Z1P.00, 1Z1Q.00, 1Z1R.00, 1Z1S.00, 1Z1T.00, 1Z1V.00, 1Z1W.00, 1Z1X.00, 1Z1Y.00, 1Z1Z.00, 2126E00, 4Z1..00, 661M200, 661N200, 66i..00, 6AA..00, 7B06300, 8L50.00, 9Ot..00, 9Ot0.00, 9Ot1.00, 9Ot2.00, 9Ot3.00, 9Ot4.00, 9Ot5.00, K01..00, K010.00, K011.00, K012.00, K013.00, K013.11, K013.12, K014.00, K015.00, K016.00, K017.00, K018.00, K019.00, K01A.00, K01B.00, K01w.00, K01w000, K01x000, K01x100, K01x111, K01x200, K01x300, K01x400, K01x411, K01y.00, K01z.00, K02..00, K02..11, K02..12, K020.00, K021.00, K022.00, K023.00, K02y.00, K02y000, K02y200, K02y300, K02yz00, K02z.00, K05..00, K05..11, K05..12, K050.00, K051.00, K052.00, K053.00, K054.00, K055.00, K0D..00, K100.00, K100000, K100100, K100200, K100300, K100400, K100500, K100600, K100z00, SP08300, TB00100, TB00111, ZV42000
Cardiovascular disease	402.01, 402.11, 402.91, 410, 411, 413, 414.0 (exc. 414.02–07), 414.02–07, V45.81–82, 440.2, 433*, 444.2, 427.3, 428	I11.0, I20–I25*, I48*, I50*, I70.2*, I73*, I74.2*, Z95.1, Z98.61	4129, 4130, 4139, 4149, 14AJ.00, 4119B, 4120A, 4129AN, 4129N, 4130E, 4139AA, 4139AT, 4139C, 4139CO, 4139E, 4139M, 4139N, 4139PA, 4139U, 662K.00, 662K000, 662K100, 662K200, 662K300, 662Kz00, 662N.00, 6A2..00, 6A4..00, 8B27.00, 8B3k.00, 8B63.11, 8CR6.00, 9Ob0.00, 9Ob8.00, G3...00, G3...11, G3...12, G3...13, G30..00, G30..11, G30..12, G30..13, G30..14, G30..15, G30..16, G30..17, G300.00, G301.00, G301000, G301100, G301z00, G302.00, G303.00, G304.00, G305.00, G306.00, G307.00, G307000, G307100, G308.00, G309.00, G30A.00, G30B.00, G30X.00, G30X000, G30y.00, G30y000, G30y100, G30y200, G30yz00, G30z.00, G31..00, G310.00, G310.11, G311.00, G311.11, G311.12, G311.13, G311.14, G311000, G311011, G311100, G311200, G311300, G311400, G311500, G311z00, G312.00, G31y.00, G31y000, G31y100, G31y200, G31y300, G31yz00, G32..00, G32..11, G32..12, G33..00, G330.00, G330000, G330z00, G331.00, G331.11, G332.00, G33z.00, G33z000, G33z100, G33z200, G33z300, G33z400, G33z500, G33z600, G33z700, G33zz00, G34..00, G340.00, G340.11, G340.12, G340000, G340100, G342.00, G343.00, G344.00, G34y.00, G34y000, G34y100, G34yz00, G34z.00, G34z000, G35..00, G350.00, G351.00, G353.00, G35X.00, G36..00, G360.00, G361.00, G362.00, G363.00, G364.00, G365.00, G366.00, G38..00, G380.00, G381.00, G384.00, G38z.00, G3y..00, G3z..00, G574011, G575.00, G575.11, G575.12, G575000, G575100, G575z00, G70..00, G700.00, G73..00, G73..12, G73y.00, G73yz00, G73z.00, G73z000, G73z011, G73zz00, G742z00, G74y300, G76z000, Gyu3.00, Gyu3200, Gyu3300, Gyu3400, Gyu3600, Gyu6200, Gyu6300, Gyu6400, Gyu6F00, Gyu6G00, Gyu7400
Cerebrovascular accident	430–432*, 433–434 (excl. 43X.X0), 436, V12.54	I60–I62*, I63*, Z86.73	1225.00, 12C4.00, 14A7.00, 14A7.11, 14A7.12, 14AK.00, 1M4..00, 661M700, 661N700, 662e.00, 662e.11, 662M.00, 662M100, 662M200, 662o.00, 7P24200, 8HBJ.00, 8Hd6.00, 8HHM.00, 8HTQ.00, 8IEC.00, 9h2..00, 9h21.00, 9h22.00, 9N0p.00, Fyu5600, G66..00, G66..11, G66..12, G66..13, G663.00, G664.00, G665.00, G666.00, G667.00, G668.00, G68X.00, Gyu6C00, L440.11, L440.12, ZV12511, ZV12512, G657.00, 9Om..00, G65zz00, 9Om1.00, 9Om3.00, G65y.00, 9Om2.00, 9Om4.00, ZV12D00, 8CRB.00, 1JK..00, 8HBJ.00, 9Om0.00, G65..00
Hypertension	401*	I10*	6627, 6628, 6629, 2126100, 1227.00, 12C1.00, 14A2.00, 212K.00, 662..12, 6624.00, 662b.00, 662c.00, 662d.00, 662F.00, 662G.00, 662O.00, 662P.00, 7Q01000, 7Q01100, 7Q01200, 7Q01300, 7Q01400, 7Q01500, 7Q01600, 7Q01700, 8B26.00, 8BL0.00, 8CR4.00, 8HT5.00, 9N03.00, 9N1y200, 9OI1.00, 9OIA.00, 9OIA.11, 9OIB.00, 9OIC.00, 9OID.00, F282.00, F404200, F421300, F450400, G2...00, G2...11, G20..00, G20..11, G200.00, G201.00, G202.00, G203.00, G20z.00, G20z.11, G21..00, G210.00, G210000, G210100, G210z00, G211.00, G211000, G211100, G211z00, G21z.00, G21z000, G21z011, G21z100, G21zz00, G22..00, G220.00, G221.00, G222.00, G22z.00, G22z.11, G23..00, G230.00, G231.00, G232.00, G233.00, G234.00, G23z.00, G24..00, G240.00, G240000, G240z00, G241.00, G241000, G241z00, G244.00, G24z.00, G24z000, G24zz00, G25..00, G250.00, G251.00, G26..00, G28..00, G2y..00, G2z..00, G2z..00, G410.00, G41y000, G41y100, G672.00, G672.11, Gyu2.00, Gyu2000, Gyu2100, J623.00, L120.00, L120000, L120100, L120300, L120400, L120z00, L121.00, L121000, L121100, L121200, L121300, L121400, L121z00, L122.00, L122000, L122100, L122300, L122400, L122z00, L123500, L128.00, L128200, Q000.00, Q043.00, Q492.00
Dementia / Alzheimer	290*, 294.1*, 331.0	F03*, F02.8*, G30.9	1281.00, 129B.00, 1461.00, 1JA2.00, 38C1000, 38C1300, 3AD1.00, 3AD2.00, 3AE..00, 67DF.00, 8BPa.00, 8CET.00, 8CMG200, 8Hla.00, 8T05.00, 8T05000, 8T05100, 8T05200, E00..11, E00..12, E000.00, E001.00, E001000, E001100, E001200, E001300, E001z00, E002.00, E002000, E002100, E002z00, E003.00, E004.00, E004.11, E004000, E004100, E004200, E004300, E004z00, E012.00, E02y100, E041.00, Eu00.00, Eu00000, Eu00011, Eu00012, Eu00013, Eu00100, Eu00111, Eu00112, Eu00113, Eu00200, Eu00z00, Eu00z11, Eu01.00, Eu01.11, Eu01000, Eu01100, Eu01111, Eu01200, Eu01300, Eu01y00, Eu01z00, Eu02.00, Eu02000, Eu02100, Eu02200, Eu02300, Eu02400, Eu02500, Eu02y00, Eu02z00, Eu02z11, Eu02z13, Eu02z14, Eu02z16, Eu04100, F110.00, F110000, F110100, F112.00, Fyu3000
Parkinson disease	332*	G20*	Eu02300, 147F.00, F12z.00, F11x900, F12..00, F120.00

(Continued on next page)

(Continued from previous page)

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
Mood and Anxiety disorders	296*, 298.0, 300.0*, 300.2, 300.4, 311	F30–F39*, F40*, F41*, F43*	Eu3z.00, Eu3y.00, 1S40.00, Eu34y00, Eu3y000, 1BT..00, 1BY..00, Eu34.00, 1S41.00, Eu3..00, 1S42.00, E292400, 225K.00, Eu34z00, 1BO..00, Eu3yy00, 3880100, Eu3y100, Eu05300, E11z100
Chronic hepatic disease	456.0–456.2; 571–573	I85.1*, K73–K75*	A709.00, J613000, J634.00, A708.00, J63A.00, J622.00, SP14200, J635100, C310400, J639.00, A705000, J637.00, J625.00, SB21100, J61y400, J61y500, J61y600, J63..00, J630.00, Jyu7500, PB6yz00, J62..00, Jyu7400, Jyu7000, J61yz00, J613.00, J635600, J635200, J612.00, J60z.00, J600.00, Jyu7100, PB6y.00, J61z.00, J612000, Jyu7200, J635300, J610.00, J61y.00, J635.00, J635400, Jyu7.00, J635500, 14C5.00, C370700, J63z.00, J62y.00, J635000, J635100, J635X00, B15..00, J61..00, Jyu7300, 7L1fy00, J63yz00
Osteoporosis	733.0*, 733.1*	M80–M81*	1229.00, 1268.00, 2126500, 585O.00, 58E4.00, 58E8.00, 58EA.00, 58EA.00, 58EE.00, 58EG.00, 58EG.00, 58EK.00, 58EM.00, 58EM.00, 58ES.00, 58EV.00, 66a..00, 66a0.00, 66a1.00, 66a2.00, 66a3.00, 66a4.00, 66a5.00, 66a6.00, 66a7.00, 66a8.00, 66a9.00, 66aA.00, 66aB.00, 7230A, 7230B, 7230D, 7230PM, 7230PT, 8B6b.00, 8I6c.00, 9kj..00, 9Od..00, 9Od2.00, 9Od3.00, 9Od4.00, 9Od5.00, 9Od6.00, 9Od7.00, 9Od8.00, 9Od9.00, 9OdA.00, 9OdB.00, 9OdC.00, N330.00, N330000, N330100, N330200, N330300, N330400, N330500, N330600, N330700, N330800, N330900, N330A00, N330B00, N330C00, N330D00, N330z00, N331200, N331300, N331400, N331500, N331600, N331800, N331900, N331A00, N331B00, N331H00, N331J00, N331K00, N331L00, N331M00, N331N00, N374600, NyuB000, NyuB100, NyuB200, NyuB800

(Continued on next page)

(Continued from previous page)

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
Malignancy	140–239*	C00–D49*	124..11, 1241.11, 1241.12, 1241.13, 1242.11, 1243.11, 124F.00, 124H.00, 142..11, 1Bb1.00, 1I2..00, 1I20.00, 1J00.00, 1J06.00, 1J07.00, 1J08.00, 1J09.00, 1J0A.00, 1J0B.00, 1J0C.00, 1J0D.00, 1J0E.00, 1J0G.00, 1J0H.00, 1J0I.00, 1J0J.00, 1J0K.00, 1O0..00, 4M0..00, 677H.00, 677K.00, 67D2.00, 67G2.00, 68W2.00, 8B3p.00, 8BAD000, 8BAV.00, 8BC3.00, 8BC6.00, 8BCF.00, 8CEB.00, 8CL0.00, 8CL1.00, 8CL2.00, 8CM0.00, 8CP0.00, 8CP1.00, 8CR8.00, 8HH8.00, 8HHt.00, 8Hn..00, 8O83.00, 9e00.00, 9h8..00, 9h81.00, 9h82.00, 9N4S.00, 9Nh1.00, 9NX0.00, 9NX1.00, 9Ok..00, 9Ok0.00, 9Ok1.00, 9Ok2.00, 9Ok3.00, 9Ok5.00, 9Ok6.00, 9Ok7.00, 9Ok9.00, 9OkA.00, 9OkB.00, A788600, B....11, B0...00, B0...11, B00..00, B00..11, B000.00, B000000, B000100, B000z00, B001.00, B001000, B001100, B001z00, B002.00, B002100, B002200, B002300, B002z00, B003.00, B003000, B003100, B003200, B003300, B003z00, B004.00, B004000, B004200, B004300, B005.00, B006.00, B007.00, B00z000, B00z100, B00zz00, B01..00, B010.00, B010.11, B010000, B010z00, B011.00, B011z00, B012.00, B013.00, B013000, B013100, B013z00, B014.00, B015.00, B016.00, B017.00, B01y.00, B01z.00, B02..00, B020.00, B021.00, B022.00, B02y.00, B02z.00, B03..00, B030.00, B031.00, B03y.00, B03z.00, B04..00, B040.00, B041.00, B042.00, B04y.00, B04z.00, B05..00, B050.00, B050.11, B051.00, B051000, B051100, B052.00, B053.00, B054.00, B055.00, B055000, B055100, B055z00, B056.00, B057.00, B05y.00, B05z.00, B05z000, B06..00, B060.00, B060000, B060100, B060200, B060z00, B061.00, B062.00, B062000, B062100, B062200, B062300, B062z00, B063.00, B064.00, B064000, B064100, B064z00, B065.00, B066.00, B067.00, B06y.00, B06yz00, B06z.00, B07..00, B070.00, B071.00, B071000, B071100, B071z00, B072.00, B072000, B072z00, B073.00, B073200, B073z00, B074.00, B07y.00, B07z.00, B08..00, B080.00, B081.00, B082.00, B083.00, B08y.00, B08z.00, B0z..00, B0z0.00, B0z1.00, B0z2.00, B0zy.00, B0zz.00, B1...00, B1...11, B10..00, B100.00, B101.00, B102.00, B103.00, B104.00, B105.00, B106.00, B10y.00, B10z.00, B10z.11, B11..00, B11..11, B110.00, B110000, B110100, B110111, B110z00, B111.00, B111000, B111100, B111z00, B112.00, B113.00, B114.00, B115.00, B116.00, B117.00, B11y.00, B11y000, B11y100, B11yz00, B11z.00, B12..00, B120.00, B121.00, B122.00, B123.00, B124.00, B12y.00, B12z.00, B13..00, B130.00, B131.00, B132.00, B133.00, B134.00, B134.11, B135.00, B136.00, B137.00, B138.00, B13y.00, B13z.00, B13z.11, B14..00, B140.00, B141.00, B141.11, B141.12, B142.00, B142.11, B142000, B143.00, B14y.00, B14z.00, B15..00, B150.00, B150000, B150100, B150200, B150300, B150z00, B151.00, B151000, B151200, B151400, B151z00, B152.00, B153.00, B15z.00, B16..00, B160.00, B160.11, B161.00, B161000, B161100, B161200, B161211, B161z00, B162.00, B163.00, B16y.00, B16z.00, B17..00, B170.00, B171.00, B172.00, B173.00, B174.00, B175.00, B17y.00, B17y000, B17yz00, B17z.00, B18..00, B180.00, B180100, B180200, B180z00, B181.00, B182.00, B18y.00, B18y100, B18y200, B18y300, B18y400, B18y500, B18y600, B18y700, B18yz00, B18z.00, B1z..00, B1z0.00, B1z0.11, B1z1.00, B1z1100, B1z1z00, B1z2.00, B1zy.00, B1zz.00, B2...00, B2...11, B20..00, B200.00, B200000, B200100, B200200, B200300, B200z00, B201.00, B201100, B201200, B201300, B201z00, B202.00, B203.00, B204.00, B205.00, B206.00, B20y.00, B20z.00, B21..00, B210.00, B211.00, B212.00, B213.00, B213000, B213100, B213300, B213z00, B214.00, B215.00, B21y.00, B21z.00, B22..00, B220.00, B220100, B220z00, B221.00, B221000, B221100, B221z00, B222.00, B222.11, B222000, B222100, B222z00, B223.00, B223000, B223100, B223z00, B224.00, B224000, B224100, B224z00, B225.00, B226.00, B22y.00, B22z.00, B22z.11, B23..00, B230.00, B232.00, B23y.00, B23z.00, B24..00, B240.00, B241.00, B241000, B241200, B241300, B241400, B241z00, B242.00, B243.00, B24X.00, B24y.00, B24z.00, B25..00, B26..00, B2z..00, B2z0.00, B2zy.00, B2zz.00, B3...00, B3...11, B3...12, B30..00, B30..11, B30..12, B300.00, B300000, B300100, B300200, B300300, B300400, B300500, B300600, B300700, B300800, B300900, B300A00, B300B00, B300C00, B300z00, B301.00, B302.00, B302000, B302100, B302200, B302z00, B303.00, B303000, B303100, B303200, B303300, B303400, B303500, B303z00, B304.00, B304000, B304200, B304300, B304400, B304z00, B305.00, B305.12, B305000, B305100, B305C00, B305D00, B305z00, B306.00, B306000, B306100, B306200, B306300, B306400, B306500, B306z00, B307.00, B307000, B307100, B307200, B307z00, B308100, B308200, B308300, B308800, B308B00, B308D00, B308z00, B30W.00, B30X.00, B30z.00, B30z000, B31..00, B310.00, B310000, B310100, B310200, B310300, B310400, B310z00, B311.00, B311000, B311100, B311200, B311300, B311400, B311500, B312.00, B312000, B312100, B312200, B312300, B312400, B312500, B312z00, B313.00, B313000, B313100, B313200, B313300, B313z00, B314.00, B314000, B314100, B314z00, B315.00, B315000, B315100, B315200, B315z00, B316.00, B31y.00, B31z.00, B31z000, B32..00, B320.00, B321.00, B322.00, B322000, B322100, B322z00, B323.00, B323000, B323100, B323200, B323300, B323400, B323500, B323z00, B324.00, B324000, B324100, B324z00, B325.00, B325000, B325100, B325200, B325300, B325500, B325600, B325700, B325800, B325z00, B326.00, B326000, B326100, B326200, B326300, B326400, B326500, B326z00, B327.00, B327000, B327100, B327200, B327300, B327400, B327500, B327600, B327700, B327800, B327900, B327z00, B32y.00, B32y000, B32z.00, B33..00, B33..11, B33..12, B33..13, B33..14, B33..15, B33..16, B330.00, B331.00, B331000, B331100, B331200, B332.00, B332000, B332100, B332200, B332z00, B333.00, B333000, B333100, B333200, B333300, B333400, B333500, B333z00, B334.00, B334000, B334100, B334z00, B335.00, B335000, B335100, B335200, B335300, B335400, B335500, B335600, B335700, B335800, B335900, B335A00, B335z00, B336.00, B336000, B336100, B336200, B336300, B336400, B336500, B336z00, B337.00, B337000, B337100, B337200, B337300, B337400, B337500, B337600, B337700, B337800, B337900, B337z00, B339.00, B33X.00, B33y.00, B33z.00, B33z000, B33z100, B33z111, B34..00, B34..11, B340.00, B340000, B340100, B340z00, B341.00, B342.00, B343.00, B344.00, B345.00, B346.00, B347.00, B34y.00, B34y000, B34yz00, B34z.00, B35..00, B350.00, B350000, B350100, B35z.00, B35z000, B35zz00, B3y..00, B3z..00, B4...00, B4...11, B40..00, B41..00, B41..11, B410.00, B410000, B410100, B410z00, B411.00, B412.00, B41y.00, B41y000, B41y100, B41yz00, B41z.00, B42..00, B420.00, B43..00, B430.00, B430000, B430100, B430200, B430211, B430300, B430z00, B431.00, B431000, B431z00, B432.00, B43y.00, B43z.00, B44..00, B440.00, B440.11, B441.00, B442.00, B443.00, B44y.00, B44z.00, B45..00, B450.00, B450100, B450z00, B451.00, B451000, B451z00, B452.00, B453.00, B454.00, B454.11, B45X.00, B45y.00, B45y000, B45z.00, B46..00, B47..00, B470.00, B470200, B470300, B470z00, B471.00, B471000, B471100, B47z.00, B47z.11, B47z.12, B48..00, B480.00, B481.00, B482.00, B483.00, B484.00, B485.00, B486.00, B487.00, B48y.00, B48y000, B48y100, B48y200, B48yz00, B48z.00, B49..00, B490.00, B491.00, B492.00, B493.00, B494.00, B495.00, B496.00, B497.00, B49y.00, B49y000, B49z.00, B4A..00, B4A..11, B4A0.00, B4A0000, B4A1.00, B4A1000, B4A1100, B4A1z00, B4A2.00, B4A3.00, B4A4.00, B4Ay.00, B4Ay000, B4Az.00, B4y..00, B4z..00, B5...00, B5...11, B50..00, B500.00, B500000, B500100, B500z00, B501.00, B501000, B501z00, B502.00, B503.00, B504.00, B505.00, B506.00, B507.00, B507000, B507100, B508.00,

(Continued from previous page)

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
			B50y.00, B50z.00, B51..00, B51..11, B510.00, B510000, B510100, B510300, B510400, B510500, B510z00, B511.00, B512.00, B512000, B512z00, B513.00, B514.00, B515.00, B515000, B516.00, B517.00, B517000, B517100, B517200, B517300, B517z00, B51y.00, B51y000, B51y200, B51yz00, B51z.00, B52..00, B520.00, B520000, B520100, B520200, B520z00, B521.00, B521z00, B522.00, B523.00, B523z00, B524.00, B524000, B524100, B524200, B524300, B524400, B524500, B524600, B525.00, B52W.00, B52X.00, B52y.00, B52z.00, B53..00, B54..00, B540.00, B540.11, B540000, B540100, B540z00, B541.00, B542.00, B542000, B542100, B542z00, B543.00, B544.00, B545.00, B545000, B545100, B545200, B545z00, B54X.00, B54y.00, B54z.00, B55..00, B550.00, B550000, B550100, B550200, B550300, B550400, B550500, B550z00, B551.00, B551000, B551100, B551200, B551z00, B552.00, B553.00, B553000, B553100, B553z00, B554.00, B555.00, B55y.00, B55y000, B55y100, B55y200, B55yz00, B55z.00, B56..00, B56..11, B560.00, B560000, B560100, B560200, B560300, B560400, B560500, B560600, B560700, B560800, B560900, B560z00, B561.00, B561000, B561200, B561300, B561400, B561500, B561600, B561700, B561800, B561900, B561z00, B562.00, B562000, B562100, B562200, B562300, B562400, B562z00, B563.00, B563000, B563100, B563200, B563300, B563z00, B564.00, B564000, B564100, B564z00, B565.00, B565000, B565200, B565300, B565z00, B56y.00, B56z.00, B57..00, B57..11, B57..12, B570.00, B571.00, B572.00, B573.00, B574.00, B574000, B574200, B574z00, B575.00, B575000, B575100, B575z00, B576.00, B576000, B576100, B576200, B576z00, B577.00, B577.11, B57y.00, B57z.00, B58..00, B58..11, B580.00, B581.00, B581000, B581100, B581200, B581z00, B582.00, B582000, B582100, B582200, B582300, B582400, B582500, B582600, B582z00, B583.00, B583000, B583100, B583200, B583z00, B584.00, B585.00, B585000, B586.00, B587.00, B58y.00, B58y000, B58y100, B58y200, B58y211, B58y300, B58y400, B58y411, B58y500, B58y600, B58y700, B58y800, B58y900, B58yz00, B58z.00, B59..00, B590.00, B590.11, B591.00, B592.00, B592X00, B593.00, B594.00, B59z.00, B59zX00, B5y..00, B5z..00, B6...00, B6...11, B60..00, B600.00, B600000, B600100, B600300, B600700, B600z00, B601.00, B601000, B601100, B601200, B601300, B601500, B601700, B601z00, B602.00, B602100, B602200, B602300, B602500, B602z00, B60y.00, B60z.00, B61..00, B610.00, B610100, B610300, B611.00, B611100, B612.00, B612400, B613.00, B613000, B613100, B613200, B613300, B613500, B613600, B613z00, B614.00, B614000, B614100, B614200, B614300, B614400, B614800, B614z00, B615.00, B615000, B615100, B615200, B615z00, B616.00, B616000, B616400, B616700, B616z00, B61z.00, B61z000, B61z100, B61z200, B61z400, B61z500, B61z700, B61z800, B61zz00, B62..00, B620.00, B620000, B620100, B620300, B620500, B620800, B620z00, B621.00, B621000, B621300, B621400, B621500, B621800, B621z00, B622.00, B622z00, B623.00, B623000, B623100, B623300, B623z00, B624.00, B624.11, B624.12, B624000, B624300, B624z00, B625.00, B625.11, B625000, B625200, B625800, B625z00, B626.00, B626000, B626500, B626800, B626z00, B627.00, B627000, B627100, B627200, B627300, B627500, B627600, B627700, B627800, B627B00, B627C00, B627C11, B627D00, B627W00, B627X00, B62x.00, B62x000, B62x100, B62x200, B62x400, B62x500, B62x600, B62xX00, B62y.00, B62y000, B62y100, B62y200, B62y300, B62y400, B62y500, B62y600, B62y700, B62y800, B62yz00, B62z.00, B62z100, B62z200, B62z300, B62z500, B62z800, B62zz00, B62zz11, B63..00, B630.00, B630.11, B630.12, B630000, B630100, B630200, B630300, B631.00, B63y.00, B63z.00, B64..00, B64..11, B640.00, B641.00, B641.11, B642.00, B64y.00, B64y100, B64y200, B64yz00, B64z.00, B65..00, B650.00, B651.00, B651.11, B651000, B651200, B651z00, B652.00, B653.00, B653000, B653100, B65y100, B65yz00, B65z.00, B66..00, B66..12, B660.00, B661.00, B662.00, B66y.00, B66yz00, B66z.00, B67..00, B670.00, B670.11, B671.00, B671.11, B672.00, B672.11, B673.00, B674.00, B675.00, B67y.00, B67y000, B67yz00, B67z.00, B68..00, B680.00, B681.00, B682.00, B68y.00, B68z.00, B69..00, B690.00, B691.00, B692.00, B6y..00, B6y0.00, B6y0.11, B6y1.00, B6z..00, B6z0.00, BBED.00, By...00, Byu..00, Byu0.00, Byu1.00, Byu1100, Byu1200, Byu1300, Byu2.00, Byu2000, Byu2100, Byu2300, Byu2400, Byu2500, Byu3.00, Byu3100, Byu3200, Byu3300, Byu4.00, Byu4000, Byu4100, Byu4200, Byu4300, Byu5.00, Byu5000, Byu5011, Byu5100, Byu5300, Byu5400, Byu5700, Byu5800, Byu5900, Byu5A00, Byu5B00, Byu6.00, Byu7.00, Byu7000, Byu7100, Byu7300, Byu8.00, Byu8000, Byu8200, Byu9.00, Byu9000, ByuA.00, ByuA000, ByuA100, ByuA200, ByuA300, ByuB.00, ByuB100, ByuC.00, ByuC000, ByuC100, ByuC200, ByuC300, ByuC400, ByuC500, ByuC600, ByuC700, ByuC800, ByuD.00, ByuD000, ByuD100, ByuD200, ByuD300, ByuD400, ByuD500, ByuD600, ByuD700, ByuD800, ByuD900, ByuDB00, ByuDC00, ByuDE00, ByuDF00, ByuDF11, ByuE.00, ByuE000, ByuF.00, ByuF100, ByuF300, ByuF600, ByuF900, ByuFA00, ByuFF00, ByuFG00, ByuG.00, ByuG000, ByuG100, ByuG600, ByuG700, ByuG900, ByuGA00, ByuGB00, ByuGC00, ByuGD00, ByuGH00, ByuGH11, ByuGJ00, ByuGN00, ByuH.00, ByuH000, ByuHD00, E202B00, F1539C, F1991MC, K217, K9611, ZG42.00, ZR38.11, ZRVy.00
COPD	491*, 492*, 494*, 496*	J41–J44*	1I70.00, 1J71.00, 2126F00, 38Dd.00, 38Dg.00, 661M300, 661N300, 66YB.00, 66YB000, 66YB100, 66Yd.00, 66YD.00, 66Ye.00, 66Yg.00, 66Yh.00, 66Yi.00, 66YI.00, 66YL.00, 66YM.00, 66YS.00, 66YT.00, 66Yz200, 679V.00, 8BMa000, 8CE6.00, 8CMV.00, 8CMW500, 8CR1.00, 8IEy.00, 8IEZ.00, 9kf..00, 9kf0.00, 9kf1.00, 9kf2.00, 9NgP.00, 9Nk7000, 9Oi..00, 9Oi0.00, 9Oi1.00, 9Oi2.00, 9Oi3.00, 9Oi4.00, H3...00, H3...00, H31..00, H310.00, H310000, H310z00, H311.00, H311000, H311100, H311z00, H312.00, H312000, H312011, H312100, H312200, H312300, H312z00, H313.00, H31y.00, H31y100, H31yz00, H31z.00, H32..00, H320.00, H320000, H320100, H320200, H320300, H320z00, H321.00, H322.00, H32y.00, H32y000, H32y100, H32y111, H32y200, H32yz00, H32z.00, H36..00, H36..00, H37..00, H37..00, H38..00, H38..00, H39..00, H3y..00, H3y..11, H3z..00, H3z..11, Hyu3100
Autoimmune disease			

(Continued on next page)

(Continued from previous page)

Disease	ICD-9-CM	ICD-10-CM	READ-CODE
Multiple Sclerosis	340*	G35*	1292.00, 1JA3.00, 666A.00, 666B.00, 8Cc0.00, 8Cc1.00, 8Cc2.00, 8Cc4.00, 8CS1.00, 8Hkv.00, 8IAb.00, 9kG..00, 9mD..00, 9mD0.00, 9mD1.00, 9mD2.00, 9mD3.00, F20..00, F200.00, F201.00, F202.00, F203.00, F204.00, F205.00, F206.00, F207.00, F208.00, F20z.00, N001000, F20..11
Rheumatoid arthritis	714, 714.0, 714.1, 714.2, 714.30, 714.32, 714.33	M05–M06*	14G1.00, 2G25.00, 2G25.11, 2G27.00, 66H..13, 7P20300, 9mM..00, 9mM0.00, 9mM1.00, 9mM2.00, 9mM3.00, 9mM4.00, F371200, F396400, G5y8.00, G5yA.00, H570.00, N005.00, N04..00, N040.00, N040000, N040100, N040200, N040300, N040400, N040500, N040600, N040700, N040800, N040900, N040A00, N040B00, N040C00, N040D00, N040E00, N040F00, N040G00, N040H00, N040J00, N040K00, N040L00, N040M00, N040N00, N040P00, N040Q00, N040R00, N040S00, N040T00, N041.00, N042.00, N042100, N042200, N042z00, N047.00, N04X.00, N04y000, N04y011, N04y012, N04y200, N362200, Nyu1000, Nyu1100, Nyu1200, Nyu1G00
Inflammatory bowel disease	564.1*	K58*	J4...11, J4...12, J40..00, J40..11, J400.00, J400200, J400300, J400400, J400500, J400z00, J401200, J401z00, J402.00, J40z.11, J41..11, J41..12, J410.00, J410000, J410100, J410200, J410z00, J411.00, J412.00, J413.00, J41y.00, J41yz00, J41z.00, J43..00, J431200, J431300, J435.00, J437.00, J438.00, J4z2.00, J4z3.00, J4z5.00, J4z6.00
Ankylosing spondylitis	720*	M45*	2377.00, 388p.00, N100.11, N100.00, 37400.0, 93639.0, 2184.0, 40946.0, M45
Myasthenia gravis	358.0*	G70.0*	Q442.00, F380.00, F380z00, F380000, F380100
Sjogren's syndrome	710.2*	M35.0*	F396700, H57y300, N002.00

Chapter 7

Acknowledgements

I am deeply grateful to Professors Giampiero Mazzaglia and Lorenzo Mantovani for everything they have taught me, both within epidemiology and beyond.

My sincere thanks also go to the entire Centro Studi Sanità Pubblica (CESP) group for their help, thoughtful feedback, and the many good moments we shared inside and outside the office.

Finally, my greatest thanks go to Erika for her unwavering support and patience throughout this journey and its challenges.