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SIMO KARINIEMI

MULTIMORBIDITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic lupus erythematosus (SLE) is a rare systemic autoimmune disease which is also associated with several comorbidities. Their occurrence among Finnish patients remains unclear.

This thesis aims to clarify the epidemiology of comorbidities among Finnish recent-onset SLE patients. The studies were retrospective case-control studies that utilized data from several national registers in Finland. SLE patients were identified through reimbursement decisions approved in 2000–2014 as recipients of new SLE medication. The study consisted of 1,006 SLE cases.

The first study assessed comorbidities among SLE patients. The information of SLE cases were linked to the Care Register, and the data on comorbidities was retrieved from the day SLE was diagnosed (index day, ID) until the end of 2017 or until death. The second study evaluated new drug purchases considering antidepressant and antipsychotic medication among SLE patients. The data on the drugs purchased was retrieved from the Drug Purchase Register maintained by Finnish Social Insurance Institution. The purchases were observed from one year before the ID until the patient died, until the end of 2015, or until five years after the ID. The quantity of drug purchases was measured by using the Defined Daily Dose (DDD) parameter. The third study examined incident malignancies among

SLE cases from the Finnish Cancer Registry. The incidence was observed from the ID until death or until the end of 2018. Moreover, information on survival among SLE patients with malignancy was retrieved from the causes of death statistics managed by Statistics Finland.

SLE cases were found to have a significant risk for multiple comorbidities. The most typical of these consisted of cardiovascular diseases (CVDs) and diseases of the genitourinary system, given that approximately half of the patients were diagnosed with them. The relative risk (rate ratio, RR) for any CVD was 1.91 (95% confidence interval [CI] 1.76–2.08), and the highest risk was recorded among patients diagnosed with SLE at a young age.

SLE patients purchased significantly more antidepressants than controls both during the year before diagnosis (62.3 DDDs) and in the years following diagnosis (87.3 DDDs). Moreover, the share of antidepressant purchasers was higher among SLE cases than controls almost throughout the observation time. There were no significant differences observed in antipsychotic purchasers between SLE cases and controls.

Among SLE cases, the most common malignancy was non-Hodgkin's lymphoma (NHL) with 12 cases, which resulted in an incidence rate and incidence rate ratio of 1.1/1,000 person years (95% CI 0.5–1.7) and 5.27 (95% CI 2.08–13.36), respectively. The adjusted survival 15 years after SLE diagnosis was 27% in SLE patients with a malignancy. This resulted in an adjusted hazard ratio (HR) of 1.68 (95% CI 1.17–2.43) for death.

Finnish patients with SLE have an increased risk of multiple morbidities. Specifically, the risk of CVDs is notable. They also use more antidepressants at the time of SLE diagnosis, likely reflecting the probability of having a notable mood disorder already at diagnosis. Lastly, SLE patients are prone to certain malignancies, and the chance of staying alive is lower among SLE patients with a malignancy than among other people with a malignancy.

Keywords: systemic lupus erythematosus, comorbidity, antidepressant drug therapy, malignancy

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TIIVISTELMÄ

Systeeminen lupus erythematosus (SLE) on harvinainen koko elimistöön vaikuttava autoimmuunitauti, johon liittyy monia liitännäissairauksia. Niiden esiintymistä suomalaisilla SLE-potilailla on tutkittu vähän.

Tämän väitöskirjatyön tavoitteena oli selvittää suomalaisten vasta diagnosoitujen SLE-potilaiden liitännäissairauksien epidemiologiaa. Tutkimukset tehtiin retrospektiivisesti käyttäen tapaus-verrokki-asetelmaa ja hyödyntäen useiden kansallisten rekisterien tietoja. SLE-tapaukset tunnistettiin perustuen erityiskorvauspäätöksiin, jotka oli hyväksytty SLE-lääkitykselle vuosina 2000–2014. Tutkimus sisälsi 1 006 SLE-potilasta.

Ensimmäinen tutkimus arvioi SLE-potilailla ilmeneviä liitännäissairauksia. Potilastiedot yhdistettiin hoitoilmoitusrekisteriin, ja tiedot liitännäissairauksista haettiin siitä päivästä lähtien, kun SLE oli diagnosoitu (indeksipäivä, ID) vuoden 2017 loppuun asti tai kunnes potilas menehtyi. Toisessa tutkimuksessa arvioitiin SLE-potilaiden uusia lääkeostoja koskien masennus- ja psykoosilääkkeitä. Tiedot lääkkeiden ostoista haettiin Kansaneläkelaitoksen lääkekorvausrekisteristä. Lääkeostojen tarkastelu alkoi vuotta ennen ID:tä ja jatkui vuoden 2015 loppuun asti tai kunnes potilas menehtyi tai kunnes ID:stä oli kulunut viisi vuotta. Lääkeostojen suuruutta mitattiin Defined Daily Dose (DDD) -työkalulla. Kolmas tutkimus tarkasteli SLE-potilaille ilmaantuvia uusia

maligniteetteja Syöpärekisteristä. Ilmaantuvuutta tarkasteltiin ID:stä lähtien kuolemaan tai vuoden 2018 loppuun asti. Tilastokeskuksen ylläpitämästä kuolinsyytilastosta haettiin lisäksi tiedot maligniteettiin sairastuneiden SLE-potilaiden eloonjäämisestä.

SLE-potilailla todettiin merkittävä riski useisiin liitännäissairauksiin. Tavallisimpia niistä olivat kardiovaskulaarisairaudet ja virtsa- ja sukupuolielinten sairaudet, sillä noin puolet potilaista sai näiden sairausryhmien diagnoosin. Suhteellinen riski (esiintyvyyssuhde, RR) kardiovaskulaaritautiin oli 1.91 (95 % luottamusväli [CI] 1.76–2.08), ja riski oli korkein potilailla, jotka olivat sairastuneet SLE:hen nuorena.

SLE-potilaat ostivat merkitsevästi enemmän masennuslääkkeitä kuin kontrollit sekä vuotta ennen diagnoosia (62.3 DDD:tä) että diagnoosin jälkeisinä vuosina (87.3 DDD:tä). Lisäksi masennuslääkitystä ostaneiden osuus oli SLE-potilailla suurempi kuin kontrolleilla lähes koko tarkastelujakson ajan. Antipsykoottien ostajien suhteen ei löytynyt merkittävää eroa potilaiden ja kontrollien välillä.

Potilaiden tavallisin maligniteetti (12 tapausta) oli non-Hodgkinin lymfooma (NHL). Sen suhteen ilmaantuvuustiheys oli 1.1/1 000 henkilövuotta (95 % CI 0.5–1.7) ja ilmaantuvuustiheyksien suhde oli 5.27 (95 % CI 2.08–13.36). Vakioitu eloonjääminen 15 vuotta diagnoosin jälkeen oli SLE:tä ja maligniteettia sairastavilla potilailla 27 %. Vakioitu riskitiheyksien suhde (HR) kuolleisuudelle oli 1.68 (95 % CI 1.17–2.43).

Suomalaisilla SLE-potilailla on kohonnut riski useisiin liitännäissairauksiin. Etenkin kardiovaskulaarisairauksien riski on merkittävä. SLE-potilaat käyttävät myös enemmän masennuslääkkeitä SLE:n diagnosoinnin hetkellä, mikä todennäköisesti heijastaa sitä, että potilaalla voi jo SLE:n toteamisvaiheessa olla merkittävä mielialaoireyhtymä. Lopuksi, SLE-potilaat ovat alttiita tietyille maligniteeteille, ja todennäköisyys pysyä elossa on SLE:tä ja maligniteettia sairastavilla matalampi kuin muilla maligniteettia sairastavilla henkilöillä.

Avainsanat: systeeminen lupus erythematosus, liitännäissairaus, masennuslääkitys, maligniteetti

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Simo Kariniemi
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LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

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II Kariniemi S, Elfving P, Virta LJ, Kautiainen H, Puolakka K, Rantalaiho V. Patients with recent-onset systemic lupus erythematosus use more antidepressant medication than matched controls – a case-control study. Submitted.

III Kariniemi S, Rantalaiho V, Virta LJ, Kautiainen H, Puolakka K, Elfving P. Malignancies among newly diagnosed systemic lupus erythematosus patients and their survival. Lupus 31: 1750–1758, 2022.

CONTENTS

ABBREVIATIONS

ACR	American College of Rheumatology
AIHA	Autoimmune hemolytic anemia
ANA	Antinuclear antibody
anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
anti-Sm	Anti-Smith
APC	Antigen-presenting cell
aPL	Antiphospholipid antibody
APS	Antiphospholipid syndrome
ARA	American Rheumatism Association
ATC	Anatomical Therapeutic Chemical
AZA	Azathioprine
BDI	Beck Depression Inventory
BEL	Belimumab
BREG	B regulatory cell
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CI	Confidence interval
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
CyA	Cyclosporin A
CYC	Cyclophosphamide
DC	Dendritic cell
DDD	Defined daily dose
DHEA	Dehydroepiandrosterone
DIL	Drug-induced lupus
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
DNASE	Deoxyribonuclease
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
ENA	Extractable nuclear antigen
ESRD	End-stage renal disease
ESRF	End-stage renal failure
EULAR	European League Against Rheumatism
GC	Glucocorticoid
GI	Gastrointestinal
GLM	Generalized linear model
HCQ	Hydroxychloroquine
HL	Hodgkin's lymphoma
HPV	Human papilloma virus
HR	Hazard ratio
HSIL	High-grade squamous intraepithelial lesion
HZV	Herpes zoster virus
IBD	Inflammatory bowel disease
IC	Immunocomplex
ICD	International Classification of Diseases
ICD-O-3	International Classification of Diseases for Oncology codes
ICD-10	10th International Classification of Diseases code
ID	Index date
IFI	Invasive fungal infection
IFN	Interferon
IL	Interleukin
IR	Incidence rate
IRR	Incidence rate ratio
IUGR	Intra-uterine growth restriction

JAK	Janus kinase
LE cell	Lupus Erythematosus cell
LN	Lupus nephritis
lncRNA	long-coding RNA
MHC	Major histocompatibility
miRNA	MicroRNA
MI	Myocardial infarction
MMF	Mycophenolate mofetil
MTX	Methotrexate
N	Number
NET	Neutrophil extracellular trap
NHL	Non-Hodgkin's lymphoma
NIHW	National Institute for Health and Welfare
NMSC	Non-melanoma skin cancer
NPSLE	Neuropsychiatric systemic lupus erythematosus
NSAID	Non-steroidal anti-inflammatory drug
PE	Pulmonary embolism
PJP	Pneumocystis jirovecii pneumonia
PNS	Peripheral nervous system
PRC	Population Register Centre
PRR	Pattern recognition receptor
PYRS	Person years
RBP	RNA-binding protein
RNA	Ribonucleic acid
RR	Rate ratio
RTX	Rituximab
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SCLE	Subacute cutaneous lupus erythematosus
SD	Standard deviation
SII	Social Insurance Institution
SIR	Standardized incidence ratio
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SMR	Standardized mortality ratio
TAC	Tacrolimus
Th cell	T helper cell
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TREG	Regulatory T cell
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
VTE	Venous thromboembolism
WHO	World Health Organization

1 INTRODUCTION

Systemic lupus erythematosus (SLE) is a rare, life-long autoimmune disease that may affect several tissues and organs. The disease course can be unpredictable and varies greatly. Moreover, sex, age, ethnicity, and socioeconomic status modify the clinical picture. Most patients are females, with an approximate sex ratio of 8:1 (1-4). SLE typically emerges between 20 to 60 and 40 to 60 years of age in females and in males, respectively, but the disease may manifest at any age (4).

However, SLE is an infrequent disease with incidence rates (IR) ranging roughly from 1.0 to 23.2 cases per 100,000 person years (pyrs) according to a meta-analysis performed by Rees et al. (4). It is also characteristic for SLE to be more common in Black and Afro-American ethnicities, whereas in White people SLE is rare (4).

In addition to clinical variability, SLE is interconnected with many comorbid conditions, which complicate the disease management. These also decrease the working ability and quality of life as well as the survival of SLE patients (2,5-18). One of the most important comorbidities are cardiovascular diseases (CVDs), as their influence on mortality is crucial, especially when combined with renal diseases (6-8,9,16). On the other hand, malignancies form a significant share of the death causes in SLE (7,8). The chronic nature of the disease increases the risk of mood disorders among SLE patients, and mood disorders may markedly affect treatment adherence (15,18).

It is pleasing to note that the survival has improved markedly in recent decades, as from the 1950s to 1980s the five-year survival in SLE was below 80%, but nowadays it is over 90% (3,5). Possible reasons for the better survival may be more efficient drug therapy and earlier recognition of the disease (3,5-8). However, mortality is still higher than among general population (6-8).

One of the most important factors increasing mortality today are comorbidities, which complicate disease management and have a major effect on the life of SLE patients. Some other studies have reported

increased risks of several comorbidities in SLE. However, no comprehensive nationwide studies have been implemented in Finland on this issue (6, 8-16).

Thus, the aim of this thesis was to clarify the epidemiology of comorbidities in recent-onset SLE patients diagnosed between 2000 and 2014 in Finland based on wide linkage of different national registers.

2 REVIEW OF THE LITERATURE

2.1 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

2.1.1 History of SLE

The first impressions of SLE may date as far back as ancient Greece, as Hippocrates appears to have been the first to describe the cutaneous ulcerations typical for SLE. In the Middle Ages, the term “Lupus” was introduced to depict the erosive facial lesions, boils, and ulcerations of SLE patients (19,20). However, in 1833, Laurent Théodore Biett and his student Pierre Louis Alphée Cazenave were the first to describe reliably the skin lesions of lupus. Cazenave described the disease as an uncommon condition which most frequently affected young females, primarily in the face. In 1866, an Austrian doctor, Ferdinand von Hebra, reported a butterfly-like malar rash. The systemic manifestations of SLE were described for the first time by Moritz Kaposi in 1872 (20).

The term “systemic lupus erythematosus” was created by Sir William Osler as he recognized pulmonary, cardiac, and renal problems as systemic manifestations of SLE at the turn of the 20th century (19). In 1948, the Lupus Erythematosus cell (LE cell) was discovered by the hematologist Malcolm Hargraves, marking the onset of the modern period of the disease. Roughly ten years later, antinuclear antibodies (ANAs) were found, which was a breakthrough in the understanding of the pathogenesis of autoimmune diseases, including SLE (20).

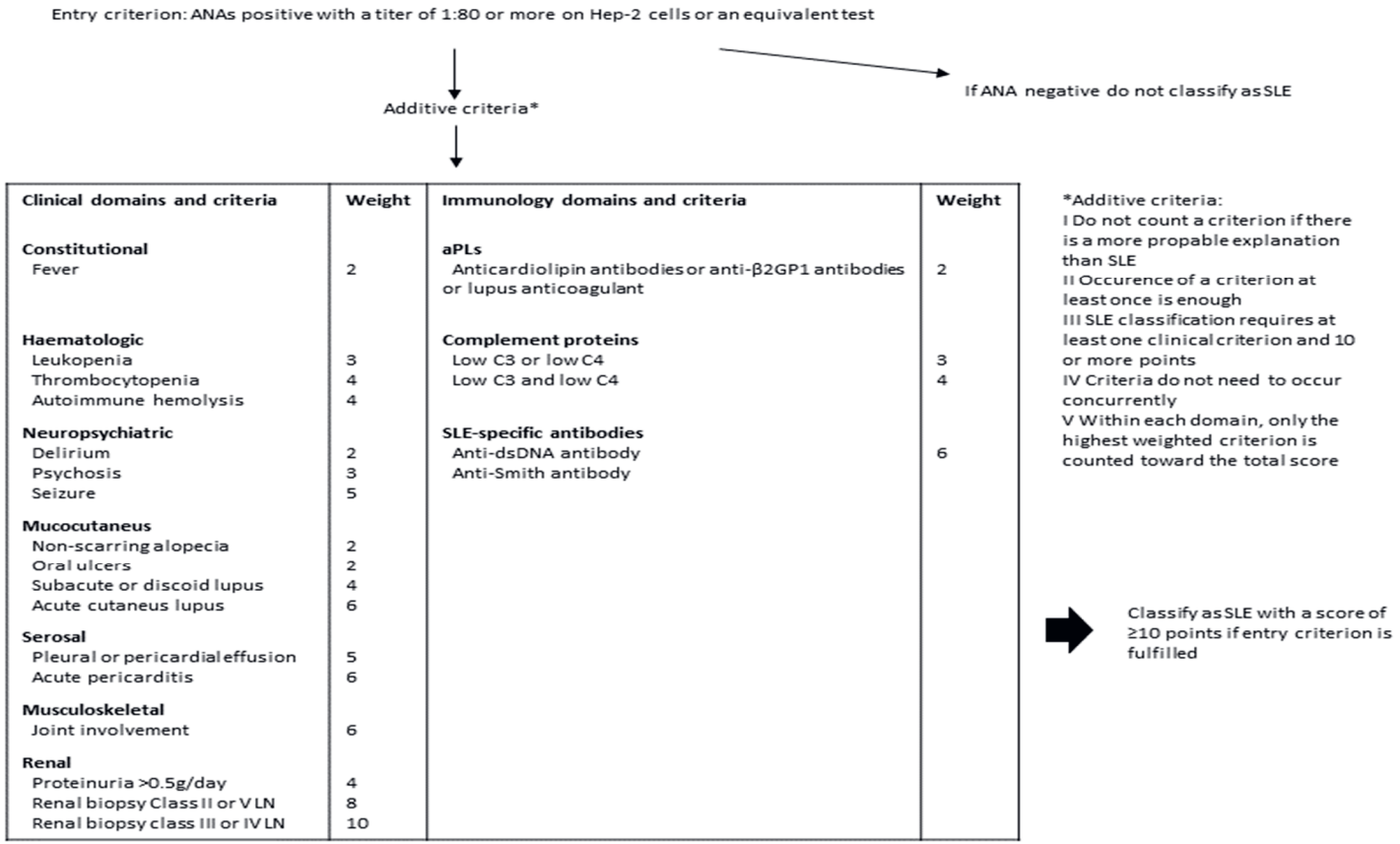
2.1.2 Classification of SLE

In 1971, the initial criteria for classification of SLE were announced by a subcommittee of the American Rheumatism Association (ARA). They were edited in 1982 by ARA, as the preliminary criteria did not include antibody testing (ARA82 criteria, which are also known as the American College of Rheumatology ACR82 criteria) (21). In 1997, the criteria were modified again, when the LE cell was replaced with the positive finding of

antiphospholipid antibodies (aPL) (22,23). In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) created new SLICC criteria based on the ACR97 criteria to improve clinical relevance and methodology, which were used alongside the ACR97 criteria in clinics worldwide (24).

In 2019, the European League Against Rheumatism (EULAR) and the ACR published the latest classification criteria for SLE (Figure 1). The 2019 EULAR/ACR criteria attempt to recognize early SLE better than the ACR97 and SLICC criteria. According to the classification criteria, ANAs should be positive at least with a titer of 1:80 to classify the disease/condition as SLE. Moreover, clinical and immunological domains are weighted, and SLE cases should fulfill at least one clinical criterion and have at least ten points. It is not required the criteria to occur simultaneously, and the occurrence of criterion of at least once is enough (25). The 2019 EULAR/ACR criteria also seem to perform well considering sensitivity and specificity across sexes and different ethnic groups (26,27). However, it is noteworthy that these classification criteria cannot be utilized when assessing incomplete or early SLE, since they are not equal to the diagnostic criteria (25,27).

Figure 1. The 2019 EULAR/ACR classification criteria for systemic lupus erythematosus. Modified from Aringer et al. 2019 (25).



Abbreviations: ANA = antinuclear antibody; aPL = antiphospholipids; LN = lupus nephritis; SLE = systemic lupus erythematosus

2.2 EPIDEMIOLOGY

Epidemiologic studies are studies examining a defined population in a certain time span. Therefore, it is impossible to determine the actual occurrence of any disease because the study results depend on the study sample, inclusion criteria, and methods (28). Especially in SLE, the estimates of incidence and prevalence are affected by the differentiations in classification criteria over time (4,21,23-25). The estimates of SLE occurrence and the occurrence of SLE-associated comorbidities are also highly affected by the diversity of the disease, as the clinical picture varies markedly according to age, sex, medication, ethnicity, and socioeconomic status (3,4,6).

2.2.1 Incidence

SLE is a rare disease which predominantly affects females, with sex ratios varying from 6:1 to 14:1 between studies (4,29-36). The disease can manifest at any age. Typically, it occurs at child-bearing age in females, while males are five to ten years older than females at diagnosis (4,29,31,33-35). The highest sex ratio has been recorded at 20 to 60 years of age, whereas in children and older patients, the ratio is lower (35,36).

SLE can manifest in any racial/ethnic population, but some of them are more prone to SLE such as Black, Hispanic, and Asian ethnicities, whereas in White ethnicities the disease is more infrequent (4,34,37,38). The incidence of SLE has been reported to vary from 4.9 to 23.2 per 100,000 pyrs and 2.4 to 8.6 per 100,000 pyrs in North America and in Europe, respectively (4,31,33-35,38,39). For example, a study from the United Kingdom (UK) reviewed the Clinical Practice Research Datalink (CPRD) records from 1999 to 2012 and reported an incidence of 4.9/100,000 pyrs for SLE. In their study, SLE was six times more common in females than in males. Black Caribbean ethnicities had the highest incidence of SLE (31.5/100,000 pyrs) whereas White patients had the lowest (6.7/100,000 pyrs). Females contracted the disease at a younger age than males (40–49 years of age vs. 60–69 years of age) (31).

In Finland, the incidence of SLE was studied between 2000 and 2007 based on reimbursement decisions for SLE medication. An incidence of 1.7 per 100,000 pyrs was recorded and 566 new SLE cases were observed. SLE was six times more common among females than males in the Finnish study, which was in line with the results of the UK study. The incidence was at its highest at the ages of 40–54 years in females and 55–59 years in males (29). A nationwide French study from 2010 reported an incidence of 3.3/100,000 pyrs. However, females contracted SLE at a slightly younger age (30–39 years) than in the UK or in the Finnish study, whereas among males the result was similar (50–59 years) (35). In Asian studies, the incidence has varied from 2.5 to 8.1 per 100,000 pyrs (30,36).

It seems that the incidence of SLE has been decreasing in recent years, as in the UK study the IRs declined steadily over time; in 1999 the incidence was 5.1/100,000 pyrs and in 2012 it was 4.6/100,000 pyrs (31). Likewise, a Taiwanese study reported a decline from 9.9/100,000 pyrs in 2001 to 6.8/100,000 pyrs in 2007 (36). One reason for the declining trend may be more accurate recognition of the disease (31,36).

In parallel to adult-onset disease, pediatric SLE is uncommon as the incidence has ranged from 0.4 to 2.8 per 100,000 pyrs (29,40-42). The Finnish study by Elfving et al. found 33 new cases of SLE among children aged under 16 years during the years 2000–2007 (29).

2.2.2 Prevalence

In contrast to incidence, the prevalence of SLE has been rising in recent years as Rees al. reported a prevalence of 65/100,000 in 1999 and 97/100,000 in 2012 in their CPRD study (31). In the French nationwide study from 2010, a prevalence of 42/100,000 was described, while in Canada, a prevalence of 48/100,000 was demonstrated in 2000, but in 2015 it had increased to 90/100,000 (35,43). In the Taiwanese study, a prevalence of 42/100,000 and 67/100,000 were recorded in 2000 and 2007, respectively (36). The only Finnish prevalence study from 1978 detected patients from nationwide hospital discharge registers and recorded a prevalence of 28/100,000 (44).

The prevalence of childhood-onset SLE is low (30,31,35). For example, the French study recorded a prevalence of 3.8/100 000 among persons aged 0–19 years. Compared to all prevalent SLE cases, the proportions of childhood-onset disease were 0.06%, 0.2%, 0.7% and 2% among persons aged 0–5 years, 0–10 years, 0–15 years and 0–19 years, respectively (35).

Possible reasons for the increased prevalence may be more efficient management, better survival and more accurate diagnostic procedures. In addition, different study strategies may explain the elevated prevalence over time (31,36).

2.3 ETIOPATHOGENESIS

The etiology of SLE remains largerly undiscovered, and it seems to be multifactorial and complex (45-48). A great mixture of several genetic, hormonal and enviromental factors are considered to have a role in causing SLE. Moreover, the pathogenesis involves various abnormalities in immune system regulation, including both the innate and adaptive immune system. Interestingly, the disordered mechanisms differ between individuals, leading to differences in clinical manifestations at the individual level. It has even been proposed that the disease that is currently called SLE may actually consist of many different heterogeneous diseases (45,48).

2.3.1 Genetic background

There are some family studies that discuss the inheritance of SLE (49-51). A Taiwanese nationwide study reported that first-degree relatives would be as much as 17 times more likely be diagnosed with SLE than general population. The risk of SLE was 300 times higher among twins and 20 times higher among siblings in that study (49). Moreover, a Danish study reported probandwise concordance rates of 25% and 8% for monozygotic and dizygotic twins, respectively, and pairwise concordance rates were 14% and 8% for monozygotic and dizygotic twins, respectively (50). In Finland, not many studies have been made considering inheritance. Yet, between 1992 and 1996, Koskenmies et al. found 53 multiplex (at least two family members were affected) SLE families and three pairs of monozygotic twins.

Interestingly, the clinical picture did not differ between familial and sporadic cases (51).

Currently, genome-wide association studies have described almost 180 genetic loci which predispose to polygenic or monogenic SLE. In addition, many of the identified risk variants are in the non-coding regions of deoxyribonucleic acid (DNA) (47). It also seems that the genetic susceptibility to SLE is mostly polygenic (46).

Some of the most interesting genes in monogenic SLE are those affecting the complement pathway (52,53). The complement system is essential in clearing out apoptotic cells and immunocomplexes (ICs), and it plays a major role in defending against pathogens. If the complement system becomes hyperactivated, the result is serious inflammatory response in many organs, particularly in the kidneys. It has been presented that the hereditary deficiency of C1q, which is a main component of the classical pathway, would be the most powerful genetic risk factor known for SLE (52-54). Interestingly, patients with C1q deficiency are younger at disease onset, and there is no tendency for female dominance compared to sporadic SLE (54).

The major histocompatibility (MHC) locus covers the most frequent genetic susceptibility to SLE. This region includes genes for antigen-presenting molecules, and some of these genes, such as HLA-DRB1, have been strongly associated with SLE in multiple ethnic groups (47).

2.3.2 Environmental factors

2.3.2.1 Epigenetics

Despite the recent advantages, there is still much missing heritability as the genetic information found covers only one third of the susceptibility to SLE. The epigenetic and environmental mechanisms could explain this missing susceptibility (47). Epigenetic mechanisms work as bridges between environmental and developmental factors and genes and play a substantial role in many life processes, such as cellular growth and immune response (55-57). Histone modification, DNA methylation and non-

coding ribonucleic acid (RNA) regulations are the primary mechanisms of epigenetic alteration (55,57).

DNA hypomethylation is one of the major epigenetic mechanisms, as notable T cell hypomethylation has been described in SLE patients (58,59). Moreover, two DNA methylation inhibitors, procainamide and hydralazine, seem to induce drug-induced lupus-like syndrome by causing hypomethylation in the T cell DNA (60).

Noncoding RNA means a large variety of transcripts which are unable to code proteins, such as microRNAs (miRNAs) and long-coding RNAs (lncRNAs). They both have decisive roles in the pathophysiology of autoimmune diseases as they regulate gene expression by suppressing or accelerating genes (61-64). Several of the miRNAs identified in SLE appear to influence pathways that are important for disease process, such as Toll-like receptor (TLR) signaling (48,62). In addition, it has recently been thought that there would be an imbalance in the expression pattern of miRNAs, in which pathogenic miRNAs are increased and suppressive miRNAs are decreased (63).

2.3.2.2 Sex and hormonal factors

As noted earlier, SLE is more common in females than in males. One appealing aspect for the female tendency is the X chromosome. In the embryonic stage, the extra X chromosome normally becomes inactivated. However, around 15% of the inactivated X chromosome's genes may escape the process (63,65,66). The inactivation of the X chromosome is significant as the chromosome contains many important gene loci that influence SLE pathogenesis, and the defective activation causes overexpression of certain genes that regulate immune responses (46,63,66-70).

Many theories about sex hormones, such as estrogen, testosterone, progesterone, dehydroepiandrosterone (DHEA) and pituitary hormones, and SLE occurrence and disease severity have been suggested, but the literature is somewhat mixed (71-75). Estrogen receptors are widely distributed in the immune system. At the cellular level, estrogen affects B cells by improving the tolerance to apoptosis. It may also promote the

maturation of pathogenic naive autoreactive B cells while restricting autoreactive B cells that potentially work in a protective way (71).

In 2007, Costenbader et al. studied more than 200,000 females aged 25–55 years and reported early age at menarche, use of oral contraceptives, surgical menopause, and postmenopausal use of hormones to be associated with the risk of SLE evolvement (73). On the other hand, the use of oral contraceptives does not appear to increase the risk of flares in premenopausal SLE females with stable disease, at least when high doses are avoided (74). Moreover, the use of hormone replacement therapy does not seem to elevate the risk of severe flares in stable SLE, but it may increase mild flares (75).

2.3.2.3 Other environmental factors

Many other environmental factors have been suggested to be associated with the onset of SLE and its flares as well (76-78). In autoimmune diseases, the immune system's ability to differentiate between host and foreign cells is diminished. This leads to formation of autoantibodies which attack the host cells and their structures. Viruses, especially Epstein-Barr virus (EBV) and cytomegalovirus (CMV), appear to affect SLE pathogenesis, whereas the roles of bacterial infections and parasites are controversial (48,76,77).

Variable results have been presented about the role of sun exposure and ultraviolet radiation (UV) in SLE development (78-83). UV radiation probably aggravates pre-existing SLE (79,82). In a Swedish study consisting primarily of Caucasian females, people with type I/II sunreactive skin type (”always burns, does not tan” or ”burns easily, tans poorly”) had a twofold increased risk of SLE (82). The mechanisms of action of UV radiation share similar characteristics with SLE pathophysiology: keratinocyte apoptosis, accelerated production of interleukin (IL)-1 and IL-6 and adjustment of lymphocyte function. Overproduction of autoreactive T cells and the formation of reactive oxygens species may also be consequences of UV radiation (78,79).

Vitamin D has been suggested to have a significant role in the pathogenesis of autoimmunity (78,79). However, its role in SLE is unknown (78,79,84). Some studies have reported lower D vitamin levels to correlate

with SLE disease activity (84,85). On the other hand, sun exposure advances vitamin D production. Thereby, low vitamin D levels may be a result of the avoidance of sun among SLE cases (79).

Smoking seems to predispose to SLE (78,82,86,87). According to a meta-analysis from 2004, current smoking increased the risk of SLE by 50%, but the results concerning previous smoking were mixed (87).

2.3.2.4 Drugs and drug-induced lupus

Some drugs can reveal pre-existing SLE or induce a usually reversible SLE-like phenomenon called drug-induced lupus (DIL) (88). Today, more than a hundred drugs have been linked to DIL, such as procainamide and hydralazine, which also bear the highest risk (89). In DIL, autoantibodies are induced, most commonly ANAs or anti-histone antibodies. Autoantibodies then lead to clinical features mimicking SLE. The features typically include arthralgias, myalgias, arthritis and fever, but major organ involvements are commonly absent (89). After the discontinuation of the drug the symptoms usually resolve. The prognosis of DIL is good in most cases (88,89).

2.3.3 Immunology

2.3.3.1 General aspects

The molecular pathogenesis of SLE is deeply complex and partly unknown. In SLE, there is a large breakdown of immunotolerance. The disordered immune system involves both the adaptive and innate immune system and many different cells, cytokines and other molecules interact with each other. The pathological processes are self-amplifying, inciting one another as well (48,90-93).

The fundamental aspects of the abnormal immune system are the wide production of different kind of cytokines, such as IFN-α and IL-17, hyperactive T and B cells, and overexpression of antigen-presenting cells (APCs) (48,92,93). The pathological hallmarks of SLE pathogenesis are also an increased rate of apoptosis, decreased removal of apoptotic cells, and

the production of autoantibodies. Autoantibodies attack the self-antigens of the cells creating ICs, which contribute to organ damage (48,90,91,94).

2.3.3.2 Apoptosis and the role of the innate immune system

Apoptosis (programmed cell death) leads to cell debris, which is cleared out in a healthy body by the immune cells and many catabolizing enzymes, such as deoxyribonucleases (DNASE) (48,92). Proper clearance of cell debris prevents the exposure and accumulation of self-antigens and hinders the activation of immune cells. However, SLE patients have an increased rate of apoptosis. Moreover, the clearance of dead cells is diminished, which leads to a stronger autoantigen exposure. As a result, an improper inflammatory response is born (48,92,93).

Pattern recognition receptors (PRR) have an essential role in the innate immune system, as they recognize the apoptotic or damaged cells and activate the immune system. Of these, TLRs play a key role in the innate immune system. SLE patients seem to have disturbances in the number of these receptors (48,92-95). More specifically, the number of TLR-9 expressing B cells and monocytes is increased when SLE is active (95). As a result, TLR-9 ligand activates plasma cell-like dendritic cells (DC), which leads to the production of a great amount of type 1 interferon (IFN). TLR-ligand can also stimulate B cells (92,93,95). Next, an increased number of autoantigen-antibody complexes is formed, activating the production of type 1 IFN. Especially IFN-α stimulates many immune cells, enhances the ability to present antigens by the DCs, and induces the production of many cytokines (48,92,93).

Neutrophils are essential components of the innate immune system. However, inappropriate activation of these cells releases chemokines, cytokines, and other tissue-injuring factors, resulting in damage in SLE (48,92,94). On the other hand, impaired phagocytosis has been described in SLE patients leading to an increased amount of cell debris and risk of infections. One of the reasons for decreased phagocytosis is the reduced function of the complement system and DNASEs (DNASE1 and 2), which are enzymes that chop cell debris for phagocytes (48,94,96).

Neutrophils also have structures called neutrophil extracellular traps (NET) which play a central role in immunity. Their function is to immobilize pathogens. In SLE, suboptimal clearance of NETs by DNASE1 has been reported. The surplus of NETs leads to autoantigen externalization, which promotes type 1 IFN production, causing further damage (48,92,93).

2.3.3.3 Lymphocyte action

Both T and B cells have key roles in SLE pathophysiology. T cells secrete cytokines and affect cell signaling inappropriately, which causes excessive recruitment and activation of B cells and DCs at the place of inflammation (93,97). T helper cells (Th cells) take part in the production of many cytokines, such as tumor necrosis factor (TNF) -α, IL-2 and -10 that are needed in activating other leukocytes. The dysfunction of Th cells and the imbalance between Th1 and Th2 subsets are believed to be important factors in SLE pathogenesis (48,93). Another imbalance is thought to exist between Th 17 cells and regulatory T cells (Treg). IL-17A, IL-17F and IL-22 are produced by Th 17 cells. Especially, the production IL-17 is important in pathogenesis as it upregulates the differentiation and survival of B cells. Tregs, on the other hand, participate in maintaining self-tolerance, and in SLE, their function is decreased (93).

Autoreactive B cells secrete a great mixture of autoantibodies (48). Activated B cells communicate with CD4+ cells and secrete cytokines, such as TNF-α (48,93). On the other hand, after activation of CD4+ cells the B cells get activated, leading to plasma cell differentiation. In the end, long-lived plasma cells are formed (48,93,98). Moreover, the number of B regulatory cells (Breg) appears to be reduced in SLE patients. They are important components of the immune system as they modulate immune response by affecting the activation and apoptosis of B lymphocytes, regulating the antigen presentation, and inhibiting the production of pathogenic Th1 cytokines (93,99).

2.3.3.4 Autoantibodies and complement system

Autoantibody production is a characteristic feature for SLE. These antibodies target many different nuclear, cytoplasmic and membrane molecules, and they can attach to proteins and lipids circulating in the bloodstream. They can form ICs, which regulate inflammation by inducing cytokines further (48,100).

It is thought that ANAs should be positive in virtually every SLE patient at least once during the disease course (20,25,100-103). They can be allocated according to their target antigen, disease association, or assumed role in the pathogenesis (100-103). Typical ANA patterns are speckled, homogenous, rim, centromere or nucleolar, the first two being the most frequent in SLE (103).

ANAs are basically divided into two groups based on the biochemical features of the molecule being targeted. The first type consists of antibodies to DNA (anti-double-stranded DNA, anti-dsDNA) and related nucleosomal components, but only anti-dsDNA antibodies are studied and routinely measured. The second ANA group includes antibodies against RNA-binding proteins (RBPs), which are also known as antibodies against extractable nuclear antigen (ENA). Furthermore, antibodies against RBPs bind to a group of RNA-binding proteins (Sm, RNP, Ro, La) (100,101,103).

ANAs typically precede the first clinical symptoms and diagnosis of SLE by several years. However, some of the autoantibodies seem to be relatively common in healthy persons, such as ANA, anti-La, Anti-Ro and aPLs, whereas anti-dsDNA, anti-Smith (anti-Sm) and anti-RNP antibodies rarely occur in healthy persons (100-104).

2.3.3.4.1 Autoantibodies and their relation to disease

Anti-dsDNA antibodies are very specific to SLE, but their sensitivity is quite low as they occur in only 50–60% of SLE patients during lifetime. Their level correlates with disease activity, at least in most of the cases, and they are positive in nearly 80% of cases when renal manifestation is present (103, 105,106). They are associated with skin disease and neuropsychiatric

manifestations, and increased levels may predict fetal loss in pregnancy (3,103,105,107). Furthermore, anti-dsDNA antibodies can be found in coincidence with certain cases of autoimmune hepatitis and infections, such as syphilis, bacterial endocarditis, and parasitic infections (103).

Anti-Ro/SSA antibodies are estimated to exist in around half of the SLE patients, and anti-La/SSB are often found in coincidence with them (3,103,107). However, neither anti-Ro/SSA nor anti-La/SSB are specific for SLE, and their role in pathogenesis is controversial (103,107). These antibodies predispose to neonatal lupus, which develops in a small proportion of children whose mothers are anti-Ro/SSA or anti-La/SSB positive (103,107).

Anti-Sm antibodies occur in around 5–30% of SLE patients, and they seem to be most frequent among African American patients. Due to their high specificity for SLE, they are included in the 2019 EULAR/ACR classification criteria (25,103,108). They are associated with lupus nephritis (LN), especially when anti-dsDNA antibodies are present, but their correlation with disease activity is uncertain (108). Anti-RNP antibodies often coexist with anti-Sm antibodies, but they are not specific for SLE. They are detected in up to half of the SLE cases. They are linked with myositis and Raynaud's phenomenon (108). Anti-ribosomal P protein antibodies target phosphoproteins. They are specific for SLE, and their levels vary with disease activity. They are associated with neuropsychiatric manifestations and liver disease (103).

aPLs (anti-cardiolipin, lupus anticoagulant and anti-β-2-glycoprotein) are often associated with SLE, but they are not specific and can occur also simultaneously with malignancy or infection. They predispose to antiphospholipid syndrome (APS) inducing thrombosis, and their role in occlusive vascular disease is important. They also predispose to miscarriage, pre-eclampsia, and preterm delivery. Their presence is associated with worse outcome and higher mortality (103,107,109).

The level of anti-histone antibodies correlates with disease activity, but they are not unique for SLE. They are associated with DIL development. C1q antibodies occur in approximately one third of SLE cases. More than 90% of proliferative LN cases have them, but they have been reported in

membranoproliferative glomerulonephritis and rheumatoid vasculitis as well (103). They are sometimes used in monitoring SLE, especially in the case of LN, as C1q level correlates strongly with disease activity (110).

2.3.3.4.2 Complement system and immunocomplex

The role of the complement system is complex in SLE. On one hand, it enhances inflammation and tissue damage, and on the other hand, a deficiency of certain parts of the system increases SLE risk (52-54,111).

The complement system consists of around 30 proteins. It has a key function in both acquired and innate immunity. More precisely, it increases the permeability of capillaries, opsonizes antigens, attacks pathogen's cell membrane, and guides other immune cells to the place of inflammation (48,92,111,112). It stimulates T and B cells, but its most important task is to clear the apoptotic cells and ICs formed by autoantibodies and self-antigens. If this task fails, dead cell debris and ICs accumulate in vascular beds leading to long-term vasculitis, tissue injury, and organ damage (111,112). With limitations, some parts of the complement system (C1q, C3 and C4) can be used in the diagnosis and follow-up of SLE (113).

2.4 DISEASE COURSE AND MANIFESTATIONS

2.4.1 Disease course and modifying factors

The manifestations of SLE can be diverse and vary between individuals, as the disease is systemic, with the ability to affect many organs and tissues. The disease course and outcome are unpredictable and depend on several factors such as ethnicity, age, sex, and medication. The onset of SLE can be insidious or acute. Usually, quiescent and active phases alternate according to disease flares. More subtle disease onset is linked with older age, White ethnicity and higher level of education (1-3,114-116).

According to the Lupus in minorities; nature vs. nurture cohort that studied differences in the clinical course and outcome of different ethnicities, the disease activity was higher among African American and Hispanic (Texas) than White patients. In general, non-White patients seem

to be younger at disease onset and have more often severe organ involvement than White patients (116,117). Moreover, predictors of greater disease activity appear to be acute disease onset and certain genetic factors. Studies have also found that Hispanic (Mexico) and African American ethnicity, low education level, older age at the onset of SLE, poverty, use of glucocorticoid (GC) therapy and immunosuppressants, hypertension, active renal disease, higher count of ACR criteria at study entry, longer disease duration and in particular, early damage, predict greater cumulated damage (116-120). Male sex has been related to higher damage accrual and end-organ damage, as CVD problems and renal manifestations seem to be more frequent among males (2,9,117,118). The use of antimalarial treatment has been linked with reduced damage accrual (117).

Childhood-onset SLE is typically more severe than adult-onset disease as children seem to have more serious disease manifestations, such as renal and neuropsychiatric involvement. These manifestations require more aggressive therapy, which may lead to increased damage over time. On the other hand, older patients may have an elevated risk of cumulative damage because they have a greater absolute risk for comorbidities, such as CVDs and malignancies. Moreover, the clinical spectrum in older-onset SLE may mimic more polymyalgia rheumatica, primary Sjögren's syndrome or DIL, whereas traditional manifestations of SLE, such as malar rash, are more infrequent (2,3,8,118-121).

2.4.2 Disease onset

In SLE, the dysregulation of immune system begins many years before the first clinical symptoms can be observed. One of the first detectable changes of the disturbed immune system is the production of autoantibodies, which may precede the clinical manifestations more than five years (102,114). The time between the first symptoms of SLE and the diagnosis seems to range two to five years, but the delay is more common in children than in adults. Many patients may require inpatient care at the time of diagnosis indicating the severity of the disease, but also likely

reflecting both the diversity of the disease and the difficulty of diagnosing SLE (3,114,122,123).

Most commonly, the onset of SLE is insidious and constitutional symptoms, such as fatigue, are common. The most typically seen disease manifestations at first are arthralgia, morning stiffness and mild synovitis accompanied with rash, photosensitivity, mucocutaneus ulcers and mild fever at least among White patients. However, SLE may also begin with renal and hematologic problems, especially among Hispanic and African American patients. Moreover, children tend to have more nephropathy and male patients may have more serositis than females at the onset. On the contrary, females seem to have more arthritis than males. It is also notable that other manifestations not included in the 2019 EULAR/ACR classification criteria are frequently present at the onset of SLE, such as sicca syndrome, Raynaud's phenomenon and livedo reticularis (3,114,122-124). In addition to ANAs, most commonly seen laboratory changes are complement deficiencies, anti-dsDNA, anemia, lymphopenia and thrombocytopenia (114,122,123).

2.4.2.1 Constitutional symptoms

The disease onset can sometimes resemble a virus infection. Mild fever, weight loss and other constitutional symptoms are frequently reported. Fatigue is one of the most commonly experienced symptoms in SLE, as more than half of the patients report suffering from it. Disease activity, organ damage, pain, comorbidities, helplessness, work disability, and poor sleep quality have been suggested to increase the risk of fatigue, indicating the problem to be multifactorial and difficult to handle (3,114,115,124).

2.4.2.2 Joint manifestations

Arthralgia and arthritis are frequently present at the onset of SLE (3,114,122,123,125). They are often migratory and prolonged morning stiffness is typical. However, swelling is not commonly as marked as in seropositive rheumatoid arthritis. In addition, the synovial fluid is in most cases only mildly inflammatory. Arthritis is most often non-erosive and can

be either asymmetrical or symmetrical. Most commonly affected joints are metacarpophalangeal and phalangointerphangeal joints and knee and wrist joints, but any joint can be affected (114,122,125).

In addition, SLE rarely causes joint deformations, and they are normally reducible. Jaccoud arthropathy is present in roughly five percent of the cases, and it may include swan neck deformities, ulnar deviation and thumb subluxation (114,125,126).

2.4.2.3 Skin and mucosal manifestations

As many as 80% of SLE cases develop skin manifestations at some point of the disease. Acute lupus, photosensitivity and alopecia are the most common features, whereas subacute cutaneous lupus (SCLE), discoid lupus and some other forms of chronic cutaneous lupus are more occasional. Acute lupus usually presents as a malar butterfly-like rash consisting of hard or flat reddish lesions. It is a specific manifestation for SLE, and skin flares often reflect systemic activity. SCLE presents as an annular, map-like lesion in areas that are exposed to light, and it may mimic psoriasis. SCLE is related to SSA antibodies. Discoid lupus is the most common form of chronic cutaneous lupus. It most often presents as an erythematous patchy-like rash with stiff hyperkeratosis in the middle. However, discoid lupus is not specific for SLE (114,123,127-129).

Mucosal lesions are typical in SLE. They primarily involve the mouth, but can also be seen in nasal, conjunctival and anogenital areas. They may present as erythematous macules, palatal erythema, ulcers, and erosions (25,114,128).

2.4.2.4 Hematological manifestations and antiphospholipids

Cytopenias are typical in SLE. Anemia, leukopenias and thrombocytopenia are usual (3,114,123,130). Anemia is frequently due to chronic disease, but sometimes it is a result of bleeding or drug toxicity (130,131). Occasionally, severe autoimmune hemolytic anemia (AIHA) is found. AIHA is frequently the warm type and commonly related to disease onset and African American origin. Usually, it coexists with thrombocytopenia (114,130,131).

Thrombocytopenia is recorded in 10–15% of the patients, and it may be related to antiplatelet antibodies and aPLs. It may have prognostic significance considering survival (130). Leukopenia is demonstrated in up to 40% of cases. Both lymphopenia and neutropenia may occur. Lymphopenia is seen in up to 80% of cases, and it is associated with disease activity, flares, and organ damage, whereas neutropenia is more uncommon but may indicate active disease or drug toxicity (130-132).

The presence of aPLs and the occurrence of arterial or venous thrombosis or pregnancy morbidity (premature birth, fetal loss, multiple abortions) is called APS. It can be primary or associated with another disease, which is most often SLE. Approximately 40% of SLE patients have been reported to have aPLs, but less than 40% of them develop thrombotic events. The risk of these events is mediated by the aPL profile: the continual presence (in two or more occasions at least twelve weeks apart) of lupus anticoagulant or double or triple aPL positivity is considered the highest risk profile (109,133).

The thrombosis manifests most often as pulmonary embolism (PE) and deep vein thrombosis (DVT), but also arterial thrombosis, such as myocardial infarction (MI), and microvascular thrombosis may occur (109,133,134). SLE patients with aPLs/APS have a higher risk for neuropsychiatric manifestations, impaired renal function and thromboses, which explain the higher mortality reported. Moreover, aPLs, especially lupus anticoagulant, are associated with heart valve disease in SLE (109,133,134).

2.4.2.5 Cardiopulmonary and gastrointestinal manifestations

Cardiopulmonary involvement may be seen in SLE as well (135,136). Virtually any part of the heart can be affected, and pericarditis, valvular heart disease, arrhythmias, myocarditis, and non-infectious endocarditis (Libman-Sacks) have all been reported (135). A common pulmonary manifestation is pleuritis, which can manifest with or without pleural effusion, whereas shrinking lung syndrome, acute pneumonitis, pulmonary hypertension, diffuse alveolar hemorrhage and chronic interstitial lung disease are less frequent (136).

Peritonitis and pancreatitis are rare manifestations of SLE while esophageal and gastric symptoms are quite common. These symptoms may occur due to the use of non-steroidal anti-inflammatory drugs (NSAID) or GCs or reduced production of saliva when secondary Sjögren's syndrome is present. Vasculitis, intestinal pseudo-obstruction, malabsorption, and protein-losing enteropathy seem to be more infrequent. Furthermore, spleno- and hepatomegaly have been reported, and elevated liver enzymes may be associated with steatosis and the use of GCs or with SLE itself (137,138).

2.4.2.6 Lupus nephritis

Renal manifestation of SLE is called LN. It is one of the most serious manifestations of SLE as it predisposes to higher mortality, particularly when coexisting with a CVD (16,139). LN seems to be more common among young patients. Other risk factors are male sex and African, Asian, and Hispanic origin. It usually presents as insidious proteinuria, but microscopic hematuria and reduced renal function are sometimes encountered. Every so often LN presents as nephrosis and may eventually lead to renal failure (3,139-141). In addition to abnormal urinalysis and decreased renal function, signs of active LN can be high anti-dsDNA and anti-C1q levels as well as decreased amount of C3 and C4. Renal biopsy is mandatory in LN diagnosis (139-142).

LN is classified according to the International Society of Nephrology/Renal pathology Society 2003 Classification of Lupus Nephritis (Table 1). These classification criteria were revised in 2018 but remain unapproved as yet (143,144). The revised version specifies certain histologic findings, eliminates class IV's segmental and global subdivisions, and suggests replacing the subclassification of classes III and IV with activity and chronicity index (144).

Recently, a new and rare form of LN has been recognized. This lupus podocytopathy presents as nephrotic syndrome. In the kidney biopsy, diffuse and severe epithelial cell foot effacement is detected on electron microscopy, while no subepithelial and subendothelial immune deposits can be observed (145).

Table 1. Lupus nephritis classification by the International Society of Nephrology/Renal pathology Society 2003 Classification of Lupus Nephritis. Modified from Weening et al. (143).

Class 1: minimal mesangial LN *Otherwise normal glomeruli, but mesangial immune deposits can be observed by IF.*
Class 2: mesangial proliferative LN *Any degree of mesangial matrix expansion or hypercellularity by LM. Mesangial immune deposits are seen.*
Class 3: focal LN *Segmental or universal, endo- or extracapillary glomerulonephritis that can be active or inactive and that involves not more than half of all glomeruli. Focal subendothelial immune deposits are commonly seen. They may be accompanied with mesangial alterations.* *The findings are classified further according to the activity of lesions.*
Class 4: diffuse LN *Diffuse, segmental or universal endo- or extracapillary glomerulonephritis that can be active or inactive affecting half or more of glomeruli. Diffuse subendothelial immune deposits are usually seen. Mesangial alterations may be present. The class is allocated into diffuse segmental (IV-S) LN and diffuse global (IV-G) LN according to the amount and site of lesions.* *The findings are classified further according to the activity of lesions.*
Class 5: membranous LN *Subepithelial immune deposits or their morphologic sequelae that are segmental or global and detected by LM and by IF or EM. Mesangial proliferation may be present.* *May appear in coincidence with Class 3 or 4.* *Class 5 LN includes developed sclerosis.*
Class 6: advanced sclerosis LN *Ninety percent or more of glomeruli are universally sclerosed and no residual activity can be observed.*

Abbreviations: EM = electron microscope; IF = immunofluorescence; LM = light microscope; LN = lupus nephritis

2.4.3 Neuropsychiatric lupus

SLE may sometimes appear as neurological or psychiatric manifestations (also known as neuropsychiatric SLE, NPSLE) affecting the peripheral and/or central nervous system (CNS). The prevalence of NPSLE varies widely depending on study population and methods. Moreover,

neuropsychiatric symptoms can also result from drug adverse effects, infections, and the burden of chronic illness and stress, but the term NPSLE is used only when the neuropsychiatric symptoms are thought to originate from SLE. Usually, NPSLE occurs at disease onset (146-150). Features can vary from mild cognitive dysfunction to acute confusional state and severe psychosis. However, mood disorder, anxiety, cognitive dysfunction, and headache are the most frequently reported manifestations. In 1999, the ACR committee published a consensus statement defining 19 NPSLE syndromes demonstrated in Table 2 (147).

However, the statement has been criticized as it includes mild symptoms that frequently occur in non-SLE populations as well (148,149). Risk factors for NPSLE are high disease activity, previous major NPSLE event, and the presence of aPLs. NPSLE is a serious manifestation that markedly affects quality of life and increases mortality (146,148,150).

Table 2. The neuropsychiatric syndromes in systemic lupus erythematosus patients according to American College of Rheumatology nomenclature and case definitions. Modified from Liang et al. (147).

Central nervous system	**Peripheral nervous system**
Seizure disorder	*Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré)*
Aseptic meningitis	*Mononeuropathy (single/multiplex)*
Demyelinating syndromes	*Autonomic disorder*
Headache	*Polyneuropathy*
Cerebrovascular disease	*Plexopathy*
Movement disorders (chorea)	*Neuropathy, cranial*
Anxiety disorders	*Myasthenia gravis*
Psychosis	
Acute confusional state	
Cognitive dysfunction	
Mood disorder	
Myelopathy	

2.5 MULTIMORBIDITY

SLE patients are susceptible to several comorbidities. Some of the most significant are cardiovascular and renal problems, malignancies, mental health concerns, and infections (6,9,11,16,151,152). Many of the comorbid conditions may exist several years before SLE diagnosis is made, but the number also increases after SLE has been diagnosed (6,152). It has been thought that in many cases, SLE itself with its wide immune system aberrancies predisposes to comorbidities, but on the other hand, some of the multimorbidity is a result of drug toxicity or organ damage. Moreover, the type of comorbidities depends on several factors such as sex, age, medications, education, and race/ethnicity (6,8,9,11,152-155). The awareness of comorbidities is essential since they increase mortality, complicate disease management, decrease quality of life, and have marked socioeconomic effects as well (6-8,10-12,15,152,156).

2.5.1 Cardiovascular morbidity

2.5.1.1 General aspects and risk factors

CVDs form a major comorbidity in SLE. SLE patients have an approximately twofold risk for CVDs compared to general population, while a study from the UK recorded a relatively high IR of 5.2/1,000 pyrs for any CVD. Their influence on mortality is crucial as they are one of the most prevalent death causes in SLE patients (6-9,16,153,157-161).

Considerable subclinical atherosclerosis among SLE patients has been shown to exist already in childhood, and relative risks are high particularly among young patients (9,16,153,157-159). For example, in the Framingham Offspring Study, young females (aged 35–44 years) with SLE studied between 1980–1993 were described to have more than 50 times higher risk for MI compared to their peers (159).

The high occurrence of CVDs can be explained by the accelerated atherosclerosis and thrombosis formation (109,133,157,158). SLE patients share same risk factors for cardiovascular morbidity as general population (hypertension, smoking, hypercholesterolemia, diabetes and high

frequency of CVDs in family), but SLE itself is a strong risk factor for CVDs as a study by Esdaile et al showed in 2001. The authors estimated the CVD risk in SLE by utilizing the Framingham risk assessment. They discovered that after controlling the traditional risk factors, SLE patients had a ten times higher risk of non-fatal MI and a 17 times higher risk of death due to coronary heart disease than expected (6,9,157,158,160,162-165).

The same mechanisms of SLE pathophysiology contribute to the CVD pathogenesis as well. It is likely that a mixed interplay of various mechanisms causes inflammation on the endothelium accelerating atherosclerosis. An impaired clearance of apoptotic cells and overload of oxidized low-densisty lipoprotein causing oxidative stress has been depicted. An imbalance of certain cytokines and different subtypes of T lymphocytes has been demonstrated as well. Moreover, aPLs can create prothrombotic states causing arterial and venous thrombosis (109,153,157,158). It has been noted that the CVD risk seems to be at its highest at the onset of SLE and decreases over time, implying the wide systemic activity of SLE at the disease onset (166,167). In addition, males with SLE seem to be more prone to CVDs than females (9,118).

The traditional risk factors may also be more common and their management more challenging among patients with SLE (6,9,157,158,160,162-164). For example, SLE is often accompanied with hypertension, which may be caused by LN, systemic inflammation and drug therapy, such as NSAIDs, GCs and cyclosporin A (CyA) (157,158,160,162). Metabolic syndrome is a frequent problem in SLE, with a worldwide meta-analysis showing a twofold risk as well (163). Moreover, diabetes and hypercholesterolemia appear to be more common among SLE patients than in general population (6,9,157,160,162-164). Furthermore, the presence of LN, renal function impairment and proteinuria have been recognized as significant risk factors for CVDs (16,160). For example, Hermansen et al. studied the risk of MI among more than 1,600 incident SLE cases with and without LN in a Danish nationwide study. The overall IR for MI was 3.4/1,000 pyrs among the SLE cases. Compared to population controls, hazard ratios (HR) of 18.3 and 2.2 were reported for MI with and without LN, respectively (16). In addition, the use

of GCs elevates the CVD risk in a dose-dependent manner, whereas the use of hydroxychloroquine (HCQ) reduces the risk (157,158,160).

2.5.1.2 Risk of myocardial infarction

An extensive meta-analysis from 2020 by Yazdany et al. reported the risk of MI to be three times higher among SLE patients than population controls (161). Furthermore, Table 3 summarizes some of the latest studies considering the incidence and risk of MI in SLE. The risk for infarction has been demonstrated to vary roughly from two to three times increased compared to other population, while IRs have ranged between 1.8 and 9.6/1,000 pyrs. Especially young patients seem to bear a high relative risk for MI (6,16,166-170). For example, Aviña-Zubieta et al. studied almost 5,000 incident SLE patients during 1990–2010 in their population-based study from Canada. They recorded an incidence of 6.4/1,000 pyrs for MI, the risk being almost three times higher than among population controls. The risk was at its highest, i.e., nearly six times elevated, during one year after the SLE diagnosis, but decreased over time. Young patients had the highest relative risk for MI, with a three to four times higher risk than their age- and sex-matched references, but the absolute risk was the highest among the oldest age group (166). Moreover, a nationwide Korean study by Lim et al. analyzed the incidence of CVDs of nearly 19,000 incident SLE patients from 2008–2015. They reported an IR of 1.8/1,000 pyrs for MI, the risk being almost three times higher than among population controls even after adjusting for traditional CVD risk factors. Similarly to the Canadian study by Aviña-Zubieta et al., the relative risk for MI was the greatest among young patients, but the absolute risk was the highest in older patients (167).

Table 3. The incidence and risk of myocardial infarction among different systemic lupus erythematosus (SLE) cohorts (6,16,166-170). Studies considering new-onset and established SLE are marked with * and †, respectively.

Author	Country and study period	Case definition	Number of cases and follow-up	Source of study material	Mean (SD)/median range age, years	Proportion of females (%)	Incidence 1,000 pyrs	Risk (95% CI)
Aviña-Zubieta et al. (166)*	British Columbia, Canada; 1996–2010	ICD-9 and -10 codes	4,863; NR	Province of British Columbia	49 (16)	86	6.4	HR 2.6 (2.1–3.2)
Bengtsson et al. (168)†	Northern-Sweden; 2001–2007	ACR 1982 and 1997 criteria	275; 7 years	Registers of 19 specialist departments, 140 primary health care centers and 1 private practitioner	39 (16)	84	NR	SIR 2.3 (1.3–3.7)
Hermansen et al. (16)*	Denmark; 1995–2011	ICD-10 codes	1,644; 7,8 years	Nationwide	SLE and no LN 48 (37-58); SLE and LN 40 (29-53)	86	3.4	HR 3.0 (2.0–4.5
Kuo et al. (6)*	UK; 1997–2013	Expert opinion	1,605; 9 years	Clinical Practice Research Datalink	51 (16)	82	NR	HR 1.7 (1.1–2.6)

Abbreviations: ACR = American college of rheumatology; CI = confidence interval; ICD-10 = 10th International Classification of Diseases code; HR = hazard ratio; NR = not reported; pyrs = person years; SD = standard deviation; SLE = systemic lupus erythematosus; SIR = standardized incidence ratio

Table 3. Continues.

Author	Country and study period	Case definition	Number of cases and follow-up	Source of study material	Mean (SD)/median range age, years	Proportion of females (%)	Incidence 1,000 pyrs	Risk
Lim et al. (167) *	South-Korea; 2008–2015	ICD-10 codes	18,575; 8 years	Nationwide	NR	91	1.8	HR 2.7 (2.3–3.4)
Lin et al. (169) *	Taiwan; 2000–2008	ICD-9 codes	1,207; 7,5 years	Nationwide	NR	82	2.1	HR 5.1 (2.6–9.9)
Tornvall et al. (170) †	Sweden; 1996–2015	ICD-8, -9 and -10	4,192; NR	Nationwide	55 (15)	84	9.6	NR

Abbreviations: ACR = American college of rheumatology; CI = confidence interval; ICD-10 = 10th International Classification of Diseases code; HR = hazard ratio; NR = not reported; pyrs = person years; SD = standard deviation; SLE = systemic lupus erythematosus; SIR = standardized incidence ratio.

2.5.1.3 Stroke

Like the risk of MI, the risk of stroke has been reported to be increased two to three times among SLE patients compared to general population (16,161,166,167). The meta-analysis from 2020 by Yazdany et al. reported a twofold risk in SLE patients versus population controls (161). Moreover, in a study from the UK with a mean follow-up of nine years, five percent of the 1,600 incident SLE cases developed a cerebrovascular disease after SLE was diagnosed. The risk was also 50% percent higher than in population controls (6). In the early study by Esdaile et al. an eight times higher risk for stroke was noted after controlling the traditional CVD risk factors (165). Moreover, the Canadian study by Aviña-Zubieta et al. reported an IR of 4.4/1,000 pyrs, and the risk was 2.1-fold for stroke compared to population controls. Similarly to MI, the relative risk was at its highest among young patients and at the onset of SLE (166). Furthermore, the Korean study by Lim reported an IR of 2.5/1,000 pyrs for stroke, the risk being over three times higher than in controls even after adjusting for the CVD risk factors. The relative risk was the greatest (nearly 18 times higher) among patients under 40 years of age (167).

2.5.1.4 Heart failure

The incidence of heart failure has been demonstrated to be two to five times higher in SLE than in other population (6,167,171,172). For example, Chen et al. reported an IR of 6.9/1,000 pyrs for heart failure in their study from the United States of America (USA) consisting of nearly 40,000 SLE patients. Curiously, the incidence was nearly the same as for patients with diabetes mellitus (172). Moreover, the Korean study by Lim et al. reported an IR of 3.1/1,000 pyrs. The risk was almost five times higher among SLE patients than controls after controlling the traditional CVD risk factors (167).

Likely, the predisposition to heart failure results from the increased prevalence of coronary heart disease and its related risk factors, such as hypertension, but also SLE itself and especially renal involvement play a key role (167,171,172).

2.5.2 Venous thromboembolism

SLE patients have an increased risk of venous thromboembolism (VTE) (109,133,173-175). A meta-analysis by Bello et al. assessed that the relative risk of VTE would be four times higher among SLE patients compared to other population. Likewise, the risk of DVT was six times higher and the risk of PE five times higher among SLE patients compared to other population (173).

Moreover, Aviña-Zubieta et al. compared the data of almost 5000 incident SLE cases to matched controls in their population-based study. The SLE cases were residents of British Columbia and diagnosed with SLE during 1996–2010. The authors demonstrated IRs of 5.3/1000 pyrs, 2.6/1000 pyrs and 3.3/1000 pyrs for VTE, PE and DVT, respectively. Compared to matched controls, SLE cases were recorded to have four, three and four times increased relative risk of VTE, PE and DVT, respectively. Interestingly, the risk was at its highest during the first year after SLE diagnosis for VTE, the risk being 13 times higher among SLE cases compared to population controls (174). In parallel, Mok et al. found that the majority of the VTEs occurred during the first couple of years after SLE was diagnosed, but they also discovered that the relative risk was at its highest among young SLE patients, while it decreased over time (175).

The increased risk of venous thromboses is explained by the systemic inflammation and hypercoagulability in SLE (109,133,157,173-175). In addition to traditional risk factors, such as immobilisation, puerperium and use of contraceptives, aPLs are a powerful risk factor for VTE. Moreover, certain disease-related factors, such as nephrosis and protein-losing enteropathy, play a role in the VTE pathogenesis (109,133,157,173-175).

2.5.3 Renal problems

SLE is associated with decreased renal funtion and failure, mostly due to LN. It is especially harmful when LN occurs in coincidence with a CVD or infection, which elevates the risk of death markedly (8,11,16,140,160,161).

A worldwide review reported that LN was already present in 7–30% of SLE patients at SLE diagnosis and around 40% of the patients developed it

within five years following the diagnosis. The risk of developing LN seems to be at its highest around the time of the SLE diagnosis and a few years after it, but appears to decrease over time as only 40–50% of patients present LN after 15 years from SLE diagnosis (141). The same review reported that around ten percent and 25% of patients with LN developed end stage renal disease (ESRD = need for chronic dialysis or renal transplantation) within five and 15 years after LN was diagnosed, respectively. However, most studies included in the review were done in specialist referral centers causing some bias (141). In the UK study by Rees et al., the IR for end-stage renal failure (ESRF) was 0.8/1,000 pyrs, which resulted in eight times higher risk compared to matched controls. After adjustments (sex, age, alcohol use and smoking, comorbidities and prednisolone use) the risk was three times increased (9).

The risk factors for renal disease and ESRD include male sex and non-White ethnicity. Hypertension, class IV LN, elevated serum creatinine and low serum C3 have also been reported to increase the risk of renal failure whereas the use of HCQ is a protective factor (2,118,176-180).

No studies have been made considering the occurrence of LN or ESRD in Finnish patients with SLE. From a Scandinavian perspective, Reppe Moe et al. studied more than 300 Norweigan SLE patients living in the city of Oslo between 1999 and 2008 and found that almost one third of them developed clinical and one fourth biopsy-proven LN during a median follow-up of 14 years. Moreover, more than 90% of the LN cases occurred within five years after SLE diagnosis. ESRD developed in six percent of all the SLE patients during a mean of 18 years of follow-up. Furthermore, it took approximately 11 years for ESRD to develop after the SLE diagnosis. The IR for ESRD was 2.3/1,000 pyrs. However, 16% of the SLE patients and around one fourth of the LN cases were of non-European origin in this cohort (181).

2.5.4 Infections

SLE patients are prone to infections, and infections have been reported to be one of the leading causes of premature mortality (6-9,11). The increased infection risk results partly from the complex dysregulation of the immune

system (48,93,182). More specifically, risk factors include lymphopenia, neutropenia, hypocomplementemia, LN, and high disease activity/lupus flare (130-132,182-184). Moreover, immunosuppressive drug treatment elevates the risk of infections in a dose-dependent manner. Especially, GCs are associated with infections at doses over 7,5–10 mg/day of prednisone or equivalent. In contrast, HCQ is beneficial for patients as it reduces infection risk and infection-related mortality (182-185).

It is challenging to estimate the overall risk of infections due to different study populations and methods (186-189). However, a worldwide meta-analysis estimated a threefold risk for severe infections in SLE compared to general population (186). Moreover, in a Canadian study, approximately one fifth of the incident SLE patients developed a severe infection during a mean follow-up of nine years. The IR was 19.7 severe infectious events/1,000 pyrs for SLE patients, and SLE was associated with a twofold risk of severe infection compared to reference individuals (187).

2.5.4.1 Bacterial infections

The most common bacterial infections in SLE are staphylococcal and pneumococcal infections (185,186,188-190). Moreover, the risk of invasive pneumococcal infections is notable, as Luijten et al. described in 2014 a 13 times greater risk in SLE patients compared to general population (190).

Tuberculosis has been a frequent issue among SLE patients in endemic areas, particularly when lymphopenia and increased use of immunosuppressives have been present, while opportunistic non-tuberculous mycobacteria infections are rarely encountered (11,185,191-194). For instance, a Columbian study concluded that the use of five mg/day of prednisolone or equivalent for one year would increase the risk of tuberculosis almost threefold in SLE, at least in endemic areas (192).

2.5.4.2 Viral infections

Herpes zoster (HZ) and HPV are the most clinically important viral infections reported (182,184,195-197). The risk for HZ infection has been reported to be twice as high among SLE compared to other population,

and the incidence has been estimated to vary between 6.4 and 14.3 cases/1,000 pyrs. Dysfunction of T cells, high GC doses and lymphopenia have been recognized as risk factors for HZ, while newly developed vaccinations seem to decrease the risk (186,195-198).

Cervical HPV infection is a major risk factor for developing cervical dysplasia and cancer, and the risk of contracting it has been reported to be increased among females with SLE (199-201). A meta-analysis from 2019 reported a pooled prevalence of 34% in SLE patients compared to 15% in controls, and the risk of cervical HPV infection was nearly threefold among SLE (199). On the other hand, a Korean study examined around 130 sexually active females with SLE between 2006 and 2007 and found that a fourth of them had high-risk HPV infection compared to 16% among controls. Moreover, the risk of HPV infection was estimated to be four times higher (201).

At the end of the year 2019, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) virus emerged. It is challenging to estimate the epidemiology of COVID-19 in SLE due to considerable heterogeneity across studies over time and limited data quality (202-206). However, SLE patients seem to have an increased risk of contracting COVID-19, and they have been hospitalized two to three times more likely. They may have a greater risk of severe disease course and death as well. Older age, comorbidities, male sex, higher disease activity and the use of GCs, cyclophosphamide (CYC) and rituximab (RTX) have been described as risk factors (202-206).

2.5.4.3 Fungal infections

Fungal infections have been found to be a rather rare issue in SLE. Still, patients have been described to be prone to them as a result of lymphopenia and the use of GC treatment (193,207-209).

The most common invasive fungal infections (IFIs) are *Cryptococcus*, *Aspergillus*, and *Candida* species typically involving the CNS, lungs, skin, and blood stream (193,207-209). IFIs may be difficult to treat, and mortality has been demonstrated to be as high as 40% (207-209).

Pneumocystis jirovecii (PJP) is rare, but more frequent among SLE patients compared to general population (210,211). A Taiwanese nationwide study

analyzed the medical records of more than 24,000 SLE patients and found that during a median follow-up of nine years, 55 patients had PJP. The age- and sex-adjusted IR for PJP was 2.63/10,000 pyrs and compared to matched controls, the risk was nearly 30 times higher. Young age, male sex, ESRD, and the use of mycophenolate mofetil (MMF), oral daily prednisone dose of ≥ 7,5 mg or pulse steroids were all risk factors for PJP, while use the of HCQ cut the risk in half. Mortality for PJP was high as nearly half of the SLE patients with PJP died (210). However, the authors did not report the number of pneumocystis prophylaxis used, which has been shown to reduce the risk of PJP considerably (211,212).

2.5.5 Malignancies

2.5.5.1 General aspects

SLE is associated with malignancies. The risk of any malignancy in SLE has been reported to be slightly higher than in general population, with the risk ranging roughly from 1.1- to 1.9-fold (9,213-230). For example, a study from the UK examined the comorbidities of nearly 8,000 prevalent SLE patients from 1999–2012 and revealed an IR of 14.8/1,000 pyrs for any malignancy, and the risk was 20% higher compared to matched controls (9). Furthermore, a nationwide study from Korea analyzed the medical records of 21,000 newly diagnosed SLE patients and recorded an IR of 6.4/1,000 pyrs for any malignancy, the risk being 1.4-fold compared to population controls (221). Moreover, a meta-analysis from 2021 estimated a pooled risk of 1.2 for any malignancy in SLE (222).

The risks of certain hematologic malignancies and lung cancer are particularly high in SLE (9,213,214,217-222,225,228-230). In addition, the risk of NMSC may be higher compared to general population (9,219,225,228). The increased risk of these malignancies probably results from chronic inflammation and SLE activity, chromosomal and cytokine abnormalities, drug therapy, and certain environmental factors, such as HPV and smoking (155,213,215,218,223-226,228-237). In contrast, the risks of melanoma and some hormone-sensitive malignancies, such as breast, prostate, and endometrial cancer, appear to be decreased or insignificant

compared to general population (9,213,218-222,225,228,229). In addition, the difference in risk for some malignancies is already seen in new-onset SLE, as depicted in Table 4 (219-221,225,228,237).

Table 4. The risk of malignancies in new-onset systemic lupus erythematosus. Risks (and 95% CI) reported as odds ratio (221) or as standardized incidence ratio (219,220,225,228,237).

		Risk (95% CI)							
Author and country	**Number of patients and study period**	**Any malignancy**	**NHL**	**Hematologic**	**Lung**	**Breast**	**NMSC**	**Melanoma**	**Cervix**
Björnådal et al., Sweden (219)	5,715 (1964–1995)	1.3 (1.1–1.4)	2.9 (2.0–4.0)	2.3 (1.8–3.0)	1.7 (1.3–2.3)	0.72 (0.54–0.98)	1.5 (0.98–2.3)	0.43 (0.14–1.01)	1.4 (0.65–2.5)
Tallbacka et al., Finland (220)	205 (1967–2013)	1.9 (1.4–2.5)	12 (5.8–22)	6.4 (3.3–11)	2.2 (0.5–6.4)[a]	0.70 (0.23–1.6)	1.7 (0.04–9.5)[b]	2.7 (0.33–9.8)	2.4 (0.06–13)
Bae et al., Korea (221)	21,016 (2008–2015)	1.5 (1.3–1.6)	NR	NR	1.3 (0.9–1.9)	0.95 (0.77–1.2)	NR	NR	3.1 (2.3–4.1)
Westermann et al., Denmark (225)	3,424 (1995–2014)	1.5 (1.3–1.6)	2.4 (0.06–14)	NR	2.6 (2.0–3.3)	0.81 (0.58–1.1)	1.3 (1.0–1.6)	1.3 (0.75–2.1)	0.88 (0.24–2.3)
Ragnarsson et al., Iceland (228)	238 (1957–2001)	1.4 (0.9–1.9)	NR	8.9 (2.5–22)	1.7 (0.4–5.0)	1.6 (0.65–3.2)	6.4 (1.3–19)	NR	NR
Dreyer et al., Denmark (237)	576 (1951–2006)	1.6 (1.2–2.0)	5.0 (1.9–13)	NR	1.4 (0.6–3.4)	0.8 (0.4–1.6)	2.0 (1.2–3.6)	1.3 (0.3–5.2)	0.6 (0.1–4.5)

Abbreviations: [a]including trachea; [b]excluding basal cell carcinoma; CI = confidence interval; NHL= non-Hodgkin's lymphoma; NMSC = non-melanoma skin cancer; NR = not reported

2.5.5.2 Hematologic malignancies

SLE patients are prone to malignancies of hematologic origin in general (6,9,213,219-223,225,227-231). In their multicenter study, Bernatsky et al. analyzed the medical records of more than 16,000 SLE patients from 1958 until 2009 and discovered that the risk of any hematologic malignancy was three times greater than expected (213). Similarly, a study from the UK by Rees et al. revealed an IR of 0.87/1,000 pyrs for hematologic malignancy, and the risk was nearly threefold compared to population controls (9). In addition, a nationwide Korean study with more than 17,000 SLE patients by Han et al. revealed an IR of 1.1/1,000 pyrs for any hematologic malignancy, and the risk was six times greater than expected (230). The reasons for the increased susceptibility to hematologic malignancies is unclear, but it may be at least partly related to the dysregulated immune system, chromosomal abnormalities, and high disease activity (154,155,223,226).

The risk of lymphomas has especially been noted to be high, and of these, NHL is the most usual (6,9,213,219-222,225,227,229-231). Standardized incidence ratios (SIR) have been reported to vary between 2.4 and 12.1 across studies (213,219,220,225,227,229-231). Furthermore, the above-mentioned studies from the UK and Korea reported IRs of 0.8/1,000 pyrs and 0.6/1,000 pyrs for NHL, respectively (9,230). The most frequent subtype of NHL appears to be diffuse large B cell lymphoma (DLBCL) and they seem to be more prevalent among White patients and males (229,230,232,233).

In addition, increased risks of Hodgkin's lymphoma (HL) and leukemias have been reported, with SIRs ranging from 2.4 to 8.1 (219,225,229,231) and 1.8 to 3.6 (213,219,225,227,229,230), respectively, whereas the risk of multiple myeloma is unclear (213,219-221,225,229-231).

2.5.5.3 Lung cancer

The results on lung cancer risk are slightly variable. Most studies have shown a positive correlation between SLE and lung cancer while a few have not (9,213,219-221,225-231). IRs of 0.9/1,000 pyrs, 0.3/1,000 pyrs and 0.6/1,000 pyrs have been recorded by Rees et al., Bae et al. and Han et al.

in studies from the UK and Korea, respectively (9,221,230). Moreover, SIRs have ranged from 1.3 to 2.6 in some of the large studies (213,219,225,229,230).

Smoking seems to be the most significant risk factor for lung cancer, and cancers are most typically small cell lung carcinomas by type (234,235). However, it is unsure whether the elevated risk is more associated with smoking than with SLE itself. For example, a study from Israel analyzed the medical records of 5,000 SLE patients and used smoking as a covariate, finding no increased risk, whereas the UK study still showed a three times higher risk after adjusting for smoking (9,231).

2.5.5.4 Skin cancers

Many studies have not found any significant difference in melanoma risk compared to general population, but Rees et al. described a relatively low incidence of 0.3/1,000 pyrs in their study from the UK (9,213,219,220,225,237). In addition, a study from California analyzed the inpatient discharge data of 30,500 SLE patients from 1991 to 2002, revealing approximately 30% decreased risk (229).

In contrast to melanoma, non-melanoma skin cancer (NMSC) risk seems to be somewhat elevated in SLE (9,219,225,228,237). Rees et al. depicted an incidence of 3.7/1,000 pyrs, and the risk was nearly significant, similarly to a Swedish study consisting of 5,700 SLE patients (9,219). In a large Danish study with more than 3,400 incident SLE patients, a 30% greater risk was observed compared to general population, whereas a study from Finland did not demonstrate any increased risk among incident SLE cases (220,225).

The decreased melanoma risk may be associated with decreased sun exposure, as SLE patients are often photosensitive and urged to avoid sunlight due to the risk of flare (80,81,236). On the contrary, immunosuppressive drug treatment and some viruses, such as HPV, may predispose to NMSC whereas HCQ may have preventive effects (226,237). However, a considerable surveillance bias may exist, as SLE patients, and especially, their skin, are controlled regularly (229).

2.5.5.5 Breast cancer and gynecological malignancies

Breast cancer is one of the most frequent cancer types described in SLE, probably resulting from the high predisposition of female sex, as many studies have reported no increased risk compared to other population (9,213,218-221,225,228,229,237). Some studies have even demonstrated a lower risk compared to general population, but only one study from Taiwan reported a 50% higher risk (213,219,227,229). Studies from Korea and the UK have reported the incidence of breast cancer to vary from 0.9 to 1.6/1,000 pyrs (9,221). The use of HCQ may decrease the risk (226).

Studies on the maligancies in gynecologial organs and their results are notably variable. Therefore, it is challenging to draw any conlusions on the risk. The reason for the mixed results is that some studies have analyzed the malignancies in an imprecise manner as a group and others, accurately with a limited number of cases. In general, the association of gynecological malignancies and SLE seems to be uncertain (9,213,219-221,225,227-231,238).

More precisely, the risk of vulvar or vaginal cancer may be slightly increased compared to general population according to some large studies (213,227,229,237). For example, in a study from California, nearly 50 cases were found during a mean follow-up of five years, resulting in a threefold risk (229). However, Bernatsky et al. found only seven cases of vulval and two cases of vaginal cancers, resulting in SIRs of 3.8 for each during a mean of seven years of follow-up. However, the risk of vaginal cancer was insignificant in their study (213).

The results on cervical cancer are unclear as well. Some studies have shown an increased risk compared to general population (221,227,231). For example, a Korean study followed 21,000 newly diagnosed SLE patients for approximately seven years and recorded an incidence of 0.7/1,000 pyrs and a three times higher risk compared to controls (221). However, several other studies have not found any significant risk of cervical cancer (9,213,219,220,225,228,229,237). On the contrary, the risk of cervical dysplasia seems to be elevated, as two studies from the Nordic countries reported two times greater risk in SLE compared to population controls (237,238). The increased risk of vulvar/vaginal cancer and cervical dysplasia

may be explained by HPV and the use of immunosuppressives, while HCQ seems to protect from malign changes (237,238).

The risk of endometrial cancer may be reduced, as the multi-international study from Bernatsky et al. and the large study from California both reported nearly 50% decreased risk compared to general population (213,229). Likewise, the risk of ovarian cancer may be decreased, although study results vary (9,213,219-221,225,227,229). The possible decrease in the occurrence of these cancer types may be linked with the decline in endo- and exogenous exposure to hormones in SLE. For instance, females with SLE may experience earlier menopause, and they are likely prescribed hormone replacement therapy and oral contraceptives more seldom than other females (213,218,222).

2.5.5.6 Cancers of digestive system

The incidence of pancreatic cancer has been recorded to be low with IRs ranging from 0.1 to 0.5/1,000 pyrs (9,221,230). However, the risk of pancreatic cancer may still be elevated as two times higher risk has been suggested among Danish, Taiwanese and Korean SLE populations compared to general population (225,227,230).

Similarly, the incidence of liver cancer has been reported to be quite low as it has varied from 0.3 to 1.0/1,000 pyrs (221,230). Only a few studies have reported a significantly increased risk of liver cancer with approximately twofold risk (221,229,230). However, others have not demonstrated any signigicant difference compared to other population (213,219,220,225).

The results of gastrointestinal (GI) tract cancers are somewhat mixed (9,213,219-221,225,227-230). The incidence of stomach cancer varies from 0.3 to 0.5/1,000 pyrs, and no increased risk appears to exist (213,219-221,229,230). Likewise, the incidence of colorectal cancer ranges from 0.5 to 0.8/1,000 pyrs, and the risk does not seem to differ from other population (9,213,219-221,225,227-230).

2.5.5.7 Other malignancies

The treatment of vasculitis and certain malignancy types may require the use of CYC, which has been associated with bladder cancer development. The same concern has existed among SLE patients as well (215,237,239). However, the incidence of bladder cancer has been demonstrated to be relatively low (0.1–0.2/1,000 pyrs) in SLE (9,221,230). Many studies have not found any significantly increased risk of bladder cancer either (9,213,219-221,225,227-229). On the other hand, in a Danish study including nearly 600 SLE patients diagnosed between 1951–2006 and with a mean follow-up of 13 years, four bladder cancers were diagnosed, resulting in a significantly increased risk with a SIR of 3.6. All the patients had been given CYC therapy (237). Thus, it seems that the risk of bladder cancer is associated with the cumulative dose of CYC given and requires a relatively long time to develop (215,237,239).

Like the incidence of bladder cancer, the incidence of kidney cancer has been described to be low (0.1/1,000 pyrs), and many studies have not found any significant difference in risk compared to other population (9,219,221,230,237). However, some studies suggest a two to seven times increased risk (220,227,229). For example, in a Finnish study with a long follow-up (almost 26 years), the medical records of 200 SLE patients were reviewed, and five kidney cancers were found, resulting in a SIR of 7.8 (220).

The risk of prostate cancer has mainly been demonstrated to be insignificant, although a few large studies have described a 20%–30% decreased risk compared to general population (213,219,221,225,227-229,237). The IR for prostate cancer was 0.7/1,000 pyrs in the Korean study (221).

Cancers of the brain and other CNS have been reported to be unusual among SLE, and the risk does not differ from other population (219,220,225,228-230,237).

On the contrary, several studies have depicted a greater risk of thyroid cancer in SLE, the risk ranging from 1.3- to 2.2-fold compared to other population (213,221,227,229,230). Likewise, the risk of malignancy in the oropharynx area may be elevated, possibly due to HPV (221,225,227).

2.5.6 Mental health concerns and dementive disorders

Chronic diseases are often interconnected with mental health concerns, which may have significant effects on quality of life (18,240). The nature of chronic diseases predisposes to mental health concerns, and a lot of anxiety may be experienced due to uncertainty about one's health. Besides the chronic nature of the disease, neuropsychiatric manifestations of SLE, high SLE disease activity and drug therapy are associated with mental health concerns (18,150,241-244). Moreover, SLE patients probably have a greater risk for dementive disorders compared to general population (245,246).

2.5.6.1 Mood disorders and anxiety

The occurrence of mental health concerns is very difficult to estimate as the rates vary considerably, which is explained by the differences in study methods, populations, and reporting styles (6,18,149-151,241-244,247-254).

In a study based on patient self-reported questionnaires from the USA including 300 White females with SLE, a lifetime prevalence of 65% for mood disorder or anxiety diagnosis was reported. Of these patients, nearly half had major depressive disorder. Specific phobia, bipolar, panic, and obsessive-compulsive disorders were more often reported in SLE patients than in control group as well (250). Moreover, a Chinese cross-sectional study found a prevalence of 23% and 18% for depression and anxiety, respectively, in a study of 350 established SLE patients without prior NPSLE. This study examined patient self-reported questionnaires as well (244). Another study from the USA by Karol et al. reported that 40% of SLE patients treated in outpatient lupus clinic had a Beck Depression Inventory (BDI) score of ≥ 18 points, implying moderate to severe symptoms of a mood disorder (243).

In a multi-international center study by Hanly et al. conducted between 1999 and 2013, around 1,800 SLE patients were studied considering mood disorders. During a mean follow-up of five years, 13% were reported to have a mood disorder, and around 40% of the cases were attributed to

SLE. Nearly one fifth of the patients developed a mood disorder in ten years, but half of the mood disorders resolved during the follow-up. However, this study lacked a control population (18). A nationwide Danish study examined 2,000 SLE patients diagnosed in 2000–2015, and during a mean of seven years of follow-up, an incidence of 5.8/1,000 pyrs was recorded for depression. The period prevalence was as low as 4.3%, but SLE patients' risk of depression was twice as high compared to matched controls (151). Another study by Van Exel et al. compared the prevalence of depression among Dutch SLE patients to general population controls from all over Europe and reported a point prevalence of 17%, which was almost three times higher than in the control group (242).

2.5.6.2 Psychotic disorders

Psychotic events and disorders have been reported to be infrequent in SLE, and the risk of these comorbidities seems to be small. However, psychosis can be a manifestation of severe NPSLE, it may be an independent disease, or may be induced by GC use. Most commonly, SLE-related psychosis occurs close to the SLE diagnosis and is associated with other neuropsychiatric events, male sex, and African origin. The recurrence rate is low, and a chronic psychotic disorder develops in only rare cases (6,251-257).

A study from the UK by Abrol et al. followed around 700 SLE cases diagnosed between 1978 and 2018 and reported that only 2.5% of them experienced SLE-related psychosis during a mean follow-up of almost 20 years, whereas a Finnish cross-sectional study found no cases of SLE-related psychosis, although their sample size was small (58 patients) (149,251). Similarly, a worldwide multicenter study of 31 centers from ten countries reported that 1.5% of the nearly 2,000 patients with SLE experienced at least one episode of psychosis. Ninety percent of these patients experienced a SLE-related psychosis during a mean of seven years of follow-up (252). Similarly, a Thai study analyzed the medical records of 750 SLE patients from 1999 to 2009 and reported that five percent of the patients had psychotic or psychotic depressive episodes (255). Finally, Appenzeller et al. described the largest number of psychoses known in

their study from Brazil. The study consisted of 520 SLE patients followed for a mean of five years. Seventeen percent of the patients experienced an acute psychosis; of the psychoses, 11% were related to SLE and five percent were GC-induced (253).

The risk of psychosis in SLE compared to general population has been scarcely studied. It seems that SLE patients may have a somewhat higher risk for this morbidity as well, as Kuo et al. reported in their study from the UK with a mean of nine years of follow-up that one percent of the 1,600 incident SLE cases developed a new psychosis. The risk was almost three times higher than in matched controls. However, the authors did not report any clinical data in relation to psychosis (6).

Drug-induced psychosis seems to be a rare adverse effect of GCs (253,256,257). In a Japanese study, GC-induced psychiatric disorders of SLE cases were assessed. Between 1999 and 2004, 135 inpatients with non-CNS SLE flare were treated with GCs and followed for eight weeks. The mean dose of prednisolone was 0.95 mg/kg/day, and nearly a third of patients were also given intravenous pulse methylprednisolone (range 0.5–1.0g/day). Only one psychotic event occured that met the criteria for GC-induced psychosis (256). Another study from China followed almost 100 SLE patients receiving a mean of 0.80 mg/kg of prednisolone for eight weeks. During the two-year study, three patients developed psychosis (257).

Hypoalbuminemia and a high dose of GCs predispose to GC-induced psychosis. Psychotic symptoms usually develop within a few weeks after GCs have been started, and they should also resolve after tapering or discontinuation of the drug (253,256,257).

2.5.6.3 The use of antidepressants and antipsychotics

Studies on the use of antidepressant and antipsychotic medication are limited and the results are variable due to the same reasons as for the occurrence of mental health concerns. It seems that the proportion of antidepressant medication users has been small considering the occurrence of mood disorders, although not all mood disorders necessarily require drug therapy (18,151,242,243). Moreover, these drugs may be used

for other indications, such as treating pain, which complicates the interpretation of the study results further (258). On the other hand, it is more evident that most of the patients experiencing psychosis need antipsychotics in a short-term manner to ease the symptoms (251-253,255).

In the multi-international study by Hanly et al., 13% of the patients had a mood disorder and around 70% of them were treated with antidepressants (18). In the Dutch study by van Exel et al. where the point prevalence of depression was estimated to be 17%, only seven percent of the patients classified as having a major depression (BDI ≥14 points) used antidepressants, while three percent with minor depression used antidepressants (242). Likewise, Karol et al. demonstrated that 40% of patients experienced moderate or severe depressive symptoms, but only 50% of them took antidepressants. Moreover, only 15% of them took the maximum dose. A quarter of patients with no symptoms or only mild symptoms had antidepressant drug therapy (243). However, SLE patients seem to use more antidepressants than general population, as the Danish study by Hesselvig et al. reported 70% higher risk for antidepressant use (151).

On the contrary, psychotic symptoms are often difficult and frequently require antipsychotic drug treatment. In the UK study by Abrol et al., half of the patients with SLE-related psychosis required antipsychotic therapy (251). Moreover, in the multi-international study by Hanly et al., nearly 70% of the patients with psychosis needed antipsychotics, but 40% of them also needed antidepressants (252). In the Thai study, all patients had antipsychotic drug therapy, and the mean duration of treatment was two to three months (255).

2.5.6.4 Dementive disorders

A few large studies and a meta-analysis have assessed that dementive disorders occur more commonly in SLE patients than in general population, with the risk estimated to be two to three times greater (245,246,259).

In a nationwide Taiwanese study consisting of patients diagnosed with SLE between 2004 and 2008, an incidence of 360/100,000 pyrs was recorded during a seven-year follow-up. The risk for dementia was also doubled compared to general population (246). In a cross-sectional study from Israel, dementia occured in 1.6% of the nearly 5,000 SLE patients studied. Also, a three times higher risk was recorded for dementia compared to controls. It was also noteworthy that dementia developed more frequently in young (< 65 years old) SLE patients than in controls (259). On the contrary, the UK study by Kuo et al. did not find any significant risk for dementia (6).

The reasons for the possibly higher risk for dementia are multifactorial. It is probable that the high risk of CVDs contributes to the risk by causing microinfarcts and vascular dementia. Some studies have also suggested that NPLSE and autoantibodies could damage CNS. A negative effect of GC treatment against CNS has also been presented (48,246,259).

2.5.7 Pregnancy complications

SLE pregnancies are high-risk pregnancies associated with many complications and adverse outcomes, such as pre-eclampsia/eclampsia and thrombosis. SLE flares, active disease, and LN are major risk factors for worse pregnancy outcome and pregnancy-related comorbidities (107,260-269). In addition, other risk factors include chronic hypertension, APS, and proteinuria (264,267). On the other hand, the use of HCQ improves obstetrical outcomes (260,261).

2.5.8 Endocrine problems

SLE patients are susceptible to several endocrine and metabolic disorders (6,9,160,163,270-279). Osteoporosis and thyroid gland dysfunction seem to be the most often reported problems of the endocrine system (6,9,270-272). Probable reasons for the susceptibility of osteoporosis may be the long-term use of GC treatment, dysregulated immune system and systemic inflammation, presence of LN, lack of vitamin D, and abnormal levels of sex hormones (271-273). A wide meta-analysis from 2019 inspected 31 reports

on the prevalence of osteoporosis and its risk and risk factors. The prevalence varied from 4% to 42% across studies, and the risk was approximately twice as high among SLE cases compared to controls (272). The study results were similar to the UK study by Rees et al. describing IRs of 12.3/1,000 pyrs and 6.2/1,000 pyrs in SLE among females and males, respectively. In the UK study, the risk was increased for both sexes, 2.5 and 5.4 times higher in females and males, respectively, compared to references (9).

SLE has been associated with hypothyroidism, hyperthyroidism and autoimmune thyroiditis (6,274-276). In a study from Taiwan, almost 3,000 SLE patients diagnosed between 2000 and 2013 were studied during an average follow-up of ten years. The overall share of SLE patients with a thyroid problem was nearly one fifth in that study. The cumulative incidences of hyperthyroidism, hypothyroidism and autoimmune thyroid disease were all significantly elevated compared to population controls, with incidences of six percent, nine percent, and five percent, respectively (274). These results were supported by a nationwide study from Korea that examined the records of more than 17,000 SLE patients. The authors reported two and three times greater risks for Graves' disease and Hashimoto's thyroiditis compared to age- and sex-matched controls (275). However, a meta-analysis from 2018 included ten studies and reported no elevated risk for hyperthyroidism but found approximately threefold risk for hypothyroidism (276).

In addition to osteoporosis and thyroid problems, it has been presented that SLE patients have aberrancies in lipid metabolism, which predispose to CVDs. Typically, the amount of triglycerides is high, whereas the levels of high-density lipoprotein are low (157,160,270,277). A review from 2016 also concluded that up to 30% of SLE patients may have dyslipidemia at the diagnosis of SLE, while the proportion may rise as high as 60% during the next few years (277). However, Kuo et al. did not find any significant difference in the risk of dyslipidemia before or after SLE diagnosis compared to matched controls (6). Many factors have been suggested to promote dyslipidemia in SLE. There may be autoantibodies hampering the normal lipid metabolism and some cytokines, such as TNF-α, may affect

the metabolism. Moreover, high doses of GCs, the use of CyA, LN, and concurrent hypothyroidism contribute to the development of dyslipidemia. On the other hand, the use of HCQ is beneficial for the lipid profile (277).

Considering the risk of diabetes, Kuo et al. found no increased risk, but they analyzed complicated and uncomplicated diabetes types separately, which may have affected the results (6). On the other hand, the prevalence of diabetes was quite high (9%) in a Greek study based on patient self-reported questionnaires (270). Furthermore, a Taiwanese nationwide study followed new-onset SLE patients for three years and described a 20% greater risk of developing the condition compared to matched controls. The IR was also high (13.0/1,000 pyrs). The authors pondered the roles of GCs and calcineurin inhibitors (CNI) in diabetes development (278). In addition, a higher rate of insulin resistance has been demonstrated in SLE (279).

2.6 TREATMENT

The basis of SLE management is the continuous use of HCQ. Moreover, due to SLE's complexity, multi-organ involvement and high variability among patients, the management of SLE should be individually tailored. The aims of management are reduction in mortality and organ damage, prevention of flares, and improvement of health-related quality of life. Management should aim to accomplish remission or at least low disease activity (179,280-282). In addition to the use of HCQ, the management of SLE has been based on GCs and immunosuppressive agents, and the role of biological drug therapy has been small. Many of the biologics have even been avoided due to concerns of inducing SLE flare (280-284).

However, the knowledge of pathophysiology has increased over time, and in the future, the roles of many novel theraphies, such as anifrolumab, Janus kinase (JAK)-inhibitors and chimeric antigen receptor (CAR) T cell therapy may become more central (280-283,285). In addition, there are other non-pharmacologic aspects of SLE management, such as vaccinations, avoidance of sun exposure and smoking, and optimization of

vitamin D levels, which are important in a holistic approach to SLE management (280-283).

2.6.1 Hydroxychloroquine

The use of HCQ is central in SLE and it should be widely used (179,280-283,286). HCQ has beneficial effects on arthralgias and skin manifestations (280-283,286). It also decreases the risk of infections, certain malignancies, CVDs, NPSLE, and chronic renal disease and has beneficial effects on lipid metabolism. HCQ has antitrombotic effects as it prevents the activation and aggregation of platelets induced by aPLs and decreases the number of them (120,133,160,178-181,182,210,226,247,277,286,287). It reduces accrual damage and mortality, improves pregnacy outcomes, and decreases the risk of congenital heart block related to anti-Ro and anti-La antibodies in neonatal children (8,117,120,261,282,288). However, more severe forms of SLE often require additional drug therapy (179,280-283,286).

HCQ seems to have an effect on immunomodulation but does not cause immunosuppression. It affects antigen processing by reducing the activation of TLRs, but also inhibits proinflammatory cytokines, such as TNF-α (282,283,286).

The optimal dose of HCQ is suggested to be five mg/kg/day, but usually not over 300 mg/day is exceeded. The side effects are rare and commonly mild. There may be loss of apetite, nausea, diarrhea, headaches and tiredness. HCQ may sensitize skin to sunlight. Therefore, use of sunscreen is strongly recommended. It may also prolong the QT interval of the heart. As HCQ has retinal toxicity properties, a follow-up by an ophthalmologist is recommended (280-283,286).

2.6.2 Glucocorticoids

GCs are very potent drugs and have strong and wide anti-inflammatory and immunosuppressive effects. GCs are essential when treating acute and severe forms of SLE, such as LN or NPSLE. As GCs are powerful drugs with many adverse effects, their use should be temporary and restricted to

induction of treatment. However, sometimes a chronic low-dose GC therapy is needed. GCs affect gene transcription, reduce non-selectively the production of cytokines, and prevent the proliferation of leukocytes. The disadvantages of chronic use of GCs are increased risk of several comorbidities, such as osteoporosis, mental health concerns, infections, cardiovascular events, and metabolic disorders, damage accrual and premature mortality (8,117,120,182,183,185,256,272,277,280-283,286).

2.6.3 Methotrexate

Methotrexate (MTX) can be used for treating mild or moderate manifestations of SLE. It is used in the management of arthritis and skin manifestations. MTX is a folic acid antagonist, which prevents inflammatory processes. The effects of MTX are dose dependent. With doses used for managing rheumatic diseases (5–30 mg once a week subcutaneously or orally), MTX affects by modifying adenosine metabolism. More in detail, it increases the amount of adenosine, which advances the production of anti-inflammatory cytokines and hinders the production of pro-inflammatory cytokines. Possible side effects are nausea and other GI tract side effects. It may cause hepatic reactions, but only rarely the treatment has to be discontinued due to this reason. Patients with severe renal impairment are at risk of myelosuppression. According to current knowledge, MTX may be teratogenous and cannot be used during pregnancy, whereas interstitial lung diseases are a relative contraindication for MTX use (280-283,286).

2.6.4 Immunosuppressives

Like MTX, azathioprine (AZA) can be used for managing mild or moderate manifestations of SLE. It is used to treat arthritis and skin manifestations. It is also sometimes used as maintenance treatment for LN. AZA is advantageous when managing SLE patients with pregnancy as it is not considered as teratogenic (280-283,286,288). It inhibits purine synthesis and prevents lymphocyte proliferation particularly. It is used 2–2.5 mg/kg/d orally. Side effects include nausea, hepatic reactions, myelosuppression, leuko- and trombocytopenia and skin reactions (179,280-283,286).

MMF is used to treat moderate to severe forms of SLE. It is especially useful when managing LN, forming the basis of treatment with CYC. It is useful in induction, but also in maintenance therapy. It can be used in managing resistant cutaneous disease, some forms of NPSLE and serositis. MMF metabolizes to mycophenolic acid, which has immunosuppressive effects. It inhibits inosine monophosphate dehydrogenase, limiting the DNA synthesis of T and B lymphocytes. The normal dose ranges 1.5–3 g/d orally. However, MMF is teratogenic and side effects include diarrhea and other GI tract symptoms, leuko- and thrombocytopenia. The risk of infection may be also higher (179,182,210,280-283,286,288).

CYC is important in managing life- and organ-threatening manifestations of SLE, such as LN, NPSLE, vasculitis, pulmonary interstitial fibrosis, and severe blood cell manifestations. The effect of CYC is based on cytotoxic alkylating metabolities. It influences lymphocytes and acts as an inhibitor against DNA replication (281-283,286). It can be used either intravenously or orally. Previously, it had a major role in managing severe forms of SLE, but due to its wide and severe adverse effects and toxicity, its role is nowadays more limited. CYC increases the risk of some malignancies and infections, is toxic for bone marrow, gonads and liver, may cause hemorrhagic cystitis, and is teratogenous (179,182,226,280-283,286,288).

CNIs are used to manage moderate or severe forms of SLE. The combination treatment of MMF and TAC may be superior to CYC in LN management (179,286). Also, topical CNI can be used to handle skin manifestations. CNIs prevent the activation, cytokine production and proliferation of T-cells. The most common CNIs used in SLE are tacrolimus (TAC) and CyA. CNIs can be used during pregnancy, but they have a number of interactions with other drugs and nephrotoxicity may limit their use. They may increase blood pressure and cause nausea, dyslipidemia, gingival hypertrophy and excess hair growth (277,280-283,286). Moreover, voclosporin is a novel CNI used in managing LN. However, studies regarding its efficacy and safety are so far limited (179,280).

2.6.5 Biological therapy

Belimumab (BEL) and RTX, seem to be efficient in SLE. They are used to manage certain moderate to severe forms of active SLE, especially when the conventional therapies fail (179,280,281,286).

A meta-analysis of seven randomized controlled trials from 2022 reported that compared to placebo, BEL, when added to standard therapy, reduced significantly disease activity, improved quality of life, and decreased the amount of GC treatment needed. No worse safety issues were recorded compared to placebo (289). BEL can be used in active severe or GC-dependent manifestations of SLE or active LN (179, 280-283,286,290). BEL is a monoclonal antibody, which prevents the stimulating effects of B lymphocyte stimulator on normal and autoreactive B lymphocytes (286). Typical side effects include nausea, diarrhea and fever (179, 280-283,286,290).

In particular, hematologic manifestations, such as severe autoimmune thrombocytopenia and hemolytic anemia, may be treated with RTX. However, the use of RTX is off-label in SLE. RTX acts by depleting B cells and predisposes to certain infections (182,280-282,286).

Anifrolumab is one of the most novel therapies approved for managing SLE. It can be used to manage active and autoantibody-positive, moderate to severe forms of SLE which are resistant to conventional therapy. However, it cannot be used to treat LN or NPSLE. It has been shown to reduce disease activity and improve life quality. It also decreases serological markers of active SLE and reduces the amount of GCs needed. Anifrolumab binds to type 1 IFN and prevents the function of all type 1 IFNs. The risk of some infections, such as HZ, may be greater among anifrolumab users. Nausea is a notable side affect (291,292).

2.7 SURVIVAL AND MORTALITY

Several studies have described that the survival rates of SLE patients have improved significantly in recent decades (3,5,293). For example, a long Canadian study showed that in 1950–1979, the five-year survival was around 60%, while in 1980–1992 it rose to over 90% (5). Furthermore, the

mortality of a thousand new-onset SLE patients was studied in Finland by Elfving et al. In that study, patients diagnosed with SLE during 2000–2014 had a five-year survival of 95% (293).

Likewise, the mortality rates have decreased in recent decades, but have still been reported to be 1.6–2.4 times greater than in general population (6-8,293-295). Another study from Canada analyzed the standardized mortality ratios (SMRs) of SLE patients diagnosed between 1971 and 2013. They found that the all-cause SMR was 13.5 in the 1970s, but decreased to 3.2 in 2000–2009. However, the SMR only decreased to 2.2 in 2010–2013 (7). A similar diminishing trend was seen in another Canadian study by Moghaddam et al. from British Columbia. The study consisted of 6,000 SLE patients and compared the mortality of two incident SLE cohorts from 1997–2005 and 2006–2014. They reported HRs of 2.0 for the former and 1.7 for the latter for death, but no significant improvement was found between the cohorts (294). Similarly, the Finnish study recorded a HR of 1.6 for death (293). In addition, many studies have reported that the mortality risk is higher at the onset of SLE and among young patients compared to controls (7,8,294,295). Frequent causes of death include CVDs, infections, malignancies, renal disease and active SLE (7,8,293-295).

CVDs and infections elevate mortality, although the significance of both has decreased over years. The risks of cardiovascular- and infection-related mortality have been reported to be 1.7–3.2-fold and 1.9–5.0-fold, respectively, compared to other population by several large studies from recent decades (7,8,187,294,295). For example, the study by Moghaddam et al. revealed SMRs of 2.1 and 2.7 for CVDs and infections, respectively (294). Mortality attributable to renal disease is also increased, the risk being 3.0–7.9-fold, although it has been suggested that studies may underestimate the renal-related risk (181,294,295).

On the other hand, mortality attributable to malignancies overall does not seem to differ from general population, but certain types of malignancies, such as NHL and lung cancer, may predispose patients to higher risk of death (7,8,294,295). Furthermore, the co-existence of SLE and malignancy may contribute to mortality, as Bultink et al. reported that a history of malignancy was linked with higher all-cause mortality in their

study from the UK (8). Similarly, Bruera et al. reported worse survival rates among SLE patients with breast cancer compared to patients with only SLE (12).

Comorbidities seem to be a major risk factor for mortality as a study from the UK described that comorbidities present at SLE onset contributed 30% of the increased mortality among SLE patients (6). This result was supported by the Finnish study in which no increased mortality was observed when it was adjusted by comorbidities present at the onset of SLE (293). Moreover, the UK study with 4,300 SLE cases reported that GC use elevated mortality risk two to three times depending on the cumulative dose, whereas the use of HCQ cut the risk in half (8).

3 AIMS OF THE STUDY

The aim of this thesis was to assess the epidemiology of comorbidities among recent-onset SLE patients in Finland.

The specific objectives were as follows:

1. To study the multimorbidity among recent-onset SLE patients in Finland
2. To evaluate the frequency, quantity and risk of antidepressant and antipsychotic drug use in recent-onset SLE
3. To assess the incidence of new malignancies in recent-onset SLE patients and compare the mortality of these cases to controls in Finland.

4 MATERIALS AND METHODS

4.1 MULTIMORBIDITY STUDIES IN RECENT-ONSET SLE (I-III)

4.1.1 Patient material (I–III)

This study was a large register-based study combining several national registers. Finnish adult (> 17 years of age) new-onset SLE cases were detected by utilizing drug reimbursement decisions for SLE management (World Health Organization's (WHO) 10th International Classification of Diseases (ICD-10) code of M32) approved between Jan 1, 2000 and Dec 31, 2014. The index day (ID) of the follow-up was the day when the reimbursement decision was granted. Every SLE case was then matched to three population controls according to sex, age, and place of residence at the ID. The ICD-10 code "M32" was used as an exclusion criterion for controls. The data from Population Register Centre (PRC) was used to select the controls randomly. The data on education level at the ID was obtained from Statistics Finland, and the levels were divided into four classes. These were basic, middle, lower and upper high level.

Permanent residents in Finland are legally entitled to National Health Insurance, and the data on these insurances is stored in a register maintained by the Finnish Social Insurance Institution (SII). Finnish patients diagnosed with chronic rheumatic diseases have a right for special reimbursement for drugs used to manage these illnesses. These certificates for compensation are applied by specialists in rheumatology or physicians working in such clinics based on general recommendations on diagnosing rheumatic diseases. Usually, SII grants the special reimbursement within a few weeks.

4.1.2 Comorbid conditions (I)

The follow-up for comorbidities began from the ID of every case and lasted until the patient died or until Dec 31, 2017. The relative risks (rate ratios, RR) of comorbidities were adjusted by the level of education at the ID.

The data regarding comorbidities was acquired from the Care Register of the National Institute for Health and Welfare (NIHW). This register contains data on all hospitalizations and outpatient visits in specialized care after 1969 and 1998, respectively. The register covers each person's personal identify code and diagnoses of medical disorders coded by ICD-10 codes.

The medical disorders of the patients were classified into twelve organ-specific groups following ICD-10 coding. The groups were: malignancies, benign neoplasias, blood diseases and immunodeficiency, endocrine disorders, psychiatric disorders, neurological diseases, ocular diseases, CVDs, asthma and chronic obstructive pulmonary disease, inflammatory bowel diseases (IBD), rheumatic diseases and osteoporosis and genitourinary diseases. Moreover, certain disease-specific groups of additional interest were examined. Systemic connective tissue disorders (ICD-10 codes M30–M36) were not included in the study. In addition, infectious diseases were excluded because the diseases diagnosed in primary health care would have been missed.

4.1.3 Antidepressant and antipsychotic use (II)

The data on the purchases of the antidepressants and antipsychotics was acquired from Jan 1, 1999 until Dec 31, 2015 from the National Drug Purchase Register. The observation time for drug purchases began one year prior to the ID, and the follow-up began from the ID. Both of them lasted until five years after the ID, until death, or until Dec 31, 2015. Patients with at least one antidepressant or antipsychotic drug purchase during the observation time, but not earlier, were included in the study. This method was used since the aim was to evaluate the drug consumption for mental health concerns associated with SLE. The analyses were implemented with six-month time frames. The cumulative shares of antidepressant purchasers after the ID were also analyzed. The patients with antidepressive drug use prior to the ID were excluded from this subanalysis.

Specific information (amount, code, date) on purchased drugs in Finland is stored in the Drug Purchase Register maintained by SII following the

Anatomical Therapeutic Chemical (ATC) classification. The information regarding the purchases of antidepressant and antipsychotic drugs were obtained from the Drug Purchase Register using their ATC codes N06A (antidepressants) and N05A (antipsychotics). The purchased antidepressant types were studied further according to their subclassification: non-selective monoamine reuptake inhibitors (N06AA), selective serotonin reuptake inhibitors (N06AB), monoamine oxidase A inhibitors (N06AG), and other antidepressants (N06AX) (296).

The Defined Daily Dose (DDD) parameter, established by WHO, was exploited to assess the drug consumption of the study subjects. The DDD is the presumed average dose for a drug utilized for its primary indication in adult persons. It is a fixed unit that can be utilized regardless of differences in medicine formulations, strengths and package sizes, which enables the comparison of drug consumption worldwide at the population level (297).

4.1.4 Malignancies and survival (III)

The follow-up for incident malignancies started from the ID of each case and lasted until death or until the end of 2018. Malignancies diagnosed before the SLE diagnosis were not included in the study.

The observed malignancies were allocated into 13 classes. These were bladder cancer, breast cancer, cancers of colon and rectum, gynecological cancer (consisting of cancers of corpus uteri, cervix and vulva), hematologic malignancy (including myeloma, myelofibrosis, leukemias and polycythemia vera), lung cancer, melanoma, NHL, NMSC, other cancers (consisting of cancers of CNS, nerve sheet and eye, meningiomas, cancers of upper respiratory tract, mesotheliomas, other cancers of GI tract and biliary duct, gallbladder and hepatic cancers, kidney cancers, HL, cancers of salivary and thyroid glands and testis cancer), pancreatic cancer, prostate cancer and stomach cancer. Additionally, malignancies which were unknown or ill-defined were categorized into the “Other” group.

Since 1953, all incident malignancies have been recorded in the Finnish Cancer registry in Finland by physicians. The register consists of definitive malignancies, but it also includes some premalign disease states and other

diseases considered as malign. In detail, severe dysplastic alterations (apart from skin cancers, where only melanoma *in situ* alterations are included), high-grade squamous intraepithelial lesions (HSIL), *in situ* cancers, benign CNS tumors and ovarian tumors classified as borderline change, are recorded. Furthermore, the register contains some other diseases, the malignancy of which is regarded uncertain (such as myelofibrosis, neuroendocrine tumors and polycythemia vera). In addition, tumors which are very likely to be malign are included even if there is no microscopic confirmation available. The observed malignancies are recorded in the registry by utilizing International Classification of Diseases for Oncology codes (ICD-O-3) or WHO's ICD-10 codes. The Finnish Cancer registry does not contain relapses (298).

The other objective of the study was to assess the survival and death causes of those SLE cases and controls who were diagnosed with a malignancy during the study period. The sex-, age- and education-adjusted survival was inspected from the SLE diagnosis until Dec 31, 2019. Considering the causes of death, the number of neoplasms and malignancies and eight other disease groups of particular interest were examined. These were infectious diseases (A00–B99), mental and behavioral disorders (F00–F99), nervous system diseases (G00–G99), CVDs (I00–I99), respiratory system diseases (J00–J99), diseases of the digestive system (K00–K93) and "unspecified", which means symptoms, signs and abnormal clinical and laboratory findings which were not otherwise allocated (R00–R99).

Death causes in Finland are reported to the causes of death register managed by Statistics Finland. They are allocated into four main categories, which are underlying cause of death, immediate cause of death, intermediate cause of death, and contributory causes of death. More specifically, the underlying cause of death is the cause which starts the cascade resulting in death, such as cancer. Immediate cause of death is the cause from which the patient instantly dies, such as pneumonia. On some occasions the underlying cause of death and the immediate cause of death can be the same. Intermediate causes of death are causes that lead from the underlying cause of death to the immediate cause of death, while

contributory causes of death are causes that contribute to the process of death, such as renal impairment. The physician who was the last to manage the deceased person determines the cause of death(s) and fills in the death certificate using the WHO's ICD-10 codes. All certificates are inspected afterwards by a forensic pathologist working in the NIHW and are revised if needed. Occasionally, autopsies are performed if the cause of death requires further clarification (299).

4.1.5 Ethical aspects (I–III)

To carry out these studies, neither patient's informed consent nor approval of an ethical committee were sought, as Finnish law does not require these when studies are register-based and performed without contacting the members of the study population. The appropriate permissions to utilize the data of the registers were required from the register holders, which were SII, NIHW and PRC.

4.1.6 Statistical methods (I–III)

In each study, the characteristics are depicted for continuous variables as means and standard deviations (SD). For categorical variables, the data is given as numbers and percentages.

In the first study, generalized linear models (GLM) and log link and binomial distribution were utilized to compute adjusted RRs for comorbidities. In case the examined event was uncommon, penalized maximum likelihood logistic regression (Firthlogit) was utilized. To assess plausible nonlinear relationship considering age at SLE diagnosis and RR for CVDs, four-knot-restricted GLMs were exploited. Knot locations were determined according to the recommended percentiles of Harrel, and the length of knots' distribution (age at the ID) was placed at the 5th, 35th, 65th, and 95th percentiles (300). As Hommel's procedure is regarded stronger than other procedures, such as the Bonferroni, Hochberg and Holm, this method was implemented to fix levels of significance for multiple testing (300). The analyses were performed using Stata 16.1 version (StataCorp LP, College Station, Texas, USA).

In the second study, the antidepressant purchases (DDD) of SLE cases and their controls were compared exploiting the Mann-Whitney test. Generalized estimating equations models and unstructured correlation structure and binomial link function were utilized to examine longitudinal measures of antidepressant purchases. Primary effects of groups and periods and their interaction were included in these models. The cumulative shares of incident antidepressant purchasers were demonstrated by Kaplan-Meier curve. To count the adjusted HRs with 95% confidence intervals (CIs), the Cox proportional hazards regression was utilized. Statistical analyses were done using Stata 17.0 version.

In the third study, the incidence of malignancies with their 95% CIs were computed assuming Poisson distribution. Thus, the results are shown as number of events per person years. Poisson regression or negative binomial regression models (when necessary) were utilized to compute the incidence rate ratios (IRRs) of malignancies. Lagrange multiplier test was utilized to check assumptions of overdispersion in Poisson model. The Kaplan-Meier method and log-rank test were exploited in evaluating the cumulative incidence of malignancies and differences between SLE cases and controls, respectively. Inverse probability of treatment weighting was applied to estimate the adjusted Kaplan-Meier cumulative survivals (301). The HRs and their 95% CIs were computed using Cox proportional hazards regression. The proportional hazards assumption was confirmed both graphically and using a statistical test based on Schoenfeld residuals' distribution. Stata version 17.0 was used to implement the statistical analyses.

5 RESULTS

5.1 MULTIMORBIDITY IN RECENT-ONSET SLE

5.1.1 Characteristics of the study population (I–III)

Each of these three studies consisted of the same population. There were 1,006 incident SLE cases whose mean age at SLE diagnosis was 45.5 years and the standard deviation (SD) was 16 years. Eighty-four percent of them were females. Likewise, the number of controls was 3,005. The characteristics of SLE patients are depicted in detail in Table 5.

Table 5. The characteristics of patients with recent onset systemic lupus erythematosus.

Sex	Female	Male
Number of patients	845	161
Age at ID in years (SD)	44.9 (15.9)	48.6 (16.4)

Abbreviations: ID = index day; SD = standard deviation

5.1.2 Comorbidities (I)

Considering comorbid conditions, 8,631 pyrs and 26,382 pyrs were recorded cumulatively for follow-up among SLE cases and controls, respectively. In other words, SLE patients and their controls were followed up for approximately 8.6 years and 8.8 years, respectively.

During the study period, 91.2% of SLE cases and 66.7% of controls were recorded to have at least one of the inspected morbidities. The share of SLE patients with multiple morbidities was larger than in controls as well (Figure 2).

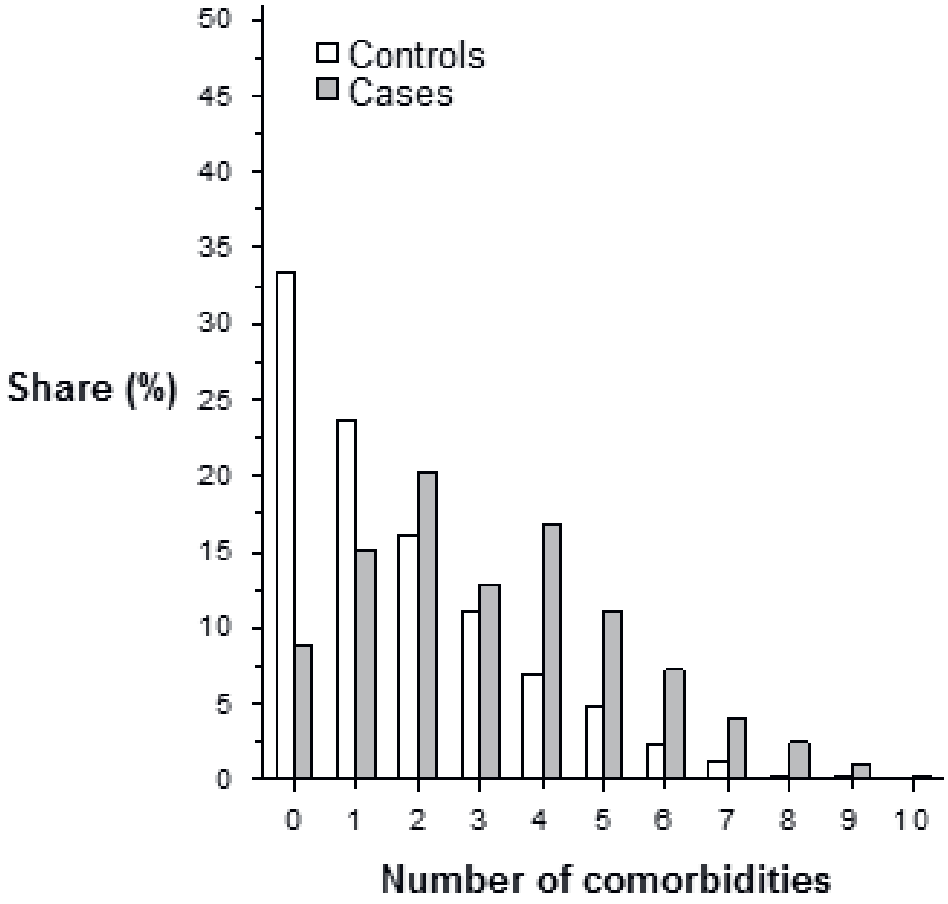


Figure 2. Cumulatively demonstrated number of comorbidities among recent-onset systemic lupus erythematosus cases compared to controls by the end of the follow-up. Systemic connective tissue disorders and infectious diseases were excluded.

CVDs, musculoskeletal disorders, and diseases of the genitourinary tract were the most commonly diagnosed diseases in both cases and controls (Table 6). SLE patients had a significantly increased relative risk for almost all of the inspected morbidities compared to controls. Only the relative risks of psychotic disorders, some neurodegenerative diseases and malignant neoplasms were insignificant. The highest relative risk was found considering blood diseases and immune disorders, the risk being

fivefold. Fifty-one percent of the SLE cases were diagnosed with any CVD, which resulted in two times increased relative risk compared to controls. More specifically, the relative risks of ischemic heart disease and cerebrovascular disease were 1.6- and 1.9-fold, respectively. Problems of the musculoskeletal and genitourinary system were typical among patients, with roughly 50% having them. Mood disorders were almost twice as frequent among SLE cases, with ten percent of patients having the diagnosis. The relative risks of osteoporosis and renal failure were approximately five times higher compared to controls. No significantly decreased relative risk was demonstrated for any of the included morbidities.

Table 6. The number, proportion and relative risks of comorbidities observed in systemic lupus erythematosus cases and their controls during the follow-up (2000-2017).

Diseases by ICD-10	Disease groups	SLE cases N=1006 (%)	Controls N=3005 (%)	RR[a] (95% CI)
C00–D09	Malignancy	117 (12)	268 (9)	1.29 (1.05–1.59)
D10–D48	Benign neoplasm	201 (20)	356 (12)	1.68 (1.44–1.97)
D50–D89	Blood disease and immunodeficiency	178 (18)	103 (3)	5.15 (4.08–6.49)
E00–E90	Endocrine, nutritional, and metabolic disease	254 (25)	388 (13)	1.90 (1.65–2.18)
E00–E07	Disorder of thyroid gland	101 (10)	120 (4)	2.49 (1.93–3.22)
E03	Other hypothyroidism	80 (8)	70 (2)	3.39 (2.48–4.63)
E10–E14	Diabetes mellitus	83 (8)	138 (5)	1.74 (1.34–2.27)
E78	Disorder of lipoprotein metabolism and other lipidemia	53 (5)	98 (3)	1.56 (1.13–2.16)
F00–F99	Mental and behavioral disease	199 (20)	399 (13)	1.46 (1.25–1.70)
F00–F03	Dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere and unspecified dementia	24 (2)	72 (2)	0.96 (0.61–1.52)
F20–F29	Schizophrenia, schizotypal and delusional disorder	15 (2)	40 (1)	1.07 (0.60–1.93)
F30–F39	Mood disorder	102 (10)	177 (6)	1.71 (1.36–2.16)
G00–G99	Disease of the nervous system	313 (31)	511 (17)	1.78 (1.58–2.01)
G30–G32	Other degenerative disease of the nervous system	16 (2)	79 (3)	0.58 (0.34–0.99)
G40–G41	Epilepsy	33 (3)	34 (1)	2.88 (1.79–4.63)

Abbreviations: [a]Education level adjusted at index day; [b] Excluding systemic connective tissue disorders (M30-M36); CI = confidence interval; CVD = Diseases of the circulatory system; IBD = Inflammatory bowel diseases; ICD-10 code = 10th International Classification of Diseases code; RR = Rate ratio; SLE = Systemic lupus erythematosus

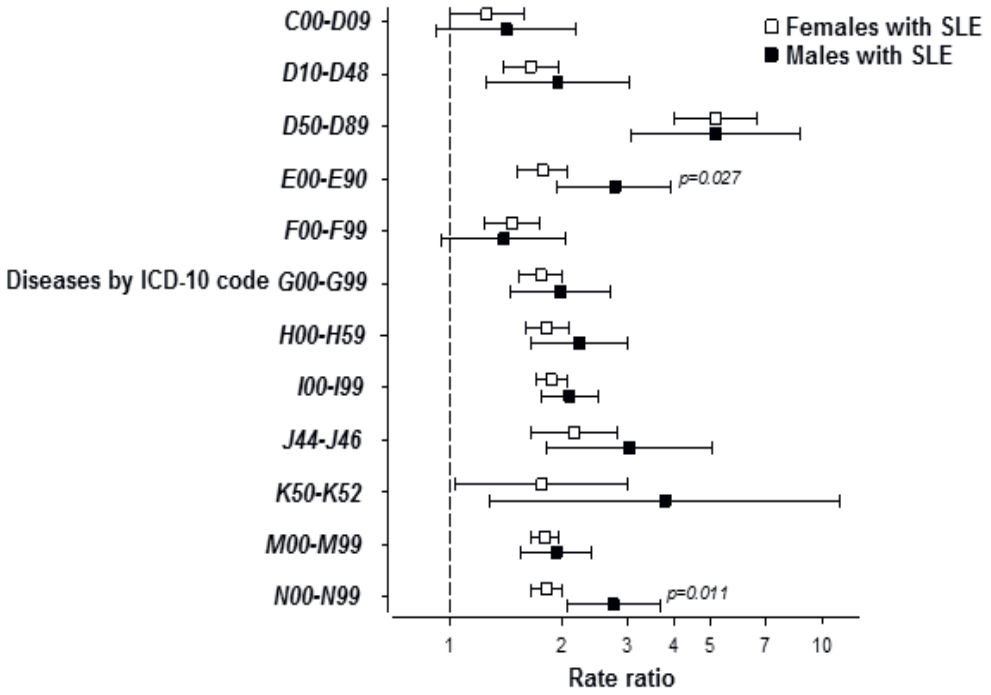
Table 6. Continues.

Diseases by ICD-10	Disease groups	SLE cases N=1006 (%)	Controls N=3005 (%)	RR[a] (95% CI)
H00–H59	Disease of the eye and adnexa	322 (32)	499 (17)	1.88 (1.67–2.12)
I00–I99	CVD	511 (51)	761 (25)	1.91 (1.76–2.08)
I10–I15	Hypertensive disease	237 (24)	351 (12)	1.93 (1.67–2.24)
I20–I25	Ischemic heart disease	100 (10)	177 (6)	1.62 (1.29–2.04)
I60–I69	Cerebrovascular disease	78 (8)	117 (4)	1.92 (1.46–2.53)
J44–J46	Other chronic obstructive pulmonary disease, asthma, and status asthmaticus	112 (11)	142 (5)	2.32 (1.83–2.94)
K50–K52	IBD	28 (3)	42 (1)	2.02 (1.26–3.24)
M00–M99[b]	Disease of the musculoskeletal system and connective tissue	532 (53)	863 (29)	1.82 (1.68–1.97)
M80–M81	Osteoporosis	61 (6)	35 (1)	5.08 (3.38–7.64)
N00–N99	Disease of the genitourinary system	456 (45)	708 (24)	1.91 (1.73–2.09)
N00–N16	Renal tubulointerstitial disease	197 (20)	94 (3)	6.15 (4.86–7.78)
N17–N19	Renal failure	53 (5)	34 (1)	4.53 (2.96–6.92)

Abbreviations: [a]Education level adjusted at index day; [b] Excluding systemic connective tissue disorders (M30-M36); CI = confidence interval; CVD = Diseases of the circulatory system; IBD = inflammatory bowel diseases; ICD-10 code = 10th International Classification of Diseases code; RR = Rate ratio; SLE = Systemic lupus erythematosus

5.1.2.1 Comorbidities by sex

No significant difference was discovered considering the number of comorbidities between SLE males and females: 3.5 (95% CI 3.1–3.8) versus 3.2 (95% CI 3.0–3.3); p = 0.10, respectively. However, males with SLE were more prone to diseases of the genitourinary and endocrine systems than females (Figure 3).



Abbreviations: ICD-10 code = 10th International Classification of Diseases code; SLE = systemic lupus erythematosus; C00-D09 = malignancies; D10-D48 = benign neoplasms; D50-D89 = diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; E00-E90 = endocrine, nutritional and metabolic diseases; F00-F99 = mental and behavioral diseases; G00-G99 = diseases of the nervous system; H00-H59 = diseases of the eye and adnexa; I00-I99 = diseases of the circulatory system; J44-J46 = other chronic obstructive pulmonary disease, asthma and status asthmaticus; K50-K52 = noninfective enteritis and colitis; M00-M99 = diseases of the musculoskeletal system and connective tissue (without systemic connective tissue disorders M30-M36), and N00-N99 = diseases of the genitourinary system.

Figure 3. The comorbidity risk among systemic lupus erythematosus cases and their controls according to sex and the 10th revision of the International Classification of Diseases codes.

Among SLE females, the highest relative risk was demonstrated considering blood diseases and immunodeficiency (RR 5.2), but the most common comorbidity group by number was diseases of the musculoskeletal system, as 53% of the patients had them (Table 7).

In many cases, the relative risk was noted to be insignificant in males (Table 8). However, similarly to females, the highest relative risk was recorded considering blood diseases and immunodeficiency (RR 5.2), while the most common disease group by number was CVDs with 67% having them.

Table 7. The number, proportion and relative risks of comorbidities observed in females with systemic lupus erythematosus cases and their controls during the follow-up (2000-2017).

Diseases by ICD-10	Disease groups	SLE patients N=845 N (%)	Controls N=2524 N (%)	RR[a] (95% CI)
C00–D09	Malignancy	91 (11)	215 (9)	1.26 (1.00–1.59)
D10–D48	Benign neoplasm	173 (21)	314 (12)	1.65 (1.39–1.95)
D50–D89	Blood disease and immunodeficiency	143 (17)	83 (3)	5.15 (3.98–6.68)
E00–E90	Endocrine, nutritional, and metabolic disease	206 (24)	337 (13)	1.78 (1.52–2.07)
E00–E07	Disorder of thyroid gland	97 (12)	117 (5)	2.46 (1.90–3.18)
E03	Other hypothyroidism	77 (9)	69 (3)	3.31 (2.41–4.53)
E10–E14	Diabetes mellitus	61 (7)	106 (4)	1.68 (1.24–2.28)
E78	Disorder of lipoprotein metabolism and other lipidemia	36 (4)	80 (3)	1.31 (0.89–1.92)
F00–F99	Mental and behavioral disease	167 (20)	334 (13)	1.47 (1.24–1.74)
F00–F03	Dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere and unspecified dementia	20 (2)	56 (2)	1.05 (0.64–1.74)
F20–F29	Schizophrenia, schizotypal and delusional disorder	13 (2)	36 (1)	1.05 (0.56–1.96)
F30–F39	Mood disorder	86 (10)	160 (6)	1.60 (1.25–2.05)
G00–G99	Disease of the nervous system	262 (31)	436 (17)	1.76 (1.54–2.00)
G30–G32	Other degenerative disease of the nervous system	13 (2)	68 (3)	0.56 (0.31–1.00)
G40–G41	Epilepsy	24 (3)	28 (1)	2.55 (1.48–4.37)

Abbreviations: [a]Education level adjusted at index day; [b]Excluding systemic connective tissue disorders (M30-M36); CI = confidence interval; CVD = Diseases of the circulatory system; IBD = inflammatory bowel diseases; ICD-10 code = 10th International Classification of Diseases code; RR = Rate ratio; SLE = Systemic lupus erythematosus

Table 7. Continues.

Diseases by ICD-10	Disease groups	SLE patients N=845 N (%)	Controls N=2524 N (%)	RR[a] (95% CI)
H00–H59	Disease of the eye and adnexa	264 (31)	425 (17)	1.82 (1.60–2.08)
I00–I99	CVD	404 (48)	617 (24)	1.87 (1.70–2.06)
I10–I15	Hypertensive disease	195 (23)	285 (11)	1.97 (1.68–2.32)
I20–I25	Ischemic heart disease	70 (8)	117 (5)	1.74 (1.32–2.31)
I60–I69	Cerebrovascular disease	64 (8)	86 (3)	2.16 (1.58–2.94)
J44–J46	Other chronic obstructive pulmonary disease, asthma, and status asthmaticus	85 (10)	117 (5)	1.32 (0.72–2.42)
K50–K52	IBD	21 (3)	36 (1)	1.77 (1.04–3.01)
M00–M99[b]	Disease of the musculoskeletal system and connective tissue	451 (53)	742 (29)	3.77 (1.28–11.09)
M80–M81	Osteoporosis	52 (6)	35 (1)	4.37 (2.87–6.65)
N00–N99	Disease of the genitourinary system	391 (46)	638 (25)	1.82 (1.65–2.00)
N00–N16	Renal tubulointerstitial disease	155 (18)	78 (3)	5.85 (4.51–7.59)
N17–N19	Renal failure	38 (5)	23 (1)	4.83 (2.90–8.05)

Abbreviations: [a]Education level adjusted at index day; [b]Excluding systemic connective tissue disorders (M30-M36); CI = confidence interval; CVD = Diseases of the circulatory system; IBD = inflammatory bowel diseases; ICD-10 code = 10th International Classification of Diseases code; RR = Rate ratio; SLE = Systemic lupus erythematosus

Table 8. The number, proportion and relative risks of comorbidities observed in males with systemic lupus erythematosus cases and their controls during the follow-up (2000-2017).

Diseases by ICD-10	Disease groups	SLE patients N=161 N (%)	Controls N=481 N (%)	RR[a] (95% CI)
C00–D09	Malignancy	26 (16)	53 (11)	1.42 (0.92–2.19)
D10–D48	Benign neoplasm	28 (17)	42 (9)	1.95 (1.25–3.04)
D50–D89	Blood disease and immunodeficiency	35 (22)	20 (4)	5.16 (3.06–8.70)
E00–E90	Endocrine, nutritional, and metabolic disease	48 (30)	51 (11)	2.77 (1.94–3.93)
E00–E07	Disorder of thyroid gland	4 (3)	3 (1)	4.98 (1.13–21.86)
E03	Other hypothyroidism	3 (2)	1 (0.2)	11.78 (1.24 ->100)
E10–E14	Diabetes mellitus	22 (14)	32 (7)	1.96 (1.17–3.28)
E78	Disorder of lipoprotein metabolism and other lipidemia	17 (11)	18 (4)	2.77 (1.46–5.26)
F00–F99	Mental and behavioral disease	32 (20)	65 (14)	1.40 (0.95–2.05)
F00–F03	Dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere and unspecified dementia	4 (3)	16 (3)	0.67 (0.23–1.95)
F20–F29	Schizophrenia, schizotypal and delusional disorder	2 (1)	4 (0.8)	1.31 (0.24–7.08)
F30–F39	Mood disorder	16 (10)	17 (4)	2.99 (1.55–5.77)
G00–G99	Disease of the nervous system	51 (32)	75 (16)	1.98 (1.46–2.70)
G30–G32	Other degenerative disease of the nervous system	3 (2)	11 (2)	0.72 (0.20–2.54)
G40–G41	Epilepsy	9 (6)	6 (1)	4.59 (1.66–12.70)

Abbreviations: [a]Education level adjusted at index day; [b]Excluding systemic connective tissue disorders (M30-M36); CI = confidence interval; CVD = Diseases of the circulatory system; IBD = inflammatory bowel diseases; ICD-10 code = 10th International Classification of Diseases code; RR = Rate ratio; SLE = Systemic lupus erythematosus

Table 8. Continues.

Diseases by ICD-10	Disease groups	SLE patients N=161 N (%)	Controls N=481 N (%)	RR[a] (95% CI)
H00–H59	Disease of the eye and adnexa	58 (36)	74 (16)	2.22 (1.66–2.99)
I00–I99	CVD	107 (67)	144 (30)	2.09 (1.76–2.49)
I10–I15	Hypertensive disease	42 (26)	66 (14)	1.86 (1.32–2.62)
I20–I25	Ischemic heart disease	30 (19)	60 (13)	1.39 (0.93–2.07)
I60–I69	Cerebrovascular disease	14 (9)	31 (7)	1.32 (0.72–2.42)
J44–J46	Other chronic obstructive pulmonary disease, asthma, and status asthmaticus	27 (17)	25 (5)	3.03 (1.81–5.07)
K50–K52	IBD	7 (4)	6 (1)	3.77 (1.28–11.09)
M00–M99[c]	Disease of the musculoskeletal system and connective tissue	81 (50)	121 (26)	1.93 (1.55–2.40)
M80–M81	Osteoporosis	9 (6)	0 (0)	..
N00–N99	Disease of the genitourinary system	65 (40)	70 (15)	2.75 (2.06–3.66)
N00–N16	Renal tubulointerstitial disease	42 (26)	16 (3)	8.06 (4.66–13.94)
N17–N19	Renal failure	15 (9)	11 (2)	4.04 (1.89–8.63)

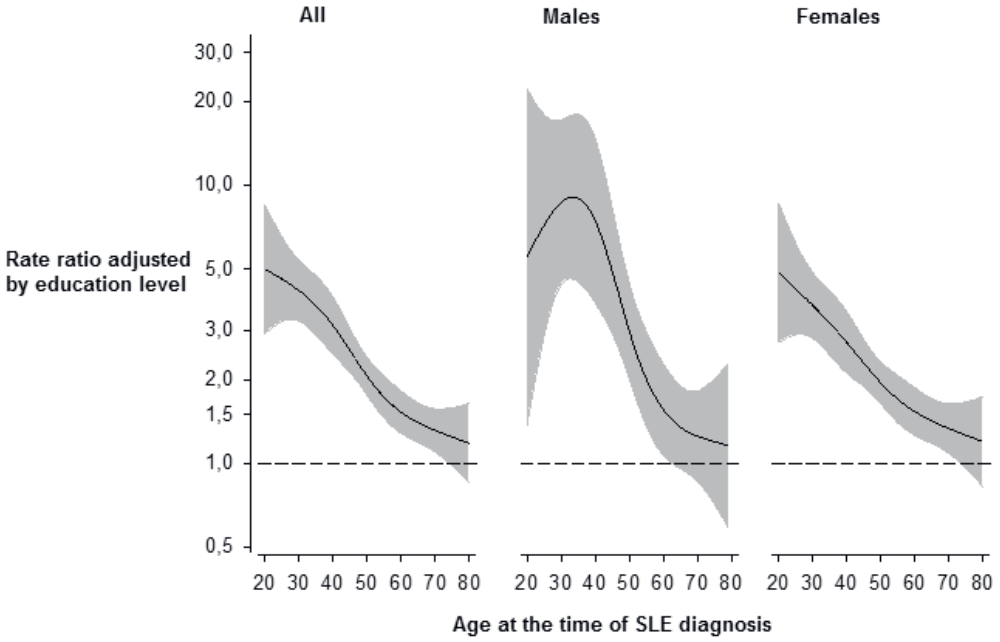
Abbreviations: [a]Education level adjusted at index day; [b]Excluding systemic connective tissue disorders (M30-M36); CI = confidence interval; CVD = Diseases of the circulatory system; IBD = inflammatory bowel diseases; ICD-10 code = 10th International Classification of Diseases code; RR = Rate ratio; SLE = Systemic lupus erythematosus

5.1.2.2 Cardiovascular morbidity

The relative risk of any CVD was 1.9-fold among all SLE cases (Table 6). There was no difference between sexes as females with SLE had 1.9-fold increased relative risk, which was nearly the same as for males with SLE (2.1). In both sexes, CVDs were prevalent as in SLE females, roughly 50% were observed to have them, whereas in males the share was almost 70% (Tables 7 and 8).

However, the relative risk of any CVD was dependent on age at SLE diagnosis. The patients who were young at the time SLE was diagnosed had the greatest relative risk. Especially, young males seemed to be high-

risk patients. The relative risk of CVDs decreased over time but remained a little higher compared to controls even among the older patients (Figure 4).



Abbreviations: SLE = systemic lupus erythematosus

Figure 4. The relative risk of any cardiovascular disease adjusted by education level at index day among systemic lupus erythematosus cases diagnosed during 2000–2014 versus controls according to age at systemic lupus erythematosus diagnosis. The 95% confidence interval is demonstrated by the grey area.

5.1.3 The use of antidepressant and -psychotic medication (II)

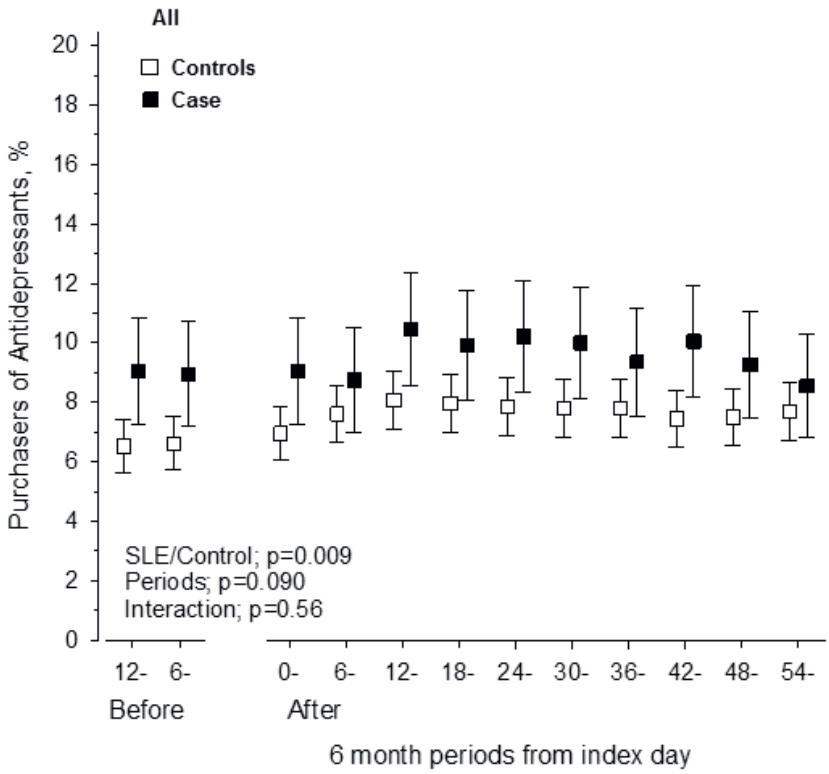
5.1.3.1 Antidepressants

During the observation, 264 (26%) patients, of whom 88% were females, purchased antidepressant drug therapy for the first time. In parallel, 571 (19%) controls, of whom 89% were females, purchased antidepressants.

The mean daily antidepressant consumption was 62.3 DDDs for cases and 57.9 DDDs for controls ($p < 0.001$) during one year prior to the ID.

During the five years since the ID, the mean antidepressant consumption increased to 87.3 DDDs in cases and 77.4 DDDs in controls ($p < 0.001$).

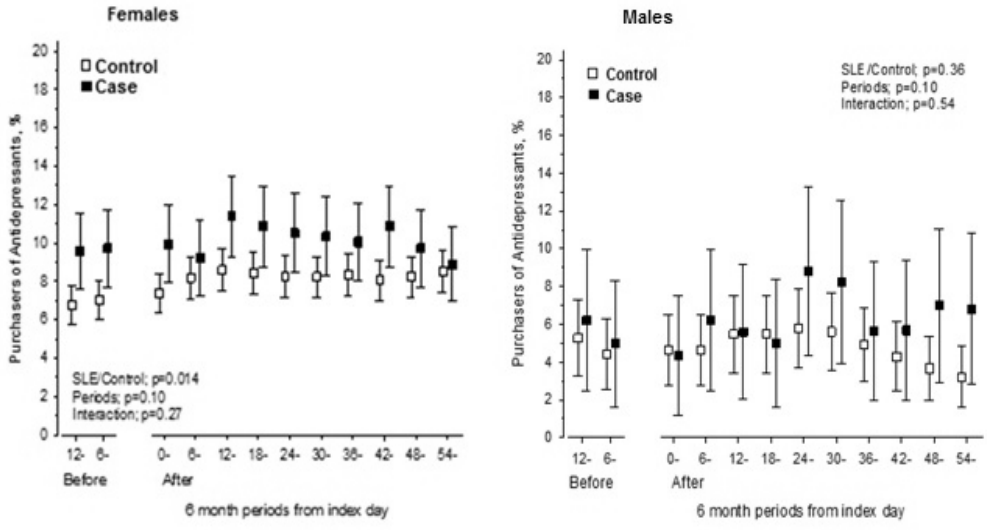
When all SLE cases and controls were compared, the share of new antidepressant purchasers was significantly greater among cases during nearly the entire observation time (Figure 5). The share was already larger one year prior to the ID (9% vs 7%) and peaked one year after the ID among cases. At the end of the observation, the share of purchasers returned to the same level as one year prior to the ID among cases. Furthermore, the difference in shares appeared to fade at the last inspection.



Abbreviations: SLE = systemic lupus erythematosus

Figure 5. The shares of new antidepressants purchasers among incident systemic lupus erythematosus cases and their controls in Finland during the observation time.

The share of new antidepressant purchasers was significantly larger among SLE females than their controls, with the difference ranging from one to three percentage points during the observation (Figure 6). The share of purchasers was already higher one year prior to the ID (ten versus seven percent). In addition, the share peaked one year after the diagnosis (12%) but decreased afterwards. At the last inspection, no difference existed between cases and controls, and the share decreased to the same amount as one year prior to the ID. Contrary to females, no significant difference was observed between SLE males and controls considering the share of new antidepressant purchasers (Figure 6).



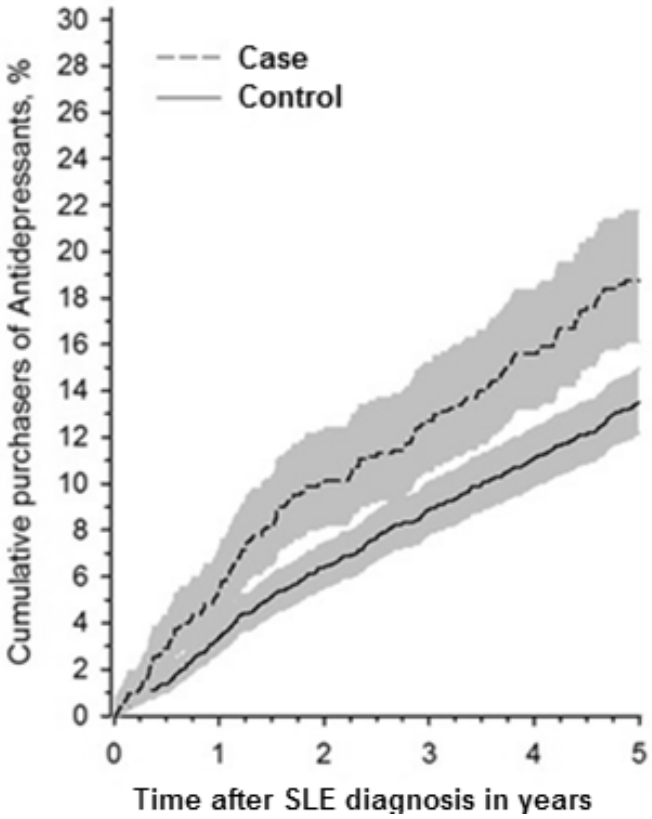
Abbreviations: SLE = systemic lupus erythematosus

Figure 6. The shares of new antidepressants purchasers among incident systemic lupus erythematosus and their controls by sex in Finland during the observation time.

A significant difference was demonstrated regarding the shares of new antidepressant purchasers between sexes, as 27.6% of females and 19.3% of males with SLE had purchased antidepressants during the observation period (p = 0.028). Similarly, the difference between sexes existed among

controls, as 20.0% of females and 13.5% of males had purchased antidepressants (p = 0.001).

When the purchasers were examined cumulatively, at least one new purchase of antidepressant medication was recorded among 18.7% (95% CI 16.1%–21.7%) of cases and 13.5% (95% CI 12.2%–15.0%) of controls during the first five years after the ID. SLE patients had a higher probability of purchasing antidepressants than controls as the sex- and age-adjusted HR was 1.45 (95% CI 1.19 to 1.77; p < 0.001) for purchasing antidepressants (Figure 7).



Abbreviations: SLE = systemic lupus erythematosus

Figure 7. The purchasers of new antidepressant drug therapy among incident systemic lupus erythematosus patients and their controls in Finland during five years after the diagnosis of systemic lupus erythematosus depicted in a cumulative manner.

The distribution of the purchased antidepressant types did not differ between cases and controls (Table 9). The most frequently purchased antidepressant type was selective serotonin reuptake inhibitors (N06AB) as nearly 50% of purchases were these drugs among both cases and controls.

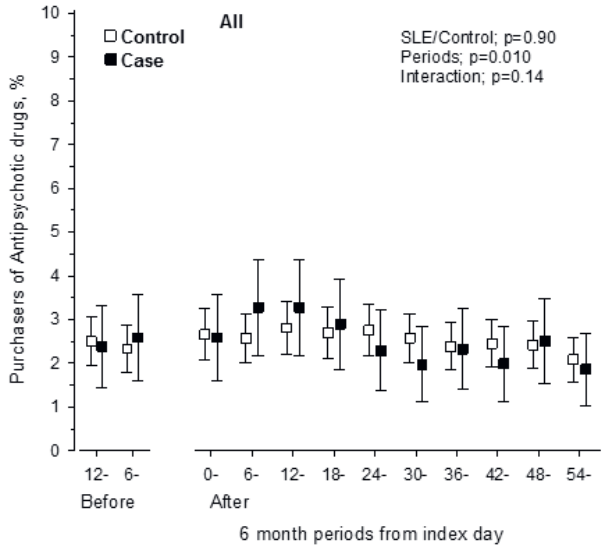
Table 9. The number of the purchased antidepressants by type and their proportions compared to all purchased antidepressants in incident systemic lupus erythematosus cases and their controls in Finland during the observation time. Data gathered Jan 1, 1999–Dec 31, 2015.

Antidepressant type	Non-selective monoamine reuptake inhibitors (N06AA)	Selective serotonin reuptake inhibitors (N06AB)	Monoamine oxidase A inhibitors (N06AG)	Other antidepressants (N06AX)
Cases N/%	55 / 16.0	164 / 47.7	5 / 1.4	120 / 34.9
Controls N/%	75 / 10.2	395 / 53.7	6 / 0.8	259 / 35.2

Abbreviations: N = number

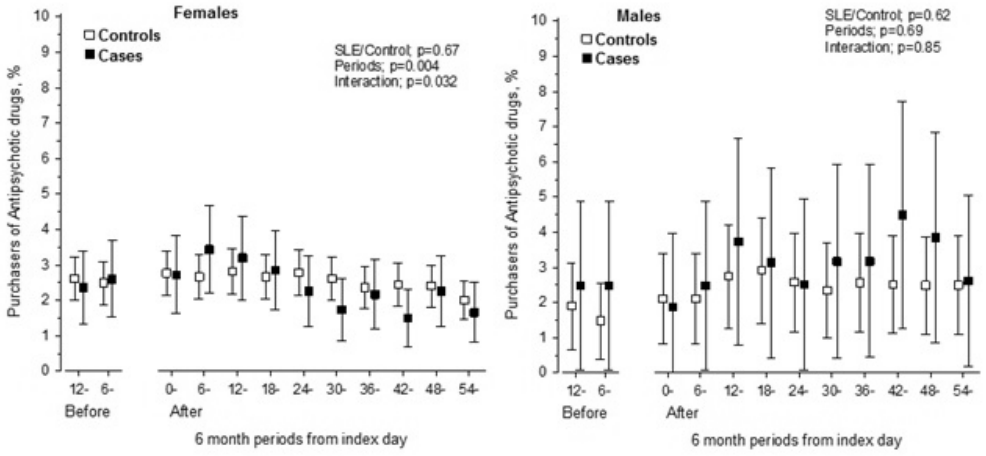
5.1.3.2 Antipsychotics

SLE cases and controls did not differ significantly when the new purchasers of antipsychotic drug therapy were evaluated. The proportion of new antipsychotic purchasers during the whole observation time was 2.5% (95% CI 1.7–3.3) among cases, while in controls it was 2.5% (95% CI 2.0–3.0) (Figure 8). Neither was any significant difference found when the purchasers were examined by sex (Figure 9).



Abbreviations: SLE = systemic lupus erythematosus

Figure 8. The shares of new antipsychotic drug purchasers among incident systemic lupus erythematosus cases and their controls in Finland during the observation time.



Abbreviations: SLE = systemic lupus erythematosus

Figure 9. The shares of new antipsychotic drug purchasers among incident systemic lupus erythematosus and their controls by sex in Finland during the observation time.

5.1.4 Malignancies in recent-onset SLE and survival (III)

5.1.4.1 Malignancies

SLE cases were followed up for 11,294 pyrs (9,782 pyrs in females and 1,512 pyrs in males). Thus, the patients were followed for approximately 11.2 years for any malignancy. Likewise, the follow-up of controls consisted of 34,734 pyrs (4,875 pyrs in males and 29,858 pyrs in females).

At least one incident malignancy was observed in 85 (8.5%) SLE cases and in 192 (6.4%) controls during the follow-up. More than one malignancy was discovered in seven SLE cases (five females and two males), whereas in controls, 15 persons developed more than one malignancy (11 females and four males). SLE cases had higher risk for any malignancy among all patients and females than controls as the IRRs were 1.41 and 1.40, respectively (Tables 10 and 11). On the contrary, no significant difference in risk of any malignancy was detected among males with SLE (Table 12).

Table 10. The observed malignancies (N), incidence rates per one thousand person years and incidence rate ratios of recent-onset systemic lupus erythematosus cases and their controls in Finland from the diagnosis of systemic lupus erythematosus until the patient died or until the end of 2018.

	Cases		**Controls**		
Malignancy type	*N*	*IR per 1,000 pyrs (95% CI)*	*N*	*IR per 1,000 pyrs (95% CI)*	*IRR (95% CI)*
Any	96	8.5 (6.6–10.4)	209	6.0 (5.2–6.9)	1.41 (1.08–1.85)
Bladder	1	0.1(0.0–0.3)	16	0.5 (0.2–0.7)	0.19 (0.03–1.45)
Colorectal	8	0.7 (0.2–1.3)	12	0.3 (0.2–0.5)	2.05 (0.79–5.34)
Hematologic	10	0.9 (0.3–1.4)	15	0.4 (0.2–0.6)	2.05 (0.92–4.56)
Lung	8	0.7 (0.2–1.2)	11	0.3 (0.1–0.5)	2.24 (0.90–5.55)
Melanoma	0	0.0	13	0.4 (0.2–0.6)	..
NHL	12	1.1 (0.5–1.7)	7	0.2 (0.1–0.4)	5.27 (2.08–13.36)
NMSC	8	0.7 (0.0–1.5)	7	0.2 (0.1–0.4)	3.51 (0.94–13.16)
Other	21	1.9 (1.0–2.7)	34	1.0 (0.7–1.3)	1.90 (1.09–3.31)
Pancreas	5	0.4 (0.1–0.8)	4	0.1 (0.0–0.2)	3.84 (1.03–14.31)
Stomach	0	0.0	9	0.3 (0.1–0.4)	..

Abbreviations: CI = confidence interval; IR = Incidence rate; IRR = Incidence rate ratio; N = Number; pyrs = person years; Any = any malignancy; bladder = bladder cancer; colorectal = cancers of colon and rectum; hematologic = hematologic malignancy consisting of leukemias, myelofibrosis, myeloma and polycythemia vera; lung = lung cancer; NHL = non-Hodgkin's lymphoma; NMSC = non-melanoma skin cancer; other = other cancers including cancers of central nervous system, nerve sheet and eye, meningiomas, cancers of upper respiratory tract, mesotheliomas, other GI tract cancers and gallbladder, biliary duct and hepatic cancers, kidney cancers, Hodgkin's lymphoma, cancers of salivary and thyroid glands and testis cancer and cancers that were ill-defined or unknown; pancreas = pancreatic cancer; stomach = stomach cancer

Table 11. The observed malignancies (N), incidence rates per one thousand person years and incidence rate ratios of females with recent-onset systemic lupus erythematosus and their controls in Finland during the follow-up.

	Cases		**Controls**		
Malignancy type	*N*	*IR per 1,000 pyrs (95% CI)*	*N*	*IR per 1,000 pyrs (95% CI)*	*IRR (95% CI)*
Any	75	7.7 (5.7–9.7)	163	5.5 (4.6–6.3)	1.40 (1.03–1.91)
Bladder	1	0.1 (0.0–0.3)	11	0.4 (0.2–0.6)	0.28 (0.04–2.15)
Breast	11	1.1 (0.5–1.8)	60	2.0 (1.5–2.5)	0.56 (0.30–1.06)
Colorectal	7	0.7 (0.1–1.3)	9	0.3 (0.1–0.5)	2.37 (0.82–6.89)
Gynecological	7	0.7 (0.2–1.2)	11	0.4 (0.2–0.6)	1.94 (0.76–5.00)
Hematologic	7	0.7 (0.2–1.2)	8	0.3 (0.1–0.5)	2.67 (0.97–7.35)
Lung	6	0.6 (0.1–1.1)	8	0.3 (0.1–0.5)	2.29 (0.80–6.58)
Melanoma	0	0.0	12	0.4 (0.2–0.6)	..
NHL	9	0.9 (0.3–1.5)	4	0.1 (0.0–0.3)	6.87 (2.12–22.25)
NMSC	8	0.8 (0.0–1.7)	4	0.1 (0.0–0.3)	6.10 (1.40–26.49)
Other malignancy	16	1.6 (0.8–2.5)	27	0.9 (0.6–1.2)	1.81 (0.96–3.42)
Pancreas	3	0.3 (0.0–0.7)	4	0.1 (0.0–0.3)	2.29 (0.51–10.22)
Stomach	0	0.0	5	0.2 (0.0–0.3)	..

Abbreviations: CI = confidence interval; IR = Incidence rate; IRR = Incidence rate ratio; N = Number; pyrs = person years; Any = any malignancy; bladder = bladder cancer; breast = breast cancer; colorectal = cancers of colon and rectum; gynecological = gynaecological cancers including cancers of cervix and corpus uteri and vulva; hematologic = hematologic malignancy consisting of leukemias, myelofibrosis, myeloma and polycythemia vera; lung = lung cancer; NH L= non-Hodgkin's lymphoma; NMSC = non-melanoma skin cancer; other = other cancers including cancers of central nervous system, nerve sheet and eye, meningiomas, cancers of upper respiratory tract, mesotheliomas, other GI tract cancers and gallbladder, biliary duct and hepatic cancers, kidney cancers, Hodgkin's lymphoma, cancers of salivary and thyroid glands and testis cancer and cancers that were ill-defined or unknown; pancreas = pancreatic cancer; stomach = stomach cancer

Table 12. The observed malignancies (N), incidence rates per one thousand person years and incidence rate ratios of males with recent-onset systemic lupus erythematosus and their controls in Finland during the follow-up.

	Cases		**Controls**		
Malignancy type	*N*	*IR per 1,000 pyrs (95% CI)*	*N*	*IR per 1,000 pyrs (95% CI)*	*IRR (95% CI)*
Any	21	13.9 (7.7–20.1)	46	9.4 (6.6–12.3)	1.47 (0.86–2.52)
Bladder	0	0.0	5	1.0 (0.1–1.9)	..
Breast	0	0.0	0	0.0	..
Colorectal	1	0.7 (0.0–2.0)	3	0.6 (0.0–1.3)	1.07 (0.11–10.27)
Hematologic	3	2.0 (0.0–4.2)	7	1.4 (0.4–2.5)	1.38 (0.36–5.32)
Lung	2	1.3 (0.0–3.2)	3	0.6 (0.0–1.3)	2.15 (0.36–12.89)
Melanoma	0	0.0	1	0.2 (0.0–0.6)	..
NHL	3	2.0 (0.0–4.2)	3	0.6 (0.0–1.3)	3.22 (0.65–15.90)
NMSC	0	0.0	3	0.6 (0.0–1.3)	..
Other	5	3.3 (0.4–6.2)	7	1.4 (0.4–2.5)	2.30 (0.74–7.18)
Pancreas	2	1.3 (0.0–3.1)	0	0.0	..
Prostate	5	3.3 (0.5–6.1)	10	2.1 (0.8–3.3)	1.61 (0.56–4.61)
Stomach	0	0.0	4	0.8 (0.0–1.6)	..

Abbreviations: CI = confidence interval; IR = Incidence rate; IRR = Incidence rate ratio; N = Number; pyrs = person years; Any = any malignancy; bladder = bladder cancer; breast = breast cancer; colorectal = cancers of colon and rectum; hematologic = hematologic malignancy consisting of leukemias, myelofibrosis, myeloma and polycythemia vera; lung = lung cancer; NHL = non-Hodgkin's lymphoma; NMSC = non-melanoma skin cancer; other = other cancers including cancers of central nervous system, nerve sheet and eye, meningiomas, cancers of upper respiratory tract, mesotheliomas, other GI tract cancers and gallbladder, biliary duct and hepatic cancers, kidney cancers, Hodgkin's lymphoma, cancers of salivary and thyroid glands and testis cancer and cancers that were ill-defined or unknown; pancreas = pancreatic cancer; prostate = prostate cancer; stomach = stomach cancer

In addition to overall malignancy, NHL, pancreatic cancer, and malignancies of the “Other” group were more prevalent among SLE cases than controls (Table 10). Furthermore, NHL was the most frequent malignancy with twelve cases and IR of 1.1/1,000 pyrs (95% CI 0.5–1.7) among SLE cases. SLE patients also developed other malignancies of hematologic origin, but the spectrum varied broadly and none of them differed from the others. As a whole group, no increased risk was observed compared to controls.

Moreover, NMSC, lung and colorectal cancers were common in SLE patients while neither cases of melanoma nor stomach cancer were observed in SLE patients compared to 13 melanoma and nine stomach cancer incidents in controls (Table 10).

The subanalysis by sex unveiled that breast cancer was prevalent in females with SLE, but also in controls. The IR was 1.1/1,000 pyrs (95% CI 0.5–1.8) in SLE cases. However, the risk was statistically insignificant. On the contrary, the likelihood of being diagnosed with NHL or NMSC was significantly higher among SLE females than their controls (Table 11). In SLE males, prostate cancer was the most typically diagnosed malignancy with five cases and IR of 3.3/1,000 pyrs (95% CI 0.5–6.1). However, SLE males did not differ from their controls considering the risk of any of the malignancy types (Table 12).

Malignancies were found to appear evenly among females with SLE during the follow-up, and the cumulative incidence of malignancies began to diverge one year after SLE was diagnosed. Furthermore, the difference remained over the years compared to controls. In male cases, the incidence peaked a few years after the ID (Figure 10).

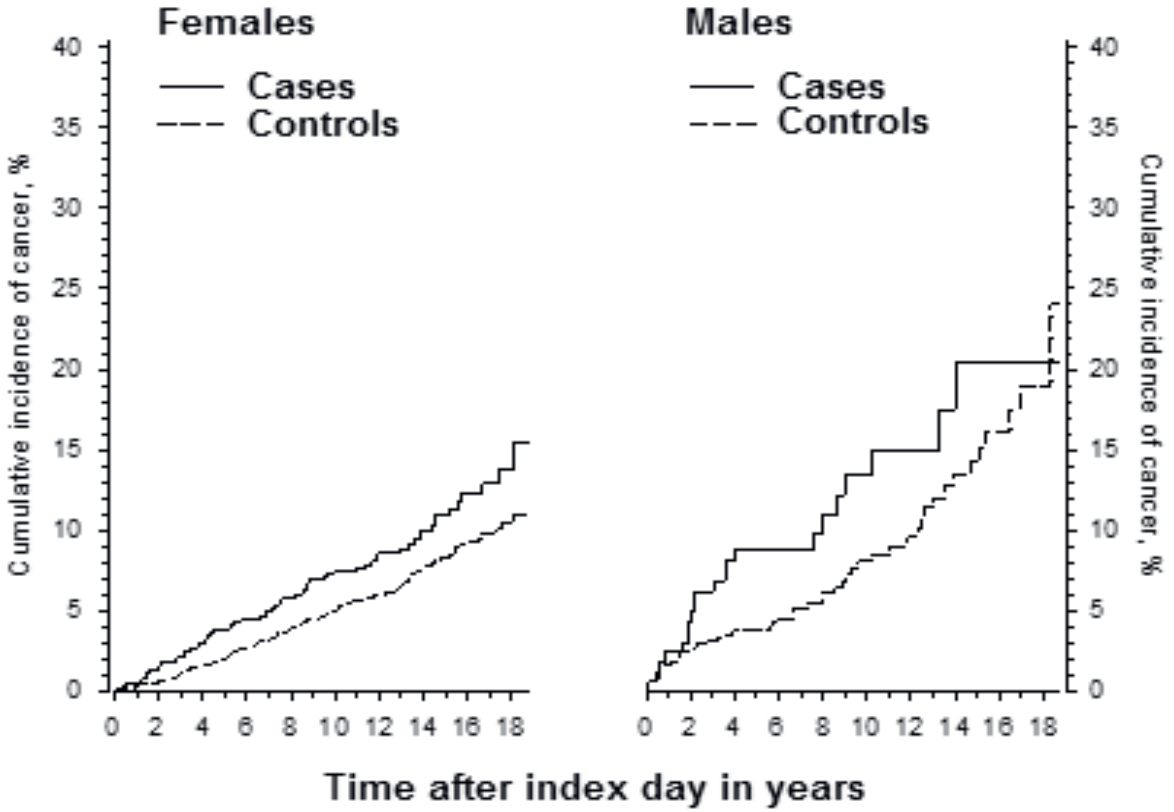
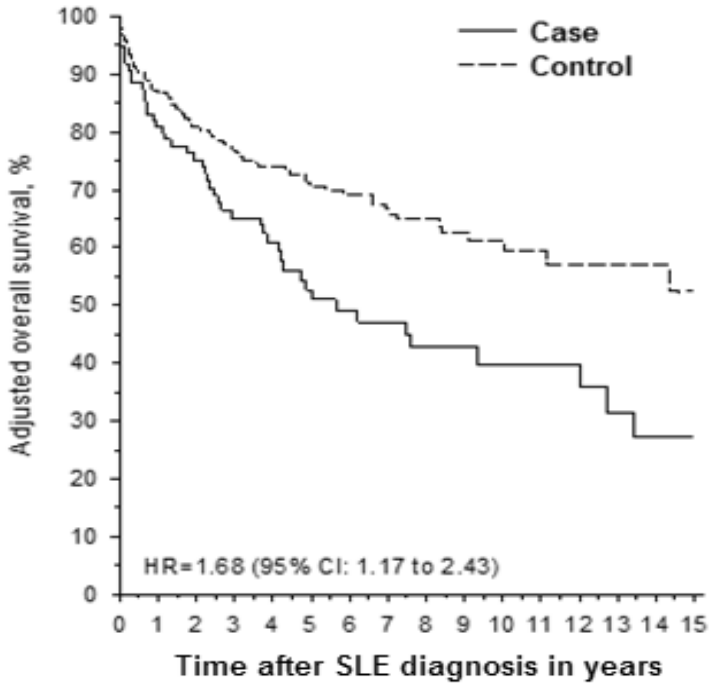


Figure 10. The cumulative incidence of malignancies among recent-onset Finnish systemic lupus erythematosus cases and their controls by sex over time.

5.1.4.2 Survival of patients with a malignancy

At the end of the follow-up, 122 of the 277 persons with a malignancy had died. Deaths occurred more often among SLE cases than controls (56.5% versus 38.5%). The crude survival for SLE cases with malignancy was lower than in controls, 30.0% (95% CI 17.4%–43.6%) versus 47.2% (95% CI 33.9%–59.4%) p = 0.020, respectively, at the end of the follow-up. The likelihood of being alive 15 years after the SLE diagnosis was worse in cases as the survival rates (adjusted by sex, age, and education) were 27.1% and 52.4% for cases and controls, respectively (Figure 11). This resulted in the adjusted HR of 1.68 (95% CI 1.17–2.43) for death.



Abbreviations: SLE = systemic lupus erythematosus

Figure 11. The overall survival, adjusted by age, sex, and education, among recent-onset systemic lupus erythematosus cases and controls with a malignancy, from the day systemic lupus erythematosus was diagnosed until Dec 31, 2019.

5.1.4.3 Causes of death in persons with a malignancy

Among people with malignancy, the most commonly registered underlying cause of death was neoplasm in SLE cases (N = 35), but also in controls (N = 58) (Table 13). Furthermore, malignancies accounted for most of these neoplasms, as the number of malignancies was 34 (70%) and 56 (76%) in cases and controls, respectively. CVDs were a notable underlying cause of death as well, as nine cases (19%) and seven controls (nine percent) died of these diseases. Other underlying death causes were sporadic in both groups. However, in four patients (eight percent) and two controls (three percent), infection was a contributory cause of death, while SLE was a contributory cause in six cases (13%).

Table 13. The underlying causes of death depicted as numbers and proportions among recent-onset systemic lupus erythematosus cases and controls with malignancy between the index day and Dec 31, 2019. The proportions are rounded off as integers.

Cause of death by ICD-10	Cause of death	Case N (%)	Control N (%)
A00–B99	Infectious	0 (0)	1 (1)
C00–D48	Neoplasm	35 (73)	58 (78)
F00–F99	Mental and behavioral	1 (2)	2 (3)
G00–G99	Nervous system	0 (0)	3 (4)
I00–I99	CVD	9 (19)	7 (9)
J00–J99	Respiratory system	1 (2)	0 (0)
K00–K93	Digestive system	2 (4)	2 (3)
R00–R99	Unspecified	0 (0)	1 (1)

Abbreviations: CVD = cardiovascular disease; ICD-10 = 10th International Classification of Diseases code; N = number

6 DISCUSSION

6.1 GENERAL DISCUSSION

The main goal of this work was to clarify the epidemiology of comorbidities in Finnish adult recent-onset SLE patients. The results of this nationwide study provide unique information on the occurrence and risk of comorbid conditions of SLE patients living in Finland.

In this case-control study, the data of a large population of recent-onset SLE patients was examined, and all the patients who had been granted the special reimbursement for SLE medication during 2000–2014 were included. These certificates for reimbursement were applied by specialists in rheumatology or physicians working in such clinics, strengthening the validity of the inclusion of SLE patients in the study. The patients were followed for a relatively long time, and control patients were individually matched for each SLE case. However, mild or incomplete SLE cases as well as fatal cases at diagnosis may have been missed if the reimbursement application had not been made or it had been made for undifferentiated connective tissue disease and had not been updated thereafter. SLE patients in this study were a little older at diagnosis compared to findings of some other studies (4,30,32,33,35,36,40). On the other hand, our results are in line with studies from the UK, Greece, and the USA (31,34,38,39). Moreover, a study from the Northern Savo region showed that the delay between the first symptoms and diagnosis of SLE was no longer than six months (302).

SLE cases had a greater risk of numerous comorbidities compared to matched controls. Especially CVDs, renal diseases, mood disorders and certain malignancies were prevalent among them. Considering mental health concerns, the consumption of antidepressants was higher among SLE cases than controls, reflecting the presence of notable mood disorders. Lastly, SLE and malignancy together had a significant effect on survival in SLE patients.

6.2 MULTIMORBIDITY

Based on the present study, SLE cases had an elevated risk for several comorbidities compared to general population. Especially, the risks of CVDs, diseases of the genitourinary system and mood disorders were notable. In addition, SLE patients had more comorbidities per single person, and more than 90% of the cases were diagnosed with at least one of the inspected comorbidities by the end of the follow-up.

Many studies have described a high number and elevated risks of certain comorbidities in SLE, such as CVDs. Instead, there is a clear lack of comprehensive long follow-up studies that consider the risk of multiple morbidities in general (6,9,11,270). However, the UK study by Kuo et al. showed that incident SLE cases had a higher number of multiple comorbidities prior to SLE diagnosis compared to controls. Furthermore, they demonstrated that the number of incident comorbidities occurring after SLE diagnosis was significantly higher than in controls (6).

The results of the present work are in line with the work by Kuo et al. as SLE cases experienced more comorbidities per individual than their controls during the follow-up. The high risk of multiple comorbidities probably results from several reasons. Firstly, the disease itself, with its wide inflammation, predisposes to comorbidities, such as inflammation in the arteries, and the formation of aPLs or the presence of LN contribute to the development of CVDs (16,109,133,157,158). The disease onset is often insidious, which may delay the recognition of SLE and the start of appropriate treatment, which gives time for the disease-related comorbidities to evolve. On the other hand, the drugs used for SLE management may predispose to comorbidities, such as GCs predisposing to CVDs, infections and osteoporosis. In addition, mental health concerns may influence treatment adherence (8,15,115,120,122,123,157,158,182,183,272,282).

The risk of almost every studied disease group was elevated in SLE cases compared to controls in the present study. SLE patients were prone to CVDs, diseases of the genitourinary system, mood disorders, endocrine disorders, and musculoskeletal disorders, such as osteoporosis. Only the

likelihoods of having a psychotic disorder, neurodegenerative disease or malign neoplasm were not significantly increased. These results are similar to other studies, although some minor variation may exist due to different study methods and populations (6,9,11,141,151,166,167,270,272,278). For example, two studies from the UK by Rees et al. and Kuo et al. studied the risk of various comorbidities by utilizing general practice data (6,9). The study by Rees et al. consisted of established SLE cases, and they found an increased risk of varying degree for every disease group studied. High risks were recorded considering CVDs and renal failure in particular (9). Similarly, Kuo et al. showed that the risks of many incident morbidities were increased, but especially, the risks of CVDs and renal diseases were notable among incident SLE cases (6).

On the contrary, there may also be some bias in the data of the studies, as SLE patients are regularly monitored and the likelihood of being tested for other morbidities is higher than in general population. Moreover, in the present comorbidity study, only diagnoses made in specialized care were included. Although this method probably increases the validity of diagnoses of comorbidities, it also excludes the diagnoses made in the primary care. Furthermore, some of the manifestations of SLE, such as hematological, cardiopulmonary and mental health problems, may be considered as comorbidities or vice versa, which may lead to slight over- or underestimation of multimorbidity also in the current study (6,25).

On the other hand, an example of the effects of study population on the spectrum and risk of comorbidities is the study by Greenstein et al. which analyzed the information of South African SLE patients attending their clinic between 1990–2015. This study consisted primarily of young females of Black ethnicity with an average follow-up of six years. More than third of the patients had at least one comorbidity at diagnosis, and nearly 80% had experienced a comorbidity by the end of the follow-up. Contrary to the present work and other studies from industrialized countries, the occurrences of CVDs and malignancies were lower, whereas hypertension and severe infections, such as tuberculosis, were more frequent (6,9,11,270).

6.2.1 Sex differences in comorbidities

SLE males appear to be prone to more severe disease course, higher amount of damage accrual, end-organ damage, and death than females. These factors may be partly related to certain comorbidities for which males seem to bear a higher risk (2,9,117,118). For example, Tan et al. described in the Hopkins lupus cohort study that SLE males experienced more commonly renal involvement, CVDs, seizures, and hematological manifestations, whereas females had a milder disease course with photosensitivity, malar rash and arthalgias (118). Cervera et al. also described more renal and pulmonary system involvement and damage in European SLE males versus females (2). In addition, in the UK study, CVDs occured more frequently in males with SLE than in females (9).

In the present study, some sex differences were observed, but they associated with diseases of the genitourinary tract and endocrine disorders. SLE males were demonstrated to be at significant risk for dyslipidemia while females were not. Moreover, contrary to above-mentioned studies, no increased risk of CVDs was found in males compared to females, and the number of comorbidities did not differ between sexes (9,118).

6.2.2 Cardiovascular comorbidities

The present study described a twice as high risk for CVDs for both female and male SLE patients compared to controls, and CVDs occurred frequently among both sexes. These results are parallel to many studies reporting two to five times higher risk of CVDs in SLE (6,9,16,161,166-169,171,172). Similary to other studies considering new-onset SLE, the risk of ischemic heart disease was twofold, as was the risk of cerebrovascular diseases (6,16,166,167,169). Moreover, in accordance with the studies by Aviña-Zubieta et al. and Lim et al., being young at the onset of SLE increased the relative risk of CVDs, with emphasis on male patients (166,167). However, even after the relative risk of CVDs decreased in older patients, it remained elevated compared to control population.

Thus, these results reinforce the conception of the high risk of CVDs even in recent-onset SLE and highlight the importance of prevention and early suspicion of them. However, there are currently no sufficiently valid risk assessment tools available for CVD risk in SLE. Instead, the EULAR guidelines from 2022 advise assessing the traditional and SLE-related risk factors to weigh the CVD risk in general. The guidelines advise using antihypertensives to lower blood pressure below 130/80 mmHg, whereas the use of lipid-lowering drugs should follow the recommendations for general population. Low-dose aspirin may be used for prevention when aPLs are present, and the use of HCQ is recommended to all patients with no contraindications for the drug. Special attention should be paid to the use of GCs, which should be decreased to the lowest dose possible (287,303).

6.2.3 Diseases of the genitourinary tract

Diseases of the genitourinary system were one of the most frequently reported disease groups in SLE cases. Approximately half of the patients had some sort of genitourinary disease diagnosis, and their risk for these diseases was twice as high compared to controls. Five percent of the SLE cases had renal failure diagnosis (acute and chronic renal failure combined), and an almost fivefold increased risk for the condition was observed. However, the data regarding the number of LN diagnoses was not available.

The elevated risk of renal diseases has also been noted in studies by Rees et al. and Kuo et al., the latter of which reported a three times higher risk for incident renal diseases (6,9). However, the authors found that the risk of renal diseases prior to SLE diagnosis was almost nine times higher compared to matched controls as well (6).

It is presumable that the somewhat lower risk in the present study may be partly explained by the fact that renal disease and LN are more common among non-White ethnicities, while the cohort of the present study presumably consisted primarily of native Finns (2,119,176,177). On the other hand, the EULAR guidelines advise starting HCQ for virtually every new SLE case as its use has been shown to diminish the risk of renal

flare, worse outcome in LN, and ESKD (178-181). In Finland, these guidelines have been implemented quite well, as up to 80 % of the new-onset SLE cases have been reported to purchase HCQ during the first year after the diagnosis (304). Thus, the high proportion of HCQ users may partly explain the lower risk of renal diseases observed in this study compared to others (6,9,11).

6.2.4 Mental health concerns

6.2.4.1 Mood disorders

Ten percent of the SLE patients were diagnosed with a mood disorder, resulting in twice as high risk compared to controls. Moreover, the risk was elevated in both sexes, with RRs of 1.6 and 3.0 in females and males, respectively. However, because of some forms of mood disorders may be treated solely in primary care, and as the data did not cover visits to primary care, the risk may be an underestimate.

The literature on the occurrence of mood disorders is mixed due to differences in study populations and methods (18,151,241-244,248-250). Moreover, there is a scarcity of studies which include a control group. Therefore, risk assessment is even more difficult. However, a few studies have shown significantly increased risks for these disorders (6,151,242). For instance, the study results of a Danish nationwide study were analogous to the present study as it pointed out a two times higher risk for depression (151). Furthermore, a Dutch study reported significantly increased BDI scores and a prevalence of depression that was ten percentage points higher (17% vs. 7%) in SLE cases than in the general population (242).

6.2.4.2 Psychotic disorders

Contrary to mood disorders, no increased risk of any type of psychotic disorder was found. Just over one percent of the patients were demonstrated to have these disorders, which was in line with other large studies (6,251,252,255). However, Kuo et al. reported an increased risk of psychosis among incident SLE cases, the risk being almost three times

elevated. Unfortunately, they did not provide any further information on the observed psychoses (6).

6.2.5 Other morbidities

Many other comorbidities were prevalent in SLE cases as well, and for most of them, a higher risk was shown compared to population controls. The risks of other autoimmune diseases were increased, since hypothyroidism was more than three times and IBDs two times more likely in SLE patients than controls. The risks of diabetes mellitus (all types combined) and lipid metabolism disorders were also elevated as the risks were increased by approximately 50% for each. The risk of osteoporosis was noted as fivefold.

Compared to the results of Kuo et al., the results of the present study are somewhat different, which may result from differences in methods. They also found a two times higher risk for hypothyroidism, but no increased risk of diabetes. However, they divided the diabetes cases into uncomplicated and complicated forms. Therefore, one could speculate whether the risk of diabetes would have been increased if they had summed up all the diabetes types, as was done in the present work (6). Noteworthy, a Taiwanese nationwide study demonstrated that SLE cases had a 20% greater risk for developing type 2 diabetes within the first few years after SLE was diagnosed compared to controls (278). Also, significant insulin resistance was found in SLE by an early study (279). In addition, the risk of hyperlipidemia was not increased in the UK study, but a twofold risk for osteoporosis was found, which was slightly lower than in the present study (6).

The high rates of other autoimmune diseases in SLE can be explained by the autoimmune diathesis, which is a theory suggesting that people with autoimmune disorders have an elevated risk of other autoimmune disorders (305,306). Moreover, autoimmune diseases are often systemic, affecting the whole body, causing damage, and predisposing to other disorders and organ problems (16,114,133,218,271,307).

It is also likely that the use of GCs has a role in the coexistence of diabetes, lipid metabolism disorders, mental health concerns,

cardiovascular events, infections, myopathy, and osteoporosis in SLE (120,286,307).

However, it is also worth mentioning that a considerable bias may exist considering some of the diagnoses, as part of the studied morbidities, such as osteoporosis and type 2 diabetes, may be diagnosed solely in primary care and may never reach the attention of specialized care. Furthermore, no clinical data was at hand. Thereby, the reasons for susceptibility to multimorbidity could not be clarified in this study.

6.3 PSYCHOACTIVE DRUGS

6.3.1 General aspects on the use of antidepressants

This study illustrated that the quantity of new purchases of antidepressant medication was significantly larger among cases than controls both one year prior to and after the SLE diagnosis. Moreover, there were more new drug purchasers among SLE patients than controls through almost the entire follow-up. However, the proportions were only significantly higher among females. The risk of antidepressant use was doubled in SLE patients compared to controls.

Some studies have described the frequency of antidepressant use among SLE patients with quite variable results (18,151,242,243). In addition, it seems that only one study from Denmark by Hesselvig et al. has approached the matter with a control group (151). Thus, there is a considerable lack of studies considering the likelihood of using antidepressant drug therapy in SLE. Moreover, one must bear in mind that a significant bias may exist in studies that examine the number of prescribed drugs as the patients do not necessarily purchase them. Hence, drug consumption should be assessed by analyzing the actual purchases and not the prescriptions, as was done in the present and in the Danish study (151).

6.3.2 The risk of antidepressant use

Since the literature on antidepressant use is limited, the results of the current study on the risk of antidepressant use are difficult to compare. However, the present results are in line with the Danish study, which included both primary and specialized care patients. They demonstrated a HR of 1.7 for antidepressant use in recent-onset SLE. Moreover, they recorded period prevalence of 38% and 24% for antidepressant use in SLE patients and controls, respectively, which were nearly the same as in the present study (26% in SLE cases vs. 19% in controls). However, they also included patients with prior diagnosis of depression or antidepressant use in these analyses, but after exclusion of these patients, the HR for antidepressant use remained at 1.7. On the contrary, the authors reported that SLE males had higher risk for antidepressant use than females, with HRs of 2.2 and 1.6, respectively. The minor differences in risk compared to the present study may be explained by the differences in study design and methods (151).

6.3.3 The temporal variation of antidepressant use

Both the quantity and frequency of antidepressant use were already higher prior to SLE diagnosis. In addition, they increased after the diagnosis, but the difference seemed to disappear in five years compared to controls.

There are several factors that explain the temporal variation in antidepressant users. It is presumable that mental health concerns start earlier than the actual diagnosis of SLE is set, as patients may experience unexplainable symptoms, such as pain and anxiety, which may lead to mood disorders and increased antidepressant use. Moreover, some of the psychiatric symptoms may be manifestations of NPSLE, at least at the onset of SLE, as the same inflammatory factors have been found to contribute to the development of mental health concerns as inflammation overall in SLE (18,114,123,151,254,308). On the other hand, patients may feel depression and anxiety after hearing that they are diagnosed with a life-long disorder, which could explain the peak in antidepressant users right after SLE has been diagnosed. Also, some of the manifestations of

SLE, such as alopecia or arthritis, may predispose more strongly to mood disorders (151,242,243).

However, as the difference in antidepressant users diminished at the end of the observation time, it may be concluded that the therapy started for SLE had eased the mood disorders associated with SLE. Although speculative, the patients may have coped better with SLE during the following years as well.

Noteworthy, antidepressant use was also greater at the end of the observation than at the beginning of it among control population. This finding probably reflects the overall increase in the prevalence of depression in Finland over time. More specifically, in 2000, the prevalence of depressive disorders in Finland was 7.3% and in 2011, it rose to 9.6% (309). Similarly, a rising trend was recorded in antidepressant purchases according to Finnish statistics on medicine in the years 1995–2015 (310).

6.3.4 Sex differences and the use of antidepressants

The current study showed that the proportion of antidepressant purchasers was larger in females than males in SLE cases. Thus, it may be that females with SLE benefit more from antidepressants than males or may be more eager to use them.

On the other hand, as the same trend was also noted in the control group, it can be concluded that the matter does not only concern SLE females, but female sex universally (311,312). Other studies have noted that females seem to use more antidepressants in general, as females with new-onset rheumatoid arthritis were shown to use more antidepressants than males with the same condition in a Finnish study in the beginning of the 21st century (311). Moreover, a two times higher likelihood of antidepressant drug use was reported in females compared to males in an Italian nationwide study in 2012 (312). Although the issue is complex, it has been suggested that females may respond better to serotonergic antidepressants than males. Furthermore, they may have better adherence to antidepressants and may utilize medical care more frequently than males (313,314).

However, as there was no clinical data and the number of males was limited, no firm conclusions can be made on sex differences. Furthermore, a mood disorder does not always require antidepressant drug treatment (315).

6.3.5 The subgroups of antidepressants used

The most frequently used antidepressant group was selective serotonin reuptake inhibitors as nearly half of the purchases were of this type in both groups. No significant differences were found considering the purchases of other antidepressant types between the study groups either. These results are in line with the Finnish study in which citalopram was the most typically used antidepressant in new-onset rheumatoid arthritis patients (311).

It is a little surprising that serotonin reuptake inhibitors were so popular among SLE patients, as these drugs are in some cases known to prolong the QT interval of the heart, which may rarely lead to ventricular arrhythmias and sudden death. Furthermore, known risk factors for QT prolongation are renal function impairment, atrial fibrillation and heart failure (316-319).

The QT prolongation is a possible disadvantage of HCQ as well. Especially, the concurrent use of HCQ and escitalopram or citalopram has been suggested to be hazardous (316-318). However, the risk of QT prolongation may be exaggerated, as Renaldi et al. showed that the QT prolongation was only subclinical in patients with SLE using HCQ and concurrent use of HCQ and antidepressants did not affect the QT interval significantly. However, their sample size was small (319). To conclude, no significant risk of dangerous arrhythmias does not seem to exist, but it may be wise to follow the QT interval of SLE patients receiving these drugs, especially when other risk factors are present (286,316-319).

On the other hand, serotonin reuptake inhibitors have several advantages, such as being mostly harmless, simple to use, effective and having fewer side effects and interactions than other antidepressant types. These general features are likely to explain the popularity of these drugs also in SLE patients (320,321).

6.3.6 The use of antipsychotics

The proportions of antipsychotic purchasers in SLE cases were similar to controls, approximately 2.5% in both groups during the entire observation period. Hence, no significant differences were observed considering the use of antipsychotics.

Multiple studies have described the occurrence of NPSLE-related and GC-induced psychosis to be approximately a few percentages and not to exceed more than ten percent for each (149,251-253,255,256). NPSLE-related psychosis most often develops close to SLE diagnosis, manifesting within a couple of years (251,252,255). Furthermore, the risk of GC-induced psychosis is at its highest at the time of SLE diagnosis or flare when high doses of GCs are used (150,253,256,257). The risk of psychosis seems to be minor, the recurrence rate of psychotic symptoms is small, and development of chronic psychotic disorder is unlikely, as was also seen in the first study of this thesis (6,149,150,251,252,255).

Only a few studies have reported the use of antipsychotics in SLE. In these studies, most of the patients have needed antipsychotics, as psychotic symptoms are often difficult and disruptive (251,252,255,322). However, only one study from Thailand clarified the duration of the antipsychotic treatment, which was roughly two to three months (255). As psychotic symptoms seem to last a relatively short time, it may be more suitable to assess the prevalence of psychotic symptoms by exploiting drug purchases than by examining the psychotic disorder diagnoses set by physicians in SLE (252,255).

The results of the present study are not directly comparable to others, since there seem to be no comparative studies of antipsychotics use in SLE patients versus controls. Moreover, the antipsychotic drugs used in the hospital wards could not be included in the analyses. Therefore, the results do not cover the amount of antipsychotics used in inpatient care. Instead, they depict the need of long-term antipsychotic treatment in SLE. Furthermore, the indication of the drugs was not available, which likely caused minor bias as some of them may be used for other purposes, such as to treat sleeping difficulties (323).

However, the share of antipsychotic purchasers was small and quite similar to the occurrence of psychosis reported in many studies (251-255). In addition, as the purchasers of antipsychotics were studied close to the SLE diagnosis, it is presumable that the results cover most of the psychoses related to NPSLE (251-253). However, contrary to the results of Kuo et al., who reported a nearly three times higher relative risk of psychosis in SLE, no increased risk of using antipsychotics was observed between the groups (6). Although a slightly increased risk of psychotic disorders in SLE may exist, the present work indicates the rarity of developing a chronic and drug-demanding psychotic condition in SLE (6,150,252,255).

6.4 MALIGNANCIES AND SURVIVAL

The present study described a slightly elevated risk of any malignancy, and the number of malignancies increased steadily over time in SLE. Furthermore, greater risks of NHL and pancreatic cancer were found, and in females, the risk of NMSC was notable. There was also a trend of higher risk of lung cancer in SLE patients. On the contrary, neither cases of melanoma nor stomach cancer were detected among SLE patients. In addition, SLE cases with malignancy had a significantly lower survival rate than controls.

6.4.1 Malignancies

6.4.1.1 Malignancies of increased risk

Multiple studies have noted a somewhat greater relative risk for any malignancy in SLE compared to general population as the risks have been not more than three times elevated (9,213,219-222,225,227,229-231,237). Furthermore, considering only incident SLE studies, the risk has varied from 1.3- to 1.9-fold (219-221,225,237). In Finland, only one large study considering malignancy risk has been conducted previously. In this study by Tallbacka et al., newly-diagnosed SLE patients treated in the Helsinki University Central Hospital were followed for a mean of almost 26 years during 1967–2013. They discovered a SIR of 1.9 for any malignancy, and it

was comparable to most of the other studies carried out in the Nordic countries (219,220,225,237). On the contrary, only one study from Iceland has not reported a significantly increased risk for any malignancy. Although this Icelandic study was nationwide and provided almost 13 years of follow-up, the number of patients was only slightly over 200, which likely affected the results (228).

Only a few comprehensive studies have reported the IRs of malignancies overall. Of these, Rees et al., Bae et al. and Han et al. reported IRs of 14.8/1,000 pyrs, 6.4/1,000 pyrs and 13.8/1,000 pyrs for any malignancy, respectively (9,221,230).

In the present study, the overall malignancy risk was approximately 40% increased compared to controls, and an IR of 8.5/1,000 pyrs for any malignancy was found. These results are in line with other studies (9,213,219-221,225,227,229-231,237). On the other hand, the results of the present study are a little different than described in the first study of the thesis, where it was reported that the risk of malignancy was only nearly significant. The difference between these studies is explained by distinctions in study methods, as in the first study, diagnoses made in specialized care were examined, while the latter study evaluated diagnoses made in both primary and specialized care. Moreover, the follow-up time was longer in the latter study. Thus, the findings of the malignancy study confirm the slightly higher overall malignancy risk even in early SLE.

The slightly higher overall malignancy risk results from the fact that for some malignancies, SLE patients undeniably have a high risk, while for others, the risk is insignificant or even decreased compared to other population (9,213,219-222,225,227-231,237). SLE patients are prone to hematologic malignancies, in particular to NHL (9,213,219-221,222,225,227-232,237). The risk for hematologic malignancies has varied from two to nine times elevated, and for NHL, two to twelve times higher rates have been demonstrated in numerous studies (9,213,219-222,225,227-231,237). In the present study, hematologic malignancies overall were prevalent, but the risk was only almost significant, while for NHL the risk was five times increased compared to controls. The risk of NHL was less than reported in the other Finnish study (12 times increased), but otherwise it was at the

same level as described in other new-onset SLE studies (219,220,225,237). In addition, the IR for NHL (1.1/1,000 pyrs) was at the same level as in studies conducted in the UK and Korea, 0.8/1,000 pyrs and 0.6/1,000 pyrs, respectively (9,230).

The insignificant finding in hematologic malignancies overall is likely explained by the inclusion methods. In this category, NHLs and other lymphomas were not included, whereas other studies have included them (213,219,220,227,228,230). It is presumable that if lymphomas had been included, the risk of hematologic malignancies overall would have been increased as well.

The risk of NMSC is difficult to compare as some studies report only the number of skin cancers overall without specifying whether melanomas were included or not (221,227). Moreover, some studies have excluded certain skin cancer types, such as the Finnish study which excluded basal cell carcinomas (219,220). Thus, only a few studies have definitely analyzed the risk of NMSC (9,225,228,237). These studies have shown a possible, slightly elevated risk for this cancer type compared to general population. For example, the UK study by Rees et al. and the Swedish study by Björnådal et al. described almost significantly increased risks with SIRs 1.1 and 1.5, respectively (9,219). Noteworthy, the Swedish study excluded basaliomas (219). Furthermore, the large Danish study by Westermann et al. discovered a 30% increased risk, and the Icelandic study depicted a six times increased risk even though all the cancers were squamous cell by type (225,228). In the present study, the increased NMSC risk concerned only SLE females, and the risk was six times elevated, although the CI was wide.

Considering these results, SLE patients may be more prone to develop NMSC than other population. The reasons for the elevated risk are unknown, but the drug therapy used and some viruses may play a role (226,237,324). CYC has been found to increase the risk of NMSC, and AZA may also elevate the risk, although the data mostly comes from studies concerning IBDs (226,324). Furthermore, another Danish study reported a two times higher risk for NMSC compared to other population and pondered the role of HPV in the cancer development (237). However, a

considerable bias may exist as the skin of SLE patients is regularly followed at the rheumatology clinics, and some of the cancer incidents of controls may remain unrecognized. In addition, early recognition and treatment of actinic keratosis may prevent the development of NMSC (325).

The risk of pancreatic cancer was nearly four times elevated, but the CI was wide and only five cases were found among SLE patients, resulting in a low IR of 0.4/1,000 pyrs. However, the literature supports that an increased risk of pancreatic cancer may exist as the risk has varied from two to three times elevated compared to general population, although the number of pancreatic cancer cases has been low (9,225,227,230). On the other hand, several studies have not reported any significant difference in risk compared to general population, leaving the matter unclear (213,219-221,229).

6.4.1.2 Malignancies of decreased risk

Curiously, no melanomas were reported in SLE cases in contrast to 13 cases in controls. Likewise, no stomach cancers were observed among SLE cases compared to nine cases in controls.

The decreased melanoma risk has been reported before by the Californian study which discovered a 30% lower risk in SLE cases compared to controls (229). Moreover, the Swedish study found a SIR of 0.4, which was almost significant (95% CI 0.14–1.01), but four other studies have reported no difference compared to general population (9,213,219,220,225). Likely reasons for the possibly decreased melanoma risk are avoidance of sun and use of sunscreen, as SLE patients are photosensitive and urged to avoid excessive sun exposure (80,81,236,281).

Contrary to the results of the present study, previous studies have mostly found neither increased nor decreased risk of stomach cancer in SLE (213,219-221,229,230). In addition, Bae et al. reported a relatively low IR of 0.3/1,000 pyrs (221). In conclusion, it appears that the risk of stomach cancer in SLE is at least not increased.

6.4.1.3 Malignancies of indeterminate risk

For some of the malignancies, SLE patients were shown to have neither increased nor decreased risk. However, for some malignancies, such as lung cancer, the risk might have been significant if the study sample had been larger. Moreover, some of the site-specific malignancy types were included in larger groups to increase the power of the analyses, which makes it impossible to compare some of the risks to other studies.

Lung cancer is one of the most common malignancy types reported in SLE. Several studies have described the risk varying from 30% to three times elevated compared to general population (9,213,219,221,225,229,230). Similarly, in the present study, SLE cases were two times more likely to develop lung cancer, but the risk was statistically insignificant. Smoking is thought to be the most crucial risk factor in lung cancer development, and the risk seems to be dose-dependent (226,231,235). Thus, it is important to urge SLE patients to avoid smoking (235). In future studies, it will be interesting to see whether lung cancer risk decreases as the prevalence of smoking is reduced over time.

The present study confirms the results of many other studies that no elevated risk of breast or prostate cancer exists in SLE, although they were the most prevalent single malignancy types in SLE females and males, respectively (9,213,219-221,225,228,229). The finding also supports the theory that the risk of hormone-sensitive cancers is decreased or does not differ from general population (213,218,219).

The present study could not clarify the risk of site-specific malignancies of gynecological origin as only sporadic cases were detected, similarly to the other Finnish study (220). However, the present study supports the results of the Swedish study, as no elevated risk of gynecological malignancies overall was found (219). Previous studies have shown mixed results, but it seems that SLE patients may be prone to HPV-associated gynecological malignancies, such as vulvar/vaginal cancer and cervical cancer (213,221,227,229,231). On the other hand, the study from California suggested a reduced risk of cervical cancer compared to general population (229). Moreover, SLE patients seem to be susceptible to cervical dysplasia, especially when immunosuppressants are used. However,

thanks to enhanced screening, the dysplasia changes may be detected earlier, preventing the development of cancer in some cases (237,238,326,327). Thus, the extensive and frequent cervical screening in Finland may have reduced the number of gynecological malignancies in the present study (328). Furthermore, it is probable that in the future, the rate of HPV-associated malignancies will diminish as the HPV vaccination has been included in the national vaccination program in Finland since 2013 (327,329,330).

6.4.2 The survival of patients with SLE and a malignancy

The likelihood of survival was markedly worse in SLE cases with malignancy than in controls. The adjusted 15-year survival was half of that of controls, and the risk of death was 70% higher in SLE cases. Malignancy was the most typical underlying cause of death in both SLE cases and controls.

It has been shown that the leading causes of death in SLE are CVDs, infections, renal disease, malignancies and SLE itself, while malignancies in general do not predispose SLE patients to premature death, apart from certain individual malignancy types such as NHL and lung cancer (7,8,293-295).

However, the present study showed that the survival of SLE cases may be decreased when a malignancy co-occurs with SLE. This result is supported by the study by Bruera et al., which reported decreased survival when SLE and breast cancer co-existed, compared to just one of them (12). Furthermore, Bultink et al. reported increased all-cause mortality among SLE patients who had been diagnosed with malignancy earlier (8).

One likely reason for the decreased survival is that the management of patients becomes more challenging when these two conditions occur concurrently (12,216). The study by Bruera et al. showed that females with breast cancer and SLE were given less GCs, antimalarial and immunosuppressive drugs and biologics than those with only SLE after cancer was diagnosed. Moreover, SLE cases with breast cancer were more rarely given radiation and endocrine therapy while the number of mastectomies was higher (12).

Thus, SLE often requires immunosuppressive therapy, and cytotoxic agents and radiation are used to restrain cancer from growing and to kill cancer cells (216,281,331,332). The immunosuppressive and cytotoxic drugs used for SLE and malignancy may increase the risk of infection and death (281,286,307,331). In addition, some chemotherapies expose patients to increased cardiovascular morbidity and mortality (333). Other comorbidities may also complicate the management of both SLE and malignancy, increasing the risk of death (6,12,281,293,331). There have also been concerns as to whether radiation therapy exacerbates SLE, although these concerns seem to be exaggerated (332).

To conclude, there may be situations where treatment options are limited and both SLE and malignancy cannot be managed properly at the same time. This may on some occasions lead to increased mortality.

6.5 FUTURE IMPLICATIONS

The studies of this thesis confirmed that SLE patients are prone to several comorbidities also in Finland. Rheumatologists and other clinicians managing SLE should be aware of the possibility of these comorbidities and screen for them, as they have been shown to have detrimental effects on the management, survival, quality of life and working ability of SLE patients (6,8-15,293). Moreover, enhanced risk assessment tools should be developed to ease the screening, and SLE patients should be treated in a holistic way at the clinics (281,303). As this may be demanding, guidelines for screening and management of comorbidities should be developed to simplify decision-making (6,12,303). Furthermore, patients with multiple severe comorbidities should be managed by a multidisciplinary team including several professionals, as they are high-risk patients. It might also be appropriate to centralize the managament of some severe and rare SLE forms to one or a few consultation center(s) in Finland.

This thesis did not concentrate on the issue of infections in SLE in Finland. In future studies, it is necessary to study the risk of infections in Finnish SLE patients as they are known to complicate the management of the disease and increase mortality (7,8,187,281,294,295). It would also be

interesting to evaluate the antibiotic choices and vaccination coverage in relation to infections (281).

Moreover, the epidemiology of LN is unclear, and the prevalence and incidence of NPSLE in Finland need clarification (149). The genetics and pathophysiology of SLE should also be clarified to provide more tailored and effective management for patients and to prevent the harms of unnecessary medication.

It is noteworthy that the number of males was limited in the studies of this thesis, as has been the case in many other studies as well. Thus, no definitive conclusions could be made considering males with SLE. To tackle this problem, it would be wise to share data with other countries, at least between the Nordic countries.

It is also important to note that it is sometimes difficult to separate a manifestation of SLE from a comorbid condition. With accumulating knowledge, it may be that some of the comorbidities may actually be considered as manifestations of SLE or vice versa in the future (6,25).

Most importantly, the studies of this thesis lacked clinical data. Thereby, the factors behind the multimorbidity could not be unraveled. Longer follow-ups with clinical data are needed, because they would also help to assess the pros and cons of SLE drug therapies considering comorbidities, such as malignancy, infections, osteoporosis, and CVD development. Fortunately, the Finnish Rheumatology Quality Register has come into effect on Jan 1, 2023 (334). With help of this register, it is possible to create high-quality studies that may answer to these questions in the future.

7 CONCLUSIONS

I Finnish SLE patients have a considerable risk of several comorbidities. Particulary, the occurrence and risk of CVDs, renal diseases, mood disorders and certain malignancies are notable, which is important to note when treating SLE in a holistic way.

II SLE patients in Finland use more antidepressants than general population before but also after the SLE diagnosis, while no difference seems to exist in the use of antipsychotics. These findings indicate that SLE patients may have significant mood disorders already at the time when SLE is diagnosed, whereas chronic psychotic disorders that require long-lasting antipsychotic treatment occur only occasionally in SLE.

III The risk of certain malignancies is increased in SLE. These malignancies include in particular hematological malignancies, such as NHL. SLE patients seem to have higher risk of lung cancer and NMSC than general population as well. Furthermore, the co-existence of malignancy and SLE appears to increase mortality. Thus, it is crucial to be aware of and search for these high-risk malignancies with a low threshold to enable early recognition and treatment.

REFERENCES

1 Tamirou F, Arnaud L, Talarico R et al. Systemic lupus erythematosus: state of the art on clinical practice guidelines. RMD Open 2018; 4: e000793.

2 Cervera R, Doria A, Amoura Z, et al. Patterns of systemic lupus erythematosus expression in Europe. Autoimmun Rev. 2014; 13: 621–629

3 Cervera R, Khamashta MA, Hughes GRV. The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. Lupus 2009; 18: 869–874.

4 Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford) 2017; 56: 1945–1961.

5 Uramoto KM, Michet Jr CJ, Thumboo J, Sunku J, O'Fallon WM, Gabriel SE. Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. Arthritis Rheum 1999; 42: 46–50.

6 Kuo CF, Chou IJ, Rees F, et al. Temporal relationships between systemic lupus erythematosus and comorbidities. Rheumatology (Oxford) 2019; 58: 840–848.

7 Tselios K, Gladman DD, Sheane BJ, Su J, Urowitz M. All-cause, cause specific and age specific standardized mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013). Ann Rheum Dis 2019; 78: 802–806.

8 Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. Rheumatology (Oxford) 2021; 60: 207–216.

9 Rees F, Doherty M, Grainge M, Lanyon P, Davenport G, Zhang W. Burden of Comorbidity in Systemic Lupus Erythematosus in the UK, 1999-2012. Arthritis Care Res (Hoboken) 2016; 68: 819–827.

10 Arnaud L, Tektonidou MG. Long-term outcomes in systemic lupus erythematosus: trends over time and major contributors. Rheumatology (Oxford) 2020; 59: 29–38.

11 Greenstein L, Makan K, Tikly M. Burden of comorbidities in South Africans with systemic lupus erythematosus. Clin Rheumatol 2019; 38: 2077–2082.

12 Bruera S, Lei X, Pundole X et al. Systemic Lupus Erythematosus is a Risk Factor for Mortality in Elderly Patients with Early Breast Cancer. Arthritis Care Res (Hoboken) 2023; 75: 559–568.

13 Al Dhanhani AM, Gignac MA, Su J, Fortin PR. Work disability in systemic lupus erythematosus. Arthritis Rheum 2009; 61: 378–385.

14 Elfving P, Puolakka K, Rantalaiho V, Kautiainen H, Virta LJ, Kaipiainen-Seppänen O. Impact of early systemic lupus erythematosus on work disability -results from the Finnish nationwide register 2000-2007. Clin Rheumatol 2018; 37: 1413–1416.

15 Julian LJ, Yelin E, Yazdany J et al. Depression, Medication Adherence, and Service Utilization in Systemic Lupus Erythematosus. Arthritis Rheum 2009; 61: 240–246.

16 Hermansen ML, Lindhardsen J, Torp-Pedersen, Faurschou M, Jacobsen S. The risk of cardiovascular morbidity and cardiovascular mortality in systemic lupus erythematosus and lupus nephritis: a Danish nationwide population-based cohort study. Rheumatology (Oxford) 2017; 56: 709–715.

17 Dietz B, Katz P, Dall'Era M et al. Major Depression and Adverse Patient-Reported Outcomes in Systemic Lupus Erythematosus: Results From a Prospective Longitudinal Cohort. Arthritis Care Res (Hoboken) 2021; 73: 48–54.

18 Hanly JG, Su L, Urowitz MB et al. Mood Disorders in Systemic Lupus Erythematosus: Results From an International Inception Cohort Study. Arthritis Rheumatol 2015; 67: 1837–1847.

19 Smith CD, Cyr M. The history of lupus erythematosus. From Hippocrates to Osler. Rheum Dis Clin North Am 1988; 14: 1–14.

20 Mallavarapu RK, Grimsley EW. The history of lupus erythematosus. South Med J 2007; 100: 896–898.

21 Tan EM, Cohen AS, Fries JF. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271–1277

22 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arhritis Rheum 1997; 40: 1725.

23 Feletar M, Ibañez D, Urowitz MB, Gladman DD. The impact of the 1997 update of the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus: what has been changed? Arthritis Rheum 2003; 48: 2067–2069.

24 Petri M, Orbai AM, Alarcón GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64: 2677–2686.

25 Aringer M, Costenbader K, Daikh D et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol 2019; 71: 1400–1412.

26 Pons-Estel GJ, Alarcón GS. How well do the new classification criteria for SLE perform? Nat Rev Rheumatol 2021; 17: 7–8.

27 Aggarwal R, Ringold S, Khanna D et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res (Hoboken) 2015; 67: 891–897.

28 Ahlbom A. Epidemiology is about disease in populations. Eur J Epidemiol 2020; 35: 1111–1113.

29 Elfving P, Puolakka K, Kautiainen H, Virta LJ, Pohjolainen T, Kaipiainen-Seppänen O. Incidence of systemic lupus erythematosus in Finland, 2000-2007, a nationwide study. Clin Exp Rheumatol 2014; 32: 953–955.

30 Shim JS, Sung YK, Joo YB, Lee HS, Bae SC. Prevalence and incidence of systemic lupus erythematosus in South Korea. Rheumatol Int 2014; 34: 909–917.

31 Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012. Ann Rheum Dis 2016; 75: 136–141.

32 Pamuk ON, Balci MA, Donmez S, Tsokos GC. The incidence and prevalence of systemic lupus erythematosus in Thrace, 2003-2014: A 12-year epidemiological study. Lupus 2016; 25: 102–109.

33 Hermansen ML, Lindhardsen J, Torp-Pedersen, Faurschou M, Jacobsen S. Incidence of Systemic Lupus Erythematosus and Lupus Nephritis in Denmark: A Nationwide Cohort Study. J Rheumatol 2016; 43: 1335–1339.

34 Feldman CH, Hiraki LT, Liu J. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum 2013; 65: 753–763.

35 Arnaud L, Fagot JP, Mathian A, Paita M, Fagot-Campagna A, Amoura Z. Prevalence and incidence of systemic lupus erythematosus in France: A 2010 nationwide population-based study. Autoimmun Rev 2014; 13: 1082–1089.

36 Chiu YM, Lai CH. Nationwide population-based epidemiologic study of systemic lupus erythematosus in Taiwan. Lupus 2010; 19: 1250–1255.

37 Hopkinson ND, Doherty M, Powell RJ. Clinical features and race-specific incidence/prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients. Ann Rheum Dis 1994; 53: 675–680.

38 Izmirly PM, Wan I, Sahl S. The Incidence and Prevalence of Systemic Lupus Erythematosus in New York County (Manhattan), New York: The Manhattan Lupus Surveillance Program. Arthritis Rheumatol 2017; 69: 2006–2017.

39 Gergianaki I, Fanouriakis A, Repa A et al. Epidemiology and burden of systemic lupus erythematosus in a Southern European population: data from the community-based lupus registry of Crete, Greece. Ann Rheum Dis 2017; 76: 1992–2000.

40 Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970-1977. Arthritis Rheum 1985; 28: 80–86.

41 Naleway AL, Davis ME, Greenlee RT, Wilson DA, McCarty DJ. Epidemiology of systemic lupus erythematosus in rural Wisconsin. Lupus 2005; 14: 862–866.

42 Kwak SG, Park SH, Kim JY. Incidence and Prevalence of Juvenile Systemic Lupus Erythematosus in Korea: Data From the 2017 National Health Claims Database. J Rheumatol 2021; 48: 258–261.

43 Fatoye F, Gebrye T, Svenson LW. Real-world incidence and prevalence of systemic lupus erythematosus in Alberta, Canada. Rheumatol Int 2018; 38: 1721–1726.

44 Helve T. Prevalence and mortality rates of systemic lupus erythematosus and causes of death in SLE patients in Finland. Scand J Rheumatol 1985; 14: 43–46.

45 Crispin JC, Liossis SNC, Kis-Toth K et al. Pathogenesis of human systemic lupus erythematosus: recent advances. Trends Mole Med 2010; 16: 47–57.

46 Rullo OJ, Tsao BP. Recent insights into the genetic basis of systemic lupus erythematosus. Ann Rheum Dis 2013; 72: 56–61.

47 Ha E, Bae SJ, Kim K. Recent advances in understanding the genetic basis of systemic lupus erythematosus. Semin Immunopathol 2022; 44: 29–46.

48 Tsokos GC, Lo MS, Costa Reis P, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nat Rev Rheumatol 2016; 12: 716–730.

49 Kuo CF, Grainge MJ, Valdes AM et al. Familial Aggregation of Systemic Lupus Erythematosus and Coaggregation of Autoimmune Diseases in Affected Families. JAMA Intern Med 2015; 175: 1518–1526.

50 Ulff-Møller CS, Svendsen AJ, Viemose LN, Jacobsen S. Concordance of autoimmune disease in a nationwide Danish systemic lupus erythematosus twin cohort. Semin Arthritis Rheum 2018; 47: 538–544

51 Koskenmies S, Widen E, Kere J, Julkunen H. Familial systemic lupus erythematosus in Finland. J Rheumatol 2001; 28: 758–760.

52 Demirkaya E, Sahin S, Romano M, Zhou Q, Aksentijevich I. New Horizons in the Genetic Etiology of Systemic Lupus Erythematosus and Lupus-Like Disease: Monogenic Lupus and Beyond. J Clin Med 2020; 9: 712.

53 Botto M, Walport MJ. C1q, autoimmunity and apoptosis. Immunobiology 2002; 205: 395–406.

54 Stegert M, Bock M, Trendelenburg M. Clinical presentation of human C1q deficiency: How much of a Lupus? Molecular Immunology 2015; 67: 3–11.

55 Xiao G, Zuo X. Epigenetics in systemic lupus erythematosus. Biomedical Reports 2016; 4: 135–139.

56 Costenbader KH, Gay S, Alarcón-Riquelme ME, Iaccarino L, Doria A. Genes, epigenetic regulation and environmental factors: Which is the most relevant in developing autoimmune diseases? Autoimmun Rev 2012; 11: 604–609.

57 Zhao M, Wang Z, Yung S, Lu Q. Epigenetic dynamics in immunity and autoimmunity. The International Journal of Biochemistry & Cell Biology 2015; 67: 65–74.

58 Richardson B, Scheinbart L, Strahler J, Gross L, Hanash S, Johnson M. Evidence for impaired T cell DNA methylation in systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 1990; 33: 1665–1673.

59 Jefrries M, Dozmorov M, Tang Y, Merril JT, Wren JD, Sawalha AH. Genome-wide DNA methylation patterns in CD4+ T cells from patients with systemic lupus erythematosus. Epigenetics 2011; 6: 593–601.

60 Yung R, Chang S, Hemati N, Johnson K, Richardson B. Mechanisms of drug-induced lupus. IV. Comparison of procainamide and hydralazine with analogs in vitro and in vivo. Arthritis Rheum 1997; 40: 1436–1443.

61 Long H, Yin H, Wang L, Gershwin ME, Lu Q. The critical role of epigenetics in systemic lupus erythematosus and autoimmunity. J Autoimmun 2016; 74: 118–138.

62 Pan W, Zhu S, Yuan M et al. MicroRNA-21 and microRNA-148a contribute to hypomethylation in lupus CD4+ T cells by directly and indirectly targeting DNA methyltransferase 1. J Immunol 2010; 184: 6773–6781.

63 Khan D, Dai R, Ahmed SA. Sex differences and estrogen regulation of miRNAs in lupus, a prototypical autoimmune disease. Cell Immunol 2015; 294: 70–79.

64 Tsai CY, Shen CY, Liu CW et al. Aberrant Non-Coding RNA Expression in Patients with Systemic Lupus Erythematosus: Consequences for Immune Dysfunctions and Tissue Damage. Biomolecules 2020; 10: 1641.

65 Nusbaum JS, Mirza I, Shum J et al. Sex Differences in Systemic Lupus Erythematosus: Epidemiology, Clinical Considerations, and Disease Pathogenesis. Mayo Clin Proc 2020; 95: 384–394.

66 Di D, Yan H, Zhang L et al. X chromosome and female bias in systemic lupus erythematosus: Focus on population-based evidence. Autoimmun Rev 2019; 18: 109–111.

67 Scofield RH, Bruner GH, Namjou M et al. Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus: support for the notion of a gene-dose effect from the X chromosome. Arthritis Rheum 2008; 58: 2511–2517.

68 Youness A, Miquel CH, Guéry JC. Escape from X Chromosome Inactivation and the Female Predominance in Autoimmune Diseases. Int J Mol Sci. 2021; 22: 1114

69 Kaufman KM, Zhao J, Kelly JA. Fine mapping of Xq28: both MECP2 and IRAK1 contribute to risk for systemic lupus erythematosus in multiple ancestral groups. Ann Rheum Dis 2013; 72: 437–444.

70 Hewagama A, Gorelik G, Patel D. Overexpression of X-linked genes in T cells from women with lupus. J Autoimmun 2013; 41: 60-71.

71 Petri M. Sex hormones and systemic lupus erythematosus. Lupus 2008; 17: 412–415.

72 Lahita RG. The immunoendocrinology of systemic lupus erythematosus. Clinical Immunology 2016; 172: 98–100.

73 Costenbader KH, Feskanich D, Stampfer MJ, Karlson EW. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. Arthritis Rheum 2007; 56: 1251–1262.

74 Petri M, Kim MY, Kalunian KC. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005; 353: 2550–2558.

75 Buyon JP, Petri MA, Kim MY. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005; 142: 953–962.

76 Illescas-Montes R, Corona-Castro CC, Melguizo-Rodríguez L, Ruiz C, Costela-Ruiz VJ. Infectious processes and systemic lupus erythematosus. Immunology 2019; 158: 153–160.

77 James JA, Neas BR, Moser KL et al. Systemic lupus erythematosus in adults is associated with previous Epstein-Barr virus exposure. Arthritis Rheum 2001; 44: 1122–1126.

78 Barbhaiya M, Costenbader KH. Environmental exposures and the development of systemic lupus erythematosus. Curr Opin Rheumatol 2016; 28: 497–505.

79 Barbhaiya M, Costenbader KH. Ultraviolet radiation and systemic lupus erythematosus. Lupus 2014; 23: 588–595.

80 Sanders CJG, Van Weelden H, Kazzaz GAA, Sigurdsson V, Toonstra J, Bruijnzeel-Koomen CAFM. Photosensitivity in patients with lupus erythematosus: a clinical and photobiological study of 100 patients using a prolonged phototest protocol. Br J Dermatol 2003; 149: 131–137.

81 Hasan T, Pertovaara M, Yli-Kerttula U, Luukkaala T, Korpela M. Seasonal variation of disease activity of systemic lupus erythematosus in Finland: a 1-year follow-up study. Ann Rheum Dis; 2004: 63: 1498–1500.

82 Bengtsson AA, Rylander L, Hagmar L, Nived O, Sturfelt G. Risk factors for developing systemic lupus erythematosus: a case-control study in southern Sweden. Rheumatology 2002; 41: 563–571.

83 Fraser PA, Ding W, Mohseni M, et al. Glutathione S-transferase M null homozygosity and risk of systemic lupus erythematosus associated with sun exposure: a possible gene-environment. J Rheumatol 2003; 30: 276–282.

84 Amital H, Szekanecz Z, Szücs et al. Serum concentrations of 25-OH vitamin D in patients with systemic lupus erythematosus (SLE) are inversely related to disease activity: is it time to routinely supplement patients with SLE with vitamin D? Ann Rheum Dis 2010; 69: 1155–1157.

85 Borba VZC, Vieira JGH, Kasamtasu T, Radominski SC, Sato EI, Lazaretti-Castro M. Vitamin D deficiency in patients with active systemic lupus erythematosus. Osteoporos Int 2009; 20; 427–433.

86 Ghaussy NO, Sibbitt WL, Qualls CR. Cigarette smoking, alcohol consumption and the risk of systemic lupus erythematosus: a case-control study. J Rheumatol 2001; 28: 2449–2453.

87 Costenbader KH, Kim DJ, Peerzada J. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. Arthritis Rheum 2004; 50: 849–857.

88 He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. Curr Opin Rheumatol 2018; 30: 490–497.

89 Xiao X, Chang C. Diagnosis and classification of drug-induced autoimmunity (DIA). J Autoimmun 2014; 48-49: 66–72.

90 Goulielmos GN, Zervou MI, Vazgiourakis VM. The genetics and molecular pathogenesis of systemic lupus erythematosus (SLE) in populations of different ancestry. Gene 2018; 668: 59–72.

91 Rekvig OP, Van der Vlag J. The pathogenesis and diagnosis of systemic lupus erythematosus: still not resolved. Semin Immunopathol 2014; 36: 301–311.

92 Biermann MHC, Veissi S, Maueröder C et al. The role of dead cell clearance in the etiology and pathogenesis of systemic lupus erythematosus: dendritic cells as potential targets. Expert Rev Clin Imnunol 2014; 10: 1151–1164.

93 Pan L, Lu MP, Wang JH, Xu M, Yang SR. Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr 2020; 16: 19–30.

94 Davis LS, Hutcheson J, Mohan C. The role of cytokines in the pathogenesis and treatment of systemic lupus erythematosus. J Interferon Cytokine Res 2011; 31: 781–789.

95 Papadimitraki ED, Choulaki C, Koutala E et al. Expansion of toll-like receptor 9-expressing B cells in active systemic lupus erythematosus: implications for the induction and maintenance of the autoimmune process. Arthritis Rheum 2006; 54: 3601–3611.

96 Lauková L, Konečná B, Janovičová L, Vlková B, Celec P. Deoxyribonucleases and Their Applications in Biomedicine. Biomolecules 2020; 10: 1036.

97 Crispin JC, Hedrich CM, Suarez-Fueyo A, Comte D, Tsokos GC. SLE-Associated Defects Promote Altered T Cell Function. Crit Rev Immunol 2017; 37: 39–58.

98 Möckel T, Basta F, Weinmann-Menke J, Schwarting A. B cell activating factor (BAFF): Structure, functions, autoimmunity and clinical implications in Systemic Lupus Erythematosus (SLE). Autoimmun Rev 2021; 20: 102736.

99 Wang L, Zhao P, Ma L, Shan Y, Jiang Z, Wang J et al. Increased interleukin 21 and follicular helper T-like cells and reduced interleukin 10+ B cells in patients with new-onset systemic lupus erythematosus. J Rheumatol 2014; 41: 1781–1792.

100 Pisetsky DS, Lipsky PE. New insights into the role of antinuclear antibodies in systemic lupus erythematosus. Nat Rev Rheumatol 2020; 16: 565–579.

101 Pisetsky DS. Evolving story of autoantibodies in systemic lupus erythematosus. J Autoimmun 2020; 110: 102356.

102 Arbuckle MR, McClain MT, Rubertone MV et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003; 349: 1526–1533.

103 Kurien BT, Scofield RH. Autoantibody determination in the diagnosis of systemic lupus erythematosus. Scand J Immunol 2006; 64: 227-235.

104 Li QZ, Karp DR, Quan J. Risk factors for ANA positivity in healthy persons. Arthritis Res. Ther. 2011; 13: R38

105 Wang X, Xia Y. Anti-double Stranded DNA Antibodies: Origin, Pathogenicity, and Targeted Therapies. Front. Immunol. 2019; 10: 1667.

106 Orme ME, Voreck A, Aksouh R, Ramsay-Goldman R, Schreurs MWJ. Systematic review of anti-dsDNA testing for systemic lupus erythematosus: A meta-analysis of the diagnostic test specificity of an anti-dsDNA fluorescence enzyme immunoassay. Autoimmun Rev 2021; 20: 102943.

107 Nahal SK, Selmi C, Gershwin ME. Safety issues and recommendations for successful pregnancy outcome in systemic lupus erythematosus. J Autoimmun 2018; 93: 16–23.

108 Miglioniri P, Baldini C, Rocchi V, Bombardieri S. Anti-Sm and anti-RNP antibodies. Autoimmun 2005; 38: 47–54.

109 Svenungsson E, Antovic A. The antiphospholipid syndrome – often overlooked cause of vascular occlusions? J Intern Med 2020; 287: 349–372

110 Trendelenburg M. Autoantibodies against complement component C1q in systemic lupus erythematosus. Clin Transl Immunology 2021; 10: e1279.

111 Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. Autoimmunity 2007; 40: 560–566.

112 Lech M, Anders HJ. The pathogenesis of lupus nephritis. J AM Soc Nephrol 2013; 24: 1357–1366.

113 Weinstein A, Alexander RV, Zack DJ. A review of complement activation in SLE. Curr Rheumatol Rep 2021; 23: 16.

114 Kiriakidou M, Ching CL. Systemic Lupus Erythematosus. Ann Intern Med 2020; 172: 81–96.

115 Ugarte-Gil MF, Pimentel-Quiroz VR, Vilá LM, Reveille JD, McGwin G, Alarcón GS. Factors associated with disease expression patterns in systemic lupus erythematosus: results from LUMINA (LXXVII), a multiethnic US cohort. Lupus 2017; 26: 650–655.

116 Uribe AG, McGwin G, Reveille JD, Alarcón GS. What have we learned from a 10-year experience with LUMINA (Lupus in Minorities; Nature vs nurture) cohort? Where are we heading? Autoimmun Rev 2004; 3: 321–329.

117 Bruce IN, O'Keeffe A, Farewell V et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis 2015; 74: 1706–1713.

118 Tan TC, Fang H, Magder LD, et al. Differences between male and female systemic lupus erythematosus in a multiethnic population. J Rheumatol 2012; 39: 759–769.

119 Fernández M, Alarcón GS, Calvo-Alén J e al. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. Arthritis Rheum 2007; 57: 576–584.

120 Tarr T, Papp G, Nagy N, et al. Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens

disease outcome in systemic lupus erythematosus. Clin Rheumatol 2017; 36: 327–333.

121 Medhat BM, Behiry ME, Sobhy N et al. Late-onset systemic lupus erythematosus: characteristics and outcome in comparison to juvenile- and adult-onset patients -a multicenter retrospective cohort. Clin Rheumatol 2020; 39: 435–442.

122 Cervera R, Khamashta MA, Font J. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 1993; 72: 113–124.

123 Sebastiani GD, Prevete I, Piga M et al. Early Lupus Project – A multicentre Italian Study on systemic lupus erythematosus of recent onset. Lupus 2015; 24: 1276–1282

124 Cleanthous S, Tyagi M, Isenberg DA, Newman SP. What do we know about self-reported fatigue in systemic lupus erythematosus? Lupus 2012; 21: 465–476.

125 Pipili C, Sfritzeri A, Cholongitas E. Deforming arthropathy in systemic lupus erythematosus. Eur J Intern Med. 2008; 19: 482–487

126 Santiago MB, Galvão V. Jaccoud arthropathy in systemic lupus erythematosus: analysis of clinical characteristics and review of the literature. Medicine (Baltimore) 2008; 87: 37–44.

127 Walling HW, Sontheimer RD. Cutaneus lupus erythematosus: issues in diagnosis and treatment. Am J Clin Dermatol 2009; 10: 365–381.

128 Obermoser G, Sontheimer SD, Zelger B. Overview of common, rare and atypical manifestations of cutaneus lupus erythematosus and histopathological correlates. Lupus 2010; 19: 1050–1070.

129 Ribero S, Sciascia S, Borradori L, Lipsker S. The Cutaneus Spectrum of Lupus Erythematosus. Clinic Rev Allerg Immunol 2017; 53: 291–305.

130 Fayyaz A, Igoe A, Kurien BT et al. Haematological manifestations of lupus. Lupus Sci Med 2015; 2: e000078.

131 Newman K, Owlia MB, El-Hemaidi I, Akhtari M. Management of immune cytopenias in patients with systemic lupus erythematosus – Old and new. Autoimmin Rev 2013; 12: 784–791.

132 Carli L, Tani C, Vagnani S, Signorini V, Mosca M. Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact–A systematic literature review. Semin Arthritis Rheum 2015; 45: 190–194.

133 Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A. The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimmun 2017; 76: 10–20.

134 İlgen U, Yayla ME, Ateş A, et al. Antiphospholipid antibodies and non-thrombotic manifestations of systemic lupus erythematosus. Lupus 2018; 27: 665-669.

135 García MA, Alarcón GS, Boggio G et al. Primary cardiac disease in systemic lupus erythematosus patients: protective and risk factors–data from a multi-ethnic Latin American cohort. Rheumatology (Oxford) 2014; 53: 1431–1438.

136 Lopez Velazquez M, Highland KB. Pulmonary manifestations of systemic lupus erythematosus and Sjögren syndrome. Curr Opin Rheumtol 2018; 30: 449–464.

137 Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. J Clin Gastroenterol 2011; 45: 436–441.

138 Li Z, Xu D, Wang Y. Gastrointestinal system involvement in systemic lupus erythematosus. Lupus. 2017; 26: 1127–1138.

139 Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. Clin J Am Soc Nephrol 2017; 12: 825–835.

140 Gasparotto M, Gatto M, Binda V, Doria A, Moroni G. Lupus nephritis: clinical presentations and outcomes in the 21st century. Rheumatology (Oxford) 2020; 59: 39–51.

141 Mahajan A, Amelio J, Gairy K. Systemic lupus erythematosus, lupus nephritis, and end-stage renal disease: a pragmatic review mapping disease severity and progression. Lupus 2020; 29: 1011–1020.

142 Misra R, Gupta R. Biomarkers in lupus nephritis. Int J Rheum Dis 2015; 18: 219–232.

143 Weening JJ, D'Agati VD, Schwartz MM. The classification of glomerulonephritis on systemic lupus erythematosus revisited. Kidney Int 2004; 65: 521–530.

144 Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int 2018; 93: 789–796.

145 Oliva-Damaso N, Payan J, Oliva-Damaso E, et al. Lupus Podocytopathy: An Overview. Adv Chronic Kidney Dis 2019; 26: 369–375.

146 Sarwar S, Mohamed AS, Rogers S et al. Neuropsychiatric Systemic Lupus Erythematosus: A 2021 Update on Diagnosis, Management, and Current Challenges. Cureus 2021; 13: e17969.

147 Liang MH, Corzillius M, Bae SC et al. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42: 599–608.

148 Ahn Gy, Kim D, Won S, et al. Prevalence, risk factors, and impact on mortality of neuropsychiatric lupus: a prospective, single-center study. Lupus 2018; 27: 1338–1347.

149 Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology 2001; 57: 496–500.

150 Bertsias GK, Ioannidis JPA, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010; 69: 2074–2082.

151 Hesselvig JH, Egeberg A, Kofoed K, Gislason G, Dreyer L. Increased risk of depression in patients with cutaneous lupus erythematosus and systemic lupus erythematosus: a Danish nationwide cohort study. Br J Dermatol 2018; 179: 1095–1101.

152 Albrecht K, Redeker I, Aringer M, et al. Comorbidity and healthcare utilisation in persons with incident systemic lupus erythematosus followed for 3 years after diagnosis: analysis of a claims data cohort. Lupus Sci Med 2021; 8: e000526.

153 Sciatti E, Cavazzana I, Vizzardi E et al. Systemic Lupus Erythematosus and Endothelial Dysfunction: A Close Relationship. Curr Rheumatol Rev 2019; 15: 177–188.

154 Bernatsky S, Ramsey-Goldman R, Joseph L, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. Ann Rheum Dis 2014; 73: 138–142.

155 Klein A, Polliack A, Gafter-Gvili A. Systemic lupus erythematosus and lymphoma: Incidence, pathogenesis and biology. Leuk Res 2018; 75: 45–49.

156 Golder V, Kandane-Rathnayake R, Hoi AY, et al. Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. Arthritis Res Ther 2017; 19: 62.

157 Frostegård J. Systemic lupus erythematosus and cardiovascular disease. J Intern Med 2023; 293: 48–62.

158 Schanberg LE, Sandborg C, Barnhart HX. Premature atherosclerosis in pediatric systemic lupus erythematosus: Risk factors for increased carotid intima-media thickness in the atherosclerosis prevention on pediatric lupus erythematosus cohort. Arthritis and Rheum 2009; 60: 1496–1507.

159 Manzi S, Meilahn E, Rairie JE. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham study. Am J Epidemiol 1997; 145: 408–415.

160 Yang L, Tao J, Tanh X et al. Prevalence and correlation of conventional and lupus-specific risk factors for cardiovascular disease in Chinese systemic lupus erythematosus patients. J Eur Acad Dermatol Venereol 2012; 26: 95–101.

161 Yazdany J, Pooley N, Langham J, et al. Systemic lupus erythematosus; stroke and myocardial infarction risk: a systematic review and meta-analysis. RMD open 2020; 6: e001247.

162 Munguia-Realpozo P, Mendoza-Pinto C, Sierra Benito C et al. Systemic lupus erythematosus and hypertension. Autoimmun Rev 2019; 18: 102371.

163 Sun C, Qin W, Zhang YH et al. Prevalence and risk of metabolic syndrome in patients with systemic lupus erythematosus: A meta-analysis. Int J Rheum Dis 2017; 20: 917–928.

164 Bruce IA, Urowitz MB, Gladman DD et al. Risk factors coronary heart disease in women with systemic lupus erythematosus. The Toronto Risk Factor Study. Arthritis Rheum 2003; 48: 3159–3167.

165 Esdaile JM, Abrahamowicz M, Grodzicky T et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001; 44: 2331–2337.

166 Aviña-Zubieta JA, To F, Vostretsova K et al. Risk of Myocardial Infarction and Stroke in Newly Diagnosed Systemic Lupus Erythematosus: A General Population-Based Study. Arthritis Care Res (Hoboken) 2017; 69: 849–856.

167 Lim SY, Bae EH, Han K-D. Systemic lupus erythematosus is a risk factor for cardiovascular disease: a nationwide, population-based study in Korea. Lupus 2018; 27: 2050–2056.

168 Bengtsson C, Öhman ML, Nived O. Cardiovascular event in systemic lupus erythematosus in northern Sweden: Incidence and predictors in a 7-year follow-up study. Lupus 2012; 21: 452–459.

169 Lin CY, Shih CC, Yeh CC. Increased risk of acute myocardial infarction and mortality in patients with systemic lupus erythematosus: Two nationwide retrospective cohort studies. Int J Cardiol 2014; 176: 847–851.

170 Tornvall P, Göransson A, Ekman J. Myocardial Infarction in Systemic Lupus Erythematosus: Incidence and Coronary Angiography Findings. Angiology 2021; 72: 459–464.

171 Kim CH, Al-Kindi SG, Jandali B et al. Incidence and risk of heart failure in systemic lupus erythematosus. Heart 2017; 103: 227–233.

172 Chen SK, Barbhaiya M, Fischer MA. Heart failure risk in systemic lupus erythematosus compared to diabetes mellitus and general medicaid patients. Semin Arthritis Rheum 2019; 49: 389–395.

173 Bello N, Meyers KJ, Workman J, Belisario JM, Cervera R. Systematic literature Review and Meta-analysis of Venous Thromboembolism Events in Systemic Lupus Erythematosus. Rheumatol Ther 2023; 10: 7–34

174 Aviña-Zubieta JA, Vostretsova K, De Vera M, Sayre EC, Choi HK. The Risk of Pulmonary Embolism and Deep Vein Thrombosis in Systemic Lupus Erythematosus: A General Population-Based Study. Semin Arthritis Rheuma 2015; 45: 195–201

175 Mok CC, Ho LY, Yu KL, To CH. Venous thromboembolism in southern Chinese patients with Systemic lupus erythematosus. Clin Rheumatol 2010; 29: 599–604

176 Petri M, Barr E, Magder LS, et al. Risk of Renal Failure Within 10 or 20 Years of Systemic Lupus Erythematosus Diagnosis. J Rheumatol 2021; 48: 222–227.

177 Luo W, Farinha F, Iseberg DA. Survival analysis of mortality and development of lupus nephritis in patients with systemic lupus erythematosus up to 40 years of follow-up. Rheumatology (Oxford). 2022; 62: 200–208.

178 Pokroy-Shapira E, Gelernter I, Molad Y. Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. Clin Rheumatol 2014; 33: 649–657.

179 Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association -European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020; 79: 713–723.

180 Londoño Jimenez A, Mowrey WB, Putterman C. Brief Report: Tubulointerstitial Damage in Lupus Nephritis: A Comparison of the Factors Associated with Tubulointerstitial Inflammation and Renal Scarring. Arthritis Rheumatol 2018; 70: 1801–1806.

181 Reppe Moe SE, Molberg Ø, Strøm EH et al. Assessing the relative impact of lupus nephritis on mortality in a population-based systemic lupus erythematosus cohort. Lupus 2019; 28: 818–825.

182 Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus 2013; 22: 1286–1294.

183 Bosch X, Guilabert A, Pallarés L et al. Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients. Lupus 2006; 15: 584–589.

184 The CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. Clin Rheumatol 2018; 37: 2081–2086.

185 Gonzalés-Echavarri C, Capdevilla O, Espinosa G et al. Infections in newly diagnosed Spanish patients with systemic lupus erythematosus: data from the RELES cohort. Lupus 2018; 2253–2261.

186 Pego-Reigosa JM, Nicholson L, Pooley N. The risk of infections in adult patients with systemic lupus erythematosus: systematic review and meta-analysis. Rheumatology (Oxford) 2021; 60: 60–72.

187 Zhao K, Xie H, Li L et al. Increased risk of severe infections and mortality in patients with newly diagnosed systemic lupus erythematosus: a population-based study. Rheumatology (Oxford) 2021; 60: 5300–5309.

188 Chen D, Xie J, Chen H et al. Infection in Southern Chinese Patients with Systemic Lupus Erythematosus: Spectrum, Drug Resistance, Outcomes and Risk Factors. J Rheumatol 2016: 43; 1650–156.

189 Wang H, Zhou Y, Yu L et al. Major infections in newly diagnosed systemic lupus erythematosus: an inception cohort study. Lupus Sci Med. 2022; 9: e000725.

190 Luijten RKMAC, Cuppen BVJ, Bijlsma JW et al. Serious infections in systemic lupus erythematosus. Lupus 2014; 23: 1512–1516.

191 Torres-Gonzalés P, Romero-Díaz J, Cervera-Hernández ME. Tuberculosis and systemic lupus erythematosus: a case-cotrol study in Mexico City. Clin Rheumatol 2018; 37: 2095–2102.

192 González-Naranjo LA, Coral-Enrïguez JA, Restrepo-Escobar M et al. Factors associated with active tuberculosis in Colombian patients with systemic lupus erythematosus: a case-control study. Clin Rheumatol 2021; 40: 181–191.

193 Nossent J, Keen H, Preen DB et al. Temporal trends in hospitalisation for opportunistic infections in lupus patients in Western Australia. Lupus 2022; 31: 1434–1440.

194 Mok MY, Wong SSY, Chan TM. Non-tuberculous mycobacterial infection in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2007; 46: 280–284.

195 Kwan A, Al Rayes H, Lazova T, et al. Herpes zoster in SLE: prevalence, incidence and risk factors. Lupus Sci Med 2022: 9: e000574.

196 Borba EF, Ribeiro ACM, Martin P et al. Incidence, risk factors, and outcome of Herpes zoster in systemic lupus erythematosus. J Clin Rheumatol 2010; 16: 119–122.

197 Chakravarty EF, Michaud K, Katz R et al. Increased incidence of herpes zoster among patients with systemic lupus erythematosus. Lupus 2013: 22: 238–244.

198 Mok CC. Herpes zoster vaccination in systemic lupus erythematosus: the current status. Hum Vaccin Immunother 2019; 15: 45–48.

199 Carcía-Carrasco M, Mendoza-Pinto C, Rojas-Villarraga A et al. Prevalence of cervical HPV infection in women with systemic lupus erythematosus: A systematic review and meta-analysis. Autoimmun Rev 2019; 18: 184–191.

200 Rojo-Contreras W, Olivas-Flores EM, Gamez-Nava I et al. Cervical human papillomavirus infection in Mexican women with systemic lupus erythematosus or rheumatoid arthritis. Lupus 2012; 21: 365–372.

201 Lee YH, Choe JY, Park SH et al. Prevalence of human papilloma virus infections and cervical cytological abnormalities among Korean women with systemic lupus erythematosus. J Korean Med Sci 2010; 25: 1431–1437.

202 Hyrich KL, Machado PM. Rheumatic disease and COVID-19: epidemiology and outcomes. Nat Rev Rheumatol 2021; 17: 71–72.

203 Mehta P, Gasparyan AY, Zimba O et al. Systemic lupus erythematosus in the light of the COVID-19 pandemic: infection, vaccination, and impact on disease management. Clin Rheumatol 2022; 41: 2893–2910.

204 Gianfrancesco M, Hyrich KL, Al-Adely S. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020; 79: 859–866.

205 Cordtz R, Kristensen S, Dalgaard LPH et al. Incidence of COVID-19 Hospitalisation in Patients with Systemic Lupus Erythematosus: A Nationwide Cohort Study from Denmark. J Clin Med 2021; 10: 3842.

206 Ugarte-Gil MF, Alarcón GS, Izadi Z et al. Characteristics associated with poor COVID-19 outcomes in individuals with systemic lupus erythematosus: data from the COVID-19 Global Rheumatology Alliance. Ann Rheum Dis 2022; 81: 970–978.

207 Lao M, Wang X, Ding M. Invasive fungal disease in patients with systemic lupus erythematosus from Southern China: a retrospective study. Lupus 2019; 28: 77–85.

208 Santamaría-Alza Y, Sánchez-Bautista J, Fajardo-Rivero JF. Invasive fungal infections in Columbian patients with systemic lupus erythematosus. Lupus 2018; 27: 1116–1122.

209 Vinicki JP, Catalan Pellet S, Pappalardo C et al. Invasive fungal infections in Argentine patients with systemic lupus erythematosus. Lupus 2013; 22: 892–898.

210 Wang WH, Lai CC, Huang YF et al. Pneumocystis Jirovecii Pneumonia in Systemic Lupus Erythematosus: A Nationwide Cohort Study in Taiwan. Arthritis Care Res (Hoboken) 2022; 74: 1444–1450.

211 Boone B, Lazaroff SM, Wheless L et al. Rates of Pneumocystis Jirovecii pneumonia and prophylaxis prescribing patterns in a large electronic health record cohort of patients with systemic lupus erythematosus. Semin Arthritis Rheum 2022; 57: 152106.

212 Park JW, Curtis JR, Moon J et al. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic disease exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis 2018; 77: 644–649.

213 Bernatsky S, Ramsey-Goldman R, Labrecque J et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. J Autoimmun 2013; 42:130–135.

214 Gayed M, Bernatsky S, Ramsey-Goldman R, et al. Lupus and cancer. Lupus 2009; 18: 479–485.

215 Kang KY, Kim HO, Yoon HS, et al. Incidence of cancer among female patients with systemic lupus erythematosus. Clin Rheumatol 2010; 29: 381–388

216 Cappelli LC, Shah AA. The relationships between cancer and autoimmune rheumatic diseases. Best Pract Res Clin Rheumatol. 2020; 34: 101472

217 Song L, Wang Y, Zhang J, et al. The risks of cancer development in systemic lupus erythematosus (SLE) patients: a systematic review and meta-analysis. Arthritis Res Ther. 2018; 20: 270

218 Choi MY, Flood K, Bernatsky S, Ramsey-Goldman R, Clarke AE. A review on SLE and malignancy. Best Pract Res Clin Rheumatol 2017; 31: 373–396.

219 Björnådal L, Löfström B, Yin L, Lundberg IE, Ekbom A. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. Scand J Rheumatol 2002; 31: 66–71.

220 Tallbacka KR, Pettersson T, Pukkala E. Increased incidence of cancer in systemic lupus erythematosus: a Finnish cohort study with more than 25 years of follow-up. Scand J Rheumatol 2018; 47: 461–464.

221 Bae EH, Lim SY, Han KD, et al. Systemic lupus erythematosus is a risk factor for cancer: a nationwide population-based study in Korea. Lupus 2019; 28: 317–323.

222 Clarke AE, Pooley N, Marjenberg Z et al. Risk of malignancy in patients with systemic lupus erythematosus: Systematic review and meta-analysis. Semin Arthritis Rheum 2021; 51: 1230–1241.

223 Hemminki K, Huang W, Sundquist J, Sundquist K, Ji J. Autoimmune diseases and hematological malignancies: Exploring the underlying mechanisms from epidemiological evidence. Semin Cancer Biol 2020; 64: 114–121.

224 Ladouceur A, Tessier-Cloutier B, Clarke AE et al. Cancer and Systemic Lupus Erythematosus. Rheum Dis Clin North Am 2020; 46: 533–550.

225 Westermann R, Zobbe K, Cordtz R, et al. Increased cancer risk in patients with cutaneus lupus erythematosus and systemic lupus

erythematosus compared with the general population: a Danish nationwide cohort study. Lupus 2021; 30: 752–761.

226 Bernatsky S, Ramsey-Goldman R, Urowitz MB, Hanly JG, Gordon C, Petri MA. Cancer Risk in a Large Inception Systemic Lupus Erythematosus Cohort: Effects of Demographic Characteristics, Smoking, and Medications. Arthritis Care Res (Hoboken) 2020; 73: 1789–1795.

227 Chen YJ, Chang YT, Wang CB, Wu CY. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. Am J Med 2010; 123: 1150.e1–6.

228 Ragnarsson O, Gröndal G, Steinsson K. Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. Lupus 2003; 12: 687–691.

229 Parikh-Patel A, White RH, Allen M, Cress R. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control 2008; 19: 887–894.

230 Han JY, Kim H, Jung SY et al. Increased risk of malignancy in patients with systemic lupus erythematosus: a population-based cohort study in Korea. Arthritis Res Ther 2021; 23: 270.

231 Azrielamt S, Tiosano S, Watad A et al. Correlation between systemic lupus erythematosus and malignancies: a cross-sectional population-based study. Immunol Res 2017; 65: 464–469.

232 Bernatsky S, Ramsey-Goldman R, Rajan R et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. Ann Rheum Dis 2005; 64: 1507–1509.

233 King JK, Costenbader KH. Characteristics of patients with systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma (NHL). Clin Rheumatol 2007; 26: 1491–1494.

234 Bin J, Bernatsky S, Gordon C et al. Lung cancer in systemic lupus erythematosus. Lung Cancer 2007; 56: 303–306.

235 Bernatsky S, Ramsey-Goldman R, Petri M et al. Smoking Is the Most Significant Modifiable Lung Cancer Risk Factor in Systemic Lupus Erythematosus. J Rheumatol 2018; 45: 393–396.

236 Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer. 1997; 73: 198–203.

237 Dreyer L, Faurschou M, Mogensen M, Jacobsen S. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term follow-up study in a Danish cohort. Arthritis Rheum 2011; 63: 3032–3037.

238 Wadström H, Arkema EV, Sjöwall C et al. Cervical neoplasia in systemic lupus erythematosus: a nationwide study. Rheumatology (Oxford) 2017; 56: 613–619.

239 Chou WH, McGregor B, Schmidt A, et al. Cyclophosphamide-associated bladder cancers and considerations for survivorship care: A systematic review. Urol Oncol 2021; 39: 678–685.

240 Airaksinen J, Gluschkoff K, Kivimäki M, et al. Connectivity of depression symptoms before and after diagnosis of a chronic disease: A network analysis in the U.S. Health and Retirement study. J Affect Disord 2020; 266: 230–234.

241 Palagini L, Mosca M, Tani C, Gemignani A, Mauri M, Bombardieri S. Depression and systemic lupus erythematosus: a systematic review. Lupus 2013; 22: 409–416.

242 van Exel E, Jacobs J, Korswagen LA, et al. Depression in systemic lupus erythematosus, dependent on or independent of severity of disease. Lupus 2013; 22: 1462–1469.

243 Karol DE, Criscione-Schreiber LG, Lin M, Clowse MEB. Depressive symptoms and associated factors in systemic lupus erythematosus. Psychosomatics 2013; 54: 443–450.

244 Xie X, Wu D, Chen H. Prevalence and risk factors of anxiety and depression in patients with systemic lupus erythematosus in Southwest China. Rheumatol Int 2016; 36: 1705–1710.

245 Zhao Z, Rocha NP, Salem H et al. The association between systemic lupus erythematosus and dementia A meta-analysis. Dement Neuropsychol 2018; 12: 143–151.

246 Lin YR, Chou LC, Chen HC, et al. Increased Risk of Dementia in Patients With Systemic Lupus Erythematosus: A Nationwide Population-Based Cohort Study. Arthritis Care Res (Hoboken) 2016; 68: 1774–1779.

247 Mok CC, Lau CS, Wong RW. Neuropsychiatric manifestations and their clinical associations in southern Chinese patients with systemic lupus erythematosus. J Rheumatol 2001; 28: 766–771.

248 Zakeri Z, Shakiba M, Narouie B, Mladkova N, et al. Prevalence of depression and depressive symptoms in patients with systemic lupus erythematosus: Iranian experience. Rheumatol Int 2012; 32: 1179–87.

249 Nery FG, Borba EF, Viana VST et al. Prevalence of depressive and anxiety disorders in systemic lupus erythematosus and their association with anti-ribosomal P antibodies. Prog Neuropsychopharmacol Biol Psychiatry 2008; 32: 695–700.

250 Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. Arthritis Rheum 2009; 61: 822–9.

251 Abrol E, Coutinho E, Chou M, et al. Psychosis in systemic lupus erythematosus (SLE): 40-year experience of a specialist centre. Rheumatology (Oxford) 2021; 60: 5620–5629.

252 Hanly JG, Li Q, Su L, et al. Psychosis in Systemic Lupus Erythematosus: Results From an International Inception Cohort Study. Arthritis Rheumatol 2019; 71: 281–289.

253 Appenzeller S, Cendes F, Costallat LT. Acute psychosis in systemic lupus erythematosus. Rheumatol Int 2008; 28: 237–243.

254 Govoni M, Bombardieri S, Bortoluzzi A et al. Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients. Rheumatology (Oxford) 2012; 51: 157–168.

255 Paholpak P, Rangseekajee P, Foocharoen C. Characteristics, treatments and outcome of psychosis in Thai SLE patients. J Psychosom Res 2012; 73: 448–451.

256 Nishimura K, Omori M, Sato E, et al. New-onset psychiatric disorders after corticosteroid therapy in systemic lupus erythematosus: an observational case-series study. J Neurol 2014; 261: 2150–2158.

257 Chau SY, Mok CC. Factors predictive of corticosteroid psychosis in patients with systemic lupus erythematosus. Neurology 2003; 61: 104–107.

258 Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. J Neurol Neurosurg Psychiatry 2010; 81: 1372-1373.

259 Gendelman O, Tiosano S, Shoenfeld Y, et al. High proportions of dementia among SLE patients: A big data analysis. Int J Geriatr Psychiatry 2018; 33: 531–536.

260 Tan Y, Yang S, Liu Q, et al. Pregnancy-related complications in systemic lupus erythematous. J Autoimmun 2022; 132.

261 Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017; 76: 476–485.

262 Joo YB, Kim KJ Park KS, et al. Pregnancy rates and perinatal outcomes in women with systemic lupus erythematosus: data from the Korean national health claims database. Clin Rheumatol 2021; 40: 2243–2250.

263 Mehta B, Luo Y, Xu J, et al. Trends in Maternal and Fetal Outcomes Among Pregnant Women With Systemic Lupus Erythematosus in the United States: A Cross-sectional Analysis. Ann Intern Med 2019; 171: 164–171.

264 Buyon JP, Kim MY, Guerra MM, et al. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. Ann Intern Med 2015; 163: 153–163.

265 Wallenius M, Salvesen KÅ, Daltveit AK, et al. Systemic lupus erythematosus and outcomes in first and subsequent births based on data from a national birth registry. Arthritis Care Res (Hoboken) 2014; 66: 1718–1724.

266 Wu J, Ma J, Bao C, et al. Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study. BMJ Open 2018; 8: e020909.

267 Phansenee S, Sekararithi R, Jatavan P, et al. Pregnancy outcomes among women with systemic lupus erythematosus: a retrospective cohort study from Thailand. Lupus 2018; 27: 158–164.

268 Clowse MEB, Jamison M, Myers E, et al. A national study of the complications of lupus in pregnancy. Am J Obstet Gynecol 2008; 199: 127.e1–6.

269 Jakobsen IM, Helmig RB, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990-2010. Scand J Rheumatol 2015; 44: 377–384.

270 Gergianaki I, Garantziotis P, Adamichou C, et al. High Comorbidity Burden in Patients With SLE: Data from the Community-Based Lupus Registry of Crete. J Clin Med 2021; 10: 998.

271 Bultink IE. Osteoporosis and fractures in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2012; 64: 2–8.

272 Gu C, Zhao R, Zhang X et al. A meta-analysis of secondary osteoporosis in systemic lupus erythematosus: prevalence and risk factors. Arch Osteoporos 2019; 15: 1.

273 Carli L, Tani C, Spera V et al. Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus. Lupus Sci Med 2016; 3: e000098.

274 Liu YC, Lin WY, Tsai MC et al. Systemic lupus erythematosus and thyroid disease – Experience in a single medical center in Taiwan. J Microbiol Immun Infect 2019; 52: 480–486.

275 Yun JS, Bae JM, Kim KJ, et al. Increased risk of thyroid diseases in patients with systemic lupus erythematosus: A nationwide population-based Study in Korea. PLoS One 2017; 12: e0179088.

276 Luo W, Mao P, Zhang L, et al. Association between systemic lupus erythematosus and thyroid dysfunction: a meta-analysis. Lupus 2018; 27: 2120–2128.

277 Tselios K, Koumaras C, Gladman DD, Urowitz MB. Dyslipidemia in systemic lupus erythematosus: just another comorbidity? Semin arthritis Rheum 2016; 45: 604–610.

278 Lin YJ, Chien CC, Ho CH, Chen HA, Chen CY. Increased risk of type 2 diabetes in patients with systemic lupus erythematosus: A nationwide cohort study in Taiwan. Medicine (Baltimore) 2022; 101: e32520.

279 El Magadmi M, Ahmad Y, Turkie W, et al. Hyperinsulinemia, insulin resistance, and circulating oxidized low density lipoprotein in women with systemic lupus erythematosus. J Rheumatol 2006; 33: 50–56.

280 Fanouriakis A, Tziolos N, Bertsias G, et al. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis 2021; 80: 14–25.

281 Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019; 78: 736–745.

282 Durcan L, O'Dwyer T, Petri M. Management strategies and future directions for systemic lupus erythematosus in adults. Lancet 2019; 393: 2332–2343.

283 Zhao X, Zhang J, Liang Y, et al. Advances in Drug Therapy for Systemic Lupus Erythematosus. Curr Med Chem 2021; 28: 1251–1268.

284 Kazzi B, Gudenkauf B, Fine D. Adalimumab-Induced Lupus Nephritis: Case Report and Review of the Literature. Eur J Rheumatol 2022; 9: 108–110.

285 Mackensen A, Müller F, Mougiakos D et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med 2022; 28: 2124–2132.

286 Sokka-Isler T, Kauppi M, Vuolteenaho K, Pirilä L, Moilanen E. Lääkehoidon periaatteet ja perinteiset reumalääkkeet. In: Kauppi M, Karjalainen A, Pirilä L, Puolakka K, Sokka-Isler T, Vähäsalo P (ed) Reumasairaudet. Kustannus Oy Duodecim. 2023.

287 Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019; 78: 1296–1304.

288 Götestam Skorpen C, Hoeltzenbein M, Tincani M, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016; 75: 795–810.

289 Chiang HY, Guo ZA, Wu TW, et al. Efficacy and safety of belimumab therapy in systemic lupus erythematosus: A systematic review and meta-analysis. Lupus 2022; 31: 666–673.

290 Rovin BH, Furie R, Onno Teng YK et al. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney Int 2022; 101: 403–413.

291 Furie R, Khamashta M, Merril JT, et al. Anifrolumab, an Anti–Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol 2017; 69: 376–386.

292 Chatham WW, Furie R, Saxena A, et al. Long-Term Safety and Efficacy of Anifrolumab in Adults With Systemic Lupus Erythematosus: Results of a Phase II Open-Label Extension Study. Arthritis Rheumatol 2021; 73: 816–825.

293 Elfving P, Kariniemi S, Kautiainen H, et al. Mortality in SLE patients compared with population controls in Finland in years 2000-2015. Rheumatology (Oxford) 2021; 60: 4238–4244.

294 Moghaddam B, Marozoff S, Li L, et al. All-cause and cause-specific mortality in systemic lupus erythematosus: a population-based study. Rheumatology (Oxford) 2022; 61: 367–376.

295 Bernatsky S, Boivin JF, Joseph L, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006; 54: 2550–2557.

296 WHO Collaborating centre for drug statistics methodology. [Internet. Accessed November 4, 2021]. Available from: www.whocc.no/atc/structure_and_principles/

297 WHO Defined Daily Dose (DDD). [Internet. Accessed May 8, 2021]. Available from: www.who.int/tools/atc-ddd-toolkit/about-ddd

298 Finnish Cancer Registry. https://syoparekisteri.fi/ (accessed May 2021).

299 Statistics Finland. https://www.stat.fi/til/ksyyt/2019/ksyyt_2019_2020-12-14_laa_001_fi.html (accessed May 2021).

300 Wright SP. Adjusted p-values for simultaneous inference. Biometrics 1992; 48: 1005–1013.

301 Cole SR and Hernan MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed 2004; 75: 45–49.

302 Elfving P, Marjoniemi O, Niinisalo H, et al. Estimating the incidence of connective tissue diseases and vasculitides in a defined population in Northern Savo area in 2010. Rheumatol Int 2016; 36: 917–924

303 Drosos GC, Vedder D, Houben E et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis 2022; 81: 768–779.

304 Elfving P, Puolakka K, Kautiainen H, et al. Drugs used in incident systemic lupus erythematosus - results from the Finnish nationwide register 2000-2007. Lupus 2016; 25: 666–670.

305 Somers EC, Thomas SL, Smeeth L, Hall AJ. Autoimmune diseases co-occurring within individuals and within families: a systematic review. Epidemiology 2006; 17: 202–217.

306 Sardu C, Cocco E, Mereu A, et al. Population based study of 12 autoimmune diseases in Sardinia, Italy: prevalence and comorbidity. PLoS One 2012; 7: e32487.

307 Ruiz-Irastorza G, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. Rheumatology (Oxford) 2012; 51: 1145–1153.

308 Figueiredo-Braga M, Cornaby C, Cortez A, et al. Depression and anxiety in systemic lupus erythematosus: The crosstalk between immunological, clinical, and psychosocial factors. Medicine (Baltimore) 2018; 97: e11376.

309 Markkula N, Suvisaari J, Saarni SI et al. Prevalence and correlates of major depressive disorder and dysthymia in an eleven-year follow-up - results from the Finnish Health 2011 Survey. J Affect Disord 2015; 173: 73–80.

310 Finnish statistics on medicine 1999-2015, Finnish Medicines Agency Fimea and Social Insurance Institution, Helsinki.

311 Jyrkkä J, Kautiainen H, Koponen H et al. Antidepressant use among person with recent-onset rheumatoid arthritis: a nationwide register-based study in Finland. Scand J Rheumatol 2014; 43: 364–370.

312 Putignano D, Bruzzese D, Orlando V, et al. Differences in drug use between men and women: an Italian cross-sectional study. BMC Womens Health 2017; 17: 73.

313 Sramek JJ, Murphy MF, Cutler NR. Sex differences in the psychopharmacological treatment of depression. Dialogues Clin Neurosci 2016; 18: 447–457.

314 Bertakis KD, Azari R, Helms LJ, et al. Gender differences in the utilization of health care services. J Fam Pract 2000; 49: 147–152.

315 Duodecim Depressio Käypä hoito. [Internet. Accessed April 18, 2023]. Available from: https://www.kaypahoito.fi/hoi50023.

316 Duodecim Lääkeinteraktiot ja -haitat -tietokanta. [Internet. Accessed April 9, 2023]. Available from: https://www.terveysportti.fi/apps/interaktio/.

317 Beach RS, Kostis WJ, Celano CM et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. J Clin Psychiatry 2014; 75: 441–449.

318 Hooks M, Bart B, Vardeny O, et al. Effects of hydroxychloroquine treatment on QT interval. Heart Rhythm 2020; 17: 1930–1935.

319 Renaldi J, Koumpouras F, Dong X. Evaluating the risk of QTc prolongation associated with hydroxychloroquine use with antidepressants in lupus patients with fibromyalgia. Lupus 2021; 30: 1844-1848

320 Van Den Berg SJ. Comparing SSRIs: From chemistry to clinical choice. Hum Psychopharmacol 1995; 10: 199–209.

321 Cipriani A, Furukawa TA, Salanti G et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018; 391: 1357–1366.

322 Suvisaari J, Isohanni M, Kieseppä T, Koponen H, Hietala J, Lönnqvist J. Skitsofrenia ja muut psykoosit. In: Lönnqvist J, Henriksson M, Marttunen M, Partonen T (ed) Psykiatria. Skitsofrenia. Kustannus Oy Duodecim, 2020, 170-189.

323 Kronholm E, Markkula J, Virta LJ. What is Behind the Seeming Cessation of the Increase in Sleep Medicine Consumption in Finland During the Last Years? J Public Health Res 2012; 1: 149–154.

324 Paz Rollan M, Cabrera R, Schwartz RA. Current knowledge of immunosuppression as a risk factor for skin cancer development. Crit Rev Oncol Hematol 2022; 177: 103754.

325 Worley B, Harikumar V, Reynolds K, et al. Treatment of actinic keratosis: a systematic review. Arch Dermatol Res 2022.

326 Lönnberg S, Hansen BT, Haldorsen T, Campbell S, Schee K, Nygård M. Cervical cancer prevented by screening: Long-term incidence trends by morphology in Norway. Int J Cancer 2015; 137: 1758–1764.

327 Giannone G, Giuliano AR, Bandini M, et al. HPV vaccination and HPV-related malignancies: impact, strategies and optimizations toward global immunization coverage. Cancer Treat Rev. 2022; 111: 102467.

328 Finnish Cancer Registry. https://cancerregistry.fi/screening/cervical-cancer-screening/ (accessed April 2023).

329 Finnish institute for health and welfare. https://thl.fi/en/web/infectious-diseases-and-vaccinations/vaccines-a-to-z/hpv-or-human-papillomavirus-vaccine (accessed April 2023).

330 Ministry of social affairs and health. https://stm.fi/en/hpv-vaccinations (accessed April 2023).

331 Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 2004; 100: 228–237.

332 Benk V, Al-Herz A, Gladman D, Urowitz M, Fortin PR. Role of radiation therapy in patients with a diagnosis of both systemic lupus erythematosus and cancer. Athritis Rheum 2005; 53: 67–72.

333 McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM, Yellon DM. Anthracycline Chemotherapy and Cardiotoxicity. Cardiovasc Drugs Ther 2017; 31: 63–75.

334 Finlex Data Bank. https://www.finlex.fi/fi/laki/alkup/2022/20220801 (accessed July 2023)

ORIGINAL PUBLICATIONS (I – III)

I

Multimorbidity among incident Finnish systemic lupus erythematosus patients during 2000–2017

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Multimorbidity among incident Finnish systemic lupus erythematosus patients during 2000–2017

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Abstract

The objective of the study was to examine the risk of other morbidities among patients with systemic lupus erythematosus (SLE). A total of 1006 adult new-onset SLE patients were identified during 1.1.2000- 31.12.2014 from the register of Social Insurance Institution. For each case three general population controls matched according to age, sex and place of residence at the index day were sampled from the population register. Both groups were followed up from the index date until the end of 2017 or until death. The national register on specialized care was explored to gather broadly their 12 organ-specific morbidities, which were found among 91.2% of SLE patients and 66.7% of comparators. The rate ratio (RR) was elevated in almost all disease groups. Musculoskeletal, cardiovascular and genitourinary conditions were the most common comorbidities with RRs of 1.82 (1.68 to 1.97), 1.91 (1.76 to 2.08) and 1.91 (1.73 to 2.09), respectively. Men with SLE had a significantly higher risk for diseases of the genitourinary system and endocrine, nutritional and metabolic diseases compared to women with SLE. The risk of concurrent morbidities is essential to note in the care of SLE patients.

Keywords

Systemic lupus erythematosus, morbidity, cardiovascular disease, gender, comorbidity

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Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can affect almost all organs and tissues. The clinical picture can vary greatly, and it is influenced by gender, age, ethnicity, residence and medication. Due to the heterogeneity of the disease, symptoms can be diverse. Most patients are female.[1–3]

Patients diagnosed with SLE have a considerable burden due to multi-organic involvement of the disease and the treatment chosen for it.[4,5] Previous studies have shown a significant risk for various diseases, such as cardiovascular diseases (CVDs), renal diseases, psychiatric disorders, infections and osteoporosis. For example, the risk for myocardial infarct has been estimated to be 2 to 9 times higher in SLE patients than in the general population.[6–11]

The European League Against Rheumatism (EULAR) recommendations from the year 2008 advise to carefully monitor certain comorbidities, and in recent years, the presence of concurrent disorders in SLE has slowly gained more attention among health care professionals.[12] Despite the recent publicity, reports on the occurrence of concomitant diseases among patients with SLE are far from ample, and

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only a few of them depict the wide spectrum of the comorbidities. In this study, we examine broadly the relations between SLE and concurrent diseases.

Patients and methods

In Finland every resident has national health insurance, and the Social Insurance Institution (SII) keeps a register of them. Patients with chronic inflammatory rheumatic disorders are entitled to a special (higher than basic) reimbursement for the cost of anti-rheumatic drugs. Identification of SLE patients was based on new special reimbursement decisions with the 10th International Classification of Diseases code (ICD-10) of M32 in the register of SII during 1.1.2000 – 31.12.2014. The date of acceptance of reimbursement was defined as the date of diagnosis (index date). For every SLE patient, three individually matched (age, gender and residence at the index date) population controls were selected from the Population

Table 1. The number of comorbidities in systemic lupus erythematosus patients and population controls and the rate ratio during 2000–2017 according to 10th revision of the International Classification of Diseases codes.

	ICD-10 disease codes	SLE patients N = 1006 N (%)	Controls N = 3005 N (%)	RR[a] (95% CI)	P-value[b]
Malignant neoplasms	C00-D09	117 (11.6)	268 (8.9)	1.29 (1.05 to 1.59)	0.057
Bening neoplasms	D10-D49	201 (20.0)	356 (11.8)	1.68 (1.44 to 1.97)	<0.001
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	178 (17.7)	103 (3.4)	5.15 (4.08 to 6.49)	<0.001
Endocrine, nutritional and metabolic diseases	E00-E90	254 (25.2)	388 (12.9)	1.90 (1.65 to 2.18)	<0.001
Disorders of thyroid gland	E00-E07	101 (10.0)	120 (4.0)	2.49 (1.93 to 3.22)	<0.001
Other hypothyroidism	E03	80 (8.0)	70 (2.3)	3.39 (2.48 to 4.63)	<0.001
Diabetes mellitus	E10-E14	83 (8.3)	138 (4.6)	1.74 (1.34 to 2.27)	<0.001
Disorders of lipoprotein metabolism and other lipidemias	E78	53 (5.3)	98 (3.3)	1.56 (1.13 to 2.16)	0.036
Mental and behavioral diseases	F00-F99	199 (19.8)	399 (13.3)	1.46 (1.25 to 1.70)	<0.001
Dementia in Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere and unspecified dementia	F00-F03	24 (2.4)	72 (2.4)	0.96 (0.61 to 1.52)	0.88
Schizophrenia, schizotypal and delusional disorders	F20-F29	15 (1.5)	40 (1.3)	1.07 (0.60 to 1.93)	0.82
Mood (affective) disorders	F30-F39	102 (10.1)	177 (5.9)	1.71 (1.36 to 2.16)	<0.001
Diseases of the nervous system	G00-G99	313 (31.1)	511 (17.0)	1.78 (1.58 to 2.01)	<0.001
Other degenerative diseases of the nervous system	G30-G32	16 (1.6)	79 (2.6)	0.58 (0.34 to 0.99)	0.14
Epilepsy and status epilepticus	G40-G41	33 (3.3)	34 (1.1)	2.88 (1.79 to 4.63)	<0.001
Diseases of the eye and adnexa	H00-H59	322 (32.0)	499 (16.6)	1.88 (1.67 to 2.12)	<0.001
Iridocyclitis	H20	18 (1.8)	21 (0.7)	2.62 (1.40 to 4.90)	0.015
Diseases of the circulatory system	I00-I99	511 (50.8)	761 (25.3)	1.91 (1.76 to 2.08)	<0.001
Hypertensive diseases	I10-I15	237 (23.6)	351 (11.7)	1.93 (1.67 to 2.24)	<0.001
Ischemic heart diseases	I20-I25	100 (9.9)	177 (5.9)	1.62 (1.29 to 2.04)	<0.001
Cerebrovascular diseases	I60-I69	78 (7.8)	117 (3.9)	1.92 (1.46 to 2.53)	<0.001
Other chronic obstructive pulmonary disease, asthma and status asthmaticus	J44-J46	112 (11.1)	142 (4.7)	2.32 (1.83 to 2.94)	<0.001
Noninfective enteritis and colitis	K50-K52	28 (2.8)	42 (1.4)	2.02 (1.26 to 3.24)	0.021
Disease of the musculoskeletal system and connective tissue	M00-M99[c]	532 (52.9)	863 (28.7)	1.82 (1.68 to 1.97)	<0.001
Osteoporosis with pathological fracture and osteoporosis without pathological fracture	M80-M81	61 (6.1)	35 (1.2)	5.08 (3.38 to 7.64)	<0.001
Diseases of the genitourinary system	N00-N99	456 (45.3)	708 (23.6)	1.91 (1.73 to 2.09)	<0.001
Renal tubulointerstitial diseases	N00-N16	197 (19.6)	94 (3.1)	6.15 (4.86 to 7.78)	<0.001
Renal failure	N17-N19	53 (5.3)	34 (1.1)	4.53 (2.96 to 6.92)	<0.001

[a]Adjusted for education level.
[b]The significance were correct for multiplicity using Hommel's multiple comparison procedure.
[c]Excluding systemic connective tissue disorders M30–M36; ICD-10 code = 10th International Classification of Diseases code; SLE=Systemic lupus erythematosus; RR = Rate ratio.

Register Centre. Only adults (age >17 years) were included. Rate ratios (RR) were standardized by education level at baseline (basic, middle, lower high and upper high level), and information about education level was acquired from Statistics Finland.

The Finnish law on personal register obligates the service providers to produce information to the Care Register of the National Institute for Health and Welfare (NIHW). The Care Register covers all hospitalizations since 1969. Outpatient visits in specialized care are included since 1998. The data contains, among others, each patient's personal identification code (PIC) and diagnoses of medical disorders according to the codes of the ICD-10.

We retrieved data on 12 organ-specific disease groups and examined some subgroups of special interest as well (Table 1). Systemic connective tissue disorders M30-M36 were excluded from the study and only disease groups of M00-M25 and M40-M99 were included to study from the group of the diseases of the musculoskeletal system and connective tissue. Infectious diseases were not included in this study because the diagnoses made in primary health care would have been missed.

The follow-up started from the index date of the each SLE patient and ended when the patient died or at end of the year 2017, whichever occurred first. Permission to use the databases were obtained from the SII and the NIHW. By Finnish law, no approval of an ethical committee nor the patient's informed consent are required for register-based studies done without contacting study subjects.

Statistical methods

Data are presented as means with standard deviation (SD) and as counts with percentages. Adjusted RRs of comorbidities were calculated using generalized linear models with log link and binomial distribution. Penalized maximum likelihood logistic regression (Firthlogit) was used if the event of interest was rare. Models included education level as a covariate. A possible nonlinear relationship between age at the index day and RR for cardiovascular diseases was assessed by using four-knot-restricted generalized linear models. The length of the distribution (age at the index day) of knots was located at the 5th, 35th, 65th, and 95th percentiles. Knot locations were based on Harrell's recommended percentiles.[13] Hommel's adjustment was used to correct levels of significance for multiple testing, because it is more powerful than alternative procedures, including the Bonferroni, Holm's, and Hochberg's procedures.[13] Stata 16.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analyses.

Results

A total of 1006 patients with newly-diagnosed SLE (mean age 45.5 years, SD 16 years, females 84,0%) and 3005 controls were included. The females were younger than the males: 44.9 years (SD 15.9 years) and 48.6 years (SD 16.4 years), respectively. The cumulative follow-up time was 8631 person years in SLE patients and 26382 person years in controls, with a mean follow-up of 8.6 years and 8.8 years, respectively.

Morbidities of interest were found among 91.2% of SLE patients and among 66.7% of comparators. Musculoskeletal, cardiovascular and genitourinary conditions were the three most common comorbidities in both groups. Number of comorbid conditions per individual was higher among SLE patients (Figure 1). Table 1 displays the numbers of the selected comorbid diseases and the respective RRs. Compared to the general population, SLE patients had elevated RRs for most of the diseases studied. Only schizophrenia, dementia, degenerative diseases of the nervous system and malignant neoplasms were not more frequent in the patient population. Men with SLE had a higher risk for diseases of the genitourinary system and endocrine, nutritional and metabolic diseases (Figure 2). After controlling confounders, no difference was

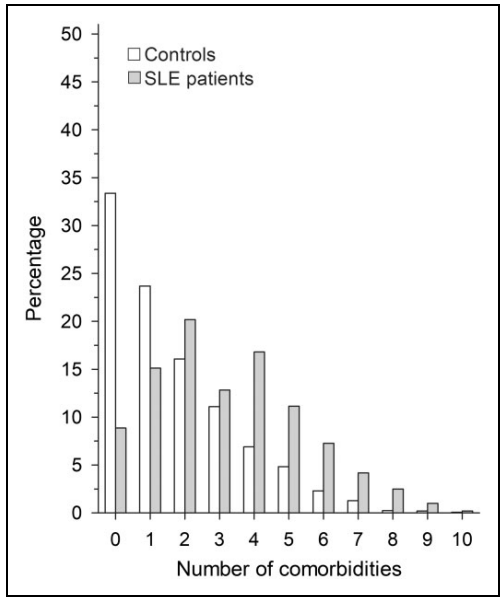

Figure 1. Cumulative number of comorbidities among new-onset systemic lupus erythematosus patients diagnosed between 2000–2014 and their controls at the end of the follow-up 2000–2017. Infections and systemic connective tissue diseases are not included.

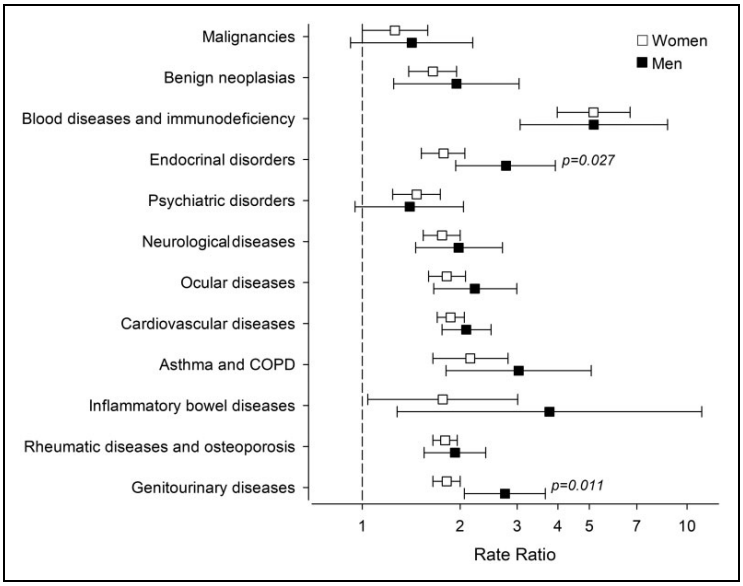

Figure 2. Education level adjusted rate ratios of comorbid diseases of systemic lupus erythematosus patients and controls by gender during 2000–2017 and according to 10th revision of the International Classification of Diseases codes.
Malignancies = malignant neoplasms C00-D09, Benign neoplasias = benign neoplasms D10–D49, Blood diseases and immune deficiency = disease of the blood and blood-forming organs and certain disorders involving the immune mechanism D50–D89, Endocrinal diseases = endocrine, nutritional and metabolic diseases E00-E90, Psychiatric disorders = mental and behavioural diseases F00–F99, Neurological diseases = diseases of the nervous system G00-G99, Ocular diseases = diseases of the eye and adnexa H00–H59, Cardiovascular diseases = diseases of the circulatory system I00-I99, Asthma and COPD = other chronic obstructive pulmonary disease, asthma and status asthmaticus J44–J46, Inflammatory bowel diseases = noninfective enteritis and colitis K50–K52, Rheumatic diseases and osteoporosis = disease of the musculoskeletal system and connective tissue M00–M99 (excluding systemic connective tissue disorders M30–M36), Genitourinary diseases = diseases of the genitourinary system N00–N99.

found between genders in the number of comorbidities: men with SLE 3.5 (95% CI: 3.1 to 3.8) and women with SLE 3.2 (95% CI: 3.0 to 3.3); $p = 0.10$.

The relative risk of CVDs depended on age. The RR was highest among patients, who were diagnosed with SLE in the young age groups (Figure 3).

Discussion

In our study, the rate of morbidities was higher in Finnish patients with newly diagnosed SLE than their population controls. Moreover, the number of morbidities per individual was higher.

Our findings are mostly in line with previous research, although some variation in morbidities has been reported depending on study design and ethnicity.[14–16] In a case-control study from UK SLE patients were compared using general practice records. The risk of comorbidities was elevated in almost all disease groups studied, but especially renal diseases and CVDs were more frequent, as it was in our cohort.[14] In a South African case-control study including mostly young black women, approximately 80% of SLE patients had more than one comorbidity after a six-year follow-up. However, CVDs, except hypertension, were rare compared to our study or studies performed in other industrial countries.[11,15,17]

SLE itself predisposes to CVDs due to endothelial dysfunction.[18,19] Again, metabolic syndrome is more frequent in SLE patients, contributing to the CVD burden.[20] In our study the relative CVD burden was substantial in young men, but young women had increased RR for CVDs as well. With advancing age the CVD risk approached but did not reach that of the general population. This age-related relative risk has also been reported from the UK.[6]

Kidney disease in SLE patients is mostly due to lupus nephritis (LN). The prevalence of LN varies depending on ethnicity, and LN is more common among non-white people.[21,22] Male SLE patients seem to have a greater risk for kidney diseases, and end stage renal disease and renal failure are common

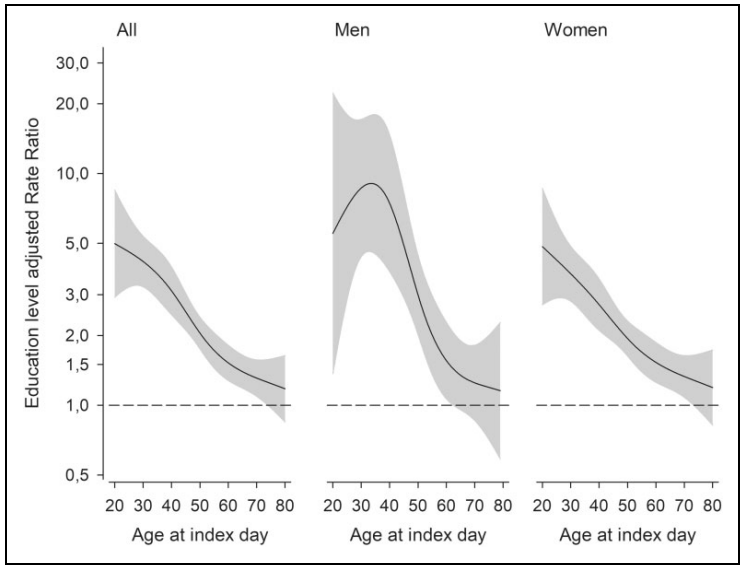

Figure 3. Education level adjusted rate ratios of cardiovascular diseases between systemic lupus erythematosus patients and controls during 2000–2014 according to age at index day. The curves were derived from a four-knot-restricted cubic splines generalized linear models. The models were adjusted for education levels. The grey area represents a 95% confidence interval.

among SLE patients.[23,24] Our study results were in line with the aforementioned, although RRs were not so high. Hydroxychloroquinine has been shown to decrease prevalence of chronic kidney disease, and at least in Finland it is often used as the primary medicine in SLE treatment.[25,26] Another explanation for our result may be that almost all of our patients were native Finnish.

SLE affects nervous system inducing neuropsychiatric disorders (neuropsychiatric SLE, NPSLE).[5,27–33] Mood disorders, and especially depression, are considered to be one of the most prevalent neuropsychiatric comorbidities in SLE.[5,34] Our study results support the aforementioned even though a considerable number of the mild cases are treated in the primary health care and never reach specialized care. However, we found no significant RR for Alzheimer's disease, vascular dementia, dementia in other diseases classified elsewhere and unspecified dementia or other degenerative diseases of the nervous system.

We found a definite risk for osteoporosis. SLE patients have been shown to be prone to osteoporosis due to systemic inflammation and glucocorticoid treatment.[4] In addition, vulnerability to osteoporosis may result from sensitiveness to sunlight, lupus nephritis and low D-vitamin levels.[35,36] SLE patients may also be screened for osteoporosis and followed more carefully than other populations.[37]

According to our study, there is a positive correlation between SLE and obstructive pulmonary disease. However, we could not differentiate between asthma and chronic obstructive lung disease (COPD). Conflicting results have been published about the risk of these conditions, and the matter needs more investigation.[38–42]

Men with SLE tend to have more severe disease course than women, at least among white and African-American patients followed in the Hopkins Lupus Cohort. Men more often had cardiovascular, renal and hematological manifestations, whereas women experienced more malar rash, photosensitivity, alopecia, oral ulcers and arthralgia at the end of the follow-up.[43] In our study, no difference was found between genders in the number of comorbidities, but men with SLE had a higher risk in genitourinary and in endocrine and metabolic diseases.

It is not clear, why SLE seems to be harsher in males. One possible explanation is that men might seek medical care later, which could delay the diagnosis and the start of proper treatment.

A weakness of this register-based study is the lack of clinical data. Therefore, we could not determine the severity of SLE and evaluate whether a harsher disease course was related to a higher morbidity rate. A major limitation in this study is the lack of infectious diseases. In addition, some diagnoses made by general

practitioners may be missing. Many SLE patients are regularly monitored in rheumatology outpatient clinics and are more prone to be diagnosed with morbidities than individuals in the general population.

The strengths of this study are the relatively long follow-up time, the case-control study design and the linkage of extensive nationwide information from different official registers. In addition, the diagnoses of morbidities were made in specialized care, strengthening the reliability of the diagnosis. Our study consisted of only new-onset SLE patients and their morbidities manifesting in the following years. This nationwide study included practically all patients using medication for SLE, but some mild forms of the disease without need for disease-modifying anti-rheumatic drugs might have been left out.

In conclusion, our study shows that SLE patients have a considerable burden of various morbidities. Particularly, CVDs are more frequent in SLE patients than in the rest of the population, but vulnerability to other morbidities is also notable.

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Supplemental material

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References

1. Tamirou F, Arnaud L, Talarico R, et al. Systemic lupus erythematosus: state of the art on clinical practice guidelines. *RMD Open* 2019; 4: e000793.
2. Schwartz N, Goilav B and Putterman C. The pathogenesis, diagnosis and treatment of lupus nephritis. *Curr Opin Rheumatol* 2014; 26: 502–509.
3. Cervera R, Abarca-Costalago M, Abramovicz D, et al.; European Working Party on Systemic Lupus Erythematosus. Systemic lupus erythematosus in Europe at the change of the millennium: lessons from the "Euro-Lupus project". *Autoimmun Rev* 2006; 5: 180–186.
4. Sarkissian A, Sivaraman V, Bout-Tabaku S, et al. Bone turnover markers in relation to vitamin D status and disease activity in adults with systemic lupus erythematosus. *Lupus* 2019; 28: 156–162.
5. Huang X, Magder LS and Petri M. Predictors of incident depression in systemic lupus erythematosus. *J Rheumatol* 2014; 41: 1823–1833.
6. Rees F, Doherty M, Grainge M, Lanyon P, Davenport G and Zhang W. Burden of comorbidity in systemic lupus erythematosus in the UK, 1999-2012. *Arthritis Care Res (Hoboken)* 2016; 68: 819–827.
7. Hak AE, Karlson EW, Feskanich D, Stampfer MJ and Costenbader KH. Systemic lupus erythematosus and the risk of cardiovascular disease: results from the nurses's health study'. *Arthritis Rheum* 2009; 61: 1396–1402.
8. Jonsson H, Nived O and Sturfelt G. Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine (Baltimore)* 1989; 68: 141–150.
9. Ward MM. Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 1999; 42: 338–346.
10. Mok CC, Ho LY and To CH. Annual incidence and standardized incidence ratio of cerebrovascular accidents in patients with systemic lupus erythematosus. *Scand J Rheumatol* 2009; 38: 362–368.
11. Bengtsson C, Ohman ML, Nived O and Rantapää-Dahlqvist S. Cardiovascular event in systemic lupus erythematosus in Northern Sweden: incidence and predictors in a 7-year follow-up study. *Lupus* 2012; 21: 452–459.
12. Bertsias G, Ioannidis JPA, Boletis J, et al.; Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR standing committee for international clinical studies including therapeutics. *Ann Rheum Dis* 2008; 67: 195–205.
13. Wright SP. Adjusted p-values for simultaneous inference. *Biometrics* 1992; 48: 1005–1013.
14. Kuo CF, Chou IJ, Rees F, et. al. Temporal relationships between systemic lupus erythematosus and comorbidities. *Rheumatology (Oxford)* 2019; 58: 840–848.
15. Greenstein L, Makan K and Tikly M. Burden of comorbidities in South Africans with systemic lupus erythematosus. *Clin Rheumatol* 2019; 38: 2077–2082.
16. Fernández M, Alarcón GS, Calvo-Alén J, et al.; LUMINA Study Group. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. *Arthritis Rheum* 2007; 57: 576–584.
17. Thorburn CM and Ward MM. Hospitalizations for coronary artery disease among patients with systemic

lupus erythematosus. *Arthritis Rheum* 2003; 48: 2519–2523.
18. Sciatti E, Cavazzana I, Vizzardi E, et al. Systemic lupus erythematosus and endothelial dysfunction: a close relationship. *Curr Rheumatol Rev* 2019; 15: 177–188.
19. Lim SY, Bae EH, Han KD, et al. Systemic lupus erythematosus is a risk factor for cardiovascular disease: a nationwide, population-based study in Korea. *Lupus* 2018; 27: 2050–2056.
20. Parker B, Urowitz MB, Gladman DD, et al. Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. *Ann Rheum Dis* 2013; 72: 1308–1314.
21. Seligman VA, Lum RF, Olson JL, Hongzhe L and Criswell LA. Demographic differences in the development of lupus nephritis: a retrospective analysis. *Am J Med* 2002; 112: 726–729.
22. Patel M, Clarke AM, Bruce IN and Symmons DPM. The prevalence and incidence of biopsy-proven lupus nephritis in the UK: Evidence of an ethnic gradient. *Arthritis Rheum* 2006; 54: 2963–2969.
23. Crosslin KL and Wiginton KL. Sex differences in disease severity among patients with systemic lupus erythematosus. *Gend Med* 2011; 8: 365–371.
24. Reppe Moe SE, Molberg Ø, Strøm EH and Lerang K. Assessing the relative impact of lupus nephritis on mortality in a population-based systemic lupus erythematosus cohort. *Lupus* 2019; 28: 818–825.
25. Pokroy-Shapira E, Gelernter I and Molad Y. Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. *Clin Rheumatol* 2014; 33: 649–657.
26. Elfving P, Puolakka K, Kautiainen H, Virta LJ, Pohjolainen T and Kaipiainen-Seppänen O. Drugs used in incident systemic lupus erythematosus – results from the Finnish nationwide register 2000-2007. *Lupus* 2016; 25: 666–670.
27. Hesselvig JH, Egeberg A, Kofoed K, Gislason G and Dreyer L. Increased risk of depression in patients with cutaneous lupus erythematosus and systemic lupus erythematosus: a Danish nationwide cohort study. *Br J Dermatol* 2018; 179: 1095–1101.
28. Tisseverasinghe A, Peschken C and Hitchon C. Anxiety and mood disorders in systemic lupus erythematosus: Current insights and future directions. *Curr Rheumatol Rep* 2018; 20: 85.
29. Sanna G, Bertolaccini ML, Cuadrado MJ, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. *J Rheumatol* 2003; 30: 985–992.
30. Hanly JG, McCurdy G, Fougere L, Douglas JA and Thompson K. Neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. *J Rheumatol* 2004; 31: 2156–2162.
31. The American college of rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. ACR ad hoc committee on neuropsychiatric lupus nomenclature. *Arthritis Rheum* 1999; 42: 599–608.
32. Lin YR, Chou LC, Chen HC, Liou TH, Huang SW and Lin HW. Increased risk of dementia in patients with systemic lupus erythematosus: a nationwide population-based cohort study. *Arthritis Care Res (Hoboken)* 2016; 68: 1774–1779.
33. Gendelman O, Tiosano S, Shoenfeld Y, et al. High proportions of dementia among SLE patients: a big data analysis. *Int J Geriatr Psychiatry* 2018; 33: 531–536.
34. Hanly JG, Su L, Urowitz MB, et al. Mood disorders in systemic lupus erythematosus: results from an international inception cohort study. *Arthritis Rheumatol* 2015; 67: 1837–1847.
35. Matsuoka LY, Wortsman J, Hanifan N and Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D. A preliminary study. *Arch Dermatol* 1988; 124: 1802–1804.
36. Bultink IE. Osteoporosis and fractures in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2012; 64: 2–8.
37. Felten R, Sagez F, Gavand PE, et al. 10 Most important contemporary challenges in the management of SLE. *Lupus Sci Med* 2019; 6: e000303.
38. Arnson Y, Shoenfeld Y and Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun* 2010; 34: 258–265.
39. Bieber V, Cohen AD, Freud T, Agmon-Levin N, Gertel S and Amital H. Autoimmune smoke and fire–coexisting rheumatoid arthritis and chronic obstructive pulmonary disease: a cross-sectional analysis. *Immunol Res* 2013; 56: 261–266.
40. Shen TC, Lin CL, Chen CH, et al. Increased risk of chronic obstructive pulmonary disease in patients with systemic lupus erythematosus: a population-based cohort study. *PLoS One* 2014; 9: e91821.
41. Shen TC, Tu CY, Lin CL, Wei CC and Li YF. Increased risk of asthma in patients with systemic lupus erythematosus. *Am J Respir Crit Care Med* 2014; 189: 496–499.
42. Sekigawa I, Yoshiike T, Iida N, Hashimoto H and Ogawa H. Allergic disorders in systemic lupus erythematosus: prevalence and family history. *Lupus* 2002; 11: 426–429.
43. Tan TC, Fang H, Magder LS and Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. *J Rheumatol* 2012; 39: 759–769.

II

Patients with recent-onset systemic lupus erythematosus use more antidepressant medication than matched controls – a case-control study

Kariniemi S, Elfving P, Virta LJ, Kautiainen H, Puolakka K and Rantalaiho V.

Submitted

III

Malignancies among newly diagnosed systemic lupus erythematosus patients and their survival

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Malignancies among newly diagnosed systemic lupus erythematosus patients and their survival

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Abstract

The objective of this study was to evaluate the incidence of malignancies among newly diagnosed systemic lupus erythematosus (SLE) patients compared to reference individuals. Another aim was to assess the survival of SLE patients with malignancy compared to references with malignancy. Finnish adult (>17 years) newly diagnosed SLE patients were identified by their drug reimbursement decisions made during 1.1.2000–31.12.2014 from the register of the Social Insurance Institution. For each case, three population controls were individually selected by age, sex and place of residence. Overall, 1006 SLE patients (women 84%), with a mean age of 45.5 years (SD 16 years) and 3005 population controls were linked to Finnish Cancer Registry, and the information about incident malignancies was retrieved from the day the special reimbursement decision for SLE medication was accepted (index day, ID) until 31.12.2018 or until death. The patients diagnosed with malignancy were followed up until 31.12.2019 considering survival. During the follow-up, 85 SLE patients (women 78%) and 192 controls (women 78%) had developed one or more malignancy after the ID. The incidence rate ratio for any malignancy was 1.41 (95% CI 1.08–1.85). The most common malignancy in SLE patients was non-Hodgkin lymphoma, with twelve cases. SLE patients with malignancy had a lower adjusted 15-year survival than controls with malignancy, 27.1% versus 52.4%, and the adjusted hazard ratio for death was 1.68 (95% CI 1.17–2.43). Our results confirm that SLE patients have a higher risk for overall malignancy. The results also suggest that SLE patients with malignancy have lower survival than their references with malignancy.

Keywords

systemic lupus erythematosus, malignancy, cancer, survival

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Introduction

Systemic lupus erythematosus (SLE) is a complex and chronic multi-organ autoimmune disease affecting primarily women.[1] Systemic lupus erythematosus is also related to a great number of comorbidities, such as cardiovascular diseases, infections and mood disorders.[2,3] Moreover, people with rheumatic diseases have a slightly higher risk for overall malignancy, and SLE is not an exception.[2,4–9] Previous studies have shown that especially lymphomas and lung cancer are overrepresented among SLE patients.[2,4]

It has also been shown that SLE patients have a decreased overall survival due to lupus activity, comorbidities and some of the medications used compared to the general population.[10–12] On the other hand, it seems that SLE patients do not experience higher mortality due to malignancy in general, but certain malignancies, such as haematological malignancies, may

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predispose SLE patients to higher mortality.[9–13] However, it is likely that SLE and malignancy combined influence survival markedly, and SLE may be a risk factor for worse survival in the presence of malignancy.[14] To our knowledge, this subject has seldom been studied.[14,15]

Thus, our aim was to depict the spectrum, number and risk of malignancies among incident SLE patients compared to reference individuals in Finland. We also aimed to assess the combined influence of SLE and malignancy on survival in this large register-based study.

Methods

Every permanent inhabitant in Finland has National Health Insurance, and the Finnish Social Insurance Institution (SII) holds a register of these insurances. SLE patients were retrieved for this study based on new reimbursement decisions of SLE medication costs during 1.1.2000–31.12.2014. The patients were identified by the World Health Organization's (WHO) 10th International Classification of Diseases (ICD-10) code of M32. The date of acceptance of reimbursement was defined as the date of SLE diagnosis (index date, ID), and it was the same for the controls.

We performed a nationwide case-control study consisting of only adults (age >17 years). For every incident SLE patient, three individually matched population controls (age, sex and place of residence at the ID) were randomly selected from the Population Register Centre. The education level was determined at baseline (basic, middle, lower high and upper high level) from information acquired from Statistics Finland.

Every new malignancy has been reported to the Finnish Cancer Registry starting from the year 1953. Besides definite malignancies, the registry includes in situ – cancers, high-grade squamous intraepithelial lesions (HSIL) and severe dysplastic alterations (except for skin cancers, where only melanoma in situ alterations are reported), ovarian tumours graded as borderline change and benign central nervous system (CNS) tumours. Moreover, some other disease states, the malignancy of which is considered unclear (such as polycythaemia vera, myelofibrosis and neuroendocrinal tumours) are recorded. Also, tumours that are highly suspected as malignant, even though no microscopic confirmation is at hand, are reported. The malignancies are reported according to the WHO`s ICD-10 codes or according to International Classification of Diseases for Oncology codes (ICD-O-3). No relapses have been recorded for this registry.[16]

The information regarding the incident malignancies was retrieved between 1.1.2000 and 31.12.2018 with the follow-up starting from the ID of each patient and lasting until 31.12.2018 or until the patient died, whichever occurred first. Malignancies that were diagnosed before the ID were excluded from this study. The survival of patients with malignancy was followed up until 31.12.2019, and it was adjusted by age, sex and education.

The reported malignancies were classified in 13 groups according to the literature as follows: breast cancer, prostate cancer, lung cancer, cancers of colon and rectum, melanoma, non-melanoma skin cancer (NMSC), haematologic malignancy (consisting of leukaemias, myelofibrosis, myeloma and polycythaemia vera), bladder cancer, stomach cancer, pancreatic cancer, non-Hodgkin lymphoma (NHL), gynaecological cancer (including cancers of cervix and corpus uteri and vulva) and other cancers (including cancers of CNS, nerve sheet and eye, meningiomas, kidney cancers, Hodgkin lymphoma, other gastrointestinal-tract cancers and gallbladder, biliar duct and hepatic cancers, cancers of salivary and thyroid glands, mesotheliomas, cancers of testis and upper respiratory tract). In addition, malignancies that were ill-defined or unknown were classified into the 'other' group.

In Finland, causes of death of all permanent Finnish residents are recorded to the causes of death statistics maintained by Statistics Finland. The causes of death are registered in four groups as follows: underlying cause of death, immediate cause of death, intermediate cause of death and contributory causes of death. The underlying cause of death is the disease that initiates the course leading to death, and it is used in official annual death certificate registers. The causes of death are recorded according to ICD-10 codes on the death certificate, and the certificate is written by the physician, who has been the last to treat the deceased patient. Every certificate is checked by a forensic pathologist from the Finnish Institute of Health and Welfare afterwards.[17]

Our aim was to evaluate the number of malignancies (C00-D48) as underlying causes of death among SLE patients and references. Furthermore, as causes of death, we inspected eight other ICD-10 groups of special interest as follows: certain infectious and parasitic diseases (A00-B99), mental and behavioural disorders (F00-F99), diseases of the nervous system (G00-G99), diseases of the circulatory system (I00-I99), diseases of the respiratory system (J00-J99), diseases of the digestive system (K00-K93) and symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99).

Since this study was register-based and done without contacting study subjects, neither approval of an ethical committee nor the patient`s informed consent was required by Finnish law.

Statistical methods

The characteristics were presented as means with standard deviation (SD) for continuous variables and as frequencies with percentages for categorical variables. The incidence of

malignancy rates (per 1000 person years) with 95% confidence intervals (CIs) were calculated assuming Poisson distribution; number of events with person-years. Incidence rate ratios (IRRs) were calculated using Poisson regression models, or negative binomial regression models when appropriate. The assumptions of overdispersion in Poisson model were tested using the Lagrange multiplier test. The Kaplan–Meier method was used to estimate the cumulative incidence and log-rank test to assess differences between groups. The adjusted Kaplan–Meier cumulative survivals were estimated using inverse probability of treatment weighting.[18] Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and their 95% CIs. The proportional hazards assumption was tested graphically and by use of a statistical test based on the distribution of Schoenfeld residuals. All statistical analyses were carried out with Stata version 17.0 (StataCorp, College Station, TX).

Results

The study included 1006 SLE patients (mean age 45.5, SD 16 years, females 84%) and 3005 controls. Mean ages were 44.9 (SD 15.9) years in women and 48.6 (SD 16.4) years in men. Among SLE patients, follow-up was a total of 11,294 person-years, 1512 in men and 9782 in women, resulting in a mean of 11.2 years of follow-up for any malignancy. Similarly, among controls, follow-up was a total of 34,734 person-years, 4875 in men and 29,858 in women.

During the follow-up, 85 patients with SLE (78% women) developed a malignancy, whereas in controls the number was 192 (78% women). Seven SLE patients (five women and two men) and 15 controls (11 women and four men) developed more than one malignancy during the follow-up. Compared to controls, SLE patients had a significantly higher IRR for overall malignancy among all patients and women, with IRRs 1.41 and 1.40, respectively (Tables 1 and 2). However, men with SLE did not differ significantly from the controls, likely due to the small number of cases (Table 3).

A significantly increased risk for NHL, pancreatic cancer and other malignancies was recorded (Table 1). The most common malignancy in SLE patients was NHL, with twelve cases. For the other haematologic malignancies, the spectrum varied widely between different types of leukaemia, myeloma and other types of malignant blood diseases. Moreover, NMSC, colorectal and lung cancers were prevalent in SLE patients. Interestingly, no melanomas were recorded among SLE patients compared to 13 melanomas in control patients.

Breast cancer was common among both SLE patients and controls in women, but no statistical difference was recorded between the groups (Table 2). Instead, women with SLE had significantly increased risk for NHL and NMSC. In men with SLE, prostate cancer was the most common malignancy, but no significant difference was recorded for any malignancy compared to controls (Table 3).

Table 1. Numbers, incidence rates per one thousand person-years and incidence rate ratios of recorded malignancies in newly diagnosed systemic lupus erythematosus patients and controls in Finland from the index day until 31.12.2018 or until the patient died, whichever occurred first. Sex-specific malignancies are presented in Table 2 (women) and in Table 3 (men).

	SLE patients		Controls		
Malignancy	N	IR per 1000 95% CI	N	IR per 1000 95% CI	IRR 95% CI
Any malignancy	96	8.5 (6.6–10.4)	209	6.0 (5.2–6.9)	1.41 (1.08–1.85)
Lung	8	0.7 (0.2–1.2)	11	0.3 (0.1–0.5)	2.24 (0.90–5.55)
Colorectal	8	0.7 (0.2–1.3)	12	0.3 (0.2–0.5)	2.05 (0.79–5.34)
Melanoma	0	0.0	13	0.4 (0.2–0.6)	
NMSC	8	0.7 (0.0–1.5)	7	0.2 (0.1–0.4)	3.51 (0.94–13.16)
Haematologic	10	0.9 (0.3–1.4)	15	0.4 (0.2–0.6)	2.05 (0.92–4.56)
Bladder	1	0.1(0.0–0.3)	16	0.5 (0.2–0.7)	0.19 (0.03–1.45)
Stomach	0	0.0	9	0.3 (0.1–0.4)	
Pancreas	5	0.4 (0.1–0.8)	4	0.1 (0.0–0.2)	3.84 (1.03–14.31)
Non-Hodgkin lymphoma	12	1.1 (0.5–1.7)	7	0.2 (0.1–0.4)	5.27 (2.08–13.36)
Other	21	1.9 (1.0–2.7)	34	1.0 (0.7–1.3)	1.90 (1.09–3.31)

SLE = systemic lupus erythematosus; N = number; IR: incidence rate; IRR = incidence rate ratio.
Note: Lung = lung cancer; colorectal = cancers of colon and rectum; melanoma; NMSC = non-melanoma skin cancer; haematologic = haematologic malignancy consisting leukaemias, myelofibrosis, myeloma and polycythaemia vera; bladder = bladder cancer; stomach = stomach cancer; pancreatic = pancreatic cancer; Non-Hodgkin lymphoma; other = other cancers including cancers of CNS, nerve sheet and eye, meningiomas, kidney cancers, other GI-tract cancers and gallbladder, biliar duct and hepatic cancers, cancers of salivary and thyroid glands, mesotheliomas, cancers of testis and upper respiratory tract and cancers that were ill-defined or unknown.

Table 2. Numbers, incidence rates per one thousand person-years and incidence rate ratios of recorded malignancies in women with newly diagnosed systemic lupus erythematosus and control women in Finland from the index day until 31.12.2018 or until the patient died, whichever occurred first.

	SLE patients		Controls		
Malignancy	N	IR per 1000 95% CI	N	IR per 1000 95% CI	IRR (95% CI)
Any malignancy	75	7.7 (5.7–9.7)	163	5.5 (4.6–6.3)	1.40 (1.03–1.91)
Breast	11	1.1 (0.5–1.8)	60	2.0 (1.5–2.5)	0.56 (0.30–1.06)
Lung	6	0.6 (0.1–1.1)	8	0.3 (0.1–0.5)	2.29 (0.80–6.58)
Colorectal	7	0.7 (0.1–1.3)	9	0.3 (0.1–0.5)	2.37 (0.82–6.89)
Melanoma	0	0.0	12	0.4 (0.2–0.6)	
NMSC	8	0.8 (0.0–1.7)	4	0.1 (0.0–0.3)	6.10 (1.40–26.49)
Haematologic	7	0.7 (0.2–1.2)	8	0.3 (0.1–0.5)	2.67 (0.97–7.35)
Bladder	1	0.1 (0.0–0.3)	11	0.4 (0.2–0.6)	0.28 (0.04–2.15)
Stomach	0	0.0	5	0.2 (0.0–0.3)	
Pancreas	3	0.3 (0.0–0.7)	4	0.1 (0.0–0.3)	2.29 (0.51–10.22)
Non-Hodgkin lymphoma	9	0.9 (0.3–1.5)	4	0,1 (0.0–0.3)	6.87 (2.12–22.25)
Gynaecological	7	0.7 (0.2–1.2)	11	0.4 (0.2–0.6)	1.94 (0.76–5.00)
Other	16	1.6 (0.8–2.5)	27	0.9 (0.6–1.2)	1.81 (0.96–3.42)

SLE = systemic lupus erythematosus; N = number; IR: incidence rate; IRR = incidence rate ratio.
Note: Breast = breast cancer; lung=lung cancer; colorectal = cancers of colon and rectum; melanoma; NMSC = non-melanoma skin cancer; haematologic = haematologic malignancy consisting leukaemias, myelofibrosis, myeloma and polycythaemia vera; bladder = bladder cancer; stomach = stomach cancer; pancreatic = pancreatic cancer; Non-Hodgkin lymphoma; gynaecological = gynaecological cancer including cancers of cervix and corpus uteri and vulva; other = other cancers including cancers of CNS, nerve sheet and eye, meningiomas, kidney cancers, other GI-tract cancers and gallbladder, biliar duct and hepatic cancers, cancers of salivary and thyroid glands, mesotheliomas, cancers of testis and upper respiratory tract and cancers that were ill-defined or unknown.

Table 3. Numbers, incidence rates per one thousand person-years and incidence rate ratios of recorded malignancies in men with newly diagnosed systemic lupus erythematosus and control men in Finland from the index day until 31.12.2018 or until the patient died, whichever occurred first.

	SLE patients		Controls		
Malignancy	N	IR per 1000 95% CI	N	IR per 1000 95% CI	IRR (95% CI)
Any malignancy	21	13.9 (7.7–20.1)	46	9.4 (6.6–12.3)	1.47 (0.86–2.52)
Breast	0	0.0 (0,0 to 0,0)	0	0.0 (0.0–0.0)	
Prostate	5	3.3 (0.5–6.1)	10	2.1 (0.8–3.3)	1.61 (0.56–4.61)
Lung	2	1.3 (0.0–3.2)	3	0.6 (0.0–1.3)	2.15 (0.36–12.89)
Colorectal	1	0.7 (0.0–2.0)	3	0.6 (0.0–1.3)	1.07 (0.11–10.27)
Melanoma	0	0.0	1	0.2 (0.0–0.6)	
NMSC	0	0.0	3	0.6 (0.0–1.3)	
Haematologic	3	2.0 (0.0–4.2)	7	1.4 (0.4–2.5)	1.38 (0.36–5.32)
Bladder	0	0.0	5	1.0 (0.1–1.9)	
Stomach	0	0.0	4	0.8 (0.0–1.6)	
Pancreas	2	1.3 (0.0–3.1)	0	0.0	
Non-Hodgkin lymphoma	3	2.0 (0.0–4.2)	3	0.6 (0.0–1.3)	3.22 (0.65–15.90)
Other	5	3.3 (0.4–6.2)	7	1.4 (0.4–2.5)	2.30 (0.74–7.18)

SLE = systemic lupus erythematosus; N = number; IR = incidence rate; IRR = incidence rate ratio.
Note: Breast = breast cancer; prostate = prostate cancer; lung = lung cancer; colorectal = cancers of colon and rectum; melanoma; NMSC = non-melanoma skin cancer; haematologic = haematologic malignancy consisting leukaemias, myelofibrosis, myeloma and polycythaemia vera; bladder = bladder cancer; stomach = stomach cancer; pancreatic = pancreatic cancer; Non-Hodgkin lymphoma; other = other cancers including cancers of CNS, nerve sheet and eye, meningiomas, kidney cancers, other GI-tract cancers and gallbladder, biliar duct and hepatic cancers, cancers of salivary and thyroid glands, mesotheliomas, cancers of testis and upper respiratory tract and cancers that were ill-defined or unknown.

Malignant cases appeared steadily among women with SLE through the follow-up. Moreover, the cumulative incidence of malignancy among women with SLE started to differ 1 year after the ID, and the relative difference persisted over time compared to control women (Figure 1).

Altogether, 122 of the 277 persons who developed a malignancy during the follow-up died. Deaths were more frequent among SLE patients (N = 48) than among controls (N = 74). By the end of the follow-up, the crude survival for persons with malignancy was 30.0% (95% CI 17.4%–43.6%) in SLE patients and 47.2% (95% CI 33.9%–59.4%) in controls, $p = 0.020$. The age-, sex- and education-adjusted 15-year survival was 27.1% and 52.4% for the SLE patients and controls, respectively (Figure 2), and the adjusted HR for death was 1.68 (95% CI 1.17–2.43).

The most common cause of death among patients with malignancy was malignancy among both SLE patients (N = 34, 70%) and controls (N = 56, 76%). Nine patients (19%) and seven controls (9%) died of cardiovascular diseases. The rest of the causes of death were divided evenly (data not shown). Infection was marked as a contributory cause of death in four patients (8%) and two controls (3%), and SLE in six patients (13%).

Discussion

In this large nationwide case-control study, we found the incidence of overall malignancies to be slightly higher among newly diagnosed SLE patients than among population controls in Finland. Although the rates for specific malignancies were quite low, we found a significantly increased risk for NHL. The risk of NMSC was also higher among women with SLE, but interestingly no cases of melanoma were found in SLE patients. SLE patients with any malignancy also had a distinctively worse survival than references with any malignancy.

We found that the risk of developing a malignancy was almost 1.5-fold higher among SLE patients. This finding is in line with previous studies, which have reported standardised mortality ratios for developing any malignancy ranging from 1.1 to 1.9 in SLE.[4,19,20] Moreover, in a nationwide Korean study from 2008 to 2014, an odds ratio of 1.4 for any cancer was recorded in newly diagnosed SLE.[21]

In our study, the most common malignancy was NHL in SLE patients. In addition, the second most common malignancy was breast cancer, but we did not record any significant difference in breast cancer between SLE patients and controls. Altogether, our study results do not differ from other studies by much. Especially NHL and lung cancer have been overrepresented among SLE patients, while no increased risk has been recorded for some other types of malignancies, such as breast cancer.[4,9,19] Moreover, in another Finnish study with almost 26 years of follow-up and conducted between 1967 and 2013, Tallbacka et al. found the risk of overall malignancy in SLE to be nearly doubled. They also found an increased risk for NHL and kidney

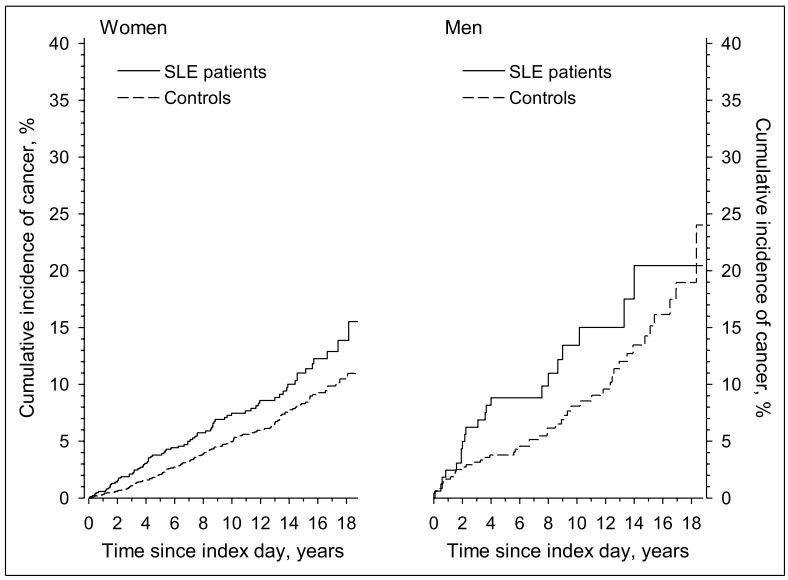

Figure 1. Cumulative incidence of malignancies along time in newly diagnosed systemic lupus erythematosus patients and controls by sex in Finland from the index day until 31.12.2018 or until the patient died, whichever occurred first.

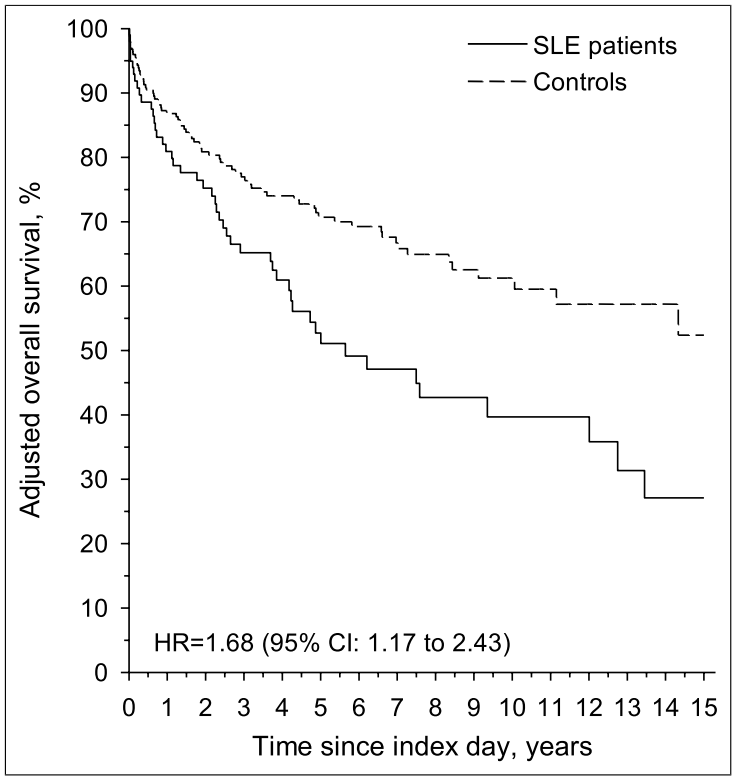

Figure 2. Adjusted (age, sex and education) overall survival in newly diagnosed systemic lupus erythematosus patients and controls with a malignancy from the index day until 31.12.2019.

cancer. However, they did not find an elevated risk for NMSC or pancreatic cancer, as we did. The minor differences between our study results and theirs may be explained by the longer follow-up time, smaller sample size and the fact that they included only SLE patients treated at Helsinki University Central Hospital.[20]

The most notable difference between SLE patients and their references was recorded for NHL risk as it was more than five times higher in SLE patients in our study. It has been shown that some of the autoimmune diseases are related to certain types of haematologic malignancies possibly due to deficiencies in immunoregulation.[9,22,23] SLE patients seem to be particularly prone to develop a lymphoma.[4,9,22–28] For instance, Bernatsky et al. showed three and four times higher risks for all haematologic malignancies and for all lymphomas, respectively, in their large international multicentre (USA, Canada, Europe and South Korea) cohort study.[4] Reasons for increased lymphoma risk are unknown, but chronic inflammation, chromosomal abnormalities, different kinds of cytokines, immunosuppressive treatment and disease activity may have a role in the pathogenesis.[4,9,22–25] In particular, SLE patients seem to be prone to NHL, as an over four times higher risk has been depicted.[4,26–28]

Interestingly, we found an elevated risk for NMSC among women with SLE, but no melanomas were recorded among SLE patients. Our results are similar to other studies from the Nordic countries which have shown the NMSC risk to be slightly increased in SLE.[29,30] It has been proposed that the increased risk could partly result from the use of cyclophosphamide. In contrast, the use of hydroxychloroquine could be a protective factor.[23,31] A slightly decreased risk for melanoma in SLE patients has been reported in a study from the state of California, whereas Bernatsky et al. showed no significant difference in risk.[4,32] We presume that the increased NMSC risk may partly be explained by immunosuppressive medication in our study, although we lacked the clinical information. On the other hand, the reduced melanoma risk could be explained by the decreased sun exposure among SLE patients to some extent.[33] However, a surveillance bias considering both NMSC and melanoma is possible, since SLE patients and

their skin are likely followed up more closely than other people.

We found that malignancy in the lungs was one of the most frequent single malignancy types, but no significant difference was recorded compared to controls among all patients or observed along sex. Our study result differed from others who have found the lung cancer risk to be approximately twice as high in SLE.[4,19,29,32]

A significantly increased risk for pancreatic cancer was found in our study, but the number of cases was limited. Previous reports on the risk of pancreatic cancer in SLE are not uniform[4,19–21,26,32], and further studies are needed to determine the actual risk.

We found only sporadic cases of gynaecological cancers of varying origin, as did Tallbacka et al.,[19] and we could not confirm any significant increased risk. Earlier findings on gynaecological cancers are not consistent.[4,20,21,32,34] Some studies have shown a higher risk for vulvar or vaginal cancer, whereas cancer risk of uterus and ovaries seem to be reduced.[4,21,32,34] Moreover, women with SLE may have an increased risk for cervical neoplasia, but the risk of developing cervical cancer is not well established.[4,21,33–35] Our study result may be partly explained by the extensive cervical cancer screening program in Finland, which prevents progression to cancer in some cases.[9,23,36,37]

Our other aim was to compare the survival of SLE patients with malignancy to general population controls with malignancy and to assess SLE as a risk factor for worse survival in coincidence with any malignant disease. We found that malignancy was the most common cause of death among both SLE patients and controls with malignancy. In our study, the risk of death was almost two-fold higher among SLE patients with a malignant disease, suggesting that SLE impairs survival among people with a malignancy. We pondered that the decreased survival may partly be explained by the complex immune dysregulation and the medication used for SLE, which both predispose to infections.[38–40]

Our study result is in line with a large study from the United States, which compared the survival of elderly women with both SLE and breast cancer to women with breast cancer or SLE alone. They discovered that patients with both SLE and cancer had a higher mortality than patients with cancer or SLE alone.[14] Moreover, one retrospective cohort study evaluated the survival of patients with both rheumatic disease and cancer compared to the general population. They showed that in certain rheumatic diseases (dermatomyositis, polymyositis and rheumatoid arthritis), the survival was decreased in coincidence with cancer. However, the number of SLE patients was limited in the study.[15]

The strengths of this study are the case-control study design and the mean follow-up of more than 11 years. The data on the incidence of malignancy and causes of death were retrieved from official registers, the reliability of which is well established and regularly monitored.[41] We also linked many different official registers and used extensive nationwide data, including all incident malignancies diagnosed both in primary and specialised care. We included all newly diagnosed SLE patients during 1.1.2000–31.12.2014 in Finland.

A major limitation of this study is the lack of clinical data. Therefore, we could not determine the severity of SLE. In addition, we were not able to investigate the effect of many acknowledged confounding factors such as smoking habits and obesity on the risk of malignancy. We also lacked the specific diagnoses and details of some malignancies, such as the stage of malignancy. There may also be some surveillance bias because SLE patients are regularly monitored.

In conclusion, we showed that SLE patients had a higher risk for overall malignancy. Especially the risk of NHL was elevated. We also showed that SLE patients with any malignancy had a worse survival than the references with malignancy. Our study results demonstrated an increased risk for certain, sometimes unscreenable, malignancies that emphasises the importance of early clinical suspicion and diagnosis.

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References

1. Cervera R, Abarca-Costalago M, Abramovicz D et al. European working party on systemic lupus erythematosus. Systemic lupus erythematosus in Europe at the change of the millennium: lessons from the "Euro-Lupus project". *Autoimmun Rev* 2006; 5: 180–186.

2. Rees F, Doherty M, Grainge M et al. Burden of comorbidity in systemic lupus erythematosus in the UK, 1999–2012. *Arthritis Care Res (Hoboken)* 2016; 68: 819–827.
3. Kariniemi S, Rantalaiho V, Virta LJ, et al. Multimorbidity among incident finnish systemic lupus erythematosus patients during 2000–2017. *Lupus* 2021; 30: 165–171.
4. Bernatsky S, Ramsey-Goldman R, Labrecque J et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun* 2013; 42:130–135.
5. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015; 17: 212.
6. Liang Y, Yang Z, Qin B, et al. Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis. *Ann Rheum Dis* 2014; 73: 1151–1156.
7. Hill CL, Nguyen AM, Roder D, et al. Risk of cancer in patients with scleroderma: a population-based cohort study. *Ann Rheum Dis* 2003; 62: 728–731.
8. Morrisroe K, Hansen D, Huq M, et al. Incidence, risk factors, and outcomes of cancer in systemic sclerosis. *Arthritis Care Res (Hoboken)* 2020; 72: 1625–1635.
9. Choi MY, Flood K, Bernatsky S, et al. A review on SLE and malignancy. *Best Pract Res Clin Rheumatol*. 2017; 31: 373–396.
10. Elfving P, Kariniemi S, Kautiainen H, et al. Mortality in SLE patients compared to population controls in Finland in years 2000–2015. *Rheumatology (Oxford)* 2021; 60: 4238–4244.
11. Tselios K, Gladman DD, Sheane BJ, et al. All-cause, cause-specific and age-specific standardized mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971–2013). *Ann Rheum Dis*. 2019; 78: 802–806.
12. Bultink IEM, de Vries F, van Vollenhoven RF, et al. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. *Rheumatology (Oxford)*. 2021; 60: 207–216.
13. Bernatsky S, Boivin JF, Joseph L et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006; 54: 2550–2557.
14. Bruera S, Lei X, Pundole X, et al. Systemic lupus erythematosus is a risk factor for mortality in elderly patients with early breast cancer. *Arthritis Care Res (Hoboken)* 2021.
15. Park JK, Yang JA, Ahn EY et al. Survival rates of cancer patients with and without rheumatic disease: a retrospective cohort analysis. *BMC Cancer*. 2016; 16: 381.
16. Finnish Cancer Registry. https://syoparekisteri.fi/ (accessed May 2021).
17. Statistics Finland. https://www.stat.fi/til/ksyyt/2019/ksyyt_2019_2020-12-14_laa_001_fi.html (accessed May 2021).
18. Cole SR and Hernan MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed* 2004; 75: 45–49.
19. Björnådal L, Löfström B, Yin L, et al. Increased cancer incidence in a Swedish cohort of patients with systemic lupus erythematosus. *Scand J Rheumatol*. 2002; 31: 66–71.
20. Tallbacka KR, Pettersson T and Pukkala E. Increased incidence of cancer in systemic lupus erythematosus: a finnish cohort study with more than 25 years of follow-up. *Scand J Rheumatol*. 2018; 47: 461–464.
21. Bae EH, Lim SY, Han KD, et al. Systemic lupus erythematosus is a risk factor for cancer: a nationwide population-based study in Korea. *Lupus*. 2019; 28: 317–323.
22. Hemminki K, Huang W, Sundquist J, et al. Autoimmune diseases and hematological malignancies: exploring the underlying mechanisms from epidemiological evidence. *Semin Cancer Biol*. 2020; 64: 114–121.
23. Ladouceur A, Tessier-Cloutier B, Clarke AE et al. Cancer and systemic lupus erythematosus. *Rheum Dis Clin North Am*. 2020; 46: 533–550.
24. Bernatsky S, Ramsey-Goldman R, Joseph L, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. *Ann Rheum Dis*. 2014; 73: 138–142.
25. Klein A, Polliack A and Gafter-Gvili A. Systemic lupus erythematosus and lymphoma: incidence, pathogenesis and biology. *Leuk Res*. 2018; 75: 45–49.
26. Chen YJ, Chang YT, Wang CB, et al. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. *Am J Med*. 2010; 123: 1150.e1–e6.
27. Bernatsky S, Ramsey-Goldman R, Rajan R, et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. *Ann Rheum Dis* 2005; 64: 1507–1509.
28. King J and Costenbader KH. Characteristics of patients with systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma (NHL). *Clin Rheumatol* 2007; 26: 1491–1494.
29. Westermann R, Zobbe K, Cordtz R, et al. Increased cancer risk in patients with cutaneous lupus erythematosus and systemic lupus erythematosus compared with the general population: a Danish nationwide cohort study. *Lupus*. 2021; 30: 752–761.
30. Ragnarsson O, Gröndal G and Steinsson K. Risk of malignancy in an unselected cohort of Icelandic patients with systemic lupus erythematosus. *Lupus*. 2003;12: 687–691.
31. Bernatsky S, Ramsey-Goldman R, Urowitz MB, et al. Cancer risk in a large inception SLE cohort: effects of demographics, smoking, and medications. *Arthritis Care Res (Hoboken)* 2020; 73: 1789–1795.
32. Parikh-Patel A, White RH, Allen M, et al. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. *Cancer Causes Control*. 2008; 19: 887–894.
33. Elwood JM and Jopson J. Melanoma and sun exposure: an overview of published studies. *Int J Cancer*. 1997; 73: 198–203.
34. Dreyer L, Faurschou M, Mogensen M, et al. High incidence of potentially virus-induced malignancies in systemic lupus erythematosus: a long-term follow-up study in a Danish cohort. *Arthritis Rheum* 2011; 63: 3032–3037.

35. Wadström H, Arkema EV, Sjöwall C, et al. Cervical neoplasia in systemic lupus erythematosus: nationwide study. *Rheumatology (Oxford)*. 2017; 56: 613–619.
36. Lönnberg S, Hansen BT, Haldorsen T, et al. Cervical cancer prevented by screening: long-term incidence trends by morphology in Norway. *Int J Cancer*. 2015; 137: 1758–1764.
37. Finnish Cancer Registry. https://cancerregistry.fi/screening/cervical-cancer-screening/ (accessed June 2021).
38. Zonana-Nacach A, Camargo-Coronel A, Yañez P, et al. Infections in outpatients with systemic lupus erythematosus: a prospective study. *Lupus*. 2001; 10: 505–510.
39. Rúa-Figueroa Í, López-Longo J, Galindo-Izquierdo M, et al. Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus. *Semin Arthritis Rheum*. 2017; 47: 38–45.
40. Danza A and Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus*. 2013; 22: 1286–1294.
41. Korhonen P, Malila N, Pukkala E, et al. The finnish cancer registry as follow-up source of a large trial cohort –accuracy and delay. *Acta Oncol*. 2002; 41: 381–388.

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease associated with many comorbidities. This thesis evaluated the multimorbidity among newly diagnosed Finnish SLE patients by utilizing many nationwide registers. An increased risk of multimorbidity was observed among SLE patients: cardiovascular diseases, mood disorders, certain malignancies and diseases of the genitourinary system were frequent among them, and they used more antidepressant drug therapy than controls. SLE patients with malignancy had also a lower survival than controls with malignancy.

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