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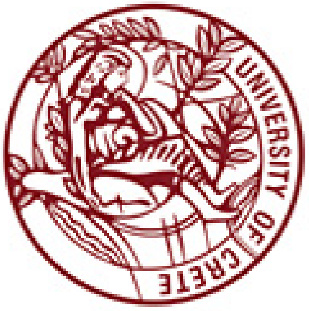

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Epidemiology of Systemic Lupus Erythematosus and Lupus Registry Establishment in Crete, Greece

A Dissertation

By

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ΠΕΡΙΛΗΨΗ

Εισαγωγή-Σκοπός Παρά τις σημαντικές επιδημιολογικές μελέτες που έχουν δημοσιευτεί τα τελευταία χρόνια για το ΣΕΛ, οι αναφορές που είναι βασισμένες στην κοινότητα και έχουν λεπτομερώς εξακριβώσει τα περιστατικά είναι σπάνιες.

Μέθοδοι: Μελετήσαμε την επιδημιολογία του ΣΕΛ και το φάσμα της νόσου στο νησί της Κρήτης την περίοδο 1999-2013. Για την εύρεση των περιπτώσεων συμπεριλάβαμε ασθενείς ≥15 ετών. Η διακρίβωση τους έγινε με τα ACR[1997], SLICC[2012] κριτήρια ταξινόμησης και τη διάγνωση από ειδικό ρευματολόγο, ενώ έγινε ενδελεχής σύνθεση επιδημιολογικών και κλινικών δεδομένων από ιατρικούς φακέλους, διοικητικά δεδομένα και ερωτηματολόγια σε ασθενείς.

Αποτελέσματα: Η προτυποποιημένη κατά ηλικία και φύλο και η αδρή επίπτωση του ΣΕΛ ήταν 7.4 ([95% CI] 6.8-7.9) και 8.6 (8.0-9.0) ανά 100,000-άτομα/χρόνο, αντίστοιχα, με μέσο όσο ηλικίας διάγνωσης 43 (±15) έτη και τάση σταθεροποίησης στις γυναίκες αλλά αυξητική στους άνδρες. Ο προτυποποιημένος και αδρός επιπολασμός (Δεκέμβριος 2013) ήταν 123 (114-133) και 143 (133-154)/10^5, με τον τελευταίο να είναι υψηλότερος σε αστικές συγκριτικά με τις αγροτικές περιοχές (165 vs. 123/10^5, $p<0.001$). Η προτυποποιημένη κατά ηλικία και φύλο επίπτωση της νεφρίτιδας ήταν 0.6 (0.4-0.8) με σταθερή τάση, ενώ του νευροψυχιατρικού ΣΕΛ ήταν 0.5 (0.4-0.7) ανά 100,000-έτος/χρόνο και με αυξανόμενη τάση. Το 50% των περιστατικών είχαν μέτριες/σοβαρές εκδηλώσεις, με το 34% από αυτούς να λαμβάνουν

ανοσοκατασταλτικές/βιολογικές θεραπείες. Μετά από 7.2 (±6.6) χρόνια μέση διάρκεια νόσου, το 30.5% των ασθενών παρουσίασε μη αναστρέψιμη βλάβη οργάνων, με τα νευροψυχιατρικά συμβάντα να είναι τα συχνότερα, ενώ το 4.4% των ασθενών με νεφρίτιδα ανέπτυξαν νεφρική ανεπάρκεια τελικού σταδίου. Τα ACR[1997] και SLICC[2012] κριτήρια ταξινόμησης εμφάνισαν μεγάλο ποσοστό συμφωνίας (87%), ενώ η διάγνωση που βασίστηκε στο γιατρό επήλθε νωρίτερα σε περίπου 20% των περιστατικών. Ο συνολικός αριθμός των συνοσυροτήτων ήταν 3.4 ± 2.4 (μέσος όρος ± SD)ενώ 42% των ασθενών είχαν >3 συνοσυρότητες).

Συμπεράσματα: Χρησιμοποιώντας ενδελεχή μεθοδολογία περιγράψαμε υψηλή συχνότητα του ΣΕΛ στην Κρήτη. Τα αποτελέσματά μας δείχνουν ότι η νόσος δεν είναι σπάνια, προσβάλει γυναίκες μέσης ηλικίας, αναγνωρίζεται αυξανόμενα στους άνδρες και έχει σημαντικό κλινικό φορτίο (μη αναστρέψιμη βλάβη, πολυνοσυρότητα) παρά την βελτίωση στην έγκαιρη διάγνωση και θεραπεία.

Λέξεις-κλειδιά: αυτοάνοσο νόσημα; επιδημιολογία; επίπτωση; επιπολασμός; νεφρίτιδα ΣΕΛ; νευροψυχιατρικός λύκος;

ABSTRACT

Objectives Several population-based surveillance studies on SLE have been reported, yet community-based, individual-case accessed, comprehensive reports are missing.

Methods: We studied the SLE epidemiology and burden on the island of Crete during 1999-2013. Multisource case finding included patients ≥15 years old. Cases were ascertained by the ACR[1997], SLICC[2012] criteria, and rheumatologist diagnosis, and validated through synthesis of medical charts, administrative and patient-generated data.

Results: Overall age/sex-adjusted and crude incidence was 7.4 ([95% CI] 6.8-7.9) and 8.6 (8.0-9.0) per 100,000-persons/year, respectively, with stabilizing trends in women but increasing in men, and an average (±SD) age of diagnosis at 43 (±15) years. Adjusted and crude prevalence (December 2013) was 123 (114-133) and 143 (133-154)/10^5, the latter being higher in urban than rural regions (165 versus 123/10^5, $p<0.001$). Age/sex-adjusted nephritis incidence was 0.6 (0.4-0.8) with stable trends, whereas that of neuropsychiatric SLE was 0.5 (0.4-0.7) per 100,000-person/years and increasing. Half of prevalent cases had moderate/severe manifestations, with 34% having received immunosuppressive/biologic therapy. After 7.2 (±6.6) years disease duration, 30.5% accrued damage with the neuropsychiatric domain most frequently afflicted, whereas 4.4% of nephritis patients developed end-stage renal disease. The ACR[1997] and SLICC[2012] classification criteria showed high concordance (87%), yet physician-based diagnosis occurred earlier than criteria-based in about 20% of cases. The total number of comorbidities was (mean ± SD) 3.4 ± 2.4 and 42% of SLE patients had multi-morbidity (>3 comorbidities)

Conclusions: By employing a comprehensive methodology, we describe high SLE occurrence in Crete. Our results suggest that the disease is not rare, it affects predominantly middle-aged women and is increasingly recognized in men. Despite

early diagnosis and treatment the clinical burden (irreversible damage, comorbidities) remains significant.

Keywords: autoimmune disease; SLE; epidemiology; incidence; prevalence; lupus nephritis; neuropsychiatric lupus;

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CHAPTER I: INTRODUCTION

Systemic lupus erythematosus (SLE) is a *complex* autoimmune disease with variable manifestations and chronic relapsing-remitting course. (1)

In our post genomic era, research has tremendously advanced our knowledge in the epidemiology, genetic susceptibility and the molecular pathways implicated in the pathogenesis of the disease.

According to the current paradigm, SLE is triggered in a genetically-susceptible person by exposure to environmental risk factors and further epigenetic modifications (2) mediate the effect of such exposures on immunologic responses, (3) eventually leading to an *inflammatory*, *autoimmune*, *multi-systemic* disease characterized by *autoantibody production* and *tissue injury*.(4)

About 90 genetic loci (5) and a number of environmental factors along with *stochastic events* (6) have been implicated in the etiopathogenesis of SLE, yet the exact etiology remains unknown.

SLE is highly perceived as a rare disease but most recent studies suggest that is not so uncommon anymore (7). Reports regarding lupus occurrence are conflicting, yet the *overall trend worldwide is increasing* (8) due to a number of factors including increased awareness and early diagnosis (9). Notably, such trend in autoimmune diseases in general is reported mostly from the more developed countries (10), highlighting the possible role of the so-called *westernized lifestyle* (10, 11).

In clinical terms, SLE is commonly described as "the disease with the 1000 faces", leading a spectrum from mild mucocutaneous to devastating life-threatening illness, such as nephritis and neurophychiatric disease.(1) Further, lupus is the disease with *the greater number of antibodies that can be detected*

[more than 100 (12)] even though practically only- the well-known anti-nuclear antibodies (ANA) remain the hallmark and the one used as screening test and detected in almost all patients (13, 14)

Diagnosis is still based on the strong clinical acumen of expert rheumatologists, since no diagnostic criteria have been validated so far (15). Both the *1997 American College of Rheumatology (ACR*) and the *2012 Systemic Lupus International Cooperating Clinics (SLICC)(16)* classification criteria sets, depict the above-described picture of the multi-faceted disease and although they were created for epidemiological studies, often are (inappropriately) used in clinical routine to support the initial diagnostic thoughts.(17)

Non unexpectedly, reports regarding the occurrence, clinical profile or the long-term outcomes of SLE are characterized by high variability (18). Illustratively, in studies conducted across the globe during the last fifteen years the prevalence of the disease ranges from 9(19)to 241/100,000 (20) and the incidence from 0.3(19) to 23.2 (21) per 100,000 person-years. (22) Moreover, the clinical phenotype displays significant heterogeneity among cohorts. (23)

This is best exemplified in the rates of severe disease, such as nephritis, which varies from affecting 20–30% of SLE patients in Europe (24) and US (25), to more than 60% in specific ethnicities (26) and as high as 70% in Asia (27).

The discrepancies described above may be due to multiple factors. First, the variance in SLE across *gender*, *age* and *race/ethnicity* groups or even socioeconomical status is consistent across studies (8). SLE is approximately *9 times more common in women* of reproductive age and about *3-5 times more common in black* people. (8) Second, the diversity in estimates is commonly due to different *study parameters* (8, 22, 28) which include the *healthcare system*

under study and the *methodology* used (i.e. case finding and ascertainment, definitions used, quality of information/data capturing systems)(8).

Rationale of the thesis.

Several population-based surveillance studies on SLE have been reported (7, 25, 29, 30), yet community-based, individual-case validated, comprehensive reports are missing.

Large administrative-sourced studies usually lack access to real word rheumatologists' data and on the other hand most SLE clinical studies include tertiary care information since *more severe patients are selected*. (28)

Updated epidemiological information at the community level may help further characterizing the burden of disease, highlight unmet needs as well as provide insights to the pathogenesis.

Given the relative closed and genetic homogenous population of Crete, the aim of this thesis was to capture meaningful data through the establishment of a *"Cretan Lupus Registry"*. The main *objective* of the thesis were to obtain estimates of SLE incidence and prevalence in Crete during 1999-2013.

CHAPTER II: BACKROUND

1. SLE: an overview

1.1 Historical milestones

The origin of the term "lupus" and the first descriptions

The Greek physician *Hippocrates* (*460-375 BC*) was the first to describe the cutaneous manifestations of a disease, calling it *herpes esthiomenos* (gnawing dermatosis, "έρπης εσθιόμενος, from the greek verb *εσθίω = κατατρώγω"*). (31) More that 15 centuries later, *Hebernus*, an archbishop from France, was possibly the one using the term "*lupus*" describing a rash that looked like a wolf 's bite (32). Biett (33) in *1833* was actually the first who named the disease "*lupus érythèmateux".* Interestingly, Biett's student Cazenave described the *preference of the disease to young women.* Finally, *Sir William Osler (1849–1919)* used the phrase "systemic lupus erythematosus." (34).

Advances which defined our current view of lupus

Interestingly, it was not until *1901*, when *Paul Ehrlich* described the concept of *autoimmunity*, coining it with the term "horror autotoxicus" to emphasize that autoimmunity would "contradict nature's aversion to self-injury". *The era of immunology* had practically begun. After a the period 1915-45, known as the eclipse of autoimmunity, an important step in determining the immunological nature of the disease (9) was taken in *1948* by Dr Hargraves, who discovered the *LE cell* (35) (a bone marrow neutrophil or macrophage with a special morphology due to phagocytosis of nuclear debris). The discovery of "ANA reaction" that followed was the key observation that linked SLE to immunological abnormality. Subsequently, the concept of *tolerance* (unresponsiveness of the immune system to substances/tissues that could

elicit an immunologic reaction) was strengthened in part due to the Burnet &Medawar's Nobel Prize in 1960 (36). Immunology then was very different from what it is today, as "there were no B lymphocytes, thymic production of T lymphocytes, major histocompatibility complex, dendritic cells nor antigen presentation, no cytokines, no inbred, congenic, transgenic nor gene knockout mice!"(37). Since 1946, thousands of studies were conducted on these subjects.(38)

Major breakthroughs through the modern period

The modern era is characterized by the development of animal models [summarized in (39)], studies showing the genetic predisposition of lupus (5) and advances on therapeutics (40)

The *HLA (*Human Leukocyte Antigen) *locus, a genetic complex encoding MHC proteins, which regulate the immune system)* was identified in '70s. The association of SLE with *HLA class I* (41-44), class II *alleles* and eventually the complement C2 and C4 genes within class III (45-49) were the key discoveries.

Nowadays, *GWAS (*Genome-wide association studies) have reaffirmed the earlier studies on the importance of genetic susceptibility in SLE and have revealed more -and more critical to the disease- risk loci associated with main immune abnormalities (B cell, T cell and innate immune system function, as well as the apoptotic and immune complex clearance (9) *Epigenetic* studies were developed along with human genome project during the last century and provided us with further understanding of lupus pathogenesis.(50)

Biologic Therapies. In 2011 *Belimumab*, a monoclonal antibody that inhibits B lymphocyte stimulator (BAFF) was approved for lupus therapy, opening a new era. (51) Nowadays a number of candidate *biologic drugs* are being investigated in clinical trials.(52)

Biomarkers

The routinely used conventional biomarkers, (i.e anti-ds DNA) are highly specific and strongly associated with the disease flaring, but they have low sensitivity and no prediction value for activity and treatment. There is an effort to discover more reliable biomarkers so that therapy can be offered in a more personalized level. Findings in novel epigenetic biomarkers (DNA methylation and miRNAs) or the combined use of different types of biomarkers (genetic biomarkers, as a predictor for organ involvement; epigenetic biomarkers, for therapy response and protein biomarkers for relapse prediction may be a promising future tool (53)

1.2 Etiopathogenesis

SLE pathogenesis is multifactorial, lying on genetic, epigenetic and environmental factors and on abnormalities of both the innate and the adaptive immune system. These factors contribute individually or synergistically to the development and progression of the disease (54).

1.2.1 Genetics

SLE presents a *complex genetic influence*: although the genetic basis of lupus is known, the way of transmission is not fully delineated so far.

Studies in *familial* SLE led to the identification of monogenic causes of SLE, which are rare inherited conditions leading to *complement deficiencies*, *interferon-α over-production* and *apoptosis defects* (55) (38).

SLE is inherited in *polygenic* way in the majority of the patients (thus controlled by many genes, each contributing to the overall phenotype) (56). Interestingly, no important differences in terms of manifestations, damage or survival exist among familial lupus and sporadic cases (57-63) with the exception of a recent study showing higher damage among African Americans SLE patients with familial versus sporadic cases (64)

Notably, even in sporadic cases, lupus occurs *more often within families (65)* A family history of SLE is significantly associated with increased risk of developing the disease (OR=6.8, 95% CI 1.4-32). (66) S*iblings* of affected individuals are much more likely to develop SLE (up to 10% of patients with SLE may have first degree family member with the disease). (67) (58, 65, 68-74). Further, monozygotic twins present a *tenfold higher* risk than dizygotic twins (24–56% versus 2–5%, respectively)(75-77).

In a recent report from Taiwan, the Relative Risks (RR 95% CIs) for SLE were *315.94* for twins of the patients, 23.68 for *siblings*, 11.44 for *parents*, 14.42 for *offspring*, and 4.44 for *spouses* without genetic similarity. (78) In the same study, ***heritability*** (defined as the proportion of the phenotypic variance explained by genetic factors (78) was estimated to be ***43.9%.*** This is lower than the estimates of *66%* that have been previously reported (but as authors suggest these older studies had not taken into account *shared environmental contributions* to the risk of SLE) suggesting that such shared environmental ("familial factors") are also contributing to SLE susceptibility for **25.8%** and non-shared environmental factors for ***30.3%*** (79, 80)

Of course, the most robust evidence for a genetic component for lupus susceptibility is the genetic variants that are now established to be statistically associated with lupus (81). The region of the genome with by far the strongest association with SLE susceptibility is the MHC(82), on *chromosome 6* (*HLA-DRB1*03:01)* (8)

Latest findings in the genetics of SLE using genome-wide association arrays are reviewed in (4). About 90 *susceptibility loci* are reported up to now as the discovery of risk variants for SLE.(83) (for interactive continuous information http://insidegen.com/insidegen-LUPUS-Associations.html). Most variants lie in non coding genome areas and are thought to affect regulatory regions (either in proximal genes or through looping, with possible role on multiple genes as well).(6, 84, 85)

Ethnic/racial differences in lupus incidence also strongly support the role of genetics, as numerous reports have shown(86) (50, 87, 88), despite the *strong linkage disequilibrium (*nonrandom association of alleles at different loci) particularly of the European population which has made very difficult to precisely assess genetic contribution of individual alleles/loci and explain differences among races and ethnicities (5, 8). Further, GWAS studies revealed that most of the genetic risk is shared across borders and ethnicities(4).

To date much effort has been done to unravel the genetic influence on clinical heterogeneity in SLE. Notably, genetic proportions of Native American ancestry, present increased and *European ancestry decreased risk* of developing severe SLE nephritis.(89) (90)

GWAS data focus on 3 main cellular pathways (each of them possibly influenced by multiple genes)

a. Lymphocyte signaling (B- and T-cells)
b. IFN signaling pathways
c. Clearance of immune complexes/other waste(6)

In conclusion, we are still in early stages of understanding how the genetic program of lupus starts and how the loci produce different phenotypes. Despite progress, GWAS have explained about 50% of lupus hereditability

(5) The *genetic risk score (GRS)* which is used to determine the risk of SLE development (based on the ORs and risk allele frequencies) is far from *the optimal* and probably needs more data on *genetic interactions* or *biological markers* that may contribute to improve the predictions (4).

Of course, lupus genetics research is moving towards a "post-GWAS era" with the main aim to identify *causal alleles* and sequencing of all exons ("next-generation sequencing"). Important *open issues* remain especially when it comes to its *utility* at the bedside level and much more needs to be done towards this direction.

1.2.2 Stochastic events

It is interesting to remember a statement of Dr. C. Garrison Fathman at the opening of a lecture on autoimmunity **a**t the Fourth International Congress of Immunology in Toronto, 1986. He characteristically said that "*autoimmunity is a combination of genetics and bad luck*."

In SLE the stochastic expression of combination of susceptibility genes is consistent with low concordance of genetic loci in twins (91, 92). This is also illustratively shown in animal models where environmental factors were tightly controlled (i.e same room/cage, identical diets, (93) (94). It is supported that the stochastic processes that lead to DNA modification may be the "lynch pins" leading the initial tolerance break (50)

1.2.3 Epigenetics

The term "epigenetics", refers to chromatin modifications that *do not alter DNA sequence* (50, 95, 96). The main epigenetic mechanisms known to be

implicated in lupus is related with DNA methylation, histone modification, and noncoding RNA which all normally play important roles in immune response. (96)

-*DNA methylatio*n (addition of a methyl group to the 5′ carbon in the pyrimidine ring of a cytosine residue) *repress the accessibility to transcriptional activators* thus inhibits the gene transcription. (97) Reversibility (demethylation process) can also occur. (50) The supported evidence for DNA methylation change in SLE and its significance has been based on a twin study reported in 2010 (98) and many others later (99) that have been extensively studied (reviewed in (100). Characteristically, T-cells from SLE patients have global DNA hypomethylation especially in nephritis cases. (6, 97, 101, 102) but also aberrant methylation is present in lupus B cells, neutrophils playing an important role in pathogenesis.(102)

-*Histone modification.* Histones are protein forming nucleosomes (the basic of chromatin subunit). This epigenetic change refers to the post-transcriptional modification (i.e acetylation) of a specific amino acid in the polypeptide chain of a histone, affecting chromatin conformation and altering its accessibility, thus influencing gene transcription. It has been also supported that is correlated with lupus pathogenesis (96, 100, 103, 104)

- *microRNAs (miRNAs)* are small noncoding RNAs which present important role in transcription through binding to messenger RNAs (mRNAs. miRNAs have a great capability in *fine tuning of gene expression*. Abnormalities in their expression contributes to dysfunction of lupus autoimmunity (105, 106) (107, 108) (109)

Notably, "cross-talks" among epigenetic abnormalities, can occur in lymphocytes and other cell types in lupus patients, further contributing to the pathogenesis (110)

1.2.4 Environmental exposures

A very interesting hypothesis that has been long supported is that environmental factors act on immune responses mediated by epigenetic changes. Via epigenetic mechanisms, a number of *internal and external risk factors* (i.e smoking, nutrition, infections and chemicals' exposures) impact on the epigenetic mechanisms, which, in turn, regulate the gene expression, and eventually trigger immunologic events. (3)

A vast number of factors has been studied in regards to SLE. They could be grouped in four large categories (Dr. Wards, presentation 9th European Lupus Congress).

a. *Physical exposures*

b. *Chemical exposures*

c. *Biological/Diet*

d. *Reproductive*

Physical exposures

Ultraviolet light is not a novel risk factor in SLE (111). It is long thought to trigger apoptosis (112) thus it is considered as a triggering stimulus. UV has immune-modulatory capabilities and may exacerbate pre-existing lupus (113, 114), yet the epidemiological data regarding its role in development of SLE are not robust or conclusive (115).

Exposure to sunlight possibly acts as a trigger for SLE especially in people who were sunburned presenting with blistering or a rash. Women with the skin type 'always burn, never/sometimes tan' (sun-reactive skin type I/II) had an increased risk of developing SLE compared with women with other skin types [OR 2.3, (95% CI 1.1-4.8)] (66) especially the white participants (116)

Further, UV is possibly associated to drug-induced lupus (6). A recent study showed that UV converts propranolol to an *aryl hydrocarbon receptor ligand*, which exerts pro-inflammatory action. Last, it has been postulated that UV have epigenetic effects, as *decrease the DNA methylation* in healthy controls and patients (117) (118)

Biological/Dietary

Infections

Long implicated in lupus pathogenesis. Epstein–Barr virus increase is considered to trigger SLE. A recent meta-analysis showed increase in seroprevalence of anti-viral capsid antigen IgG (OR 2.08; 95% confidence interval (CI) 1.15 – 3.76, p = 0.007) (119). Cytomegalovirus human endogenous retroviruses (HERVs) has also been implicated(120) (121) Notably, a single study from Taiwan showed that tuberculosis (TB) was a risk factor for precipitating SLE (OR = 2.11, 95% CI = 1.49–3.00).(122). Other infections (i.e Helicobacter pylori, hepatitis B virus, and some parasite infections) (123-125) are suggestive to be protective.

A general role of infections (and not a single infection) are suggested in SLE although mechanisms are not fully elucidated e. g serum levels of lipopolysaccharide-a gram negative bacteria cell wall component which can act as an TLR4 activator- are increased in patients with SLE; amyloid-DNA

complexes found in biofilms trigger the autoantibodies production in mice)(6, 126)

Microbiome

The microbiota (a term for collectively all microbes inhabiting the gut) is a study field of emerging interest. The human gut microbiome (as named collectively the microbes' genes) is suggested to present immunomudulatory role revised recently in(127).Gut microbioma is highly influenced from diet, drinking water,(128) use of antibiotics and probiotics and it is a challenging future theurapeutic goal.(129)

Gut microbial composition is altered in SLE vs. healthy people. (129) Using next-generation sequencing techniques to explore the potential dysbiosis (a shift in microbial composition) Arancha el al. revealed lower levels of *Firmicutes to Bacteroidetes ratio (130)* Although this was replicated (131), there is inconsistency in the results in humans. (129) Mouse SLE models also exhibits altered microbiome and interestingly differences among genders. (129, 132).

The gut microbiota interacts both with the host and other organisms, i.e. the virome (the genomes of all the viruses that inhabit a host) interacts with the gut microbiota. To this end, a *chronic trigger* seems likely as a mechanism in SLE (133)

Interestingly, the long standing "Hygiene Hypothesis" (which attributes the increase of immune reactivity to reduced exposure to microorganisms in industrialized countries, due to improved sanitary conditions) linked with the emerging role of the *microbiome diversity* (suggesting that the gut microbiota was affected from population migration from rural areas in contact with

animals and environmental flora to more sanitized urban areas) (134) (135) represent *fields of growing interest in the context of lupus research*(129).

Vitamin D (VitD)

The epidemiological data regarding the role of VitD as an SLE risk factor are not strong (136, 137) being difficult to delineate whether the VitD insufficiency commonly described in lupus patient is a risk factor or a consequence of sun avoidance of the patients due to photosensitivity/photoprotection, renal insufficiency and/or some medications used. Most of such studies are cross sectional, so that a risk of reverse causality cannot be always avoided.(138) Reports showing low vitamin D level in new-onset Lupus, support a role of vitamin D as an environmental trigger of the disease in genetically susceptible patients (137) (139, 140)

Diet

Diet as also mentioned previously may have an epigenetic role, influencing i.e the DNA-methylation, which has critical role to SLE pathogenesis. Additionally, dietary habits -even water- are suggested to have an effect on gut microbiota and subsequently this has been extensively studied in both SLE humans and lupus-prone animal models (141) (142) but no causative epidemiological data linking diet or dietary elements with lupus development has been revealed. For example, dietary antioxidant intake was studied by Constenbader et al.(143) but it was not found to be associated with the risk of developing systemic lupus erythematosus. Alike, no evidence of associations between intake of antioxidants from foods and supplements (vitamins A, C,

and E and α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin) and the risks of SLE was found in Nurses' Health Study cohort.(144) Last**,** no associations were revealed between dietary vitamin D intake in adolescence and adult female SLE (145)

Obesity

Obesity has not been found to be related with increased lupus risk as it has been shown with i.e Rheumatoid Arthritis in earlier studies. (146) In a study published in 2017 with data from incident SLE cases from NHS (n=153) and NHSII (n=151), during 5,602,653 person-years of follow-up, the authours showed that cumulative average obesity was significantly associated with SLE risk in NHSII [HR = 1.85 (1.17-2.91)], but not in NHS [HR = 1.11 (0.65-1.87)] vs to normal BMI. In the meta-analysis of these cohorts, obesity was not significantly related with increased risk of SLE [HR = 1.46 (0.88-2.40)]. (147)

Alcohol, Tea and Coffee

Several epidemiologic studies have investigated the relationship between alcohol consumption and the risk of developing SLE. Most reported an inverse association and dose-response relationship between alcohol and SLE susceptibility, suggesting a possible protective effect, (148) (66, 149) (150) although there was some inconsistency in the results. (151) Interestingly, in a recent report performed in two large prospective cohorts (NHS (1980-2012) and NHSII (1989-2011), an inverse association between moderate alcohol consumption (≥5 grams or 0.5 drink/day) and SLE risk in women. [HR: 0.61 (95% confidence interval [95% CI] 0.41–0.89)] was clearly demonstrated. (147)

Further, consumption of black tea (odds ratio [OR] 1.88, 95% confidence interval [95% CI] 1.03-3.41) and coffee (marginal association OR 1.57, 95% CI 0.95-2.61), was associated with an increased risk of SLE. (152) In contrast, findings regarding the consumption of green tea drinking are not conclusive (152, 153)

Salt

Last, an interesting study by Wu et. all showed the role of salt in SLE development (in mice). As a possible mechanism it was suggested that salt acts possibly by promoting follicular helper T cells (that act by helping B cells, leading an important role in autoimmunity).(154)

Vaccinations

A recent systematic review and meta-analysis findings suggested that vaccinations significantly increased risk of SLE (RR=1.50; 95%CI 1.05-2.12, P=0.02).(155)

Chemical exposures

Silica

Crystalline silica is a well-known adjuvant, with the highest exposures in construction, ceramics, mining stone masonry or tile work. Acts by inducing pro-inflammatory cytokines, stimulating T-cell (decreasing regulatory T cells)

and also increases oxidative stress and induces apoptosis. (156). Robust epidemiologic data provide evidence of the silica role to lupus development (OR RR 1.6, 2.1, 4.6, 10)(116, 144, 157-161). Yet, some important questions remain: First, whether it is the quantity (dose) or the duration of the exposure that it is important, second the exact mechanisms: evidence supports that likely the inhaled silica dust is trapped in the respiratory system, and the resulting apoptosis, may leads to development/ acceleration of autoimmunity pathways. In conclusion silica is a robust but not specific environmental factor for lupus (162)

Asbestos

Additionally, exposures to other silicates may act similarly. Illustratively, there is scarce evidence relevant to exposure to *asbestos*, a long-chain silicate, which is associated with increased risk of rheumatoid arthritis, systemic sclerosis, and SLE). (combined OR 2.1; 95%CI 0.9,5.1); Yet, further investigation of their effects on SLE risk is needed.(162)

Smoking

Smoking has been long implicated as a trigger factor for lupus development. A meta-analysis of the available studies up to 2005, had found a *modestly increased risk posed by current smoking* (RR 1.5 [95% CI 1.09, 2.08]) (163) Notably, after adjustment for alcohol and socioeconomic status (as smoking status confounders) the OR was 2.07 (95% CI: 1.33–3.23) and 1.76 (95% CI: 1.09–2.83), respectively. Subsequent meta-analyses confirmed this association between smoking and SLE (OR=1.31-1.9). (146, 164, 165)

Additionally, smoking cessation was found to be associated with a risk reduction of SLE development. (149). Moreover, the risk of SLE was related with the average number of cigarettes/ day, smoking cigarette-years, and smoke inhalation amount (OR 3.73, 95% CI 1.46-9.94) for moderate inhalation; OR 3.06, 95% CI 1.81-5.15 for deep inhalation)(149)

The finding of increased ds-DNA antibodies that has been found in current and past smokers SLE patients (OR 4.0 and 1.4 respectively)(166) was not further replicated. Young et al. did find any clear association between smoking status and auto-antibodies neither in lupus patients, nor in unaffected relatives or healthy controls, concluding that the effect of tobacco on SLE may manifest its risk through mechanisms that do not include the autoantibody production per se.(167)

The actual mechanism through which tobacco contributes to autoimmunity is not fully understood up to now. It is supported that smoking is associated with an increased pro-inflammatory (TNF-α, IL-1, IL-6, IL-10) and reduced production anti-inflammatory cytokines (IL-10).(168, 169) (170). When the exposure to tobacco is sustained for longer, a chronic inflammatory process emerges that may enhance microbial colonization/infection and abnormal processing of apoptotic cellular debris leading to autoimmunity. Another mechanism postulated is that smoke provokes oxidative stress, possibly contributing to SLE by DNA demethylation and immune gene up-regulation (171). Characteristically, smoking has been described as *"the fire behind the disease" (171).*

Organic Dust

In line with hygiene hypothesis, an interesting case-control study reported that farm *contact with livestock* was significantly and inversely associated with

SLE risk (OR = 0.55), after adjusting for silica exposure. (172). This association was stronger among those with childhood farm residence and both childhood and adult livestock exposure (OR = 0.19; 95% CI 0.06, 0.63). In another study, however, the early and extended childhood farm residence (i.e. prenatal/maternal farm exposure and longest childhood farm residence) increased SLE risk (OR = 1.8; 95% CI 1.1, 3.0) vs neither. (173) Notably, such association was not seen with only prenatal/maternal exposure (173)

Hair Dyes

The use of hair dyes as a lupus risk factor have come into attention and of interest, due to the fact that they contain aromatic amines (known to induce lupus symptoms)(174) and an early study in 1989 that pointed to a positive association (175). Subsequent reports thought did not replicate the result.(176-178) or found a week association with SLE (OR 1.5, 95% CI 1.0, 2.2) which increased with longer use. (179) Interestingly some newer studies show some weak association with ANAs (180) and reveal some of the possible the immunologic effects of hair dyes (in mice: pro-inflammatory immune response; increase of Tregs).(181)

Solvents (hydrocarbons), pesticides and cosmetics

Environmental contaminants exist in pesticides, hazardous waste sites and several products (such as cosmetics) with main mechanisms of action the oxidative stress or discuption of endocrine homeostasis (182, 183)

Hydrocarbons refer to organic compounds with diverse industrial uses which broadly include fuels, solvents, lubricants, emulsifiers/ waxes. Organic solvents are popular in both work and household settings as cleaning

products (i.e dry cleaning, nail polish removers) and in chemical products (i.e in paints, varnishes, perfumes).

Increased SLE risk has been found to be associated with jobs/tasks involving solvent exposures (116, 184): relatively strong associations were reported with working with *paints* or *dyes* or developing film (OR 3.9; 95% CI 1.3, 12.3) and *applying nail polish/nail applications* (OR 10.2; 95% CI 1.3, 81.5) (116); repair/cleaning machinery or metal (OR=1.9) and dry cleaning (OR=1.5).(116) These findings should be accepted with caution as there are inconsistencies in literature. (158) To this end, animal studies regarding specific compounds i.e trichloroethylene reviewed by Cooper et al. (185) warrants further investigation. (162)

Dioxins, furans, polychlorinated biphenyls, and other polycyclic aromatic hydrocarbons are organic pollutants (organohalogens) that can be found widespread in the environment due to their ability to accumulate in the food chain. Interestingly, increased SLE mortality was observed in long-term follow-up of a Taiwanese population exposed to very high levels of polychlorinated biphenyls and dibenzofurans through contaminated rice (186). Similar findings from animal studies warrants furher investigation. (162) Also, results from animal studies on mineral oil exposures (mixtures of alkanes and cyclic paraffins with various industrial uses) in relation to SLE risk, leads to a need for further human studies.

To our knowledge a single study has reported an SLE cluster (13 SLE cases who were found on two blocks alone, OR 19.33; 1.96, 190.72) in a neighborhood which was built on an abandoned oil field waste site (Hobbs, known as the "oil capital of New Mexico" where oil was discovered in 1928) Impressively, higher than usual levels of various hydrocarbons (including benzene, xylene, toluene, pristane, phytane and aromatic hydrocarbons) have been reported. (187) One important limitation of this study was the difference

in ethinicity in exposed vs. non exposed people (about 50% vs. 4% of Hispanics respectively, thus exposed was related with an ethnicity with increased lupus prevalence. Futher, no association was found between proximity of the residence to hazardous waste sites (defined as sites where oil or hazardous material has been deposited, stored or disposed, known as E21 sites) and the risk of SLE diagnosis in an urban setting in African American population.(188)

Pesticide use has been reported as a risk factor for SLE in a number of studies This was shown in women with *at least monthly use* [(OR = 2.3; 95% CI 1.3, 4.1) (173) and with *mixing pesticides-but not with mere application- for agricultural use.* [(OR 7.4, 95% CI 1.4, 40.0] (184). Notably in the second study (184) there was not adjuststment for other agricultural exposures i.e organic dust (livestock/grain dust) which was only some years later found to be protective (162, 172).) Further, in a prospective study in 2011 by Parks et al. in post-menopausal women, (ages 50-79) ever mixing/applying insecticides (mostly at home setting) increased risk of SLE development,, with increasing trends by cumulative use; p-trend 0.06)(189) and similarly with insecticide application by others (p-trend=0.10). Of course, because of the sample characteristics (older post-menopausal women), it is not clear whether these results can be generalized.

To this end we have to notice that some other studies did not find association between lupus development and pesticides use (116) highlighting possibly the fact that there is a great diversity among exposures in a farm setting (which may result in confounding). Relevant findings from studies on individual pesticides' effects show that that their role on autoimmunity are likely to be very complex and still no specific substance has been identified as a lupus causal agent, as reviewed by Parks. (162)

An interesting metanalysis suggests that toxic effect influences those who are already genetically susceptible. (190) Additionally, a recent study suggested a dose-related elevation in SLE risk with *early life pesticide exposure*.(173)Regarding cosmetics, the use of *lipstick* was associated with increased risk of lupus development [OR = 1.71, 95% CI = 1.04–2.82 with at least 3 days/week use], with a trend of greater risk with earlier age of initiation (<16 years vs. never use; OR = 1.95, 95% CI = 1.01–3.76, *p* trend = *0.02*) and with greater frequency [OR = 1.75, 95% CI = 0.89–3.44, *p* trend = 0.07 with 7 days/week vs. never use]. No association was reported between cosmetologists' occupation and SLE occurrence. (184)

Heavy metals (mercury), uranium

Mercury-exposed gold miners had higher anti-nuclear antibodies (ANA) and higher concentrations of pro-inflammatory cytokines, as compared to diamond and emerald miners with no mercury exposure. Associations with SLE were seen with self-reported occupational exposure to mercury (OR 3.6, 95% CI 1.3, 10.0) (184) and similarly in a case-control study (OR 3.1; 95% CI 0.77, 12.7) (116). Hg exposure was also associated with ANA positivity in NHANES (1999-2004) (191)

Interestingly, a nested case-control study using data from a population that had resided near a uranium ore-processing plant in Ohio (Fernald Community Cohort (FCC) reported an association of SLE with higher levels of uranium exposure (OR 3.92, 95% CI 1.13-13.59).(192)

Pollution

Limited studies have investigated whether exposure to air pollution is associated with lupus incidence. Particulate air pollution has been linked to the development of systemic autoimmune rheumatic diseases, including lupus, in Canada (193) Further studies are needed to examine these findings with a focus to SLE patients. Interestingly PM10, NO2, and CO were suggested to have a role as risk factors for juvenile-onset SLE disease activity (estimated with SLEDAI-2K score >8) approximately 2 weeks after exposure in a large urban area in San Paolo. (194)

Reproductive exposures

Endometriosis

Laparoscopically confirmed endometriosis was significantly associated with SLE diagnosis (HR=2.03; CI 1.17- 3.51) in a large prospective cohort (Nurses' Health Study II), although risk was attenuated after adjustment for hysterectomy and oophorectomy (195). Similarly, a case-control study from Sweden demonstrated a positive association between endometriosis and SLE (OR 1.39, 95% CI1.09–1.78).(195)

Oral contraceptive use, early menarche, parity, perinatal factors, post menopausal hormones

Two large prospective studies [Nurses' Health Study (NHS) and NHSII cohorts] reported in 2007 a significant increase in SLE development with ***age≤10 years at menarche*** (pooled RR 2.1, 95% confidence interval [95% CI] 1.4-3.2), ***oral contraceptive use*** (pooled RR 1.5, 95% CI 1.1-2.1), and ***postmenopausal hormones use*** (RR 1.9, 95% CI 1.2-3.1).(196). In the same study SLE risk was increased among postmenopausal women after surgical

menopause (RR 2.3, 95% CI 1.2-4.5), and with earlier age at natural menopause (*P for trend<0.05*). (196).

Two years later data from UK's General Practice Research Database found that the adjusted rate ratio of incident SLE associated with any ***use of combined oral contraceptives (COCs)*** was 1.19 ([95% CI] 0.98-1.45), whereas with current use it was 1.54 (95% CI 1.15-2.07). (197) The assosiation was further increased in current users who had recently started COC (RR 2.52, 95% CI 1.14-5.57) compared with longer-term current users (RR 1.45, 95% CI 1.06-1.99). The risk was particularly elevated with current exposure to first- or second-generation contraceptives (RR 1.65, 95% CI 1.20-2.26). (197) Additionally, a strong dose-response association between the oral contraceptives (ethinyl estradiol dose) and SLE new cases was shown. (197) A resent metanalysis (198) did not showed a significant association among OC users and lupus risk, revealing the existing inconsistency with previous studies.(199) (200)

On the contrary, a resent metanalysis (198) confirmed a significant association between **Hormonal Replacement Therapy** exposure and an increased risk of SLE (Rate Ratio: 1.96; 95%-CI: 1.51-2.56; p-value<0.001)

Reports on other **reproductive factors** in relation to SLE development are inconsistent (156, 201). Some some of relevan findings include: menstrual irregularity was found associated with an increased risk (RR 3.79; 95% CI 1.43-10.01).(202); breast-feeding was associated with a decreased risk of developing SLE (OR 0.6, 95% CI 0.4-0.9) (200); and last, the number of ovulatory years and parity [women with at least one liveborn child were at lower risk than nulliparous women (RR 0.74; 95% CI 0.64-0.86)]. (203)

Further, SLE was related with **low birth weight** (OR = 2.2; 95% CI 1.2, 3.9), with a linear dose response (*p*-trend = 0.008) as well as with **preterm birth**

[(OR = 3.4; 95%CI 1.6, 7.4)]. (173) a result towards the theory of early environmental exposures which lead to lupus (204, 205), that warrants further investigation. (201, 206) Birth order was inversely associated with SLE in one study particularly among girls (first born vs. not, OR = 0.77, 95% CI 0.64, 0.94; with the odds of SLE increased by 12% for every additional birth, as Arkema et al. reported in 2015 with data from a Swedish population study (207) Additionally, in a recent study it was found that pregnancy induced hypertension may be an independent risk factor for the development of SLE (hazard ratio [HR]=2.87, 95% CI 2.07-3.98, P<0.0001) (208)

In conclusion,

a. the strongest association with SLE incidence has been shown for the associations of **silica**, **smoking**, oral **contraceptives**, **postmenopausal hormone therapy** and **endometriosis**

b. robust evidence exist for the association between **alcohol consumption** and decreased SLE risk.

c. data regarding other factors, including air pollution, ultraviolet light, infections, vaccinations, solvents, pesticides, mercury, obesity, perinatal risk factors and various occupational exposures in relation to SLE risk are not consistent.

Biologic **mechanisms** suggested to link environmental exposures and SLE include:

-increased oxidative stress

-systemic inflammation

-cytokine up-regulation, and

-hormonal triggers

1.3 Pathogenetic mechanisms

The hallmark of SLE pathogenesis is the ***loss of tolerance*** and the **sustained production of antibodies**

Recent studies support that main disturbed pathways leading to tolerance break and subsequent tissue damage (6) are:

a. Defects in immune complexes (or other waste i.e apoptotic cells) clearance
b. Neutrophil extracellular traps (NETS)
c. Nucleic acid sensing
d. Lymphocyte signaling
e. Type I Interferon production pathways

The **SLE pathogenic model** that was suggested during the previous decade (6) (based on genetic data, mouse models and in vitro observations) supports that one key mechanism is an *imbalance in apoptotic cell production and disposal*. More specifically, under normal circumstances, during apoptosis, nuclear antigens are not accessible and blebs are created on the cell's surface containing nuclear material among other cellular debris which rapidly disappears, before the immune system recognize it. **Increase in this "apoptotic load"** can be produced by UV and toxins/infections-all known exposures that have been associated with SLE-(6). In case that such apoptotic debris persist for longer than expected time interval, an **inflammatory response** can be elicited through receptors that recognize nucleic acid (i.e *toll-*

like receptors family), leading to the production of Interferon 1 (IFN-1). *IFN-1* among other cytokines leads to ***B cell differentiation*** and *loss of tolerance*.

Antibodies The increase in serum of antinuclear andibodies' (ANA) levels as a subsequent event to self-tolerance loss is considered as the initial step in the disease development. Interestingly, in most cases autoantibodies can be detected before clinical syndrome (209, 210).

1.4 Manifestations

Commonly described as "the disease with the 1000 faces", lupus leads a spectrum from mild mucocutaneuous to devastating illness, such as *nephritis* and *neurophychiatric disease*.

The general constitutional symptoms include: fever, malaise, arthralgias, myalgias, headache, loss of appetite, weight loss and fatigue.(211) In the course of SLE, patients may present with arthritis, dermatologic minifestations, serositis, cytopenias, kidney disease. (1) Fatigue is reported up to 90% of women with SLE (212)

1.5 Diagnosis

Diagnosis is still based on strong clinical acumen of expert rheumatologists, since no diagnostic criteria have been validated so far (15). Both the *1997 American College of Rheumatology (ACR*) and the *2012 Systemic Lupus International Cooperating Clinics (SLICC)* classification criteria sets, depict the above-described picture of the multi-organ autoimmune disease and although they were created for epidemiological studies, often are (inadequately) used in clinical routine to support the initial diagnostic thoughts.(17)

Notably, manifestations and serological abnormalities do not always occur at the same time period, leading to a *continuum of a disease* from a milder connective tissue syndrome (CTD) or pre-lupus to the full-spectrum of a severe case. Often times the diagnosis is ongoing (17) and challenging as a "fine balance between over-diagnose SLE and under-diagnose early disease/ incomplete lupus (213). Last, not rare are the cases with *preclinical disease* presenting with autoantibodies but are asymptomatic (213)

1.6 Course –Prognosis-Outcomes

Symptoms can vary from person to person and may be intermittent (*flares and remissions*) (214) with various patterns, with prolonged remission to be an infrequent feature. (215) (213) The disease in overall can be *mild, moderate, or severe* or lead to different degrees of *non-reversible organ damage.(216-218)*

Flares An international consensus definition describes SLE flare as "a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements, which must be considered clinically significant and usually there would be at least consideration of a change or an increase in treatment". (215) What provokes this flaring process is not completely understood and possible triggers includes infections, drugs hormones or other environmental exposures. (219) *Notably, flares lead to more damage accrual.(220)* A recent review estimated that flare incidence rate was 0.11 flare per patient-year (range 0.19-1.76 patient-year).(221)

The *concepts of flaring and remission* are often time complex and to approach them appropriately, a validated index must be used [i.e systemic lupus

erythematosus disease activity index (SLEDAI or SLEDAI-2K); British Isles lupus assessment group (BILAG) 2004 (222); European consensus lupus outcome measure (ECLAM)] combined with physician's global assessment. (223, 224) According to a large international task force on definitions of remission in SLE (DORIS), a distinction should be made between*: remission off therapy* (which requires no other SLE treatment than maintenance antimalarials) and *remission on therapy* [which allows maintenance antimalarials, low-dose corticosteroids (prednisone ≤5 mg/day), maintenance immunosuppressives and/or maintenance biologics](223)

Non reversible Organ Damage The commonest score used in studies to estimate non reversible damage is the "SLICC/ACR Damage Index (SDI) score"(225). On average, the SDI score increased at a rate of 0.13 per year. Higher rates of damage have been reported in older patients, male and those of African American origin. Further *higher SDI* has been associated with *lower financial status* or *education* attainment as well as with *hypertensive* lupus patients, those who had more *disease activity*, *lower complement*, were positive for *anti-double-stranded DNA*, satisfied *more ACR criteria*, or were receiving *corticosteroids*. On the contrary lower risk was reported among patients who were receiving therapy with hydroxychloroquine. Petri et all suggested that among variables, *age, hypertension, and corticosteroid use* emerged as the most significant predictors of damage accrual in SLE patients. (226)

Hospitalizations A recent study by Busch et al reported that 65% of lupus patients had one or more hospitalization during a 5-year study period (2007-2012) corresponding to *incidence rate of hospitalizations: 0.50 per year* (227) Compared with non SLE hospitalized patients, SLE patients are younger (51

vs. 62 years), mostly female (89% vs. 54%), and more likely to be of racial/ethnic origin. (228) The most common reason for hospitalization of lupus patients is infections. Further, admissions are a source of high direct and indirect costs: illustratively, the annual cost per patient for hospitalization was was US$51,808.41 and the average length of stay was 8.5 days per admission. Notably, SLE patients with organ involvement rather than active disease at initial hospitalization are likely to have a poor outcome, especially for those with renal insufficiency cardiopulmonary involvements and neuropsychiatric events (229) As expected, SLE was not a significant prognostic factor for outcomes in patients admitted for non-related causes. Interestingly, men lupus patients have a worse prognosis during hospitalization when compared to females, (230)

1.7 Health Related Quality of Life

SLE is associated with low health-related quality of life (HRQOL) which is significantly worse at an earlier age, as compared to patients with other common chronic diseases. (231) (232, 233) HRQOL is one of the most important outcomes in lupus patients. (232) Older age of SLE patients is associated with lower physical, but not mental, HRQOL independently of damage and disease activity.(234) Fatigue is recognized as an important factor for daily life of patients independently from disease flaring. (235)

In a recent study by Caldero et al. (236) HRQoL was associated with depressive symptoms, higher activity and organ damage whereas impairments in attention and memory did not decrease the HRQoL. (236) In addition, active lupus nephritis and musculoskeletal manifestations were associated with physical limitations, emotional difficulties, increased pain and poor social functioning. (237, 238) HR-QOL of SLE patients is influenced by

self-efficacy in the management of the disease (239) No association of hydroxycloroquine concentrations with current or longitudinal HRQOL has been found in SLE. (240) The associations of older age with lower physical, but not mental, HRQOL were independent of accumulated SLE damage and current SLE activity.(234)

Furthermore fibromyalgia is associated with poorer HRQOL. (241) Not unexpectedly, the quality of life and psychological status in relatives of lupus patients are adversely impaired, as reported by Zeng et al.(242) HR-QOL of SLE patients is influenced by self-efficacy in the management of the disease and problematic support. (239) No association of HCQ concentrations with current or longitudinal HRQOL were found in SLE. (240) The associations of older age with lower physical, but not mental, HRQOL were independent of accumulated SLE damage and current SLE activity. (234)

Successful management of complex conditions such as systemic lupus erythematosus (SLE) benefit from patient-reported outcomes (PRO). Measuring health-related quality of life with PROs provides SLE patients with an opportunity to participate in their treatment and to facilitate better communication with the multidisciplinary team involved in their care. Health outcomes research has produced well-validated instruments that can be used across diseases; others have been specifically developed for SLE. (243)

1.8 Survival-mortality

Despite the continuing progress, the all-cause *mortality* in lupus patients is 3-fold greater than the general population, as estimated in recent metanalyses. (244). Noteworhy, between the '50s and the 2000s, SLE survival rates increased [(from 74.8% to 94.8% and 63.2% to 91.4% for the 5-year and 10-year survival, respectively ($P < 0.001$)]. To this end, a population-based study

published in 2017 by Jorge et al. (245) showed that mortality due to SLE has not improved during recent years, with mortality hazard ratios estimated as 2.15 (95% CI 1.63, 2.83) and 2.12 (95% CI 1.61, 2.80) in the early (1999-2006) and late lupus cohorts (2007-2014) respectively.

Further, Tektonidou et all reported that during the period 2008-2016, the 5-year, 10-year and 15-year survival in SLE adult patients from high-income countries 0.95, 0.89 and 0.82, thus higher than those in low/middle-income countries which were 0.92, 0.85 and 0.79, respectively.(246) Noteworthy,, mortality is associated with ethnicity (higher in Native Americans and blacks and lower in Whites, Asian and Hispanics) (247) Last, Fallasinou et al suggested that there are gender differences and reported that the most frequently causes of death among female SLE patients were septicemia (4.32%) and hypertension (3.04%) whereas in men lupus patients heart disease (3.70%) and complicated diabetes mellitus with complications (3.61%) were the most common. (248)

1.9 Comorbidities

SLE remains a *complex* disease with long-term course, burdened with various *comorbidities* (*cardiovascular disease*, *metabolic syndrome* (249), *malignancies* (250-254), *infections* (255) and *osteoporosis*, among others)(256) especially in late onset-disease (<50) (1, 213, 257). Comorbidities decrease quality of life (258), work productivity (259), overall outcomes and survival rates (260, 261) leading to increased needs of more complex management, hospitalizations and higher costs. (262).

In particular, the *cardiovascular risk for lupus patients* is at least double as a recent metanalysis suggested, with the elderly patients having the highest absolute risks and young women presenting very high relative risks (in

comparison with the general population). (263) Traditional risk factors do not fully explain the increased risk and autoimmunity (anti-phospholopid antibodies, disease activity and inflammation) is suggested to play an important role. (257)

Notably, hypertension may be as high as 75% in SLE cohorts. (257) The prevalence of dyslipidemia in lupus patients ranges from 36% at diagnosis to 60% after 3 years. Numerous mechanisms are implicated in its pathogenesis, including antibodies against lipoprotein lipase, as well as, cytokines that affect the balance of lipoproteins. (264) Prevalence of diabetes ranges from 2.7% to 7% and increases over time after diagnosi,s up to 14% (265). Obesity is prevalent in about one third of patients (if defined with Body Mass Index by body mass index [BMI >30 kg/m2] (266)

One more systematic review studying *the risk of stroke in SLE* patients revealed a twofold higher risk of ischaemic stroke, a threefold higher risk of intracerebral haemorrhage, and an almost fourfold higher risk of subarachnoid haemorrhage compared to the general population. (267) Additionally, the incidence of peripheral arterial occlusive disease was 9.39-fold higher (95% confidence interval [CI]=7.70-11.15) in a study, suggesting that SLE is an independent risk factor. (268)

Further, the pooled Risk Ratio (RR) for overall cancer has been estimated 1.28 (95% CI, 1.17–1.41)(250-254). *Malignancy risk* is related to the pathology of the underlying rheumatic disease including the inflammatory process, immunological abnormalities, and exposures such as smoking and viral infections. (269)

Interestingly, SLE patients have a higher rate of atopic dermatitis (6.81% vs. 3.06%), and asthma (10.6% vs. 7.64%) -approximately 2 times- more common that controls. (270) Further, the overall incidence rate of Chronic Obstructive Pulmonary Disease was found to be 1.73-fold higher in SLE patients than

controls. (17.4 vs. 10.1 per 10,000 person-years, 95% CI=1.62-1.84)(271). Additionally, fibromyalgia has been reported to be prevalent in about 13 % of SLE patients. (272)

Infections are an emerging problem for SLE patients. It is estimated that 14–52% of SLE hospitalizations are for infections (pneumonia, opportunistic infections among others (228). More specifically, Pneumonocystis Pneumonia, herpes zoster and cytomegalovirus are seen in high rates in lupus patients. (228) Interestingly, from 2000 to 2011, SLE hospitalization rates for herpes zoster increased whereas for pneumonocystis decreased (228).

An interesting recent study by Gu et. al. in Toronto (273) identified that 19.3% patients suffered ≥1 severe infection with incidence rate to be 29.2 (95% CI: 27.6-30.9) infections per 1000 patient/years. Notably, time interval from first to second infection was shorter than time from diagnosis to first infection. In the same study, respiratory infections were the most common (35.5%) and bloodstream infections were the most common infectious cause of death (42%). Severe infection was suggested to be a predictor of poor prognosis in lupus, it is more common in Latin-Americans and it is associated with *age*, previous *infection*, and *smoking* whereas antimalarials have a protective effect. (273)

As far as ***mental comorbidities*****,** a meta-analyses revealed that the prevalence of depression was 30-39% and the prevalence of anxiety was 40% (95% CI, 30%-49%, $I^2 = 93.0\%$). (274) which were higher than the general population and higher than other rheumatic diseases. (274) Additionally, Bipolar Disorder was found in a higher prevalence in SLE patients compared to

controls (0.62% vs. 0.26%, respectively, P<0.001). (275). Patients with SLE had a higher suicide risk than the general population.(276)

Interestingly, SLE patients have a higher rate of atopic dermatitis (6.81% vs. 3.06%), and asthma (10.6% vs. 7.64%) -approximately 2 times- more common that controls(270) Further, the overall incidence rate of Chronic Obstructive Pulmonary Disease was found to be 1.73-fold higher in the SLE patients than controls (17.4 vs. 10.1 per 10,000 person-years, 95% CI=1.62-1.84). (271). Additionally, *fibromyalgia* has been reported to be prevalent in about 13 % of SLE patients (272)

1.10 Pregnancy in lupus-offspring health

As SLE is mostly diagnosed during the childbearing years, issues around reproductive health are common in everyday practice (277). While *fertility is preserved* and live births occur in most times (85-90%), *pregnancy* remains a *high-risk situation for female SLE patients*. (278). Illustratively, SLE carries higher risk of flaring and pregnancy-related complications such as preeclampsia (278). Fetal morbidity includes higher occurrence of preterm birth (*double pooled relative risk (RR)* of *preterm birth* in SLE vs. controls [RR 2.05 [95% confidence interval (CI): 1.72–3.32)(279)], intrauterine growth restriction, and neonatal lupus (particularly heart block).

A recent systematic review also suggested that maternal SLE is associated with *increased learning disorders (dyslexia*), increased rate of autism spectrum disorders in the offsprings, although further research is necessary to substantiate such evidence. (277) Additionally, the risk ratio for childhood asthma was 1.46 (95% CI 1.16-1.84) in a study by Rossides et. al (280) and for allergic conditions versus control children was 1.35, 95% CI 1.13, 1.61).(281)

1.11 Antiphospholipid syndrome (APS)

APS is the association of thrombosis and/or pregnancy morbidity with antiphospholipid antibodies (aPL) (lupus anticoagulant [LA], anticardiolipin antibodies [aCL], and/or anti-β_2-glycoprotein-I antibodies [aβ_2GPI]) and can occur as secondary disease in SLE (282). SLE patients with aPL have a higher prevalence of thrombosis, pregnancy morbidity, valve disease, thrombocytopenia, hemolytic anemia, renal lesions, and cognitive impairment and higher tissue and organ damage. (282) (283).Longitudinal studies show that APS may develop in 50 to 70% of patients with both SLE and aPL after 20 years of follow-up.(284)

1.12 Financial Burden.

Lupus patients on average have *double medical visits* (outpatient or emergency) and hospitalizations (285) translated into $10,229 more healthcare costs per patient annually. (286) Further, indirect costs of *work a*bsenteeism and *short-term disability* have been estimated to be $1867 and $1602 higher, respectively, for lupus patients vs. non-lupus controls (287). Medical expenses increase steadily over the years with the diagnosis, and this is true particularly for SLE nephritis (288). Notably, the cost of flares increase with disease severity (285) with the average unadjusted cost per mild, moderate, and severe flare, respectively, reaching $909, $1539, and $17,059. Annual total costs for patients with severe flares can be as high as $49,754 (289)

In addition, the socioeconomic and psychosocial impact of SLE should be emphasized. In overall, SLE is associated with a decline on quality of life, *high health-care costs* and *significant productivity loss* thus holds a great burden on both the patient and society.(290)

1.13 Advances in SLE Therapeutics

The burden of SLE remains substantial, both for patients and the health services. After an extended period in which few therapeutic advances were made, fundamental developments are finally on the way. These new treatments will need to be evaluated for both clinical and cost effectiveness if their use is to be widely implemented (291)

New biological agents are being developed which *target the lymphocytes, accessory molecules and cytokines* and aim to enhance the therapeutic efficacy when combined with conventional therapies. B cells remain one of the main target with *belimumab* to have proven its superiority to placebo, when added to the standard of care. On the contrary, the phase III trials of *epratuzumab* and *blisibimod* did not achieve the primary endpoints.

Finally, recent data on the *inhibition of type I interferons (anifrolumab)* appear promising. *Newer calcineurin inhibitors* and combination with conventional immunosuppressive agents are being tested in nephritis.

2. SLE Epidemiology

2.1 Classification criteria

Classification criteria for Systemic Lupus Erythematosus have long been designed for research use with the objective to provide comparable definitions among epidemiological studies or clinical trials, evolving from 1971 ACR criteria, (292) 1982 ACR criteria (293), to their 1997 revised ACR criteria. (294) The latest, althought never validated, are the one mostly used until today in most studies, "shaping our understanding of SLE"(13) . Depicting the immunogenic nature of SLE they involved anti-nuclear antibody as a separate item and need 4 out of 11 items to exist in order the

case be classified as SLE, but no single criterion is thought essential even the hallmark of ANA. (295)

In 2012, SLICC/ACR criteria (16) were introduced, after 8 years of top-field researchers and subsequent validation studies, and were shown to present more sensitivity (94% versus 86%) and similar but less specificity (92 vs. 93%) with ACR-1997. (16, 296). Notably, Ines et. al (296) showed that of patients *not* fulfilling the ACR 1997 (n=296), more than 60% could be SLICC 2012-classified. The subgroup of patients in earlier disease (the first five years), presented the greatest difference in sensitivity (89.3% vs. 76.0%) between the SLICC-2012 and the ACR 1997 classification. On the contrary, the difference was diminishing as with disease duration increased, with no significance difference for patients with more than twenty years after disease diagnosis. (296)

The same research group (297) using a relatively small sample of patients, reported that patients meeting ACR criteria as compared to those with SLICC criteria only, presented with more nephritis (35.1% v. 13.8%, $p < 0.01$), but less thrombotic antiphospholipid syndrome (4.5% vs. 17.2%, $p < 0.01$) during follow-up. Cox models used in the study (297) showed no significant differences in risk for non reversible organ damage [hazard ratio (HR) (95% CI) 0.991 (0.453-2.167)] or mortality [hazard ratio (HR) (95% CI) 0.694 (0.107-4.506)]. Further, the SLICC- 2012 criteria were suggested to perform better in *juvenile populations* at first visit and one year follow-up.(298) Alike in pediatric populations SLCC-2012 criteria performed well but again they showed greater sensitivity ($p<0.001$) an less specific ($p<0.001$) than the ACR criteria. One more report suggested a correlation of SLICC-2012 with SLEDAI Index, although these results need further study (299). Interestingly in the most recent European Medicines Agency (EMA) guidelines the use of either

SLICC-2012 or the ACR 1997 classification use for clinical trials with adherence to one of them during the trial. (300)

Mainly, due some methodological reasons the new criteria has been criticized (301). The main issue is that although they incorporated some new concepts practically did not manage to perform much better that the 1997-ACR criteria (13) showing very low specificity. This would be a "sword of double" edge in case of the SLICC-criteria misuse for diagnostic reasons (302). A new approach is underway since 2014 supported by a Steering Committee appointed by both the European League Against Rheumatism (EULAR) and the ACR working on new classification criteria (13)

It is noteworthy that diagnostic criteria remain an unmet need for lupus which is difficult to attain: Almost 100% specificity and 100% specificity is needed and they should apply universally (ie in every person irrespectively of the settings). As characteristically Larosa et al. report in an interesting review regarding the advances in classification and diagnostic criteria, it is too simplistic to dichotomize as present or absent a disease that may evolve.(302, 303)

2.2 SLE Incidence and prevalence worldwide

SLE is perceived as a rare disease. Notably, there is high variability in reports regarding the occurrence of the disease.(18) Illustratively, in studies conducted across the globe during the last fifteen years the prevalence of the disease ranges from 3.2 (304)to 241/100,000 (20) and the incidence from 0.3 (19) to 23.2 (21) per 100,000 person-years. (22)

A number of population-based surveillance studies on SLE have been reported especially from *countries with public health systems*, including studies from Denmark, Finland, Norway, Sweden and the UK (7, 25, 29, 30). Still reliable studies of the incidence and prevalence of Systemic Lupus Erythematosus remain few, due to a number of mainly methodological issues as reviewed by Lewis et al. (8) with most important the following ones:

a. a number of cohorts are in fact incomplete or from populations that are not closed or have unclear boundaries

b. in some countries census high-quality data are not provided, leading to non accurate incidence and prevalence estimates

c. few studies have used the capture–recapture technique to increase validity

d. Studies use different case definitions (based on different criteria based definition)

e. Variability on case finding methods (population-based studies, administrative-only sources, medical records review among others)

More specifically, in **USA** there has been a considerable variation in estimates. Illustratively prevalence/100,000 has been estimated at a range of 42.0–300.0 in overall, 45.0–408.2 in females and 4.4–54.0 in males (18). Two comprehensive studies supported from CDC from Michigan (305) and Georgia (306) both published in 2014, reported the incidence of SLE to be 5.5 and 5.6 per 100 000, respectively, and the prevalence of SLE as 72.8 and 73.0 per 100 000, based on data from 2002–4 (305).

In 2017, two more studies were published providing estimates of age-standardized SLE incidence and prevalence rates of 4.6-6.2 and 62.2-73.8 per 100,000 person-years respectively among residents of New York County

(Manhattan) (307) and 4.6 and 84.8 per 100,000 persons in San Francisco County, California (308) during the same study period. (2007-2009). Although these reports are very comprehensive and strict methodology was followed there were performed for only two years, so that no information about the trends is provided.

Furthermore, a study from Medicaid nationwide population estimated SLE incidence to be as high as 23.2 per 100,000 person-years and SLE prevalence as 143.7 per 100,000 (25). In general the estimates described above are increased in comparison with previous ones. Particularly, the increase in SLE incidence that has been reported in previous decades (from 50s to 90s) (309) were attributed to classification criteria use, awareness and recognition of milder forms of the disease and better diagnostic approach as reviewed in (21) and (8).

Notably, when some ethnicities were overrepresented in studies, the estimates were higher. Illustratively, a study from Medicaid nationwide population estimated the SLE incidence to be as high as 23.2 per 100,000 person-years and SLE prevalence as 143.7 per 100,000. (25). In Alaska, the age-adjusted incidence and prevalence of SLE was 7.4 per 100,000 person-years (95% CI 5.1-10.4) and the prevalence was 178 per 100,000 person-years (95% confidence interval [95% CI] 157-200), in 2007. (310). Last, the age-adjusted prevalence and incidence of SLE according to the primary definition were 178 per 100,000 person-years (95% confidence interval [95% CI] 157-200) and 7.4 per 100,000 person-years (95% CI 5.1-10.4) in a population-based registry of American Indian and Alaska Native people, 2007-2009.(310)

In **Canada**, the incidence was estimated at 3.0/100,000 person-years [95% confidence interval (CI) 2.6-3.4] and the prevalence at 32.8/100,000 persons, in 2003, by Bernansky et. al (30).

In **Central and South America**, lupus incidence ranges from 4.6-6.64 (in Caribbean) (311, 312) to up to 8.7/100,000 in Brazil (313) and prevalence from 64.2 in Martinique (1999)(314) to 150 per 100,000 in Puerto Rico (2003)(315)

In **Europe** the incidence ranges from 1.9 in Greece (2001)(316) to 4.9 per 100,000 in UK (2012) (7) and the prevalence from 28.3 in Denmark (2003)(317) to *110/100,000 in Greece*, as estimated by Anagnostopoulos et. al in 2008.(318)

Estimates from European countries include (per 100,000 population): Germany (prevalence: 36.7)(319); Sweden (39-68)(320-323); France: 40.8 (324) Greece: 39.5-110 (316, 318) Denmark: (22.2-48) (29, 317, 325, 326); Finland: 28(29); Iceland: 35.9 (327); Italy: 39.2-81 (328-331); Lithuania: 16.2 (332); Norway: 49.7-64.1(333-335); Spain:17.5-34.1(321, 336-338); and UK: 6.5-97(7, 339-345)

In **Asia** the incidence rates ranges from 3.1 (*China*, 2000-2006)(346) and 8.1 (*Taiwan*) (347). The lowest prevalence has been reported in *India* (3.2/100,000 in 1993)(304) and the highest in *Taiwan* (97.5/100.000, study period 2003-2008). (348) In a recent study from United Arab Emirates, a wealthy country with access to health care system, the age-standardized incidence per 100,000 population for the period 2009-2012 was *8.6 (95% confidence interval 4.2-15.9)* and the age-standardized prevalence was 103/100,000 population (95% confidence interval 84.5-124.4).(349)

In **Africa** the prevalence is very low (0.3/100,000 in Zimbabwe) (350)

In general, European countries have less incident cases than Americas, Asia and the Australasia. (313)

Occurrence trends

Although current metanalysis are lacking, a systematic review by Rees (313) points out that it appears to be an *increase in prevalence over time,* about 3% in UK annually [(from 64.63/100 000 in 1999 (95% CI 61.74 to 67.62) to 97.04/100 000 in 2012 (95% CI 94.19 to 99.94) (p for trend<0.001)](7) Similarly in Sweden prevalence doubled from 1955 to 1961(351) and rose from 39 to 68/100,00 from 1982 to 1991. (321).

Regarding incidence there are inconsistencies in the epidemiological reports. There is a difficulty for direct comparisons as a few number of studies have examined the same population across time. Uramoto et all reported an incidence rate (age- and sex-adjusted) to be 5.56 per 100,000 (95% confidence interval [95% CI] 3.93-7.19) in Ronchester, Minesota for the period 1980-1992. This as increased compared with the incidence of 1.51 (95% CI 0.85-2.17) in the previous 1950-1979 cohort (352).(309) corresponding to *almost tripled occurrence of new cases* in this four decades. This dramatic increase was attributed mainly to better recognition of milder forms of the disease. Finally, in a more recent study by Jarukitsopa et. al, the age- and sex-adjusted incidence of SLE in the same area and project was found to be 2.9 per 100,000; [95% CI] 2.0-3.7) for the period 1993-2005.(353)

Furthermore, in Denmark there was a (non-linear) increase in incidence from 1980 to 1994 from 1.0/100,000 to 3.6/100,000 (325). Similarly, in Greece, Alamanos et al(316) who studied the lupus incidence in north-west Greece (Ioannina region) showed a non statistical significant increase (incidence 1.41/100,000 in the period 1982-1986 to 2.19/100,000 person-years in 1997-2001. Also, in UK a non-significant increase in lupus incidence was noted in women (but not in men) from 1990-1999. (354). Last, Rees et all. reported incidence decline from 1999 to 2012 of 1,8% per year.(7)

Although direct comparison is not clear in most areas, Lewis at. Al (8) in a recent systematic review concludes that over time there is an increase in incidence(8) Last, an interesting study from Germany projects that prevalent SLE cases will increase in the country until 2020 and then will stabilizise(319)

2.3 The role of ethnicity

Numerous studies consistently find that SLE is more common in black people [(5 to 9-fold increased incidence and 2-to 3-fold increased prevalence)] and in some ethnicities such as South and East Asians among others non-whites. (305-308, 355, 356) (357). Further, South and East Asians and SLE patients with Hispanic race present with more severe disease, higher activity and damage accumulation. (8, 358) (356, 359) (360) as well as with more comorbidities (risk of CVD events was higher among blacks SLE patients (HR 1.14 [95% CI 1.03-1.26]) as compared to whites). Most importantly mortality rates also differed [62.5% higher in blacks](247, 361)

Possible explanations for the above described differences include an increased genetic risk coupled with increased autoantibody reactivity (8) as well as reasons related with ethnicity such as socioeconomic status, acess to care or adherence to therapy among other reasons. (362)

Race-Ethnicity-Ancestry Terms. As comprehensively explained in a review by Lewis et. al (8) we have to note that the term "race", although originally describes people with biologic similarities i.e skin colour, can often times be confused with the term "ethnicity". Ethnity which can be defined as a "biological and a social construct which encompasses ancestral genes, cultural, geographic and socioeconomic characteristics shared within a population" (359) which it can be differently categorized especially in countries such as in the USA, where description of mixed populations turns to

have loose boundaries. (8) On the other hand "ancestry" is mostly determined from geographical regions i.e. northern Europe which of course has many subdivisions. According to US guidelines, there are at least five racial categories (White, American Indian/Alaska Native, Black/African American, Asian and Hawaiian/Pacific Islander)(8) According to the same guidelines, "*Hispanic*/Latino" refers more to an ethnicity and in particular people of South/Central American, Mexican or other Spanish culture (independently of their race). The term "*Mestizo*" is used under the "Hispanic ethnicity" umbrella, meaning people with combines European and *American Indian* (indigenous of America). Another variously used term is "Asian" which in studies from the UK it is used referring to individuals from India/Pakistan/Bangladesh, whereas in the USA for people of Chinese/Japanese/Korean origin.

Some of the most characteristic studies include the following:

-Two interesting UK studies in Birmingham (342) and Nottingham (341) et al. showed an up to *9-10-fold increase in lupus occurrence in Afro-Caribbean compared to white individuals.*

-Increased incidence (up to 6-fold) and prevalence (up to more than 2-fold) was also noted in *South Asian individuals*. (342) (341)

-LUMINA studies have provided insights for the epidemiology of lupus in Hispanics. (359) Hispanics is a very heterogeneous group (363) and differences between subgroups (i.e. Texan and Mexican) are not uncommon (364) with Texan Hispanics presenting with more severe disease than Puerto Rican Hispanics(26)

-A population-based study from *Canada* (over 120,000 North American Indians) reported that *native American-Indians* present double

incidence and prevalence and 4-fold mortality compared with white patients. (365) More recently, another population-based study in the *US American Indian and Alaska Native population* reported high prevalence and incidence of SLE [178 per 100,000 person-years (95% confidence interval [95% CI] 157-200) and 7.4 per 100,000 person-years (95% CI 5.1-10.4) respectively. These estimates are as high as or ever higher than the occurrence rates that have been reported for US black people (310).

It is of interest to comment that *before the '80s connective tissue disease was thought to be low in black people* but this revealed not to be the case as numerous studies showed that black people in Europe and America resent more frequently with lupus in comparison with European descents(366) (342) (341, 355). Interestingly, SLE appeared to be rare in west Africa, but shows increasing occurrence in central and south parts of Africa as Symmons et all concluded in a study published in 1995, with the first lupus identified in 1961(367). An explanation of the rarity of autoimmune disease was supported by malaria-endemic areas coupled with infection-induced immunosupression (368) A "gradient hypothesis" was formed suggested that there is increased occurrence of SLE within people of African descent when they were not living in Africa with a very interesting critical review on the "gradient hypothesis" published in 1998 by Bae, who supported that appraise the epidemiologic studies of SLE in African population it is rather complicated including the understanding of the origin of African Americans and even the historic perspectives of the dark period of transatlantic slave trade(369).

More recent studies tend to challenge the gradient hypothesis(370) suggesting that the main issue is the underdiagnosis of the condition and other practical or methodological factors(368). Scarce data is available regarding the incidence and prevalence of SLE in Africa but a clear ethnic distribution was reported in a recent study, with the disease being mostly

prevalent among Sudanese Arabs compared to those of central African descent (371)

Furthermore, a recent sle epidemiological study from UK reported lupus occurrence in South Asian subgroups with Indian ethnicity presenting higher incidence (9.9/100.000) which was of course much lower than Afro-Caribbean people (incidence 31.5/100.000). UK Pakistanis also had high incidence (10/100,000). These results should be taken in consideration with caution as there were many patients with unknown ethnicity in the study (7) In addition, *Arab origin was 2-fold* increased in southeastern Michigan as compared with whites.(372) Interestingly, the incidence rate (7.6) was similar to the one found in United Emirates among native Arabs (8.6)(349)

Further, racial differences occur in the incidence of systemic lupus erythematosus which occurs at a higher prevalence(373) and with greater severity in Aboriginal Australians(374) First Nations ethnicity was associated with lower survival and an increased increased mortality compared to Caucasians as Hurd et al suggested in a recent review(375)

Final, a recent study found differences among Roma and Caucasian SLE patients with Roma patients from Spanish Hospitals presenting increased risk (odds ratio 2.56, 95% CI 1.02-6.39) of antiphospolipid syndrome (APS) and abortions (23.5% vs. 10.2%, P = 0.049)(376)

2.4 Gender differences

A recent review by Rees et. all(313) on worldwide SLE incidence and prevalence confirms that in all relevant studies female gender had higher incidence than males.

Notably, the female to male incidence ratio of SLE *varies with age*, being approximately 1 during the first decade of life, followed by a sharp increase to 9 during the 4th decade, and then decline in subsequent years before a again increase during the 7th-8th decade. (377) On average systemic lupus erythematosus predominantly resents with females to male ratio F:M = 10-15:1 in adults and F:M = 3-5:1 in children.(378)

Interestingly, the female to male ratio varies also among geographical different countries. Although mostly centered around 1:9-10, prevalence male-to-female ratios such as 1:4 have been reported in Germany(319) to 1:28 in Manila, Philippines (379).

The background reason for these differences in gender is not totally understood up to now, although studies support that this "gender bias" may result from a complex interaction including sex hormones, genetics and epigenetics, and even the gut microbiota as interestingly summarized by Krasselt a al in a recent review.(380) Moreover, time of disease onset, the clinical manifestations, co-morbidities and overall the course of the disease differ between male and female lupus patients.(381) For instance there is a tendency for male SLE patients to have more abrupt onset (382) and manifest more severe disease such as nephritis, pleuritis and serositis, although these findings are not consistent among studies.(380, 383) Pons et al (384) describes individual manifestations' differences between gender among settings and countries. Some studies suggest that male is a subgroup of lupus patients with distinct characteristics.(385)

2.5 The role of age

SLE may develop in any age (383) but in most cohorts the peak incidence occurs during the reproductive years (383). In most studies a peak incidence

age exist and then there is a decline and often times a second smaller peak. (313) Men have their peak at later age group (5-7th decade) vs. women lupus patients (range 3-7th decade). (313)

There is no official consensus regarding the cut-off age defining "pediatric" or "childhood" SLE, although most studies use the age of 16-18 to categorize it from "adult" lupus.

Childhood lupus refers to about 10-20% of all SLE cases (386) and similarly to adult cases, Caucasian children present less frequently and less severe disease. (387) Notably, ethnic and race differences do exist in pediatrics lupus patients. (388, 389) Further children present with more renal involvement [OR = 1.549, 95% CI (1.397-15.856)] and neurological involvement [OR = 1.642, 95% CI (1.689-15.786)](390) (391) (392-394) in comparison with adults SLE. As a recent systematic review suggest, hematologic manifestations (hemolytic anemia, thrombocytopenia, leucopenia, lymphopenia) were also higher in childhood-onset SLE. On the contrary, photosensitivity, pulmonary manifestations and Raynaud were significantly higher in adult-onset lupus patients.(395) Furthermore children with SLE present with higher disease activity (396), receive more corticosteroids and present more damage (up to 65%) than adults (390, 391)

Late-onset lupus refers to age-onset of >50 years old. Lupus in this age group is suggested to present with more insidious way, with not specific symptoms and this is one reason of being undiagnosed in greater level. (397) Late-onset lupus manifest itself with less nephritis, less severe course and disease activity.(396, 398, 399) Unfortunately the overall outcome is poorer probably due to aging, comorbid situations and higher mortality in these age groups (383) with a recent study by Martinez-Mario reporting that age at disease onset over than 50 years is an independent risk factor for damage

(OR, 2.2; 95%CI, 1.1-4.6; p=0.029) and mortality (OR, 2.6; 95%CI, 1.1-6.3; p=0.03). (400)

2.6 The role of place of residency

Scarce previous epidemiological studies suggest that SLE is more frequent in urban than rural regions (16) (17). Although urban-rural differences could provide an insight in the effect of the risk/protective factors associated on SLE, the role of the place of residence *per se* has not been examined in detail up to date. A few previous studies have reported higher disease activity at diagnosis, increased occurrence of renal disease (12) and depression (13) in rural vs. urban regions, yet similar rates regarding the delay in the diagnosis (14), disease activity over the disease course, hospitalizations, damage or mortality (12). As expected, findings from some relevant studies, most of them performed in heterogeneous multiethnic environments with immense inequalities, suggest that patients from underprivileged residential areas may experience worse clinical outcomes due to their low socioeconomic status, educational level or inadequate access to health care. (15) (14) (8).

2.7 The role of education

Many lupus studies including those derived from LUMINA and GLADEL cohorts, have suggested that low educational attainment is associated with higher disease activity, damage and mortality. Underdiagnosis and worse interaction with their physicians has been described in low educated non-white lupus patients. Notably, ethnicity remains a stronger factor for mortality in spite of higher educational level (18)

2.8 The impact of SES and poverty on SLE

Poverty has been associated with higher disease activity, damage and mortality as reviewed by Carter et al. (18, 401) Studies from LUMINA, a cohort started in 1994 including 600 patients from Alabama, Texas and Puerto Rico of white, Hispanic and African America ethnicity illustratively showed that *lupus patients below poverty line, were four times more likely to die* in comparison with patients with better financial status (18). It has been postulated by some authors that genetic factors are stronger at the disease onset, whilst socioecomic factors at the course of the disease over time.Further, poverty has also been linked with worse mental functioning of lupus patients (402) and lupus nephritis progression (403)

2.9 Epidemiology of lupus nephritis

Lupus nephritis (LN) is the most severe complication of systemic lupus erythematosus (SLE), accounting for increased *morbidity*, including end stage renal disease, and mortality (404, 405) (406). LN refers to inflammation of the kidney that encompasses various patterns of renal disease including glomerular, tubulointerstitial and vascular. (407).

The *pathogenesis* of nephritis in lupus patients lies on a number of mechanisms such as complement activation and immune-mediated injury to the renal parenchyma. (408) Notably**,** if these inflammatory processes are not controlled, then *glomerulosclerosis*, *interstitial fibrosis and tubular atrophy* will possibly occur , leading in many cases to end-stage renal failure (408)

Renal involvement manifests itself with *haematuria*, *proteinuria* or *decreased renal function,* and requires confirmation by renal biopsy. (409) The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system is widely accepted for therapeutic and prognostic

guidance. (409). In a few cases, patients may have "*silent lupus nephritis,*" which refers to histopathologic disease without clinical manifestations. LN can occur at *any time in the disease course*. When early after SLE diagnosis, it is considered as a significant predictor of *poor prognosis*. (410) In about 5 % of the lupus patients, LN may appear more than 5 years after the SLE diagnosis (*delayed LN*). (411). Unfortunately, the risk of myocardial infarction and cardiovascular mortality, is significantly higher in SLE patients with LN than SLE patients without (412). Further, lupus nephritis has a *6-fold increase in mortality* compared with the general population, although, nowadays, early mortality or acute renal failure is rare (413) (404)

***Prognostic factors of LN occurrence*:** LN demonstrates familial aggregation and a genetic susceptibility. *Hispanic race* (odds ratio (OR) 2.71, 95% CI 1.07-6.87), *African-American ethnicity* (OR 3.13, 95% CL 1.21-8.09), *not married/living together* (OR 3.45, 95% CL 1.69-7.69), *higher activity* (OR 1.11, 95% CL 1.02-1.19), *higher anti-dsDNA* (OR 3.14, 95% CL 1.50-6.57) and anti-RNP antibodies (OR 4.24, CL 1.98-9.07) are suggested to be significant predictors of the lupus nephritis development. (414).(415). Mestizo ethnicity (HR 1.61, 95% CI 1.19–2.17), hypertension (HR 3.99, 95% CI 3.02–5.26) and activity (SLEDAI index) at diagnosis (HR 1.04, 95% CI 1.01–1.06) are also associated with a shorter time to nephritis occurrence; older age at onset (HR 0.90, 95% CI 0.85–0.95, for every 5 years) and photosensitivity (HR 0.74, 95% CI 0.56–0.98) were associated with a longer time interval (416)

Prevalence of LN mainly depends on the selected population and the diagnostic criteria for defining SLE: Renal disease affects patients, with a

range from **~20 to 60%**, but frequencies as low as 12 and as high as 100% have

been reported in studies. (417, 418). Prevalence (% of total SLE cases) is about 20-30% in Europe (23), 30-40% in USA (25, 418) as high as 50-60% in Asia. (27). The annual lupus nephritis point prevalence in Norway was LN point prevalence of 13.8/100 000 (in 2007), five times higher for women than men (22.8 vs. 4.4 per 100 000) and increased. (407)

Gender: Notably, male SLE patients tend to have more frequent (OR 1.51, 95% CI 1.31-1.75) (419) and more severe renal involvement [renal insufficiency (42% vs. 11%, $p<0.01$) and end-stage renal disease (33% vs. 6%, $p<0.01$) in men vs. women (420). This sex bias has been not fully clarified, with an interesting report showing that *Estrogen Receptor α-deficient female mice* show protection from renal disease (421).

Age of onset: Nephritis is *a common problem in* ***childhood onset SLE*** (50% in a French cohort, (422) 49% in GLADEL cohort in Latin America (388); and it is *more common* than in late onset SLE [20% in children-onset vs. 9% in adult onset in a Spanish cohort (OR:2.7; 95% CI :1.1, 7), (423); 60.6% vs. 26.6% respectively, ($p < 0.001$) in a Brazilian cohort, 50% vs. 29% in Iran].(396, 424) Age of the disease onset also is suggested to play a role: age <33 years has been found to be associated with nephritis development (HR = 2.1; 95% CI: 1.8- 2.4)(417)

Ethnicity/Race: The highest *risk* of renal disease (and renal failure) has been described in **black patients** [40.5% and 15.3%, respectively) as compared to white SLE patients (18.8% and 4.5%, respectively) (305, 306). In GLADEL study in Latin America (G: rupo L: atino A: mericano D: e E: studio del L: upus, an inception cohort that started in 1997 including patients in first two years of diagnosis), the prevalence of lupus nephritis was 69% in Africans-Americans (blacks), 60% in Hispanics and 29% in Caucasians (414) Additionally, *black and Hispanic SLE patients develop LN earlier* (425) and have

worse outcomes than white patients with SLE, including death and ESRD (426)

Dramatic differences in occurrence of LN in various ethnicities were revealed also from a a study by Patel et al. who estimated that the *prevalence* of biopsy-proven LN in the UK (study period: 2001) was higher in *Chinese* women compared to Indo-Asian and white women (110.3 vs. 21.4 and 5.6 per 100,000 patients, respectively). Similarly, it was higher in Chinese men compared to Indo-Asian and white men (20.3 vs. 4.1 and 1.1 per 100,000 patients, respectively), but similarly high in Chinese and Afro-Caribbean patients.(427)

In comparison to whites, the age-standardized prevalence of LN was 3.8 times higher in Indo-Asian, 18.6 times higher in Afro-Caribbean and 19.2 times higher in Chinese (citizens of the UK) (427). The overall prevalence was 4.4 per 100,000 population (95% confidence interval [95% CI] 3.8-5.0), 7.1 per 100,000 (95% CI 6.1-8.2) in women, and 1.4 per 100,000 (95% CI 1.0-2.0) in men. (427) Notably, in an older study the UK, lupus nephritis (LN) was *twice as frequent in blacks* with SLE compared to whites (62 vs. 32%)(354)

Interestingly, Jakes et. al in a metanalysis in **Asian countries** reported a prevalence of 21-65% at diagnosis and 40-82% over time which is much higher than whites [(New Zealand: 14% at diagnosis and Australia: 30% over time. (428)

Further, in a US study which included people 18-65 years old enrolled in Medicare in **2000-2004**, 34,339 individuals with SLE were identified and 7,388 **(21.5%)** of them with LN (this corresponds to prevalence **30.9 per 100,000).**(25) The prevalence was **four times higher among African Americans** compared to Whites (25) with highest frequencies among **African American women (74.6 per 100,000)** and **Asian women (*80.7* per 100,000). (25)** In general, higher

occurrence was noticed among all racial/ethnic minority groups compared to whites. (25) There are two interesting points in this study-first the LN prevalence, especially among African Americans (***26.7%),*** was lower than prior estimates (414). Second, the higher frequency of LN in black populations persisted after adjustment for socioeconomic factors.(25)

An other interesting study from California reported **Hazard Ratios of different ethnicities in relation to LN development**: Hispanic American (HR = 1.2; 95% CI: 0.9 to 1.6), African American (HR = 1.6; 95% CI: 1.2 to 1.9), and Asian American ethnicity (HR = 1.9; 95% CI: 1.6 to 2.1); (417) Renal disease in SLE was less frequent in patients with SLE of *European origin* both in Latin America and the USA (43.7 and *22.7%* of SLE patients affected, respectively) compared to patients of *Hispanic* (Mestizo; *58.3%* and *59%* of SLE patients affected, respectively) and of *African ancestry* (*55.3%* or *54.4%* of SLE patients affected(363, 429)

In a recently published report (study period: 2007-2009), from Manhattan Lupus Surveillance Program, renal disorder was prevalent in 42.4 % (in overall cohort), 25.4% in non-Hispanic white, 50.7% in non-Hispanic black, 49.4% in Hispanics, 53.2% in non-Hispanic Asian (307) Similarly, renal disorder was prevalent in 44.6% (35.6–53.6) in overall, 51.9%(32.7–71.0) in black, 39.5% (24.7–54.4) in white and 51.3% (35.4–67.2) in Asian/ Pasific islander [2017 publication,: (study period: 2007-2009) data from San Francisco Lupus Surveillance Project].(430)

Furthermore, in Alaska SLE patients in a study from 2007 to 2009, nephritis was documented in 39.6% whilst data from the Georgia (GLR) and Michigan lupus registries (MILES) showed that LN was present in ***36.7%*** and ***40.5%*** of blacks with SLE (310) suggesting that **renal disease may be as common in American Indian/Alaska Native as in black patients with SLE**.(310) ESRD

was noted in 5.6% of patients with SLE in Indian-Alaska registry, in comparison with 8.4% of black patients in the GLR (306) and 15.3% of black patients in MILES (305) (although this difference possibly is due to methodological reasons i.e better access to national renal databases)

Additionally, of the highest frequencies of renal disease are reported in the Caribbean (78% in Curacao); Jamaica with 75%(431) (but, 28% in a more recent study) (432). Further, in Barbados and Martinique the frequency was estimated at 47% (312) and 48.6%, (314) respectively. Last, during a long study period (1980-2006), the prevalence of LN was estimated to be 47.9% in a lupus cohort in Riyadh, Saudi Arabia (433)

Polymorphisms of genes involved in the immune response, might be partly responsible for the differences in prevalence between the *different ethnic groups*. ***European ancestry*** *is generally associated with a decrease in the risk of LN,* even after adjustment for genes most associated with renal disease.(434) *European ancestry is suggested to be protective* [10% increase in the proportion of European ancestry is associated with a 15% reduction of LN (odds ratio 0.85, 95% confidence interval 0.82-0.87] (89).

It should be pointed out that **ethnicity accounts for less than 8%** of the total variance (435) in the risk for renal involvement (436). Out of this ethnicity-related variance, **14.5% could be attributed to socioeconomic factors,** and **36.8% to the genetics** (African or American Indian background); and **12.2% to the combination** of both. Thus, 40% of the ethnicity effect on renal risk remains unexplained.d (436) (435) At this point we have to note that, also considerable **interethnic variation** is evident in the efficacy/tolerability of the various immunosuppressive therapiesgiven for nephritis. (406)

LN Incidence.

Scarce is the evidence regarding incidence of lupus nephritis. The first relevant epidemiological study available, was performed in the UK and estimated the annual incidence of LN to **0.4 per 1 000 000** in 2001. In **Norway**, the estimated incidence of LN was **0.6** (CI 0.4–0.8) and it was higher in females (1.0, CI 0.6–1.4) vs. males (0.2, CI 0.1–0.4). (407) Interestingly, in Norway the incidence decreased from **0.7 to 0.45/100 000** between 1978 and 2006. (407) In **Denmark** the mean annual incidence rate of lupus nephritis was estimated to be **0.45** per 100,000 (95% CI 0.38-0.53); 0.20 (95% CI 0.13-0.28) for men and 0.69 (95% CI 0.57-0.83) for women (29). In **Denmark** the mean annual incidence rate of lupus nephritis was estimated to be **0.45** per 100,000 (95% CI 0.38-0.53); 0.20 (95% CI 0.13-0.28) for men and 0.69 (95% CI 0.57-0.83) for women (29). The annual incidence LN in French Polynesia was **0.96** per 100,000 (time period 1993-2014) (437)

The average incidence rate of LN was **6.9 per 100,000** person-years in US (Medicaid population, 2000-2004) **(25)**, highest in the older age groups (5.14 in 18-29 vs. 5.52 in 30-49 and 8.60 in 50-64 age group). (427) Further, in the same study, LN incidence was higher in females (8.98/105 vs. 1.47 in men) **(25)** and in African Americans (**10.65**).(25) (407)

In conclusion, as systematic review by Anders *et al.* highlights, Lupus nephritis remains a kidney disease with *significant unmet medical needs* despite *extensive clinical and translational research* over the past decade. More accurate epidemiologic research will help towards this direction. (438)

2.10 Epidemiology of Neuropsychiatric Lupus

Patients with systemic lupus erythematous (SLE) with one or more of neurologic and/or psychiatric manifestations during the disease course represent a sub-phenotype os SLE called “neuropsychiatric lupus” (NPSLE).

(439) NPSLE comprises a wide range of clinical conditions affecting the **central**, **peripheral**, or **autonomic** neurological system. Manifestations of this unique entity may present with various severity from mild to life-threatening, including cognitive dysfunction, psychosis, depression (440), acute confusional state, stroke, seizures (441), chorea, or transverse myelitis. (442)

Notably, neurological disease is less frequent in European American SLE patients (at disease onset) compared to other ethnicities. **African American** ethnicity is an **independent risk factor** for the NPSLE development early in the disease course. (443) Further, previous neuropsychiatric lupus events, higher SLE activity or damage and positive antiphospholipid antibodies are other well-established **risk factors** for NPSLE development (444).

Regarding pathogenesis, the exact mechanisms underlying NPSLE are not fully clarified, although, a number of pathways have been linked to clinical profile including antibody-mediated neurotoxicity and vasculopathy due to anti-phospholipid and cytokine-induced neurotoxicity (439). Histological examinations reveal cerebral edema, loss of neurons and myelin, microglial proliferation and astrocytosis as well as ischemic changes-microinfarcts or diffuse in the brains of neuropsychiatric lupus patients (Ercan et al., 2016)

From clinic-epidemiological point of view, the definition of NPSLE is challenging due to the broad spectrum of neuropsychiatric symptoms that may occur, with the majority of them of them being non-specific or mild (i.e headache, cognitive dysfunction). The most widely accepted classification scheme, up to date, is the one of American College of Rheumatology (ACR) that was created in 1999 (445) and identifies 19 neuropsychiatric conditions, (12 relevant to central nervous system (CNS) and 7 the peripheral nervous system). This criteria set has been criticized that is not very useful in every day practice due to low specificity. (446)

Correct attribution of neuropsychiatric events to lupus is often challenging: the use of magnetic resonance imaging (MRI) (442) -although not always very well correlating with severity- (442) in combination with *attribution algorithms* (447, 448) expertise multi-disciplinary approach, and often neuropsychiatric specialized tests (batteries) can successfully lead to appropriate classification case by case (442, 449)

Even in more clearly defined manifestations i.e **seizures** the range of prevalence is very broad ranging from 6% (450) (in adults) to 51% (451)(in paediatric population) (418), mainly due to methodological reasons. Interestingly, large studies reveal a cumulative frequency of seasures from 4.6% (441) to 6.7% (452) in the first 3-5 years of diagnosis, with more than half of them occuring within the first year of diagnosis and 53% re-occuring (453) (444).

Prevalence of NPSLE has still ranged considerably from 14%- 91% of SLE patients (435, 440). Unterman et al (454). in a meta-analysis published in 2011 estimated the prevalence of NPSLE manifestations is as high as 56%. The most frequent manifestations were headache (28.3%), mood disorders (20.7%), cognitive dysfunction (19.7%), seizures (9.9%), and cerebrovascular disease (8.0%). As expected the epidemiological studies that exclude minor symptoms present lower prevalence estimates.

Importantly, the prevalence of neuropsychiatric damage has been **significantly increasing** over the past 5 decades (216) A meta-regression by Mak et. al revealed that neuropsychiatric damage **negatively affected the overall 5-year survival** (216)

2.11 SLE in Greece

Clinico-epidemiological studies in Greece are scarce and mostly from tertiary health care level. The ESORDIG study estimated **a lupus prevalence of 50 per 100,000 with sampling from different parts of Greece** (study period 1993-1996) (455)

In 1993, Vlachoygianopoulos et al., (456) published a comprehensive clinical description of a series of unselected 292 lupus patients from all over Greece, examined between 1982 and 1992. The retrospective analysis of their files revealed a female-to-male ratio of 5.3:1, mean disease onset at 31.2 years old (30.8 in women and 33.8 in men).(456) After a mean disease of about 8 years, patients presented arthritis in 78%, photosensitivity in 40%, renal disease in 50% and neuropsychiatric disease in 12.3%. Interestingly, ANA was positive in 89.1%, anti-ds DNA in 65%, decreased complement (C4) in 46.6%, anti-Sm 8% and Coombs in 21.7%. (456)

In 2001, Voulgari et. al investigated 489 lupus at presentation and during follow-up. Female to male ratio was 1: 7 with no differences in the mean age at diagnosis between genders. Younger men had more serositis and discoid lupus, whereas women had more malar rash at presentation. During follow-up, men had more renal disease and serositis and women more photosensitivity, oral ulcers and hematologic abnormalities. Both gender and age were not found to affect the damage score.(457)

A year later an epidemiological study **in Greece estimated the annual SLE incidence to be 1.9 cases/100,000 inhabitants** (95% CI 1.49-2.31). (178 cases in Ioannina Region, northwest Greece, period 1982-2001). In this study female to male ratio was 7.4:1 and the mean age at the time of diagnosis was 39.1 (SD 16.9, range 6–68) years for male patients and 38.8 (SD 18.4, range 2–81) years for females. **The point prevalence of SLE for women was 69.27 and for men 9.46 cases/100,000, and the total 39.51, in 2001**. Other interesting points in

from the study was that **incidence rates were higher for urban people** and that the peak of incidence was observed in the 30-49 age group for both men and women. Small increase in the incidence was noted during the study period. 15.2% of patients presented with renal involvement at diagnosis. Final, the 5 year survival rate was 96.8% and the 10 year survival rate was 90.3%. (316). Last, a survey study in Greece estimated the **prevalence of lupus as high as 110 per 100,000 people** (2 cases only) in Central Greece (318).

In 2011, a study by Stefanidou et. al (398) also reported that male patients had a higher prevalence of nephropathy, stroke, thromboses, and antiphospholipid syndrome in comparison with female lupus patients, but less mucocutaneous symptoms (arthralgia, hair loss, Raynaud's phenomenon and photosensitivity) at the initial clinical presentation (n=594, Thessaloniki Region hospitals, female: male 9:1, mean age at diagnosis:31 in women, 34 in men). During the 5-year follow-up, male gender was found to be associated with nephropathy (27.1 % in men and 16.6% in women, p=0.002) and infections, especially of the respiratory tract (14.3% vs. 4.8%, p0.008) Interestingly, no statistical significant differences were reported in comorbidities among genders (398)

Kampylafka et al reported clinically severe CNS involvement in Greek SLE patients, to be 7.8/100 person years (n=370 patients followed at tertiary center in Athens). Female-to-male ratio was 8:1, with a mean age of 32±14 years, 44% prevalence of lupus nephritis (disease duration about 9 years), 13% secondary ARS, 11% pericarditis, 11% pleurishy, 47% arthritis and CNS involvement in 4.3%. Regarding therapy corticosteroids were reported for most patients (92%), Azathiprine in 35%, Hydroxychloroquine in 62%, Methotrexate in 17%, Cyclophospamide Mofetil in 32% and Rituximab in 9.5% (458) Damage accrual was similar in both groups.

Further, a study from Thessaloniki compared 121 late onset patients with 430 early onset patients reported that elderly patients had less malar rash, nephropathy, fever and lymphadenopathy, while pericarditis, sicca syndrome and lung involvement were more frequent.(398) Last, elderly showed more cardiovascular damage as well as higher hypertension and osteoporosis incidence at 5 years. (398)

A more recent study was contacted by Bertsias et all (chart-based review, n= 215 adult SLE patients with active disease, with predefined 30% severity, seven tertiary Greek centres). Notably, severe patients had more chronic active disease (22.4% vs 4.7%), higher disease activity index and damage in comparison with non-severe patients. Damage accrued in 67% of severe and 36% of non-severe patients. The mean annual direct medical cost was E3741 for severe vs. E1225 for non-severe ones. Active renal disease, severe flares, and non-reversible organ damage were independent predictors for cost. Among patients, the percentage of 30% who display chronic activity, in spite of standard care, represents an important unmet medical need.(459)

3. Lupus Registries-Surveillance Projects: Challenges and Unmet needs.

A *lupus registry* can be defined as "an organized system for the collection, storage, retrieval, analysis, and dissemination of information on a group of predefined SLE patients'. (460) Registries are multi-purpose tools that can be used to recruit patients into clinical trials, monitor main outcomes of diseases and study quality of care. (461) (462) They may focus on a specific research question or capture data on a continuous basis, addressing emerging research issues. They may also include the collection of tissues or blood samples (biobanking) (463).

The terms “SLE cohort” and “SLE database” have been used alternatively for a “registry”, even if they are not totally interchangeable. A cohort can be described as a well-defined group of participants or patients “who have had a common experience or exposure and are then followed for the *incidence* of new diseases or events in clinical research”. A database can be defined as “an organized set of data or collection of files that can be used for a specified purpose” and is a more general term which can be thought as a collection of registries.(464)

Up to now, some well-conducted registries have received recognition for their contributions to lupus research in epidemiology, genetics, clinical features, or outcomes: LUMINA Cohort, Hopkins Lupus Cohort Toronto Lupus Database, Birmingham Lupus Cohort, SLICC, Euro-Lupus Cohort GLADEL Cohort (460) and the more recent Spanish RELESSER, Georgia Lupus Registry and Michigan Lupus Epidemiology and Surveillance Program which offer important advantages and strengths over previous efforts.(305, 306)

Critical to the success of a patient registry is the digital technology used to enable researchers, physicians or patients to enter search, report or store the data, display information, link to other resources and/or share meaningful information in a secure way.(460)

CHAPTER III. OBJECTIVES OF THE STUDY

The main objectives of the thesis were:

a) to obtain estimates of SLE incidence and prevalence in Crete during 1999-2013 across gender and age groups

b) to describe the main clinical and immunological features, including trends of severe disease manifestations (lupus nephritis, neuropsychiatric lupus)

c) to explore main outcomes (organ damage, severity) in prevalent SLE population

c) to describe the burden of the disease and unmet needs at the community level (diagnosis delay, comorbidities, preventive measures, health-related risk factors, hospitalizations and treatments needed).

c) to examine whether the *place of residency (urban-rural)* influence occurrence, phenotype and outcomes of SLE patients (to formulate an hypothesis for the impact of urbanicity)

CHAPTER IV: METHODOLOGY

1. Source population and settings

The setting of Crete island offers advantages to study epidemiologically complex diseases, such as SLE. First of all, it is a *geographically isolated region* with a *stable, genetically homogeneous population* of approximately 0.65 million. Crete is the fifth largest (8,303 km2 or 3,206 sq mi) southernmost island in the Mediterranean. The capital of the island is Iraklion and there are four more main cities, each at the four prefectures of the island.

The majority of the inhabitants are white Caucasians. 53% of the inhabitants reside in rural, 8% in suburban (10,000-15,000 dwellers) and the remaining 39% in urban areas (>15,000 dwellers) with low migration and translocation rate (2011 National Census, http://www.statistics.gr/en/statistics/pop). The health care system is mixed public/private and patients can visit a specialist at hospital or in private office without necessarily prior consultation with a general practitioner. The Rheumatology Clinic at the University Hospital of Iraklio was founded in 1990 (465) and serves as the single referral center for Crete, with strong connections to primary and secondary care units. From 1999 the clinic has a special academic interest for SLE, providing expertise case. This is another more reason of low rate of SLE patients translocation to tertiary hospital rheumatology centers outside Crete.

2. Case finding and patient recruitment

Multiple case-finding sources were utilized (**Figure 1**). This is an ongoing program that started in 2012 and included an initial retrospective search (period 1999-2011) followed by a more active surveillance (2012-2015) for identification of cases (irrespective of the year of diagnosis).

Our **primary source** was the archive of medical charts of the Rheumatology Clinic, University Hospital of Iraklio (as in Greece national electronic health records were still in pilot phase). *More than 10,000 paper records were manually screened for "SLE" and related diagnoses such as "incomplete lupus", "possible lupus", "lupus-like" and "undifferentiated connective tissue disease".* All the potential cases were sorted in a "SLE archive".

***Second**, the program was communicated to nephrology and rheumatology departments* (**Figure 1**) across the island who possibly followed patients that have never been referred to rheumatology department (i.e cases with renal/skin problems being more intense, so the treating physician was not a rheumatologist). To this end, we contacted the Heads and staff physicians of the Nephrology (4 in each hospital of four prefectures) and Dermatology Clinics (single referral unit at the University Hospital of Iraklio) to provide their data (i.e. biopsies archives, medical records of SLE patients) and most importantly, to refer their patients to our center.

The third source of cases were private rheumatologists in Crete (Figure 1) following SLE patients without necessarily having referred them to our clinic. The majority of these patients had mild disease with no major organ involvement. Of note, several of these patients could still pay visit (and thus, be registered) at the Rheumatology Clinic due to administrative reasons, an emergency visit or hospitalization. Nevertheless, we contacted ***all*** private rheumatologists at the beginning of our study since the exact number of SLE patients being followed exclusively by them was unknown and this could contribute to under-ascertainment or selection bias-if we including only patients from the tertiary referral unit). It appears that the vast majority of SLE patients had at least one registered visit at the Rheumatology Clinic, University Hospital of Iraklio. Still, our communication with the treating private rheumatologist was helpful in obtaining more accurate/updated

clinical data especially for the time period that these patients were followed at the community.

Complementary data were retrieved from hospitals/health system, renal biopsy archives, and the National Renal Data System for end-stage renal disease (ESRD). Other hospital databases (mortality, hospital discharge, laboratory) were used as available. Administrative hospitalization data were queried for relevant International Classification of Diseases (ICD-9) and billing codes. The aforementioned sources were used also to gather *mortality data.* Medical chart review was done by dedicated physicians (IG, AF, AC, GB).

3. Interviews-Questionnaires

To the patients who were recruited a structure questionnaire was given **(*Supplementary Material*)** and an 1h-interview was conducted by the main researcher (IG). For the patients that were not recruited to face-to-face-interview, residential data were captured from the administrative database or the medical records. *All participants signed an informed consent.*

4. Registry establishment, variables and information synthesis

For each potential case, we reviewed all available paper and electronic files. Data were entered into a secure electronic database (**Supplementary Material-snapshots**) to enable cross-checking and synthesis of the information from variable sources. *The database was developed in SQL.* Rigorous quality control and raw data management (control of duplicates, handling of missing data, regular edits through dynamic communication with physicians and patients) enabled high level of *information integrity*. Data from medical records vs. patients' interviews were differentiated (levels of accuracy).

A biobanking database was also established as SLE projects in "Aristeia" program were running, linking clinical and biological data and be able to provide anonymous datasets to collaborative researchers. Analyzable Exports for analysis were extracted per project and research questions.

Last update (4/08/2017 of total number of SLE/CDT patients included in database is n=1548)

The registry was named "Leto" after the Greek mythology goodness who had to give birth in a place without sun, transforming to a wolf and eventually gave birth to Apollo and Artemis.

The variables we captured were the following The ACR[1997](466) and SLICC[2012](16) classification criteria, validated activity (SLE Disease Activity Index 2000(467) and organ damage (SLICC/ACR damage index [SDI](225) indices were recorded.

The paper medical chart that is used for monitoring SLE patients at the Rheumatology Clinic (University Hospital of Iraklio) includes the SLEDAI-2K and the SLICC/ACR damage Index (SDI), which are filled by the treating physicians on every visit (SLEDAI-2K) or every 6-12 months (SDI) (**Supplementary Material**). Dedicated researchers abstracted data per item of these indexes and entered them into the electronic version of the indexes in our registry database so that the scores were calculated. In case the treating physician had not filled the paper index (es), the researchers abstracted the relevant data from the medical records.

SLE was characterized as mild, moderate or severe by integration of data on **severity of disease manifestations** according to the BILAG glossary,(222) the use of lupus medications, and physician's global assessment. LN was diagnosed according to kidney biopsy and/or the classification criteria. ESRD was defined according to the respective SDI item.(225) Diagnosis of

neuropsychiatric SLE (NPSLE) (i.e. attributed to the disease) was according to the ACR case definitions,(445) following multi-disciplinary approach and validated with existing attribution models.(448, 468) Time-relevant data included dates of SLE diagnosis, any previous diagnoses, and dates for major clinical features and score items described above.

Detailed data on demographics, residence, family and personal history, disease manifestations, body mass index (BMI) and tobacco use were obtained from the questionnaires.

5. SLE definitions and case ascertainment –Inclusion/exclusion criteria

Cases were counted as incident at the year of diagnosis of SLE (clearly reported for the first time in patient's medical records) and/or at the year the 4th criterion was fulfilled in the ACR or the SLICC classification criteria. The Rheumatology Department, University Hospital of Iraklio from 1990 and onwards had started following patients who had been diagnosed even before this (even in the 1970s). In fact, we systematically searched all available paper medical records but included in the study incident and prevalent SLE cases from 1999 and onwards to ensure the completeness of data. Likewise, although we included in the study patients diagnosed up to 2013, we extended our surveillance period by another two years to increase the possibility of a patient to visit our referral center at least once.

Primary analyses were based on cases that fulfilled the ACR^{1997} criteria during the period 1999-2013 (up to 31 December, 2013). Secondary analyses used rheumatologist*- and SLICC^{2012} criteria-based diagnosis. Cases were counted as incident at the year the diagnosis was clearly reported for the first time in patient's medical records and/or the 4th criterion was fulfilled. To count a

case (incident or prevalent) for a specific calendar year, a patient had to reside in Crete at least one year before of this calendar year and be over 15 years old.

If SLE was diagnosed before the age of 15 years, the case would still be included in the calculation of the disease prevalence but only at the time the patient became 15 years old (i.e., age at which there is transition of pediatricians to adult rheumatologists). Patients who died still counted as prevalent in the same year of death but not in the ensuing year(s). Drug-induced SLE and cutaneous SLE without systemic manifestations were excluded. The flow chart of the case finding and validation process is shown in **Figure 1**.

Physician diagnosis was based on the treating rheumatologist of the Department of Rheumatology, University Hospital of Iraklio, except for a few cases who were initially diagnosed by nephrologists (n=14) or dermatologists (n=2), later confirmed by the Department's rheumatologists. The study doctor did not modify any diagnosed cases as reported in the medical charts. In a number of patients who were followed exclusively by private physicians, there was re-evaluation from a rheumatologist of our Department.

6. Statistical analysis

All SLE cases contributed to the prevalence numerators, for every year (from diagnosis onwards) of residence in the source population during 1999-2013, and to the incidence numerators for the year of diagnosis. Age-, sex-, region of residence- specific denominators were calculated based on Greece National Census data (2001, 2011) and interim population estimations. *

The interim estimations are publicly distributed by the University of Thessaly, Greece (http://www.e-demography.gr) and have been generated based on the

official Hellenic Statistical Authority (ELSTAT; http://www.statistics.gr/en/home/). Specifically, the inter-censal population estimates were based on the population figures from the decennial Census of Population updated annually at the national and local level from the births, deaths occurring meanwhile as recorded in the vital statistics movements from municipalities registers and estimated migration. The annual population estimates are calculated for a reference date of 1st January on the basis of the events of vital statistics of the previous year. The annual mid-year inter-censal population estimate results from the sum of two consecutive years' annual population estimates divided by 2.

Crude and stratum-specific average annual incidence and prevalence together with 95% confidence intervals (95% CIs) were calculated. *Age-standardized rates were calculated using the direct method* (using 3-year intervals). Direct standardization by age and gender for SLE, lupus nephritis and NPSLE was performed using the *European Standard Population* as a reference.

Capture-Recapture. Because of the possibility that LN cases followed exclusively in nephrology departments may have received care outside our capture area and thus, have been missed, we evaluated for possible underestimation of LN prevalence using multiple two-source capture-recapture analysis.(469) We calculated the Chapman's estimator (95% CI) using the Rheumatology Clinic as the primary source (since it yielded most of the cases) and each one of the remaining eight sources as a secondary source. We used the STATA median and centile commands in these results to obtain the final estimator. In addition, we applied latent class Bayesian models (GLLAMM module) in our data to generate LN prevalence estimates, adjusting for the imperfect sensitivity and specificity of the different sources and without relying on a gold standard, as described elsewhere.(30, 470).

The SPSS (version 22) and STATA SE (version 12) software were used.

Comparison of classification criteria subanalysis

Inclusion criteria for this analysis were registered patients ≥15 years old, diagnosed with SLE by the opinion of an experienced consultant (drug-induced lupus and cutaneous only lupus were excluded) Both the SLICC[2012] and the ACR[1997] classification criteria were applied. Classified SLE cases (*n=907)* were assessed *at the end of 2015* in terms of individual items of classification criteria, disease severity (determined by the severity of manifestations and the use of lupus treatments) and organ damage (assessed by the SLICC/ACR damage index).

Two main comparisons were made: The first comparison was **among "ACR-only", "SLICC-only" and both criteria groups.** Further, those cases who fulfilled both criteria during the observation period were categorized according to **which set of criteria came first** and then compared for the frequency of individual criteria.

Baseline characteristics were expressed as the **mean (±SD), median (IQR) or percentages (%)**. The Student's t-test or Mann-Whitney test were applied as appropriate for continuous variables, and the Chi-Square or Fisher's exact test for categorical variables.

Effect of rural-urban place of residency on lupus occurrence, clinical pictures and outcomes substudy

Demographics/detailed residency history was obtained from consecutive interviews at enrolment (2012-2015) whereas clinical data from medical records reviews (n=399 patients).

Patients that have lived in exclusively urban (>10,000 people), exclusively rural (<10,000) or mixed residence (translocations) throughout all their lifespan (up to enrolment), were compared regarding disease risk (24) (25) and disease characteristics.

The *risk* is a ratio between the conditional probability of the outcome for those with a positive predictor relative to the same probability for those with a negative predictor a/(a+b)/c/(c+d)=PPV/(I-NPV). If the two conditional probabilities are equal, the relative risk = 1.0. (24) (25). At our analysis, we estimated SLE exclusively lived in urban areas/general population in urban areas)/SLE having lived exclusively in rural areas/general population in rural areas. The population in the denominator was based on estimations of Hellenic Statistic Authority for population (≥15 years old) (National Census 2011).

Baseline characteristics were expressed as the mean (±SD), median (Interquartile Range, IQR) or percentages (%) as appropriate. The Student t-test or Mann-Whitney test were applied for continuous variables, and the Chi-Square or Fisher's exact test for categorical variables. *Bonferroni correction was used in case of multiple comparisons*.(26) Missing values were mostly due to missing data in questionnaires (i.e do not know answers and was handled by complete case analysis method).(27)

A ***stepwise binary logistic regression analysis*** (unadjusted and adjusted for gender, age at diagnosis, disease duration, total number of ACR and smoking was performed to determine if the place of residence influences damage

accrual (SDI=0, no damage accrual, SDI≥1 any damage accrual up to last follow-up).

In a second regression model, SLE *severity* was treated as outcome and was categorized in mild/moderate vs. severe disease and was adjusted for *total ACR criteria, gender, disease duration and age at disease onset*. The results from the multivariate logistic regression are presented as the exp (B) coefficient with 95% Confidence Interval and p-values.

7. Ethics

Study approval. The study was approved by the Ethics Committee of the University Hospital of Iraklio (*no. 20/03/2012*)

CHAPTER V. RESULTS

1. Incidence of SLE in Crete 1999-2013

The *overall crude and age-/sex-adjusted incidence rate* of SLE (ACR[1997]-based) in Crete during 1999-2013 was 8.6 (95% CI 8.0-9.0) and 7.4 (95% CI 6.8-7.9) per 100,000 person-years, respectively. *There was an about 3fold increase* in SLE incidence during the years 1999-2010, which stabilized afterwards. The incidence female-to-male ratio was 13:1 (**Figure 2, Table 3**)

2. Incidence of severe SLE (LN, NPSLE)

Incidence of Lupus Nephritis

Overall age-/sex-adjusted incidence of LN during 1999-2013 was 0.6 (95% CI 0.4-0.8) per 100,000 person/years, corresponding to incidence rates of 1.0 (95% CI 0.7-1.3) and 0.2 (95% CI 0.1-0.4) per 100,000 person/years in women and men, respectively. Rates of incident nephritis remained stable during the whole study period. The female-to-male ratio of incident nephritis was 4.2:1. **(Figure 3, Table 3)**

NPSLE Incidence rates

Adjusted NPSLE incidence rates in the total, female and male population were 0.5 (95% CI 0.4-0.7), 0.8 (95% CI 0.5-1.1) and 0.3 (95% CI 0.1-0.4) per 100,000, respectively. Temporal trends of incident NPSLE resembled those of general SLE, i.e. increasing during 1999-2010 and remaining stable afterwards. The female-to-male ratio of incident NPSLE cases was 3:1 **(Figure 4, Table 3)**

3. Age at diagnosis of SLE, LN and NPSLE

The mean (±SD) age at the time of SLE diagnosis was 43 (±15) years (range 9-81), with a *peak at the age group 45-54* years for both males and females **(Figure 5)**

LN occurred earlier in men than in women, with most cases diagnosed at the age group of 15-24 versus 45-54 years, respectively **(Figure 6)**

In NPSLE, the peak age of diagnosis was also lower in men than in women (30-39 versus 50-59 years, respectively) **(Figure 7)**

4. Prevalence of SLE

During the study period, there was a steady increase in SLE prevalence (ACR[1997]-defined) from 22 (95% CI 18-26) (crude point prevalence) in 1999 to 143 (95% CI 133-154) per 100,000 individuals aged ≥15 years old in 2013. **(Tables 1 and 2)**

The age-/sex-adjusted prevalence was 19 (95% CI 15-23) in 1999 and 123 (95% CI 114-133) per 100,000 in 2013. The increasing trend was noted in both genders.

Crude Prevalence also varied across 4 prefectures of Crete: Heraklion: 153 Rethymnon:147 Chania:121 and Lasithi:110 per 100,000. **(Figure 8)**

SLE prevalence was calculated as high as 165 per 10^5 inhabitants in urban vs. 123 per 10^5 in rural areas [$p<0.001$].

5. Prevalence trends of LN

Age-/sex-adjusted prevalence of LN in 2013 was 14.5 (95% CI 11.1-17.6) per 100,000, which corresponds to prevalence of 24.0 (95% CI 18.0-29.9) and 4.3 (95% CI 1.8-6.8) (per 100,000) in women and men, respectively. The total number of prevalent cases (n = 90) was very close to the median number of expected LN patients according to capture-recapture for all sources (89.5, 95% CI 73.0-105.9). Also, the Bayesian model-derived estimate of prevalent LN cases was 86 (95% CI 83-89). The prevalence of nephritis was increasing throughout the study period (2-fold). **(Tables 1 and 2)**

6. Prevalence trends of NPSLE

As for NPSLE, adjusted prevalence (year 2013) in the total, female and male population were 9.7 (95% CI 7.0-12.3), 14.9 (95% CI 10.3-19.5) and 4.3 (95% CI 1.8-6.9) per 100,000 people, respectively. Prevalence NPSLE increased throughout the study period (6-fold). **(Tables 1 and 2)**

7. Trends in SLE incidence and prevalence using different case definitions

To validate our findings, we further estimated the disease incidence and prevalence using *alternative case definitions.* Time trends in SLE incidence were *similar according to all three definitions*, namely ACR[1997], SLICC[2012] classification criteria and physician diagnosis **(Figure 9)**

Within cases who fulfilled both the ACR[1997] criteria and rheumatologist-based diagnosis, 68% had the diagnosis by these two definitions in the same year; in 22%, clinical diagnosis preceded that of ACR[1997] criteria and in the remaining 10% the ACR-based diagnosis preceded the clinical one. The respective percentages were 70%, 19%, and 11% for the comparison of SLICC[2012] criteria

against rheumatologist-based diagnosis, and 87%, 5% and 8% for the comparison of ACR[1997] against SLICC[2012] criteria. By use of any of the three disease definitions, SLE prevalence estimates demonstrated a steady increase during 1999-2013. **(Figure 10)**

Incident cases were defined by rheumatologist diagnosis on average 3 months earlier than with the ACR[1997] criteria, and cases were defined by the ACR[1997] criteria on average 3 months earlier than the SLICC[2012] criteria

8. Demographics of prevalent cases, smoking and obesity **(n=750)**

The ACR[1997]-based prevalent population residing permanently in Crete (December 2013) comprised 750 patients and was homogenous in terms of sociodemographic characteristics: 97% Greek, 93% women, 81% married, 70% with <12 years of education, and 80% with Cretan descent (defined as past 3 generations). **(Table 4)**

Current smoking and obesity (BMI >30 kg/m^2) were each found in 30% of the patient. **(Table 4)** (n=399)

9. Clinical and immunological features of the prevalent cases

The most frequent clinical features (cumulative incidence of ACR[1997] criteria) were *arthritis* and *mucocutaneous manifestations*. In particular, malar rash: 58%, discoid rash: 12%, photosensitivity: 83%, oral ulcers: 48%, arthritis: 88%, serositis: 15%, renal disorder: 13%, neurologic disorders: 4%, hematologic abnormalities: 29% (ACR-1997 criteria defined, prevalent cases n=750) **(Figure 11)**

The *mean disease duration of the disease was 7.2 (± 6.6) years* and 68.4% of the patients had disease duration longer than 5 years.

ANA was positive (>1/80) in 92% of prevalent cases (n=750). **(Figure 11)** Anti-dsDNA (*Crithidia luciliae*): 23%; aPL (aCL/aβ2GP1/LA): 14.3%. Low complement was found in 21.3% of prevalent patients.

10. Severity

Based on the severity of manifestations and the use of lupus treatments, the disease was classified as *mild, moderate and severe* in 50%, 33% and 17% of all prevalent SLE cases.

11. Organ damage **(n=613)**

Data for organ damage were available in 613 patients. At the year of diagnosis, 84.0% of SLE patients were free of damage, whereas 12.6%, 2.9% and 0.5% had SDI scores of 1, 2 and 3, respectively. Three years after diagnosis, the respective figures were 76.7%, 18.3%, 3.8%, and 1.3%. At last follow-up, 30.5% of SLE patients had accrued organ damage **(Figures 12 and 13)**

The most frequent component of the SDI (11.75%) was the *neuropsychiatric* (cognitive impairment, seizures, cerebrovascular accident) followed by the musculoskeletal (4.89%) and malignancy (4.24%). Skin non reversible damage was found in 3.92%, cardiovascular 3.26% ocular 2.28% and pulmonary 2.12% Diabetes with onset at least 6 months was found in 1.63% **(Figures 14)**

In the prospective part of the study (2012-2015) we also estimated *transition rates of damage accrual*. SDI increased from 0 (at baseline) to >0 in 8.2% of the patients. In patients with damage in 2012, there was 2.4% more increase in SDI damage index.

Within the subgroup of patients with LN, 4.4% developed ESRD.

12. Gender Differences (n=750)

The following manifestations occurred more frequently in men versus women: *serositis* (28% versus 14%, p<0.001), *renal involvement* (26.4% versus 11.8%, p<0.001), *neurological manifest*ations (13.3% versus 3.3%, p<0.001) and *hematological abnormalities* (47.2% versus 28.0%, p<0.001). **(Figure 11)**

Significantly *more men than women* displayed moderate (30.2% versus 25.8%) or severe (34.0% versus 13.5%) forms of SLE (p<0.001 for both comparisons).

Men accrued more damage (SDI>0) than women: 28% versus 18% (p<0.003) at the year of diagnosis, 34% versus 22% (p<0.005) after 3 years' follow-up, and 38% versus 30% (p<0.005) at last follow-up.

Men and women had differences also in *use of treatment* (ever, patient reported at enrollment 2012-2015) Rituximab was used from 8.6% males vs. 7.1% of females (p=0.005). Cyclophospamide 31.4% among males vs. 8.2% in females (p=0.005). Belimumab 2.9% in men vs. 0.5% in women (p=0.001);AZA 25.7% in males and 12.9% in females (*p=0.001*).

The following results derived from the analyses of questionnaires' data (n=399)

13. Prevalence of self-reported symptoms/manifestations and events related to SLE

The mean number of presenting symptoms were 2.27± 1.19.

Self-reported symptoms as patients reported them: anorexia: 12.8%; weight loss: 14.5%; fever: 18.8%; anemia: 15.3%; arthritis:81.6%; oral ulcers:41.9%;

malar rash: 59.4%; ptotosensitivity:72.9%;dermatologic symptoms:23%;low platelets' count 14.5%; low WBCs:16.3%; renal disturbances:9.3%; pleuritis:4.8%;DVT 3%; valve disease:5%; arrhythmia:7%; acute myocardial infarction:1.8%; angina:0.3%; pericarditis 9.8%; chronic diarrhea: 2%;ulcer: 6%; dyspepsia 9.5%; retinopathy:1%; cataract:12.3%; memory disturbances: 10.3%; epilepsy: 1.8%; neurological symptoms: 11.3%; cerebrovascular events: 2.5%; tenontitis 23.3%; fibromyalgia: 19%.

14. Therapy

14.8% of prevalent cases had received azathioprine or mycophenolate, 9%cyclophosphamide and 3.6% rituximab. In total, 34% of the moderate/severe cases had received potent immunosuppressive drugs.

15. Trends in damage, severity and therapy over cohort periods

To further clarify to which extent milder cases might have been missed during the first year we compared severity (mild-moderate-severe categories, as described in methodology section), immunosuppressive drugs (ever use, any of cyclophosphamide, mycophenolic, rituximab, belimumab) and damage trends (ACR/SLICC score). The estimates refer to the last year of each 5-year-period and the average duration for the cases was about 2.5 years in each of the three periods.

Regarding severity, the ratio of mild/severe cases were 3.80 during the first five years of the study (1999-2003), 4.17 during next five years (2004-2008) and 3.85 during the third period (2009-2013). Further, the ratio of mild/ moderate+severe was 1.32 during the first five years of the study (1999-2003),

1.38 during next five years (2004-2008) and 1.23 during the third period (2009-2013).

Regarding the use of potent immunosuppressive drugs the ratio of incident cases that had never received to those that received potent immunodepressant treatment was 10.11 during the first five years of the study (1999-2003), 10.32 during next five years (2004-2008) and 10.62 during the third period (2009-2013).

Last, in incident cases the ratio of patients without non-reversible damage (SLICC/ACR SDI=0) to those that have damage (SDI>0) was 2.69 during the first five years of the study (1999-2003), 2.73 during next five years (2004-2008) and 2.66 during the third period (2009-2013). **(Table 5)**

16. Prevalence of Comorbidities

Comorbidities were patient-referred at the time of the enrollment (n=399). 21.1% of the patients report an allergic disease (allergic rhinitis: 10.5%; asthma: 5%; knidosis: 3.5%; use of antiallergic drugs: 8%). Drug-allergies were reported in 17.5% of the patients. Diabetes mellitus: 7. 8%, use of anti-diabetic therapy: 6.5%. A percentage of 24.3% of patients reported hypertension, 20.8% use of anti-hypertensive medication. Hyperlipedaemia: 31.8%; anti-hyperlipedaemic treatment: 21.3%. *Thyroid disturbances* were the commonest comorbidity (44%). **(Figure 15, Table 6)**

Other comorbidities included: osteoporosis: 17.3%; osteoporotic fracture: 6.3%; heart disease: 12%; neurologic comorbidities: 8.8%; cancer: 4.8%; kidney problems: 9.5%; lung diseases: 9.3%; Liver disorders: 4.3% gallbladder disturbances: 4%; peptic ulcer: 5.8%; blood disorders: 2.3%

Regarding *infections* 2% of the patients reported tuberculosis, 0.5% hiv/aids, 9% recurrent respiratory and 10.8% recurrent urinary tract infections. Thalassemia trait was reported in 3.3% of interviewed patients. From their past medical history 26.8% of patients reported measles, 22.8% mumps, 4.3% infectious mononucleosis, 13.3% rubella and 10% chickenpox.

The most commom combinations of comorbidities are depicted in **Table 6.**

Mental comorbidities in SLE patients *At least one mental disorder* was reported in 34.8% of patients yet only 13.8% reported regular visits to a mental health professional. *Depression* was referred from *25%* of SLE patients; Generalized Anxiety Disturbance 10%; *suicidal attempt: 4%*; bipolar disorder: 0.8%; eating disorder: 0.3%; alcohol addiction: 0.3%; drug-addiction: 0.3% **(Figure 16)**

17. Obstetric Events, pregnancy outcomes, off-springs health status

The mean (±SD) number of children of SLE patients is 1.97±1.36. A percentage of 24.3% has more than three children. In female lupus patients that had at least one pregnancy, maternal hypertension were reported from 2.3%; preterm delivery: 5.8%; low birth weight: 7.8%. Menses problems (current or past) was reported from 23.8% women.

18. Hospitalizations

38.6% of the patients had at least one lupus-related hospitalization since the disease diagnosis (in a mean 7 years duration of the disease). Mean hospitalizations up to the enrolment were 1.42±3.7 per patient. Further, 69% of the patients had at least one surgery up to enrollment.

19. Health Care Utilization

Based on our data, over two thirds of all prevalent SLE patients were regularly followed at the Department of Rheumatology, University Hospital of Iraklio outpatient clinics. From the remaining cases, about 70% are followed exclusively by private physicians and 30% were lost to follow-up. However, even these patients have at least one visit at our department (mostly for diagnosis confirmation or second opinion visits) or have occasional visits for other reasons (e.g. hospitalizations, retirement due to disability etc).

Twenty-three out of 90 lupus nephritis cases are followed exclusively by nephrology departments, 20 patients by both nephrology and rheumatology departments, and the remaining 47 by rheumatologists as main treating physicians and nephrologists as consultants.

20. Preventive measures

Mammography was perfomed from 67.7% (194 out of 278 that had indication for mammography),pap-smear in 70.9%; sun-protection in 63.9%, colonoscopy in 29.0% of those that had indication. Immunization for influenza had been performed in 38.8% and influenza immunization in 44.1%.

21. Diagnosis Delay

A percentage of 6.8% of patients had a delay (from symptoms to definite diagnosis) >1year; 34.5% wait for >2years for definite diagnosis, 28.1% 1-5 months and 5.8% for 6-12 months.

22. Performance of ACR-1977 vs. SLICC-2012 classification criteria (n=907)

In a second analysis, performed to *907* SLE patients (*irrespective of residency*) Two main comparisons were made: The first comparison was **among "ACR-only", "SLICC-only" and both criteria groups.** 224 of them (24.70%) fulfilled ACR-only criteria, 615 (67.81%) fulfilled both, and 68 (7.5%) fulfilled SLICC-only. *Significant differences* were resulted in individual manifestations. Illustratively, renal disease were 4.9% in ACR only patients, 15% in those with both criteria and 10.3% in SLICC only. **(Table 7).** Further, 23.9% of the ACR-only group vs. 35.2% in both group and 38.1% in SLICC-only group had damage [(SDI>0, *(p=0.03*).] **(Figure 17)** Individual items of either ACR-1997 or SLICC-2012 are shown in **Tables 8 and 9,** respectively**.**

Further, *those cases who fulfilled both criteria* during the observation period were categorized according to **which set of criteria came first** and then compared for the frequency of individual criteria. SDI>0 was 40.9%, 34.4% and 19.44% in those that ACR came first, concurrent or SLICC-came first criteria, respectively (p=0.03). **(Figure 18)** In these groups, severe disease was described in 37.5%, 19.59% and 13.16% (n=515, *p<0.001)* **(Figure 19).** The percentage of moderate and severe disease was 33.53% among ACR-only patients, 26.3% in both-criteria group and 55.9% in SLICC only group (*p=0.40*). No statistical significant difference was found among SDI items.

23. Severity burden at the community level (n=737)

The objective of this subanalysis was to provide a comprehensive assessment of the burden and severity of SLE manifestations at the community level. A total 737 SLE patients irrespectively of the place of their residency (98% with ≥ 4 ACR-1997 criteria, 74% fulfilling both ACR-1997 and SLICC-2012 criteria) were included with a median (interquartile range) age at diagnosis of 43 (21)

years and disease duration of 8 (7) years. Regarding disease severity, 49% of the patients had mild, 32% moderate and 19% severe lupus.

Within the severe cases, most frequently afflicted systems were the *hematological* (4.6%), *renal* (3.6%), *cardiovascular* system (2.8%), and *neurological* (2.3%). Mycophenolate was administered in 0%, 2.7% and 8.5%, and rituximab in 0%, 7.1% and 15.3% of patients with mild, moderate and severe disease, respectively ($p<0.01$ for both).

Disease severity did not differ according to age of SLE diagnosis (before or after 50 years). Instead, *female predominance was more pronounced in mild cases (31:1)* as compared to moderate (12:1) or severe (5:1) ($p<0.001$).

Notably, more severe disease correlated with shorter time interval from symptoms onset to SLE diagnosis (delay >12 months: 56% in mild, 39% in moderate, 27% in severe, $p<0.001$). Unemployment and smoking status (n=399 patients) tended to be higher in the moderate/severe group (54% versus 44% and 34% versus 28%, respectively).

Regression analysis showed that moderate/severe as compared to mild disease is strongly associated (odds ratio 2.5, $p<0.001$) with organ damage accrual (SDI>0).

24. Risk of developing SLE in urban than rural regions

By comparing the relative distribution of residence in our SLE patients against the population distribution in Crete, we found that the *risk of SLE for those lived all their lifetime in urban versus a rural region* was estimated at 2.08 (95% confidence interval [95% CI] 1.66–2.61, $p<0.001$).

25. Demographic and clinical differences across place of residency (n=399)

Patients in rural differed significantly than those in urban areas regarding their *educational* (9.6% vs. 42.1% with >12 education years, p<0.001) and *employment* status (26.4% vs. 39.5% paid work, p<0.001). **(Table10)**

No significant differences in diagnosis delay (59.1% of rural-living patients delayed >1 year until diagnosis vs. 49.6% in urban-living, p=0.41).

Notably, patients who had exclusively lived in urban regions had lower female-to-male ratio (7: 1 in urban vs. 15:1 in rural *vs*. 19:1 in mixed , *p=0.05*)

A *significantly lower age of disease diagnosis* was found in patients who lived exclusively in urban [median (IQR), 39 (19) years] as compared to rural areas [median (IQR) 46(24) years], *p<0.001*)]. Notably, SLE patients whose upbringing was exclusively at urban place (n=193) had about *five years earlier age of diagnosis*, compared to those who had grown up in a village (n=188) with median (IQR), 41.00 (19.50) vs. 46 ± (23.71) years, *p<0.001*).

At the year of SLE diagnosis, *renal disorder was twice as common in urban* than rural environment (2.06:1, p<0.02). In terms of cumulative disease characteristics, malar rash, photosensitivity and arthritis were collectively more prevalent in exclusively rural SLE patients **(Figure 20)** Sunsensitivity and malar rash were more frequent in rural than urban environment (80% vs. 77% in mixed and 64% in urban, p=0.001 and 70% vs. 54 % equally in mixed and urban, p=0.03, respectively). Antiphospholipids antibodies were found positive in 21% urban vs. 14% in rural SLE vs. 9% in mixed population (p=0.04) **(Figure 21).**

Among comorbidities assessed, *Hashimoto thyroiditis* was most common in patients that had lived exclusively in urban regions (12.2% vs. 1.6% in rural, p<0.001). *Allergic rhinitis* was 2-fold higher in urban SLE patients (57.1% vs. 28.6% in rural, *p=0.04*). Urban dwellers reported more frequently past

infection from *rubella* (17.3%, 15.7% vs. 7% in rural, p=0.02) and *chicken-pox* (25.6% vs. 12.4% respectively *p=0.03*). Infectious mononucleosis was also higher in urban SLE patients (6.4% vs. 1.6% in rural, p=0.02). Hospitalizations due to active lupus differed significantly between the two groups (38.8% in rural versus 37.2% in urban *p<0.001*). **(Table 22)**

Rural dwellers reported *increased use of preventive measures* such as pap-smear test (52.3% vs. 48.0% in urban dwellers, p=0.001), mammography (46.9% vs. 41.6%, p=0.007), colonoscopy (13.1% vs. 11.6%, p=0.7) immunizations against influenza and pneumoniococcus (39.2% vs. 24.9%, p=0.009 and 32.3% vs. 23.7%, p=0.014, respectively). Prevalence of obesity (BMI>40 kg/m2) was higher in rural (39.8% vs. 28.7% in urban, p=0.049), whereas of past/current smoking was lower (36.9% vs. 45.5 % in urban, p=0.07).

As for disease outcome, in a crude, unadjusted analysis, SLE patients from rural environments had less mild and *more moderate/severe disease* as compared with in those from urban areas. (**Figure 23**) In multivariable-adjusted analysis showed that *urban living was associated with lower risk for moderate/severe forms of SLE* (OR 0.5 CI 95% 0.28-0.90) **(Table 11)**

In addition, 45.3% of the patients living in exclusively urban and 51.9% of patients in rural areas were free of organ damage (SDI=0) at the last follow-up (p=0.89). In multivariate analysis, the place of residency was not predictive for non reversible organ damage

Similar results were revealed when *exclusive urban vs. else* were performed: No statistical significant differences in diagnosis delay or in damage prevalence/damage items. Female to male difference is 6.8:1 in exclusively urban vs. 18:1 in other (p=0.008)

Similar results were revealed when *exclusive urban vs. else* were performed: No statistical significant differences in diagnosis delay or in damage

prevalence/damage items or even in hospitalizations. Female to male difference is 6.8:1 in exclusively urban vs. 18:1 in other (p=0.008) In univariate analysis exlusively-urban had 50.6% mild disease vs. 42.6% in other places of living **(Table 12).** In multivariate analysis (adjusted for disease duration, age at diagnosis anf gender) living up to enrolment in any other than exlusively urban is associated with higher severity [OR 1.7 (CI 95% 1.05-2.75 (**Table 13)**

CHAPTER VI. DISCUSSION-IMPLICATIONS

Occurrence. By employing a comprehensive methodology we describe high SLE occurrence in Crete in line with recent estimates from other regions suggesting that SLE should no longer be considered a rare disease.(471) [The average prevalence threshold for characterization of a rare disease across organizations lies within a range from 5 to 76 cases/100,000 people, most jurisdictions (66%) support an average prevalence threshold between 40 and 50 cases per 100,000 people with a global average of 40 cases/100,000]

Our incidence is higher than overall estimates from Nordic countries and Europe,(322) albeit lower than ethnic minorities' rates in UK,(342) USA,(25) and elsewhere.(18, 472) The observed adjusted incidence rates ($7.4/10^5$ persons-year) exceed those from previous decade studies in our country ($1.90/10^5$ persons-year, period 1982-2001).(316) Likewise, our prevalence estimates are higher than those previously reported in Greece (50 to 110 per 100,000).(316)

Increasing Trends. We found a 3fold increase in SLE incidence in our region during 1999-2010, which stabilized thereafter. Relevant reports worldwide (472) are conflicting (309, 473) (7, 316, 317, 335, 336) but the overall trend is suggesting that is increasing(8, 313) Increasing trends that had been reported during the previous decades (1950-1990) were attributed to wider use and improvements in ANA testing and diagnosis of milder cases.(309) In our study, the observed rise might be –at least partially– explained by better disease awareness and recognition.

The analysis in differences in disease severity, damage and need for potent immunossupresants provided further support that there was not

ascertainment of milder cases at earlier years. Further, as sensitivity analyses showed that changes in sources (i.e more active surveillance after 2012, added sources) did not had an effect on estimations.

Increasing prevalence may be due also to reduced mortality in our SLE population but unfortunately, detailed mortality data were not available especially for the first decade of the observation period. This is a limitation but during the more recent five years (2008-2013) for which we have more accurate data, we had only a few deaths (9 patients). Due to this low number of deceased cases, we do not think that mortality causes important differences in the results.

Effect of urbanicity on SLE occurrence. Notably, and in agreement with other reports (316, 474) we have found a higher prevalence in urban than rural regions (165 versus $123/10^5$, $p<0.001$) in 2013 (475). We also demonstrated that having lived exclusively in an urban environment almost doubles the risk of SLE diagnosis in comparison to rural living. This is consistent with previous studies in Greece (Ioannina Region), where Alamanos et al (16) showed that disease incidence was higher among the urban population (2.25 vs. 1.68 per 100,000 in the rural population) as well as international studies i.e 2- to 3-fold higher SLE occurrence rates in New York City than in Jefferson county(17) and a similar trend in Canada (28).

Possible mechanisms. To this end, the possible effect of environmental factors cannot be excluded. In Crete, there was a *profound urbanization* during the previous decades not only in terms of people migrating to larger cities but also in lifestyle changes. Illustrative examples are vitamin D deficiency (severe in 21% (476), westernized diet and lifestyle,(477) and smoking (44%

among parents of preschool children (478) in general population of Crete). These changes could possibly contribute to the increase, an hypothesis that needs further investigation.

Clinico-epidemiological features. The average age of SLE diagnosis in our prevalent cases was 43 years, which approximates the findings of other European studies (46 years in Spain, (336) 49 years in UK (7)). The peak incidence of the disease was noted in the age group of 45-54 years as compared to 30-49 years reported in a previous decade study in Greece.(316)

Our results confirm the female predominance in SLE with a male-to-female incidence ratio of 1:13. This lies within the range of ratios described in cohorts from Spain (1:5.5)(336) and a previous Greek study (1:7.5)(316) to those in Arabs (1:23) and USA Hispanics (1:25).(472) interestingly, the gender ratio declined from 1:16 during 1999-2001 to 1:8.6 during 2011-2013, which concords with the increasing SLE incidence rates in males. In agreement with previous reports (479) male *SLE patients had more severe disease* as evidenced by the increased frequency of renal and CNS involvement as compared to females. We also demonstrated *higher damage accrual* in men than women with SLE. Together, these results suggest more aggressive disease in males, thus highlighting the need for vigilant follow-up in this group.

Lupus nephritis and NPSLE comprise subgroups of patients with significant morbidity and mortality.(216) Our estimated incidence of lupus nephritis (0.6 per 100,000/year) is higher than those in the UK (2001),(427) Denmark (2004-2011)(29) and Norway (1996-2006)(407) (incidence rates in the range of 0.40-0.45 per 100,000/year). Accordingly, prevalence of lupus nephritis in Crete in 2013 (14.5 per 100,000) is higher than in the UK (5.6 per 100,000 white individuals)(427) and Denmark (6.4 per 100,000)(29) but lower than in white US Medicaid-enrolled adults (15.8 per 100,000) in 2002-2004.(25)

Regarding NPSLE, epidemiological studies are scarce and their results are highly variable, probably due to the heterogeneity in event classification and attribution.(454) Herein, *we provide for the first time, sex- and age-adjusted incidence and prevalence estimates for NPSLE*, and demonstrate increasing trends during 1999-2010, possibly due to better awareness and increasing use of neuroimaging.

Although direct comparisons among studies are difficult, one could argue that SLE in our region is not as severe as in North/Latin America or other parts of Europe.(23, 435) This can be extrapolated by the lower percentage among prevalent cases of nephritis (13%), NPSLE (7.8%), anti-DNA autoantibodies (23% by *Crithidia luciliae*), irreversible organ damage (30.6%), and the increased prevalence (50%) of mild disease forms. In accordance, the rate of ESRD in our lupus nephritis patients was 4.4%, which is lower than the rates reported elsewhere (typically 10-15% after 5 years).(480-482) Alamanos *et al*. also reported a milder SLE profile in northern Greece due to lower prevalence of nephritis (15% at diagnosis) and lower standardized mortality ratio,(316, 483). Further, previous studies in rheumatoid arthritis have also suggested milder disease in Greek versus British populations.(484)

Classification Criteria Comparison. By using rheumatologist diagnosis, the ACR[1997] and SLICC[2012] criteria for case definition, we noted concordant time trends in SLE. There were differences in the timing of diagnosis with physician-based preceding criteria-based diagnosis in about 20% of cases. Furthermore, at the end of 2013, fewer SLE patients had been classified with the SLICC[2012] than with the ACR[1997] criteria. Our data suggest that this is largely due to lack of inclusion of photosensitivity and of malar rash in the former, which agrees with a previous report.(485)

Our findings reveal that at all time periods, at community level physician diagnosis is more "sensitive" (i.e., diagnosing more cases of SLE or some months earlier) than the classification criteria and that both sets of criteria (ACR, SLICC) agree on the majority of cases. In clinical practice, rheumatologists usually apply clinical diagnoses rather than diagnosing patients based on the classification criteria. In addition, the revised SLICC classification criteria were published/ introduced in 2012, just one year before the end of our study observation period (2013). Together, we suggest that in complex diseases like SLE, continuing education and training of the practitioners is of central importance for more accurate and timely diagnoses.

Effect of rural vs. urban environment on clinical expression. In overall, urban versus rural place of living has not been frequently studied as a modifier of SLE expression and long term outcomes. In the GLADEL cohort (12) researchers found that the patients living in rural areas had less education, lower SES and medical insurance and were younger and with more disease activity at diagnosis and had more comorbid conditions such as hypertension and renal involvement Further, there was no impact on the rates of hospitalization, disease activity over the disease course, renal damage, overall damage and mortality (33). These results in part were attributed to inequalities to health care access that rural inhabitants of large and remote rural areas of Latin America face.

In our study, we also examined the role of the place of residency on the expression and outcome of SLE, in a genetically homogenous south European population. In our results, the age at diagnosis was higher in rural dwellers and there was also a trend towards chronic comorbid conditions. SLE patients with exclusively rural residence present with higher photosensitivity and a "pattern" including mucocutaneous manifestations and arthritis. More

importantly, rural dwellers possibly manifest more severe disease and more frequent hospitalizations due to active disease that urban participants.

We confirm that patients compared by residence did not present worse outcomes on damage index, even though also in our region patients residing in rural area had lower SES (estimated by educational level and work employment). We have to note that our SLE population is rather homogenous not only genetically but also socio-demographically. No ethnicity or race effect could act toward a biased estimation because of these two strong confounders. In addition, access both to primary and specialized (rheumatogical) care is not so hampered in Crete, due to the health care system which is characterized by a public large referral clinic, geographically approximately in the centre of the island plus a highly cooperative network of private rheumatologists and general physicians working in rural health centers. This accessibility is probably shown indirectly by no significant differences in mean delay between urban and rural districts in diagnosis, which is a finding consistent with a study from Austria showed no association of delay in diagnosis and rural or urban residency (14).

Possible mechanisms. It would be interesting for future research to investigate possible mechanisms explaining the differences between urban-rural dweller, as the place of residency may reflect environmental exposures that may trigger or influence the disease different patterns of disease expression in SLE. Our finding that SLE in people who spend all their life in a village have more than 6 years later occurrence in SLE can lead us to the assumption that maybe there are protective factors in rural lifestyles or a triggering urban lifestyle. Interestingly, Parks et al(172) reported that farm contact with livestock was inversely associated with SLE (OR = 0.55, 95% CI 0.35, 0.88). This effect was most pronounced among those with childhood farm residence and both childhood and adult livestock exposure (OR = 0.19; 95% CI 0.06, 0.63). In the

same study, an inverse association was seen among non-smokers (OR = 0.59; 95% CI 0.33, 1.1), particularly for textile work (OR = 0.34; 95% CI 0.19, 0.64).

In addition, a residential area is possibly associated with environmental exposures that may trigger different patterns of SLE expression (36). Most characteristic factors include: work-related increase in the levels of sun light (37) and exposures to pesticides (38) or insectides (39) which are more likely to occur in rural areas. In contrast, other factors like air pollution levels (40), occur more frequently in cities. Finally, factors such as smoking(41) (42) (43) or infections associated with lupus -such as Epstein Barr virus(44) may be observed equally in urban and rural areas.

Strengths. This study has several strengths; it included multiple sources to ensure data completeness and integrity.(305, 306) Demographics (and most importantly information about residence) were determined from self-reports and not exclusively from administrative data.(28) Chart review and face-to-face interviews were performed,(28) further contributing to data reliability. (354) as well as the use of three alternative case definitions facilitated disease ascertainment. Most importantly, although this is a referral-center study, *we adopted a community-based method which avoids the biases from tertiary settings*.

Limitations. One of the study limitations is that capture-recapture methods were not used in the total SLE population. Yet it was mainly LN cases that were more likely to have been missed. Accordingly, we used *capture-recapture analysis and Bayesian model statistics* both showing no missing renal cases. Regarding rural-urban effect *a more sophisticated index rather that the dichotomous we used* maybe would clarify better the results. Another limitation of our study was that we were unable to include in our analyses detailed data on specific environmental exposures. However, the place of residency may be

a surrogate measure for these variables in multivariable models thus our study offers an updated picture of the similarities and differences present in SLE patients living in urban and rural south European settings. Among the strengths of our study was that because of the monoethnic and genetically homogenous environment with low rates of translocations there was a reduction of any bias due to ethnicity/race that multiethnic studies carry.

CHAPTER V. CONCLUSION

Addressing the need for meaningful data on the epidemiology of SLE at the population level, we established the Cretan Lupus Registry "Leto" providing retrospectively (up to 2012) and prospectively data (2012-).

Our project offers robust, updated estimates of SLE burden. Alike other studies, we document that *SLE frequency may be higher than previously considered*. Despite the increased mild-to-severe ratio of disease manifestations in the community as compared to tertiary centers, a *considerable proportion of patients develop organ damage*. Our data corroborate previous findings on the *emerging burden of NPSLE* which clearly represents an unmet need. These results confirm that SLE affects also older ages and is *increasingly recognized in men.*

SLE epidemiological profile is possibly changing. Application of the SLICC[2012] criteria may result in classification of SLE patients with more severe disease as compared to those who fulfill the ACR[1997] criteria, which may have important implications in terms of trial design. Lack of inclusion of malar rash in the SLICC[2012] criteria and of non-scaring alopecia in the ACR[1997] criteria may result in delays in the classification of SLE patient.

Urban environment is associated with increased risk, although there is no significant difference in the delay of diagnosis and increased nephritis but less overall severity. In general SLE in Crete has less severe characteristics and less mortality as compared with other regions although damage percentage is relatively high and is accrued early in the course of the disease. Our results suggest the existence of different phenotypes of SLE with different clinical and immunological features, age of onset/diagnosis and possible risk factor burden. Considering the rather homogenous genetic background of our

population, these results imply a possible effect of the living environment on SLE risk and phenotype, which warrants further investigation.

Unmet needs remain toward earlier diagnosis, comorbid risk factors control and prevention.

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TABLES AND FIGURES

Table1 Prevalence of Systemic Lupus Erythematosus, SLE nephritis and Neuropsychiatric Lupus in Crete from 1999-2006

	Year	1999	2000	2001	2002	2003	2004	2005	2006
Prevalent Patients N (ACR1997)	Male	6	7	8	12	14	16	20	23
	Female	100	120	136	157	196	238	279	348
	Total	106	127	144	169	210	254	299	371
Age-Sex Adjusted Prevalence/100.000 (ACR1997)	Male	1,7 (0,0 3,4)	2,1 (0,2 3,9)	2,5 (0,5 4,4)	4,0 (1,5 6,5)	4,6 (1,9 7,3)	5,1 (2,3 8,0)	6,6 (3,4 9,8)	7,7 (4,3 11,1)
	Female	35,7 (28,1 43,2)	42,7 (34,5 50,9)	48,5 (39,8 57,3)	54,8 (45,6 64,0)	68,0 (57,8 78,2)	82,5 (71,3 93,7)	96,6 (84,6 108,7)	118,6 (105,3 131,9)
	Total	18,7 (14,8 22,6)	22,4 (18,2 26,6)	25,4 (20,9 29,9)	29,1 (24,4 33,9)	36,0 (30,7 41,3)	43,6 (37,8 49,3)	51,4 (45,2 57,7)	63,0 (56,1 69,9)
Crude Prevalence/100000 (ACR1997)	Male	2,6 (0,5 4,6)	2,9 (0,8 5,1)	3,3 (1,0 5,6)	4,9 (2,1 7,7)	5,7 (2,7 8,6)	6,4 (3,3 9,6)	8,0 (4,5 11,4)	9,1 (5,4 12,8)
	Female	41,3 (33,2 49,4)	49,1 (40,3 57,9)	55,6 (46,3 65,0)	63,3 (53,4 73,2)	78,4 (67,4 89,4)	94,3 (82,3 106,3)	109,3 (96,5 122,2)	135,0 (120,8 149,2)
	Total	22,2 (18,0 26,4)	26,4 (21,8 31,0)	29,7 (24,9 34,6)	34,3 (29,1 39,4)	42,2 (36,5 47,9)	50,6 (44,4 56,9)	59,0 (52,4 65,7)	72,6 (65,2 80,0)
Prevalent Patients N (Clinical Dx)	Male	5	7	9	13	14	17	21	25
	Female	109	133	150	181	223	269	329	399
	Total	114	140	159	194	237	286	350	424
Crude Prevalence/100000 (Clinical Dx)	Male	2,1 (0,3 4,0)	2,9 (0,8 5,1)	3,8 (1,3 6,2)	5,3 (2,4 8,2)	5,7 (2,7 8,6)	6,8 (3,6 10,1)	8,4 (4,8 11,9)	9,9 (6,0 13,7)
	Female	45,0 (36,6 53,5)	54,5 (45,2 63,7)	61,3 (51,5 71,2)	73,0 (62,4 83,6)	89,2 (77,5 100,9)	106,6 (93,8 119,3)	128,9 (115,0 142,9)	154,8 (139,6 169,9)
	Total	23,9 (19,5 28,3)	29,1 (24,3 33,9)	32,8 (27,7 37,9)	39,3 (33,8 44,9)	47,7 (41,6 53,7)	57,0 (50,4 63,6)	69,1 (61,9 76,3)	83,0 (75,1 90,9)
Prevalent Patients N (SLICC 2012)	Male	5	6	6	11	12	13	15	17
	Female	79	101	114	138	169	201	226	264
	Total	84	107	120	149	181	214	241	281
Crude Prevalence/100000 (SLICC 2012)	Male	2,1 (0,3 4,0)	2,5 (0,5 4,6)	2,5 (0,5 4,5)	4,5 (1,8 7,1)	4,9 (2,1 7,6)	5,2 (2,4 8,1)	6,0 (2,9 9,0)	6,7 (3,5 9,9)
	Female	32,6 (25,4 39,8)	41,4 (33,3 49,4)	46,6 (38,1 55,2)	55,7 (46,4 64,9)	67,6 (57,4 77,8)	79,6 (68,6 90,6)	88,6 (77,0 100,1)	102,4 (90,1 114,8)
	Total	17,6 (13,8 21,4)	22,2 (18,0 26,4)	24,8 (20,3 29,2)	30,2 (25,4 35,0)	36,4 (31,1 41,7)	42,7 (36,9 48,4)	47,6 (41,6 53,6)	55,0 (48,6 61,4)
Prevalent SLE Nephritis Cases (N)	Male	5	5	5	7	8	9	9	9
	Female	35	40	43	44	48	49	53	58
	Total	40	45	48	51	56	58	62	67
Crude Prevalence SLE Nephritis Cases/100,000	Male	1,4 (0,0 3,0)	1,4 (0,0 3,0)	1,4 (0,0 2,9)	2,2 (0,3 4,0)	2,6 (0,6 4,6)	2,8 (0,7 4,8)	2,8 (0,7 4,8)	2,7 (0,7 4,8)
	Female	11,9 (7,5 16,2)	13,3 (8,7 17,9)	14,3 (9,6 19,1)	14,8 (10,0 19,5)	16,0 (11,0 20,9)	16,2 (11,3 21,2)	17,7 (12,5 22,8)	19,2 (13,8 24,5)
	Total	6,6 (4,3 8,9)	7,3 (4,9 9,7)	7,8 (5,3 10,3)	8,3 (5,8 10,9)	9,2 (6,5 11,8)	9,4 (6,7 12,1)	10,1 (7,4 12,9)	10,9 (8,0 13,7)
Prevalent NPSLE Cases (N)	Male	2	3	3	4	5	5	6	7
	Female	8	8	12	13	14	18	21	25
	Total	10	11	15	17	19	23	27	32
Crude Prevalence NPSLE Cases/100,000	Male	0,6 (0,0 1,5)	0,9 (0,0 2,1)	0,9 (0,0 2,1)	1,4 (0,0 2,9)	1,8 (0,1 3,5)	1,8 (0,1 3,4)	2,1 (0,3 3,9)	2,3 (0,4 4,2)
	Female	2,7 (0,6 4,8)	2,7 (0,7 4,8)	4,2 (1,6 6,7)	4,5 (1,9 7,2)	4,8 (2,1 7,6)	6,3 (3,2 9,4)	7,3 (4,0 10,6)	8,5 (5,0 12,1)
	Total	1,6 (0,5 2,8)	1,8 (0,6 3,0)	2,5 (1,1 3,9)	2,9 (1,4 4,4)	3,3 (1,7 4,9)	4,0 (2,3 5,8)	4,7 (2,8 6,6)	5,4 (3,4 7,4)

Table2 Prevalence of Systemic Lupus Erythematosus, SLE nephritis and Neuropsychiatric Lupus in Crete from 2007-2013

	Year	2007	2008	2009	2010	2011	2012	2013
Prevalent Patients N (ACR1997)	Male	26	28	31	35	43	50	53
	Female	377	436	490	549	597	654	697
	Total	403	464	521	584	640	704	750
Age-Sex Adjusted Prevalence/100.000 (ACR1997)	Male	8,4 (4,9 12,0)	9,1 (5,4 12,8)	10,2 (6,3 14,1)	11,5 (7,4 15,7)	14,0 (9,4 18,6)	16,3 (11,4 21,3)	17,3 (12,2 22,4)
	Female	127,1 (113,5 140,8)	146,3 (131,7 160,9)	164,3 (148,8 179,7)	183,4 (167,1 199,7)	197,2 (180,3 214,1)	213,3 (195,8 230,8)	225,5 (207,6 243,5)
	Total	67,8 (60,7 74,9)	77,8 (70,2 85,4)	87,6 (79,5 95,6)	98,3 (89,8 106,8)	106,7 (97,8 115,5)	116,4 (107,1 125,6)	123,4 (113,9 132,9)
Crude Prevalence/100000 (ACR1997)	Male	10,2 (6,3 14,1)	10,9 (6,9 14,9)	12,0 (7,8 16,3)	13,6 (9,1 18,1)	16,7 (11,7 21,7)	19,5 (14,1 24,9)	20,7 (15,1 26,3)
	Female	144,9 (130,3 159,5)	166,3 (150,7 181,9)	185,8 (169,4 202,2)	207,3 (190,0 224,7)	224,6 (206,6 242,5)	244,8 (226,1 263,5)	259,9 (240,6 279,2)
	Total	78,2 (70,5 85,8)	89,4 (81,2 97,5)	99,9 (91,3 108,5)	111,8 (102,7 120,8)	122,3 (112,9 131,8)	134,4 (124,5 144,3)	143,1 (132,9 153,3)
Prevalent Patients N (Clinical Dx)	Male	31	34	38	47	54	61	67
	Female	459	537	591	654	696	759	817
	Total	490	571	629	701	750	820	884
Crude Prevalence/100000 (Clinical Dx)	Male	12,1 (7,9 16,4)	13,2 (8,8 17,7)	14,7 (10,1 19,4)	18,2 (13,0 23,5)	21,0 (15,4 26,6)	23,8 (17,8 29,7)	26,2 (19,9 32,5)
	Female	176,4 (160,3 192,5)	204,8 (187,5 222,1)	224,1 (206,0 242,1)	247,0 (228,1 265,9)	261,8 (242,4 281,2)	284,1 (263,9 304,3)	304,6 (283,8 325,5)
	Total	95,0 (86,6 103,5)	110,0 (101,0 119,0)	120,6 (111,2 130,0)	134,2 (124,3 144,1)	143,4 (133,1 153,6)	156,5 (145,8 167,2)	168,7 (157,6 179,8)
Prevalent Patients N (SLICC 2012)	Male	20	22	25	30	38	42	44
	Female	292	338	388	438	474	522	558
	Total	312	360	413	468	512	564	602
Crude Prevalence/100000 (SLICC 2012)	Male	7,8 (4,4 11,3)	8,6 (5,0 12,1)	9,7 (5,9 13,5)	11,6 (7,5 15,8)	14,8 (10,1 19,5)	16,4 (11,4 21,3)	17,2 (12,1 22,3)
	Female	112,2 (99,4 125,1)	128,9 (115,2 142,7)	147,1 (132,5 161,7)	165,4 (149,9 180,9)	178,3 (162,3 194,3)	195,4 (178,7 212,1)	208,1 (190,8 225,3)
	Total	60,5 (53,8 67,2)	69,3 (62,2 76,5)	79,2 (71,5 86,8)	89,6 (81,5 97,7)	97,9 (89,4 106,4)	107,7 (98,8 116,5)	114,9 (105,7 124,0)
Prevalent SLE Nephritis Cases (N)	Male	9	10	11	12	14	15	14
	Female	60	61	65	68	69	72	76
	Total	69	71	76	80	83	87	90
Crude Prevalence SLE Nephritis Cases/100,000	Male	2,8 (0,7 4,8)	3,1 (0,9 5,2)	3,3 (1,1 5,5)	3,6 (1,3 5,9)	4,2 (1,7 6,7)	4,6 (2,0 7,3)	4,3 (1,8 6,8)
	Female	19,8 (14,4 25,2)	19,8 (14,4 25,2)	21,2 (15,6 26,8)	21,8 (16,2 27,5)	22,1 (16,4 27,7)	23,0 (17,2 28,7)	24,1 (18,2 29,9)
	Total	11,2 (8,3 14,1)	11,4 (8,5 14,3)	12,2 (9,2 15,2)	12,7 (9,7 15,8)	13,2 (10,1 16,3)	13,9 (10,7 17,1)	14,4 (11,1 17,6)
Prevalent NPSLE Cases (N)	Male	9	9	9	11	12	13	13
	Female	28	33	35	40	42	44	46
	Total	37	42	44	51	54	57	59
Crude Prevalence NPSLE Cases/100,000	Male	2,9 (0,8 5,0)	3,0 (0,9 5,1)	3,0 (0,9 5,1)	3,6 (1,3 5,9)	3,9 (1,5 6,3)	4,3 (1,8 6,8)	4,3 (1,8 6,9)
	Female	9,5 (5,7 13,2)	11,1 (7,0 15,1)	11,7 (7,5 15,8)	13,3 (8,9 17,7)	13,8 (9,3 18,3)	14,3 (9,7 18,8)	14,9 (10,3 19,5)
	Total	6,2 (4,0 8,3)	7,0 (4,7 9,3)	7,3 (5,0 9,6)	8,4 (5,9 10,9)	8,9 (6,3 11,4)	9,3 (6,7 11,9)	9,7 (7,0 12,3)

Table 3 Incidence Rates of Systemic Lupus Erythematosus, SLE nephritis and Neuropsychiatric Lupus in Crete from 1999-2013

	Year	1999 2001	2002 2004	2005 2007	2008 2010	2011 2013
Incident Caces N (ACR1997)	Male	3	8	10	9	18
	Female	48	102	139	172	155
	Total	51	110	149	181	173
Age-Sex Adjusted Prevalence/100.000*year	Male	0,4 (0,0 0,8)	0,9 (0,2 1,5)	1,1 (0,4 1,9)	1,0 (0,3 1,7)	1,9 (1,0 2,9)
	Female	5,7 (4,0 7,4)	11,7 (9,2 14,1)	15,6 (12,8 18,4)	19,1 (16,1 22,2)	16,5 (13,7 19,3)
	Total	3,0 (2,1 3,9)	6,2 (5,0 7,5)	8,3 (6,9 9,7)	10,1 (8,5 11,7)	9,3 (7,8 10,8)
Crude Incidence Rate/100000 (ACR1997)	Male	0,4 (0,0 0,9)	1,1 (0,3 1,8)	1,3 (0,5 2,1)	1,2 (0,4 1,9)	2,3 (1,3 3,4)
	Female	6,6 (4,7 8,4)	13,6 (10,9 16,2)	18,0 (15,0 21,0)	21,8 (18,5 25,0)	19,3 (16,3 22,4)
	Total	3,5 (2,6 4,5)	7,4 (6,0 8,7)	9,7 (8,2 11,3)	11,6 (9,9 13,3)	11,0 (9,4 12,7)
Incident Caces N (Clinical Dx)	Male	5	8	14	15	20
	Female	59	120	189	197	167
	Total	64	128	203	212	187
Crude Incidence Rate/100000*year (Clinical Dx)	Male	0,7 (0,1 1,3)	1,1 (0,3 1,8)	1,8 (0,9 2,8)	1,9 (1,0 2,9)	2,6 (1,5 3,7)
	Female	8,1 (6,0 10,1)	16,0 (13,1 18,8)	24,4 (21,0 27,9)	24,9 (21,4 28,4)	20,8 (17,7 24,0)
	Total	4,4 (3,3 5,5)	8,6 (7,1 10,1)	13,2 (11,4 15,1)	13,6 (11,7 15,4)	11,9 (10,2 13,6)
Incdence Patients N (SLICC 2012)	Male	2	7	7	10	14
	Female	47	88	91	147	123
	Total	49	95	98	157	137
Crude Incidence Rate/100000*year (SLICC 2012)	Male	0,3 (0,0 0,7)	0,9 (0,2 1,6)	0,9 (0,2 1,6)	1,3 (0,5 2,1)	1,8 (0,9 2,8)
	Female	6,4 (4,6 8,3)	11,7 (9,3 14,2)	11,8 (9,3 14,2)	18,6 (15,6 21,6)	15,4 (12,6 18,1)
	Total	3,4 (2,4 4,3)	6,4 (5,1 7,6)	6,4 (5,1 7,7)	10,0 (8,5 11,6)	8,7 (7,3 10,2)
Incident SLE Nephritis Cases (N)	Male	1	4	0	4	2
	Female	10	8	12	6	10
	Total	11	12	12	10	12
Age-Sex Adjusted Nephritis Incidence Rates /100.000*year	Male	0,1 (0,0 0,3)	0,4 (0,0 0,9)	0,0 (0,0 0,0)	0,4 (0,0 0,8)	0,2 (0,0 0,5)
	Female	1,1 (0,3 1,9)	0,9 (0,2 1,5)	1,4 (0,6 2,2)	0,6 (0,1 1,2)	1,1 (0,4 1,8)
	Total	0,6 (0,2 1,0)	0,6 (0,2 1,1)	0,7 (0,3 1,1)	0,5 (0,1 0,8)	0,7 (0,3 1,0)
Incident NPSLE Cases (N)	Male	2	2	4	2	2
	Female	2	5	10	12	7
	Total	4	7	14	14	9
Age-Sex Adjusted NPSLE Incidence Rates /100.000*year	Male	0,2 (0,0 0,6)	0,3 (0,0 0,6)	0,4 (0,0 0,8)	0,2 (0,0 0,6)	0,2 (0,0 0,5)
	Female	0,2 (0,0 0,6)	0,6 (0,1 1,2)	1,1 (0,4 1,8)	1,3 (0,5 2,1)	0,7 (0,1 1,3)
	Total	0,2 (0,0 0,5)	0,4 (0,1 0,8)	0,7 (0,3 1,2)	0,8 (0,3 1,2)	0,5 (0,1 0,8)

Table 4. Demographics and main clinical features of prevalent cases at baseline (n=750)

Demographics	
Nationality, Greek	97%
Gender, Female	93%
Marital Status, Married	81%
Education, <12 years	70%
Descent, Gretan	80%
Life-style factors	
Smoking, current	30%
Obesity (BMI >30 kg/m2)	30%
Clinical-Laboratory Features	
Disease Duration, ys	*7.2 (± 6.6)*
ANA, positive (>1/80)	92%
Anti-dsDNA (Crithidia luciliae)	23%
aPL (aCL/aβ2GP1/LA)	14.3%
Low complement	21.3%
Severity	
mild	50%
moderate	33%
severe	17%
Organ Damage (SDI>0, at last follow up)	30.5%
Therapy (potent immunosuppresants)	
Azathioprine or Mycophenolate	14.8%
Cyclophosphamide	9%
Rituximab	3.6%
Hospitalizations	1.42±3.7 per patient

Table 5. Trends in damage, severity and therapy over cohort periods

	1999-2003	2004-2008	2009-2013
Patients without damage/with damage (SDI>0)	2.69 (n=96)	2.79 (n=194)	2.66 (n=245)
Patients no use of immunosuppresants/pts received immunossupressants	10.11(n=100)	10.32(n=215)	10.62(n=279)
Patients Mild/ Severe	3.80 (n=100)	4.17(n=215)	3.85(n=279)
Mild/Moderate&Severe	1.32(n=100)	1.38(n=215)	1.23(n=279)

Table 6. Comorbidities in SLE prevalent cases

Cancer										5%
Diabetes									8%	1%
Lung Diseases								9%	1%	1%
Heart Disease							12%	2%	2%	1%
Osteoporosis						18%	4%	3%	2%	1%
Allergies					19%	4%	4%	2%	1%	1%
Hypertension				25%	5%	6%	5%	5%	5%	2%
Hyperlipedemia			32%	15%	6%	8%	5%	3%	4%	1%
MentalDisease		36%	13%	9%	8%	7%	4%	5%	3%	2%
Thyroid Disorders	45%	19%	16%	12%	11%	10%	8%	3%	4%	3%
	Thyroid Disorders	Mental Disease	Hyper-lipedemia	Hyper-tension	Allergies	Osteopo-rosis	Heart Disease	Lung Diseases	Diabetes	Cancer

Table 7. Comparison of classification criteria items by which set came first

	ACR-first	Concurrent	SLICC first	p-value
ACR-1977	(%)	(%)	(%)	
Renal	16.67	13.96	9.30	0.02
Neurologic	13.33	3.75	0	<0.001
SLICC-2012				
Renal	13.33	13.33	9.30	0.01
Neurologic	10	6.88	4.55	0.02
Leukopenia	23.33	21.04	13.93	0.03

Table 8. Comparison of ACR-1997 individual items in classification criteria sets.

ACR-1997 items				
	ACR only (%)	Both (%)	SLICC only (%)	P-value
Malar rash	65.6	55.1	10.3	<0.001
Discoid rash	12.5	11.9	2.9	0.07
Photosensitivity	85.3	80.5	50	<0.001
Arthritis	86.2	90.1	58.8	<0.001
Serositis	15.6	16.4	1.5	<0.001
Renal	4.9	15	10.3	<0.001
Neurological	3.1	4.9	1.5	0.22
Hematologic	24.6	31.2	14.7	0.01
Leukopenia	15.6	18.4	7.40	0.06
Lymphopenia	4.9	4.9	1.5	0.44
Thrombocytopenia	6.3	13.3	11.8	0.02
Immunologic	18.3	47.2	26.5	<0.001
anti dsDNA	11.2	29.8	14.7	<0.001
antiphospholipid antibodies	5.4	19	13.2	<0.001
ANA	55.8	94.3	85.3	<0.001

Table 9 . Comparison of SLICC-2012 Items in classification criteria sets.

SLICC-2012 items				
	ACR only (%)	Both (%)	SLICC only (%)	P-value
Acute Cutaneous Lupus	58.9	79.9	55.9	<0.001
Chronic Cutaneous Lupus	8.9	10.7	88.8	0.70
Oral or nasal ulcers	26.3	42.3	23.5	<0.001
Non scarring alopecia	29	57.1	61.8	<0.001
Synositis	59.4	89.1	63.2	<0.001
Serositis	8.5	14.8	1.5	<0.001
Renal	1.8	14.3	10.3	<0.001
Neurological	1.3	8	7.4	<0.001
Hemolytic anemia	0.4	1.7	0	0.8
Leukopenia OR Lymphopenia	9.8	19.2	13.2	<0.001
Thrombocytopenia	4.0	13.0	14.7	<0.001
ANA	31.7	94.3	85.3	<0.001
anti dsDNA	4.5	29.9	17.6	<0.001
antiSm	0.4	5.0	4.4	<0.001
antiphospholipid antibodies	3.1	18.2	13.2	<0.001
Low complement	2.2	29.3	45.6	<0.001
Direct Coomps	0.4	4.4	5.9	0.01
Biopsy Proven Nephritis	0.0	9.8	10.4	<0.001

Table 10. Difference in demographics and life-style risk factors across living places.

Occupation	Exclusive Rural	Mixed	Exclusive Urban	Total
Unemployed	9.6% (12)	12.63% (12)	13.33% (22)	11.95% (46)
Farmer	24% (30)	5.26% (5)	2.42% (4)	10.13% (39)
Self-employed	8.8% (11)	13.68% (13)	10.91% (18)	10.91% (42)
Trainee/Student	0.8% (1)	1.05% (1)	5.45% (9)	2.86% (11)
Emploees	17.6% (22)	23.16% (22)	40% (66)	28.57% (110)
Housewife	21.6% (27)	17.89% (17)	13.94% (23)	17.4% (67)
Retired	17.6% (22)	26.32% (25)	13.94% (23)	18.18% (70)
Total	100% (125)	100% (95)	100% (165)	100% (385)
Maritual Status	**Exclusive Rural**	**Mixed**	**Exclusive Urban**	**Total**
Unmarried	9.45% (12)	10.31% (10)	18.82% (32)	13.71% (54)
Married	75.59% (96)	80.41% (78)	71.18% (121)	74.87% (295)
Divorced	2.36% (3)	5.15% (5)	7.65% (13)	5.33% (21)
Widow	12.6% (16)	4.12% (4)	2.35% (4)	6.09% (24)
Total	100% (127)	100% (97)	100% (170)	100% (394)
Educational Level	**Exclusive Rural**	**Mixed**	**Exclusive Urban**	**Total**
Illiterate	4% (5)	2.11% (2)	2.44% (4)	2.86% (11)
High School	34.4% (43)	36.84% (35)	40.24% (66)	15.1% (58)
Elementary School	52% (65)	27.37% (26)	15.24% (25)	30.21% (116)
University	9.6% (12)	33.68% (32)	42.07% (69)	51.82% (199)
Total	100% (125)	100% (95)	100% (164)	100% (384)
Obesity	**Exclusive Rural**	**Mixed**	**Exclusive Urban**	**Total**
BMI 18.5-24.9	7.41% (8)	8.7% (8)	6.1% (10)	7.14% (26)
BMI 25-29.9	25% (27)	23.91% (22)	40.24% (66)	31.59% (115)
BMI 30-34.9	27.78% (30)	31.52% (29)	25% (41)	27.47% (100)
BMI 35-39.9	0.00% (0)	1.09% (1)	0.00% (0)	0.27% (1)
BMI >40	39.81% (43)	34.78% (32)	28.66% (47)	33.52% (122)
Total	100% (108)	100% (92)	100% (164)	100% (364)
Pesticides, use	**Exclusive Rural**	**Mixed**	**Exclusive Urban**	**Total**
Never	63.53% (54)	79.22% (61)	90% (117)	79.45% (232)
Ever	36.47% (31)	20.78% (16)	10% (13)	20.55% (60)
Total	100% (85)	100% (77)	100% (130)	100% (292)
Smoking	**Exclusive Rural**	**Mixed**	**Exclusive Urban**	**Total**
Never	63.11%(77)	54.95%(50)	49.7%(84)	55.24%(211)
Current	27.05%(33)	26.37%(24)	34.91%(59)	30.37%(116)
Past	9.84%(12)	18.68%(17)	15.38%(26)	14.4%(55)
Total	100%(122)	100%(91)	100%(169)	100%(382)

Mixed,patients have lived both in rural or urban areas. Rural, Urban, patients that have been living all their lives up to the enrollment day in a rural (<10.000 inhabitants) or an urban region (>10,000). *P-values* for the comparisons of employment status ($p<0.001$), marital status ($p<0.001$), educational attainment ($p<0.001$) BMI ($P<0.001$) and pesticide use $p<0.001$)

Table 11. The effect of residence on SLE Severity.

Predictors	B	p-value	OR	95% C.I.	
Disease duration	.049	0.017	1.05	1.01	1.09
Age of diagnosis	-.011	0.265	0.99	0.97	1.01
Gender	1.876	0.001	6.53	2.08	20.5
Residence (Rural as reference)		0.046			
Mixed Rural/Urban	-.102	0.747	0.90	0.48	1.68
Urban	-.691	0.021	0.50	0.28	0.90
No. ACR criteria	.495	0.000	1.64	1.25	2.14

Table 12. Severity Prevalence across place of residency (Exclusively Urban Living until enrollment vs. Other)

			Urban or other		Total
			Other	Exclusively urban	
Severity	Mild	Count	78	80	158
		% within Urban or other	42.6%	50.6%	46.3%
	Moderate	Count	75	43	118
		% within Urban or other	41.0%	27.2%	34.6%
	Severe	Count	30	35	65
		% within Urban or other	16.4%	22.2%	19.1%

P = 0.027 (χ2 test)

Table 13. The effect of residence on SLE Severity (Exclusively Urban Living vs. Other)

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	SLE duration (per 1-year)	.072	.021	12.138	1	.000	1.075	1.032	1.120
	Age of SLE diagnosis (per 1-year)	-.010	.009	1.313	1	.252	.990	.973	1.007
	Φύλο: male verus female	2.007	.573	12.280	1	.000	7.443	2.422	22.871
	Residence: Rural/mixed versus Urban	.536	.244	4.814	1	.028	1.709	1.059	2.758
	Constant	-.561	.476	1.385	1	.239	.571		

a. Variable(s) entered on step 1: duration, Age Dx, Gender, Urban or other.

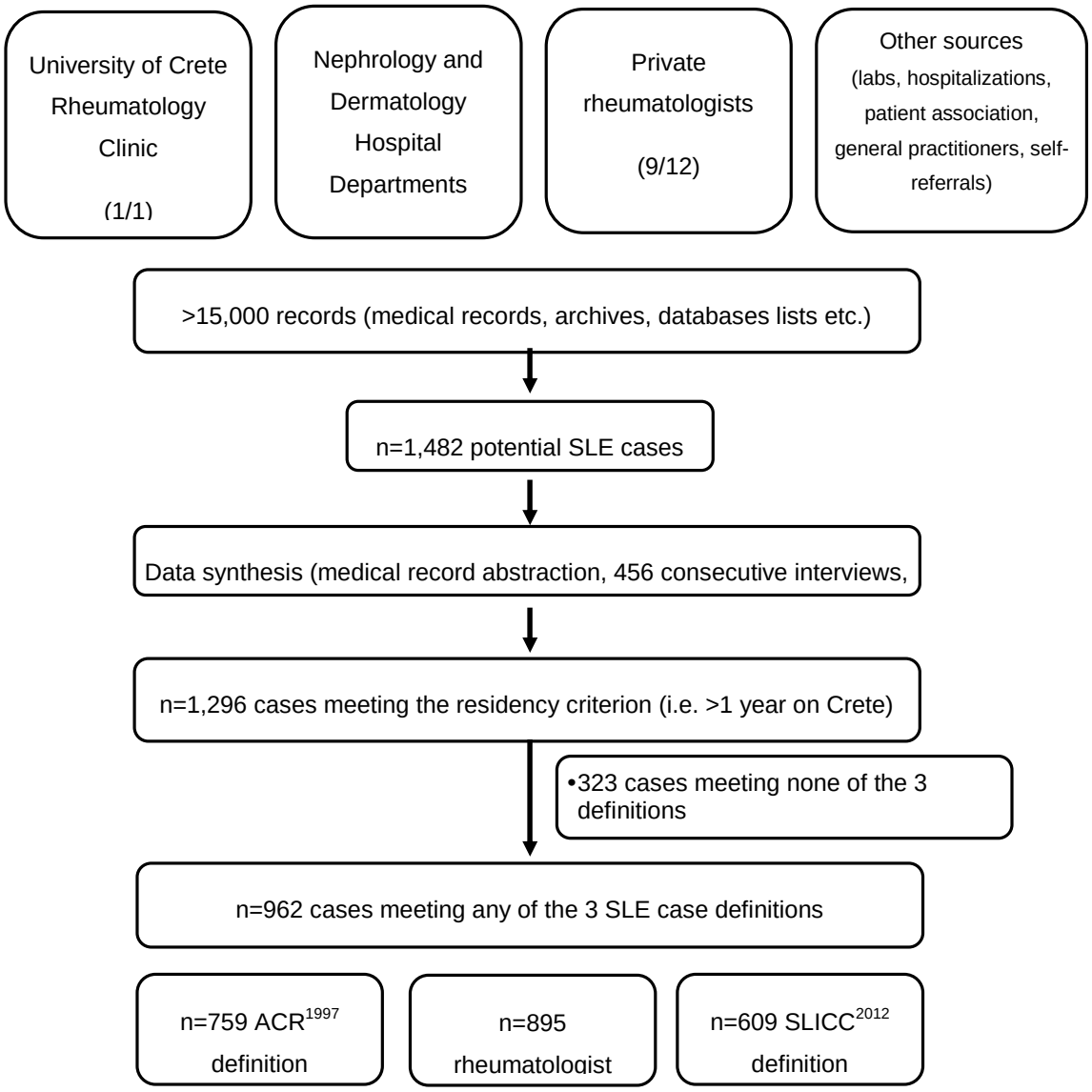


Figure 1. Flow chart with case-finding and ascertainment procedures. Three SLE definitions were used: SLE cases fulfilling the ACR 1997 (primary definition), rheumatologist SLE diagnosis (secondary definition) or fulfilling the SLICC Classification Criteria 2012 (third definition). From 962 cases, 537 met all three definitions, 230 cases met two out of the three definitions and 195 met only 1 of the 3 definitions.

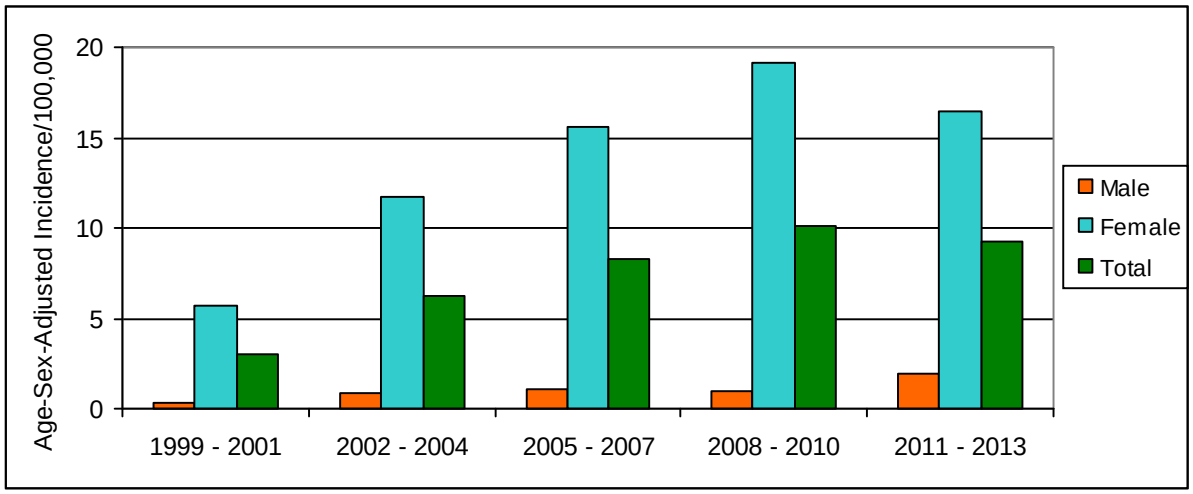


Figure 2. Age- and Sex- Adjusted Incidence of SLE cases (ACR-1997 based definition) per 100,000 person/years 1999-2013

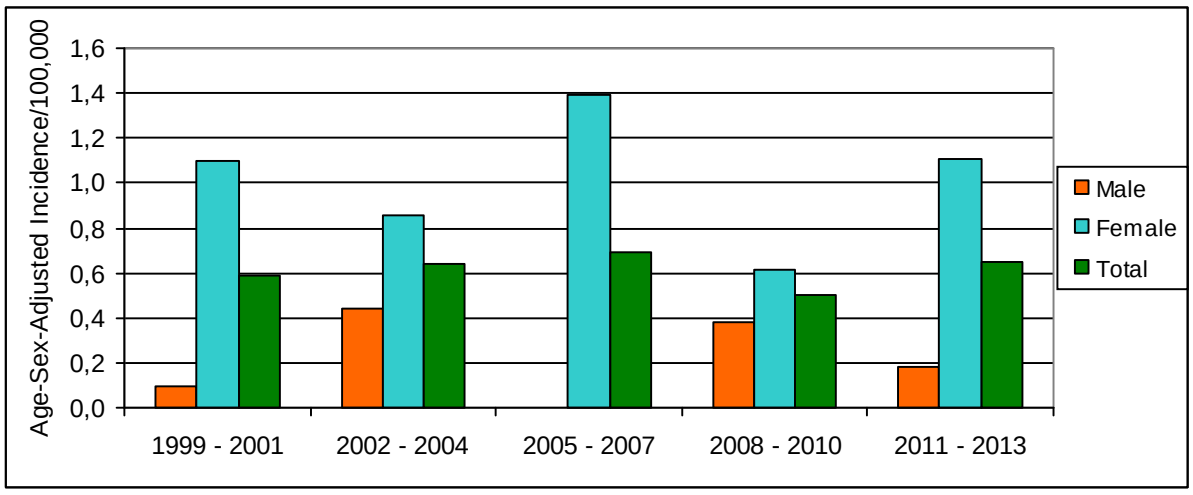


Figure 3. Age- and Sex- Adjusted Incidence of SLE nephritis cases (biopsy-based) per 100,000 person/years 1999-2013.

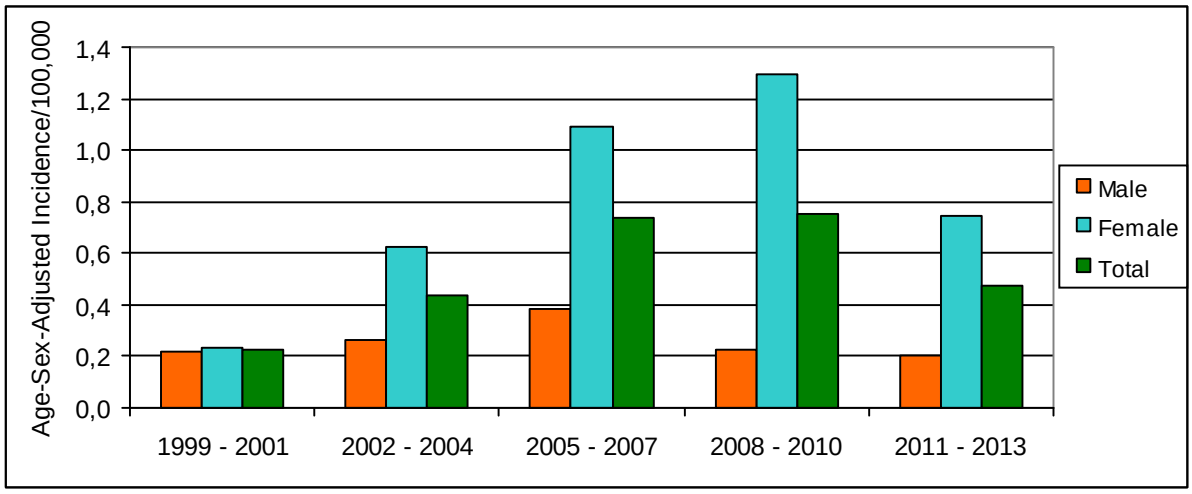


Figure 4. Age- and Sex- Adjusted Incidence of SLE NPSLE cases per 100,000 person/years 1999-2013

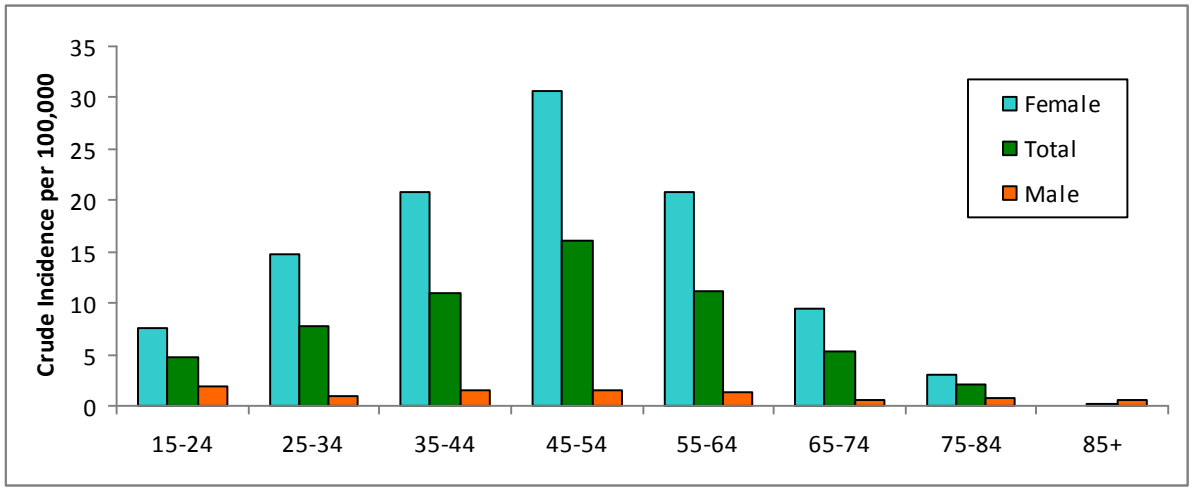


Figure 5. Crude Incidence of SLE cases per age group per 100,000/year, through 1999-2013.

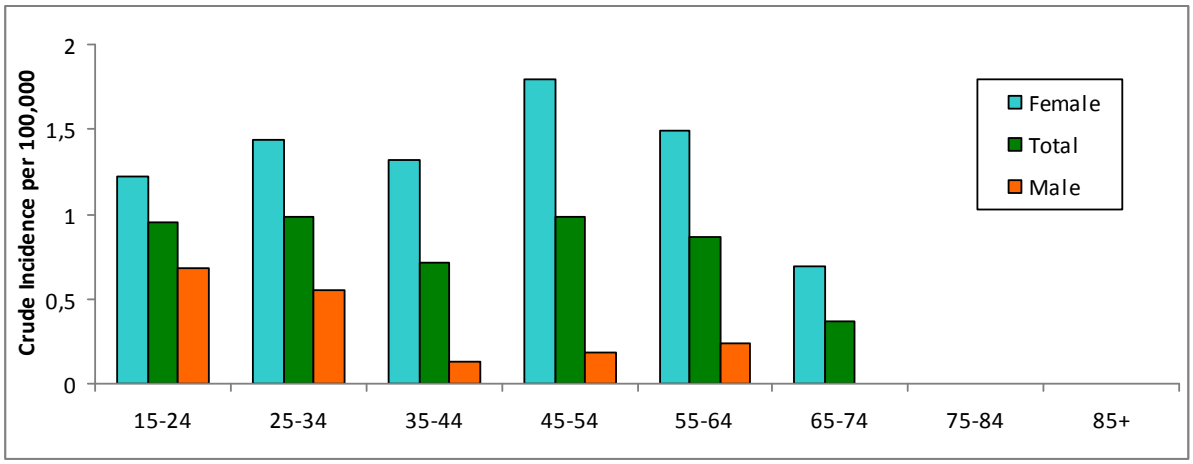


Figure 6. Crude Incidence of SLE nephritis cases per age group per 100,000/year, through 1999-2013.

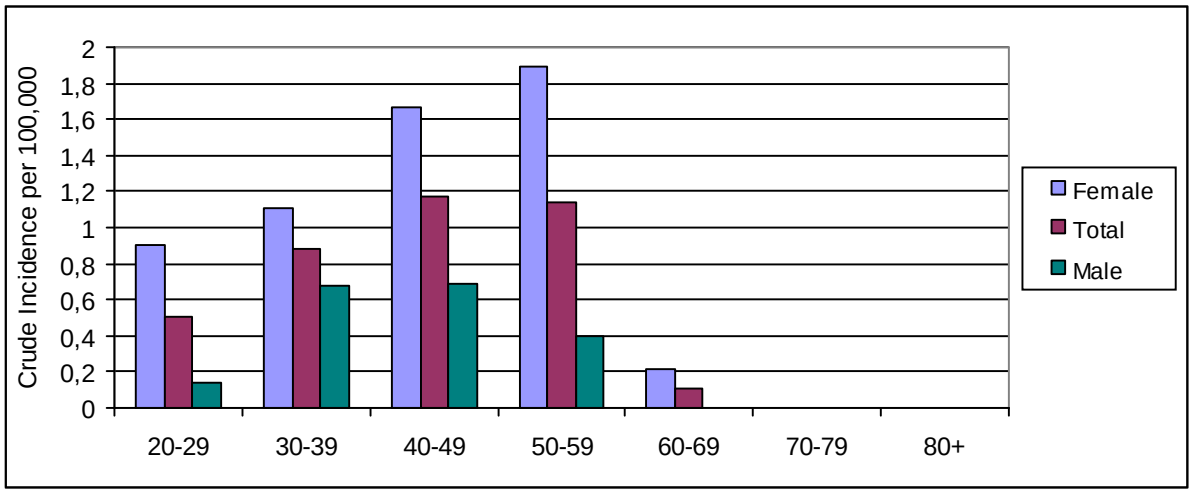


Figure 7. Crude Incidence of NPSLE cases per age group per 100,000/year, through 1999-2013.

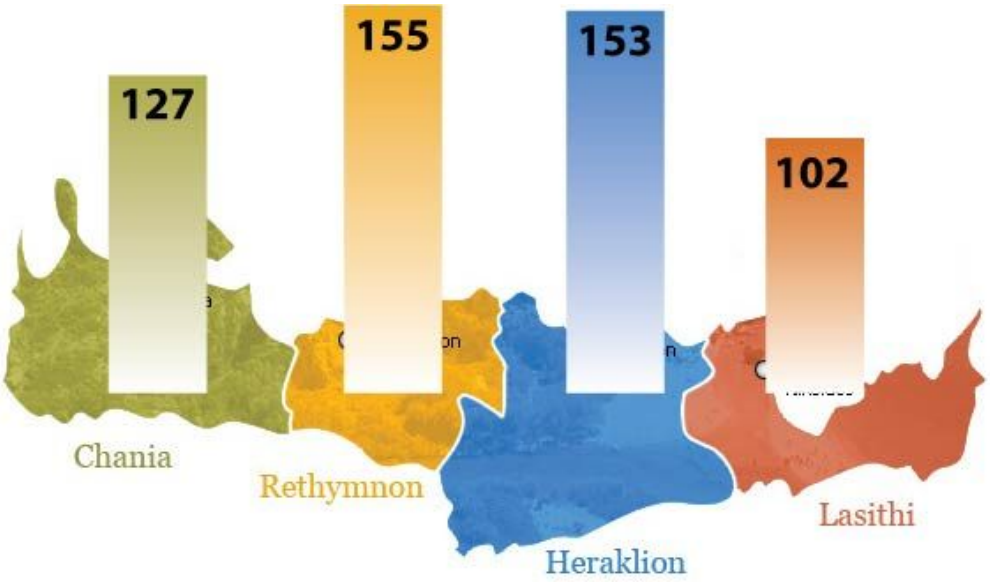


Figure 8. Crude Prevalence of SLE cases (ACR-1997 based definition) in four Cretan Prefectures' per 100,000 people in December, 2013.

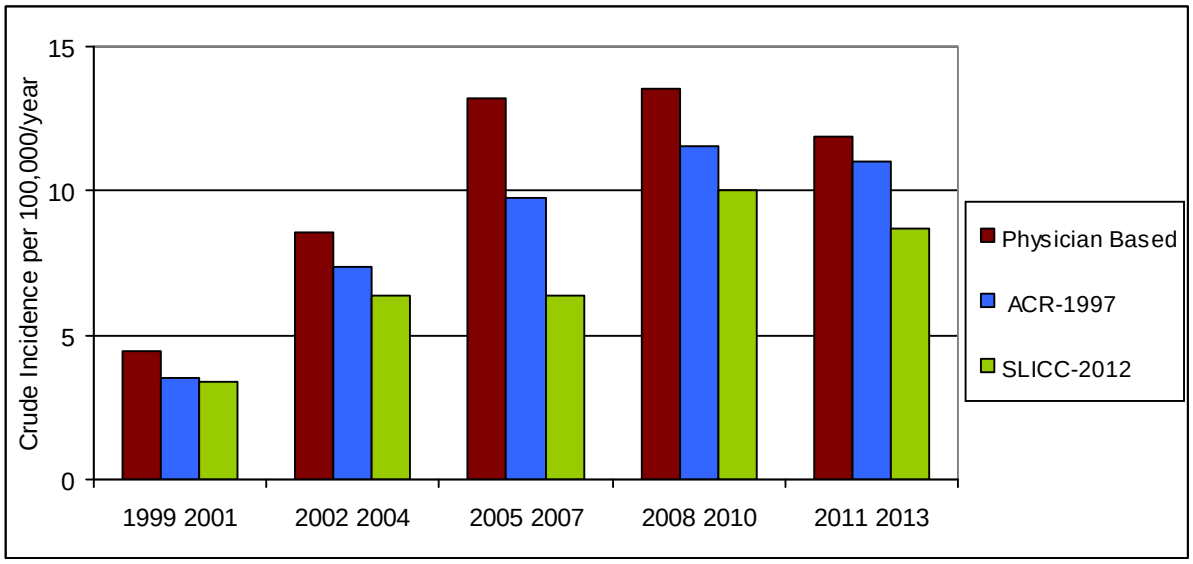


Figure 9. Crude Incidence Estimates of SLE cases per 100,000 per year for the period 1999-2013, comparing 3 definitions

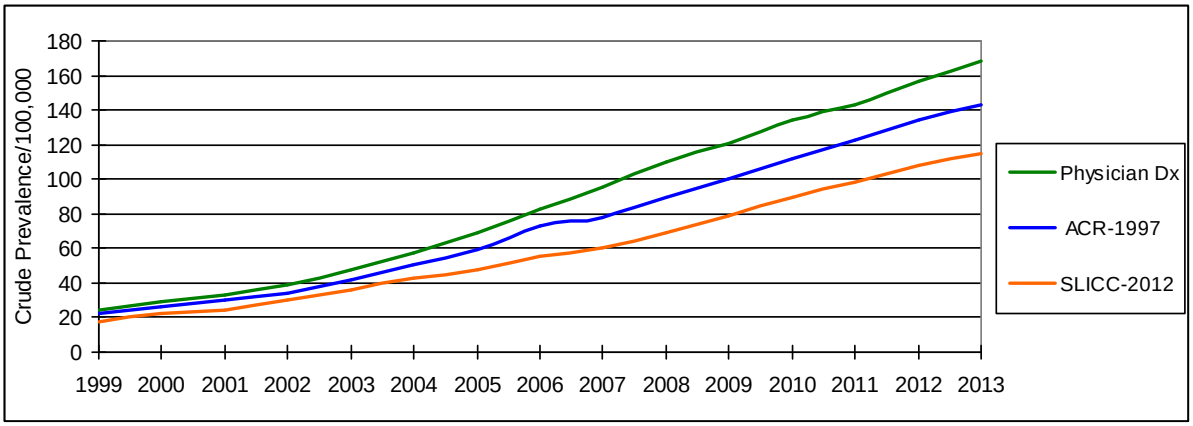


Figure 10. Annual Prevalence of SLE cases per 100,000 for the period 1999-2013, comparing 3 definitions in December, 2013.

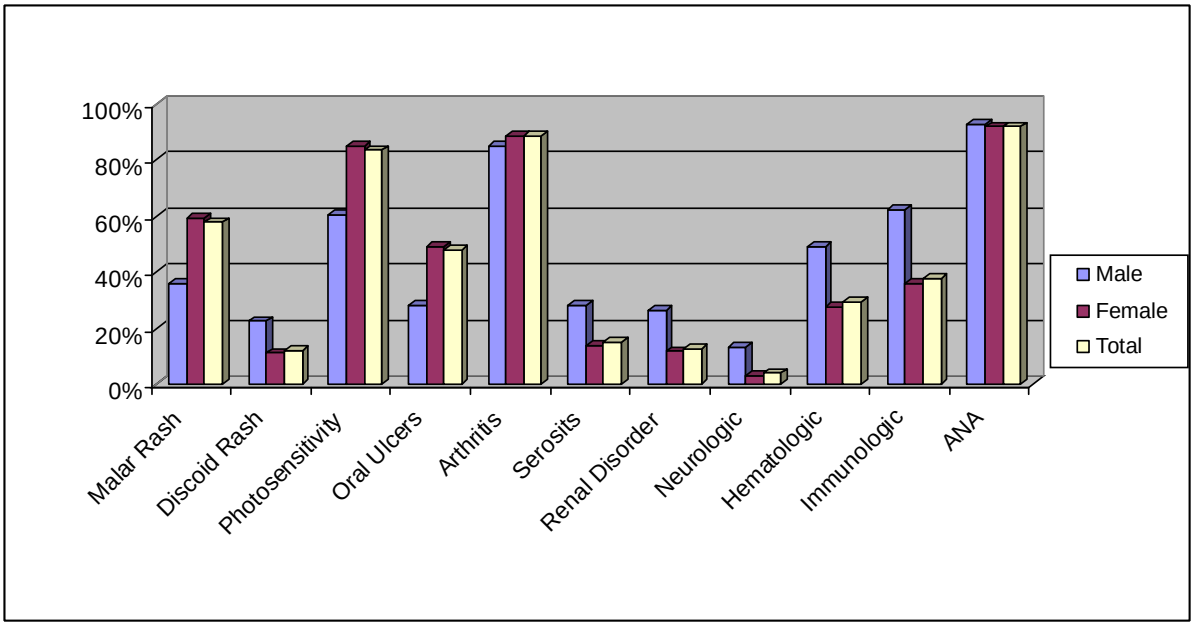


Figure 11. Clinical and serological manifestations in prevalent SLE cases (ACR 1997 criteria definition, 2013)

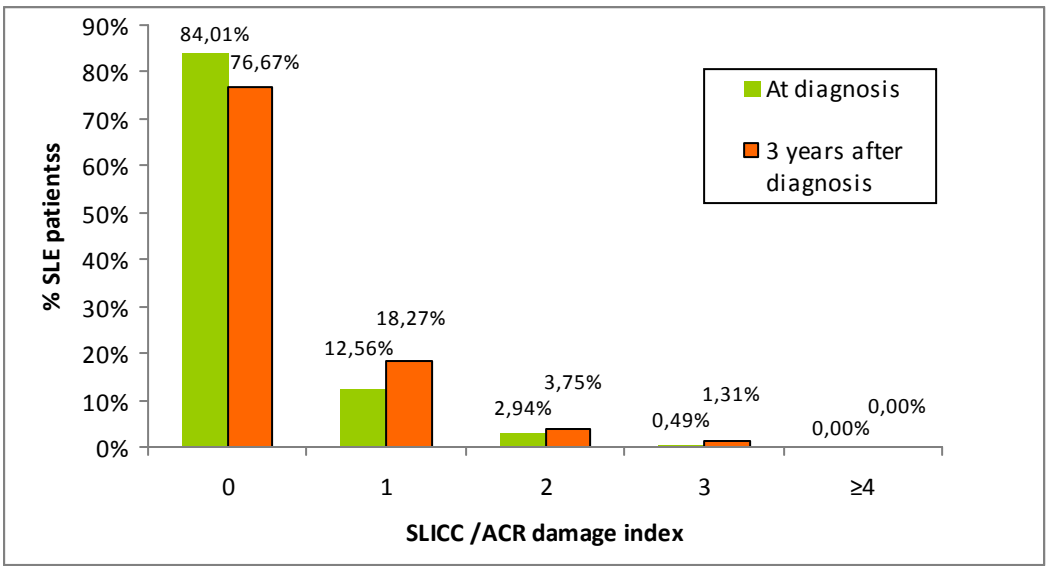


Figure 12. Frequency of non-reversible organ damage (assessed by the SDI) in prevalent SLE cases at at the time of diagnosis and after 3 years. Results are from 613 patients with available data at both time points. No deaths occurred during this period.

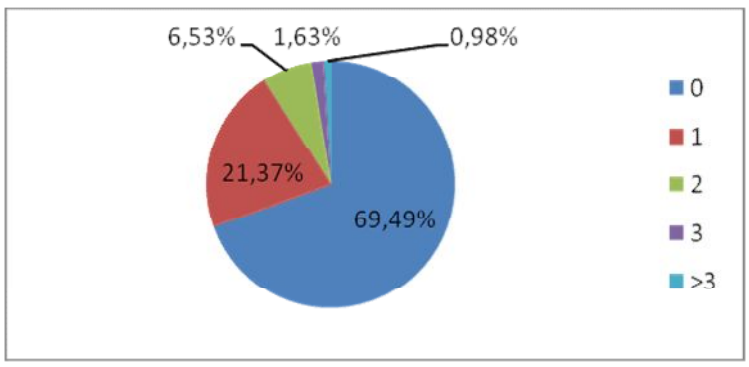


Figure 13. Frequency of organ damage (SDI) in prevalent SLE cases at last follow-up. Results are from 613 patients with available data at both time points. No deaths occurred during this period**.**

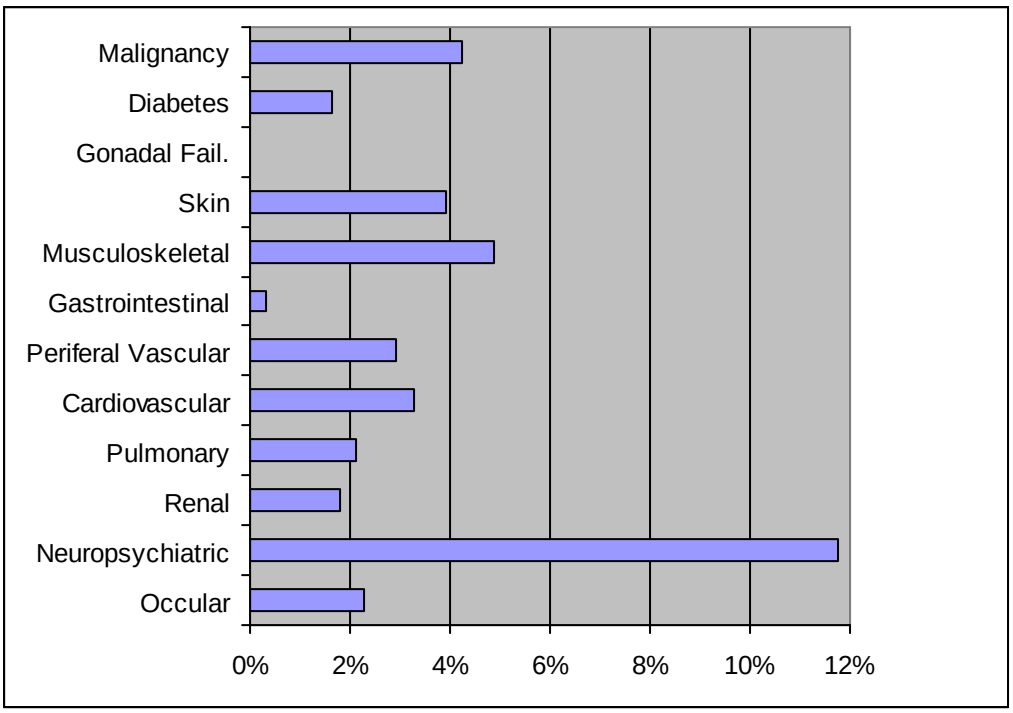


Figure 14. Individual damaged domains (SDI) in prevalent SLE at last follow-up. ACR American College of Rheumatology; SDI, SLICC/ACR Damage Index; SLE, systemic lupus erythematosus.

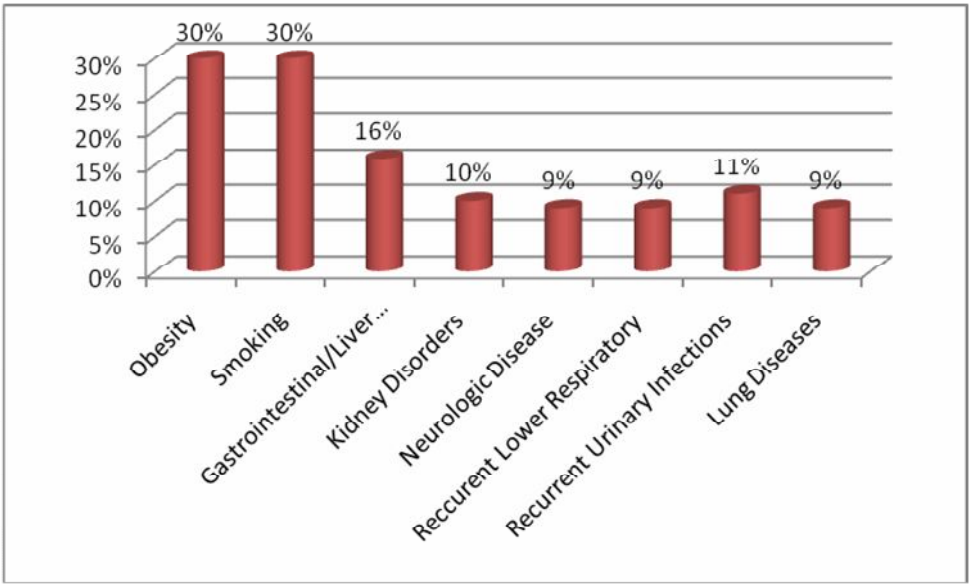


Figure 15 Prevalence of Physical Comorbidities in SLE patients (n=399)

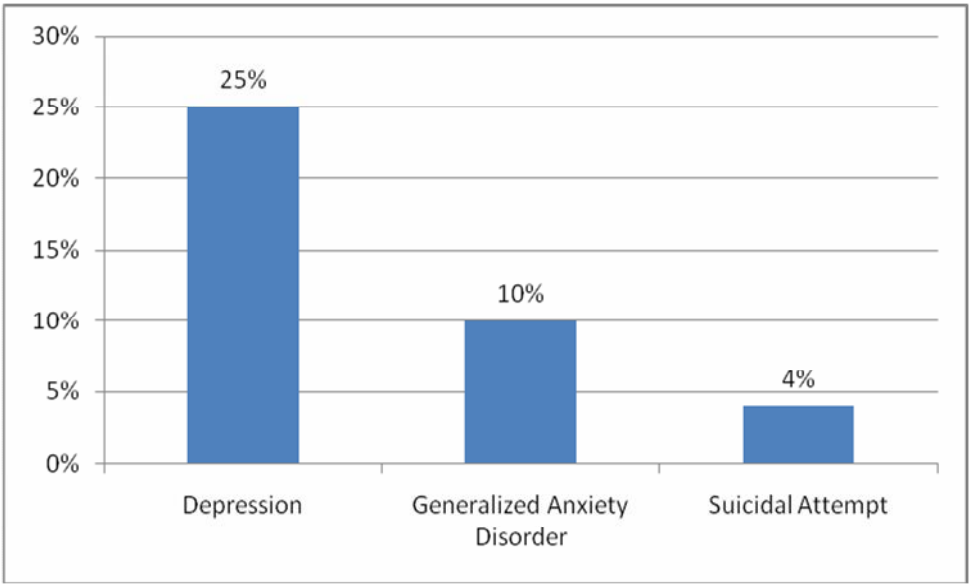
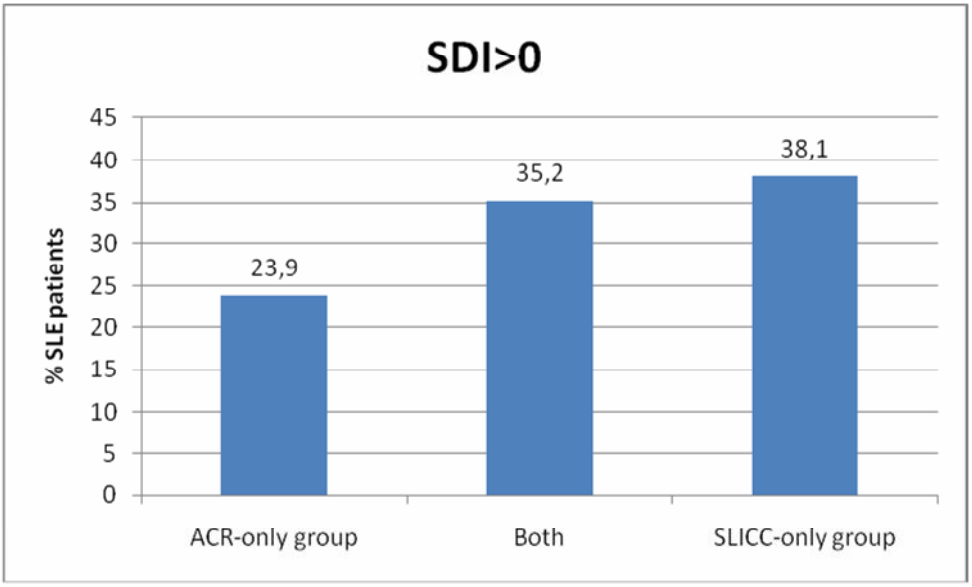
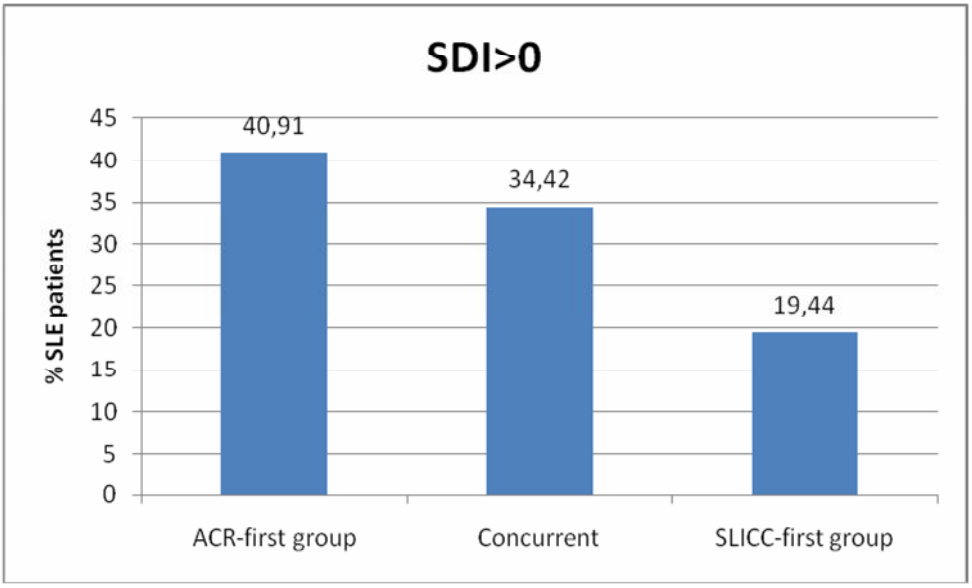


Figure 16. Prevalence of mental comorbidities in SLE patients (n=399)



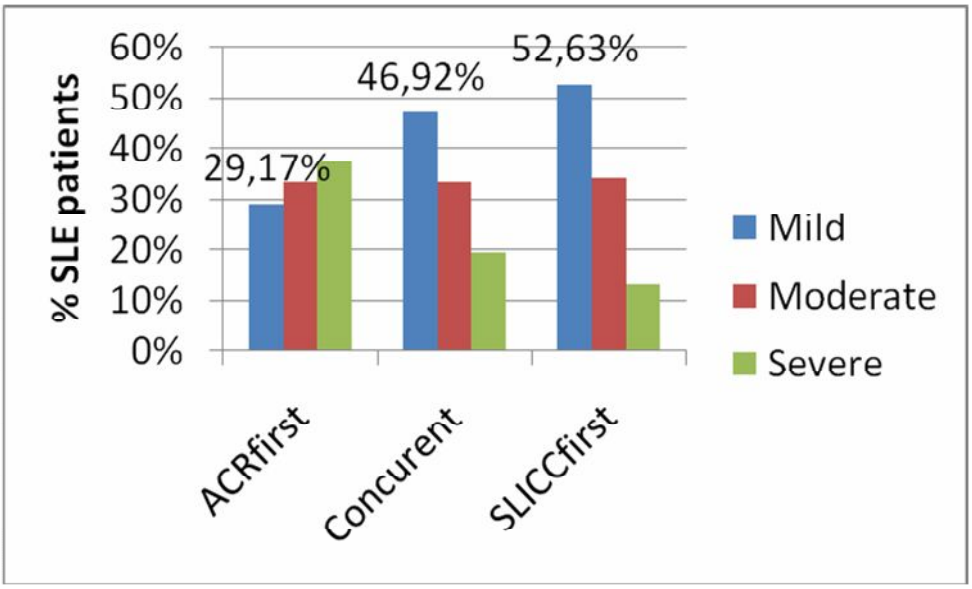
p=0.03

Figure 17. Percentage of SLE patients with non-reversible damage (SDI>0) on last follow-up by ACR-only, SLICC-2012 only or both classification criteria (n=907)



(*p=0.03*)

Figure 18. Percentage of SLE patients with non-reversible damage (SDI>0) by which criteria came first criteria. (n=515)



p<0.001.

Figure 19. Comparison of severity in SLE patients fulfilling both ACR-1997 and SLICC-2012 classification criteria by which came first (n=515)

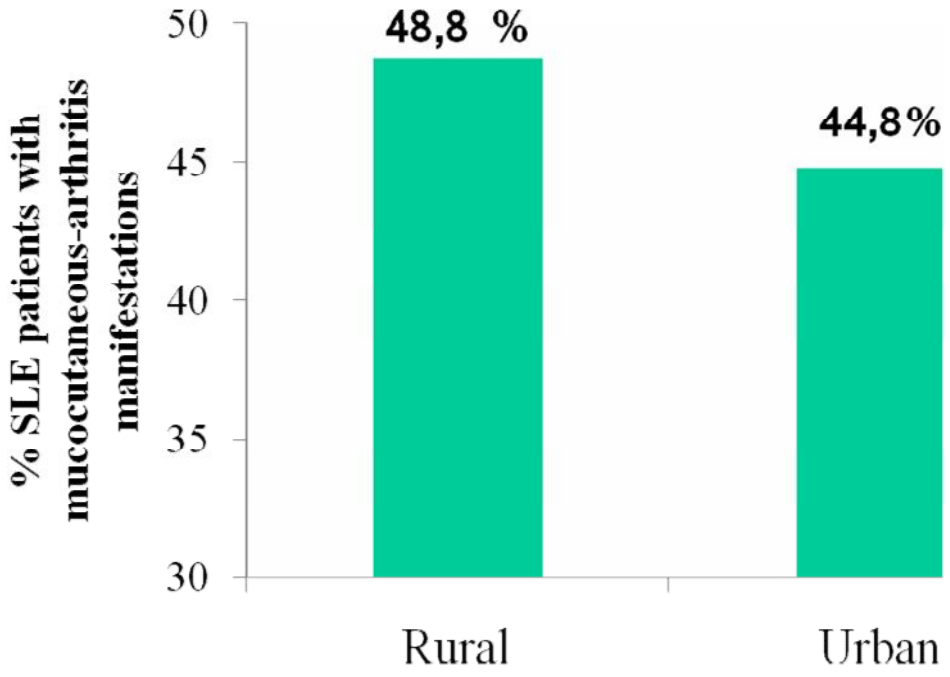
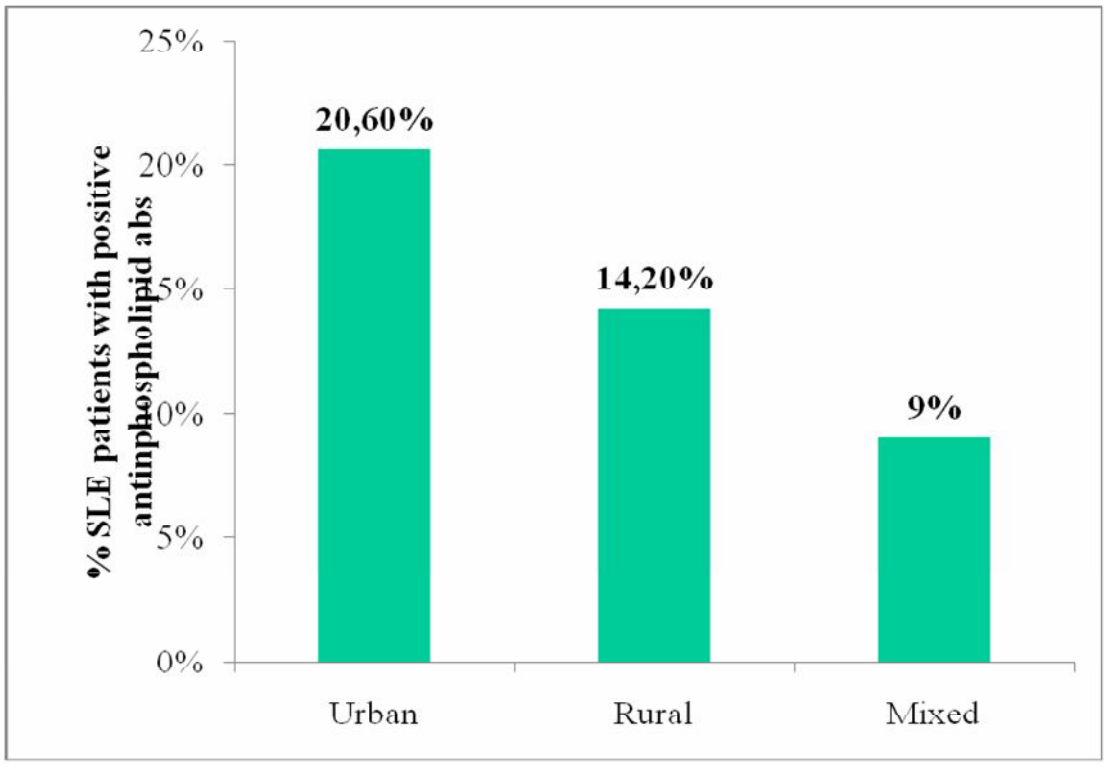
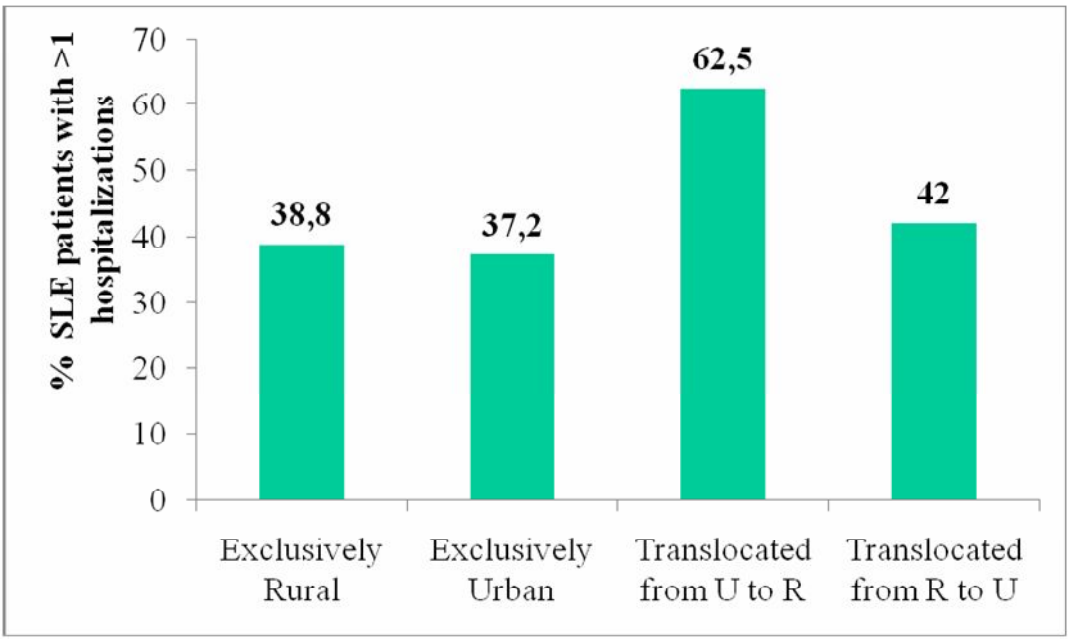


Figure 20. Disease pattern of malar rash, photosensitivity and arthritis in patients having lived exlusively in rural vs. exclusively in urban regions



p=0.04

Figure 21. Prevalence of antiphospholipids by residence



p<0.001

Figure 22. Hospitalizations by residence

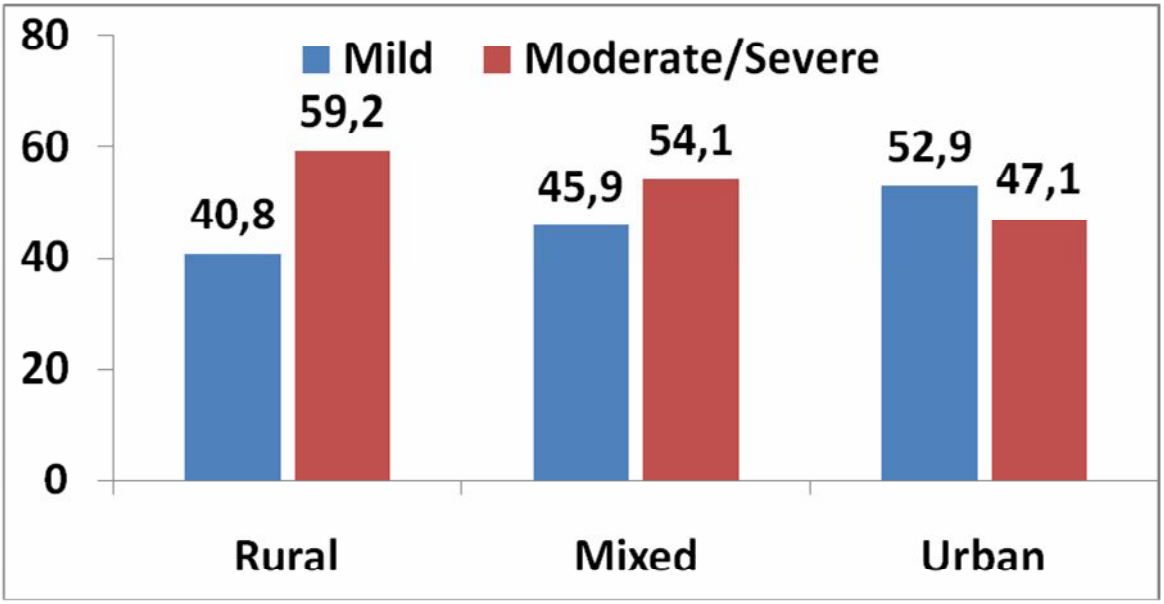


Figure 23. The effect of place of residence on SLE severity.

APPENDIX (SUPPLEMENTARY MATERIAL)

1. SLE PATIENT QUESTIONNAIRE (BASELINE EVALUATION)

ΕΠΙΔΗΜΙΟΛΟΓΙΚΗ ΜΕΛΕΤΗ ΚΟΟΡΤΗΣ ΣΥΣΤΗΜΑΤΙΚΟΥ ΕΡΥΘΗΜΑΤΩΔΟΥΣ ΛΥΚΟΥ ΣΤΗΝ ΚΡΗΤΗ

ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΑΣΘΕΝΟΥΣ ΚΑΤΑ ΤΗΝ ΕΙΣΑΓΩΓΗ ΣΤΗΝ ΜΕΛΕΤΗ (VERSION 17.4.2013drf)

Αρ. ερωτηματολογίου | | | | |

Ημερομηνία συνέντευξης | | | | | | | | |
ημέρα *μήνας* *έτος*

Νοσοκομείο / Παραπέμπων Ιατρός

1. ΠΑΓΝΗ……..
2. Βενιζέλειο……..
3. Ιδιωτικό Ιατρείο ……..
4. Άλλο……..

ΕΝΟΤΗΤΑ 1. ΠΡΟΣΩΠΙΚΑ ΚΑΙ ΔΗΜΟΓΡΑΦΙΚΑ ΣΤΟΙΧΕΙΑ

1.1.1 Φύλο: ☐ Άρρεν ☐ Θήλυ

1.1.2 Επώνυμο:……..……**1.1.3 Όνομα:**…….

1.1.4 Πατρώνυμο:…….... **1.1.5 Ημερομηνία Γέννησης** ……..

1.5. Που μένετε;

1.5.1. ΝΟΜΟΣ : ☐ Ηράκλειο ☐ Ρέθυμνο ☐ Χανιά ☐ Λασίθι ☐ Άλλο…….

1.5.2. Διεύθυνση (Οδός – Αριθμός) ……

1.5.3. Κοινότητα/Πόλη…… **1.5.4. Δήμος**……

1.5.5 Η περιοχή μόνιμης κατοικίας σας είναι: ☐ Αστική ☐ Ημιαστική ☐ Αγροτική

1.6. Τηλέφωνο Οικίας: …….. **1.7. Κινητό τηλέφωνο:** ……

1.9. Ποια είναι η εθνική σας καταγωγή ;

☐. Ελληνική ☐. Άλλο ……..…… ☐. Δ.ξ./Δ.α.

(Αν η καταγωγή είναι Ελληνική συνεχίζετε στην ερώτηση 1.11)

1.10. Αν η καταγωγή σας δεν είναι Ελληνική, πόσο καιρό μένετε στην Ελλάδα;

☐. Γεννήθηκα στην Ελλάδα / Μένω εδώ από παιδί ☐ χρόνια/μήνες……/…… ☐ Δ.ξ./Δ.α.

1.11 Σε ποιο μέρος γεννηθήκατε:……..……☐ Πόλη ☐ Χωριό ☐ Δ.ξ./Δ.α.

1.12 Μένετε μόνιμα στην Κρήτη; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

1.12.1 Αν ναι, πόσο καιρό μένετε στην Κρήτη;

☐ Γεννήθηκα στην Κρήτη / Μένω εδώ από παιδί ☐ χρόνια/μήνες……/…… ☐ Δ.ξ./Δ.α.

1.12.2 Ζούσατε στην Κρήτη, ένα χρόνο πριν τη διάγνωση της ασθένειας σας;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(Εάν ο ασθενής δε δηλώσει μόνιμη κατοικία στην Κρήτη τουλάχιστον ένα χρόνο πριν τη διάγνωση εξαιρείται από τη μελέτη επίπτωσης)***

1.12.3 Που μεγαλώσατε και σε ποιες περιοχές έχετε διαμείνει έως τώρα και για ποια χρονικά διαστήματα;……
……
…… ☐ Δ.ξ./Δ.α.

1.12.4 Έχετε κατά τη διάρκεια της ζωής σας διαμείνει σε μεγαλύτερη πόλη;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

1.12.5 Είστε κρητικής καταγωγής; (και οι τρεις γενιές πριν από εσάς ήταν από και διέμεναν στην Κρήτη;)

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

1.13. Ποια είναι η οικογενειακή σας κατάσταση. Είστε :

☐ Άγαμη/ος ☐ Αρραβωνιασμένη/ος ☐ Έγγαμη/ος ☐ Διαζευγμένη/ος

☐ Χήρα/ος ☐ Δ.ξ./Δ.α.

1.14. Ποια είναι η πιο υψηλή βαθμίδα εκπαίδευσης που έχετε συμπληρώσει ;

☐ Δεν πήγα σχολείο ☐ Δημοτικό σχολείο ☐ Γυμνάσιο ☐ Λύκειο

☐ Ανώτερη Σχολή ☐ ΤΕΙ/ΑΕΙ ☐ Δ.ξ./Δ.α.

1.15. Πόσα κιλά ζυγίζετε αυτή τη στιγμή;…… kg ☐ Δ.ξ./Δ.α.

1.15. Τι ύψος έχετε ; ……cm ☐ Δ.ξ./Δ.α. **BMI: ΣΒ/Υ^2** ……

<u>Θα θέλαμε τώρα να σας κάνουμε μερικές ερωτήσεις για την εργασία σας</u>

1.17. Εργάζεστε, τώρα ; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

1.18 Πως θα περιγράφατε την απασχόλησή σας;

☐ Μισθωτός ☐ Αυτοαπασχολούμενος ☐ Άνεργος ☐ Οικιακά ☐ Στρατιώτης

☐ Αγρότης/Αγρότισσα ☐ Μαθητής, φοιτητής, μετεκπαιδευόμενος, εργαζόμενος χωρίς αμοιβή

☐ Συνταξιούχος ή έχετε διακόψει τις εργασίες της επιχείρησής σας

☐ Ακατάλληλος για εργασία ή έχετε μόνιμη αναπηρία ☐ Άλλο……..……..

☐ Δ.ξ./Δ.α.

Εάν δεν εργάζεσθε:

1.19.1 Περιγράψτε τον λόγο που δεν εργάζεσθε:

☐ εξαιτίας του λύκου ☐ απολύθηκα ☐ προσωπική επιλογή/οικογενειακοί λόγοι

☐ συνταξιοδότηση ☐ άλλα προβλήματα υγείας ☐ δεν βρίσκω εργασία

☐ Άλλο, προσδιορίστε ……..

1.19.2. Ποια ήταν η παλαιότερη σας εργασία ……

1.19.3 Εάν είστε άνεργος, πόσος καιρός έχει περάσει από την τελευταία σας εργασία;

☐ 1-6 μήνες ☐ 6 μήνες-1 χρόνο ☐ Πάνω από ένα χρόνο

<u>Θα θέλαμε τώρα να σας ρωτήσουμε για την εργασία του συζύγου/(πατέρα σας σε περίπτωση μη έγγαμου)</u>

1.21 Τι δουλειά κάνει; ☐ Σύζυγος ☐ Πατέρας

☐ Δεν εργάζεται ☐ Μισθωτός ☐ Ελεύθερος επαγγελματίας ☐ Αγρότης

☐ Άνεργος, που ψάχνει για εργασία ☐ Άνεργος λόγω προβλημάτων υγείας ☐ Συνταξιούχος

☐ Έχει εξασφαλισμένο εισόδημα και δεν χρειάζεται να εργάζεται.

☐ Άλλο (διευκρινίστε)…….. ☐ Δ.ξ./Δ.α.

Θα θέλαμε τώρα να μιλήσουμε συγκεκριμένα για το είδος της εργασίας σας. Επίσης αν κάνατε περισσότερες από μία εργασίες συγχρόνως θα θέλαμε να μιλήσουμε για αυτές ξεχωριστά.
(Εάν είναι αγρότισσα πηγαίνετε στην αντίστοιχη ενότητα (8).

	ΕΡΓΑΣΙΑ						
ΕΡΓΑΣΙΑ	**1.22.1** Τι ***δουλειά*** κάνετε;	**1.22.2** Πόσα ***χρόνια*** κάνετε τη συγκεκριμένη εργασία;	**1.22.3** Σε ποια ***εταιρία/ υπηρεσία*** εργάζεστε;	**1.22.4** *Τι,* ακριβώς, κάνετε στη δουλεία σας;	**1.22.5** ***Το ωράριό σας είναι:*** 1. Σταθερό ημερήσιο 2. Σπαστό ημερήσιο 3. Σταθερό νυχτερινό 4. Κυκλικό χωρίς να περιλαμβάνει νυχτερινή εργασία 5. Κυκλικό που περιλαμβάνει νυχτερινή εργασία	**ΣΗΜΕΙΩΣΤΕ ΤΙΣ ΩΡΕΣ ΠΟΥ ΕΡΓΑΖΕΣΤΕ ΑΝΑ ΕΒΔΟΜΑΔΑ** **ΩΡΕΣ/ΕΒΔΟΜΑΔΑ** **1.22.6** ΠΡΙΝ ΤΗΝ ΝΟΣΟ	**1.22.7** ΚΑΤΑ ΤΗΝ ΝΟΣΟ
	ΟΝΟΜΑ	**ΧΡΟΝΟΣ**	**ΥΠΗΡΕΣΙΑ**	**ΔΡΑΣ/ΤΗΤΑ**	**ΩΡΑΡΙΟ**		
1						<20 20-40 >40	<20 20-40 >40
2							
3							

ΕΝΟΤΗΤΑ 2 ΟΙΚΟΓΕΝΕΙΑΚΟ ΚΑΙ ΑΤΟΜΙΚΟ ΙΣΤΟΡΙΚΟ

Τώρα θα ήθελα να μιλήσουμε για το ιατρικό ιστορικό το δικό σας και της οικογένειάς σας

2. Πάσχει άλλο μέλος της οικογένειάς σας από ρευματολογικό ή αυτοάνοσο νόσημα όπως λύκο, ρευματοειδή αρθρίτιδα, ψωρίαση κτλ; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.1 Αν ναι περιγράψτε: Μέλος Οικογένειας / Νόσος ……../……

……/…… ……/……

2.1.1 Έπασχε / Πάσχει άλλο μέλος της οικογένειας από άλλο κληρονομικό /σοβαρό νόσημα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.1.1.2 Αν ναι περιγράψτε: Μέλος Οικογένειας / Νόσος ……../……

……/…… ……/……

Τώρα θα ήθελα να μιλήσουμε για το δικό σας ιστορικό

2.2 Έχετε στο ιστορικό σας κάποια ασθένεια αλλεργικής φύσης;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.3)***

2.2.1 Αν ναι περιγράψτε ποια:

☐ Αλλεργική ρινίτιδα ☐ Αλλεργικό άσθμα ☐ Κνίδωση ☐ Άλλο ……..

2.2.2. Παίρνετε κάποια φάρμακα γι αυτήν την ασθένεια;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.3)***

2.2.3 Αν ναι, πείτε μας την ονομασία του φαρμάκου και την εβδομαδιαία δοσολογία του (*υποσημείωση να συμπληρώνεται με βάση το βιβλιάριο ασθενείας-ιατρικό φάκελο)*

……

……

…… ☐ Δ.ξ./Δ.α.

2.2.4 Έχετε αλλεργία σε κάποιο φάρμακο; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.2.4.1 Αν ναι σε ποιο, περιγράψτε:…… ☐ Δ.ξ./Δ.α.

2.3. Έχετε σακχαρώδη διαβήτη; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(εάν όχι πηγαίνετε στην ερώτηση 2.4) **Αν ναι από πότε;**……

Παίρνετε φάρμακα για την υψηλή γλυκόζη αίματος / σακχαρώδη διαβήτη;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.4)***

2.3.2 Αν ναι, πείτε μας την ονομασία του φαρμάκου και την εβδομαδιαία δοσολογία του (*υποσημείωση να συμπληρώνεται με βάση το βιβλιάριο ασθενείας-ιατρικό φάκελο)*

……

……

…… ☐ Δ.ξ./Δ.α.

2.4Έχετε αρτηριακή υπέρταση; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(εάν όχι πηγαίνετε στην ερώτηση 2.5) **Αν ναι από πότε;**……

2.4.1 Παίρνετε φάρμακα για την αρτηριακή υπέρταση ; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(εάν όχι πηγαίνετε στην ερώτηση 2.5) **2.4.2 Αν ναι, πείτε μας την ονομασία του φαρμάκου και την δοσολογία του (*να συμπληρώνεται με βάση το βιβλιάριο ασθενείας-ιατρικό φάκελο)***

…… ☐ Δ.ξ./Δ.α.

2.5 Έχετε υψηλές τιμές χοληστερόλης/τριγλυκεριδίων; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(εάν όχι πηγαίνετε στην ερώτηση 2.6) **Αν ναι από πότε;**……

2.5.1 Παίρνετε φάρμακα για την υψηλή χοληστερόλη/ τριγλυκερίδια;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.6)***

2.5.2 Αν ναι, πείτε μας την ονομασία του φαρμάκου και την ημερήσια δοσολογία του

…… ☐ Δ.ξ./Δ.α.

2.6 Σας έχει πει ποτέ γιατρός ότι πάσχετε από θυρεοειδοπάθεια;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.7)***

2.6.1 Τι είδους θυρεοειδοπάθεια έχετε; ☐ Υπερθυρεοειδισμό ☐ Υποθυρεοειδισμό

☐ Βρογχοκήλη ☐ Οζώδης βρογχοκήλη ☐ Αυτοάνοση θυρεοειδοπάθεια (Hashimoto)

☐ Ca θυρεοειδούς ☐ Άλλο …….. ☐ Δ.ξ./Δ.α.

2.6.2 Λαμβάνετε φάρμακα για θυρεοειδοπάθεια; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(εάν όχι πηγαίνετε στην ερώτηση 2.7)

2.6.3 Αν ναι, πείτε μας την ονομασία του φαρμάκου και την ημερήσια δοσολογία του (*να συμπληρώνεται με βάση το βιβλιάριο ασθενείας-ιατρικό φάκελο ασθενή-να συμπεριληφθεί και η χορήγηση ραδιενεργού ιωδίου)*

……

……

…… ☐ Δ.ξ./Δ.α.

2.7 Έχετε οστεοπόρωση; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(εάν όχι πηγαίνετε στην ερώτηση 2.8) **Αν ναι από πότε;**……..

2.7.1 Αν ναι, έχετε κάνει ποτέ κάποιο κάταγμα λόγω της οστεοπόρωσης;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2. 7.1 Έχετε πάρει φάρμακα για οστεοπόρωση κατά την διάρκεια των τελευταίων 12 μηνών ;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.8)***

2.7.2 Αν ναι, πείτε μας την ονομασία του φαρμάκου και την ημερήσια ή εβδομαδιαία δοσολογία του (***να συμπληρώνεται με βάση το βιβλιάριο ασθενείας-ιατρικό φάκελο ασθενή)***

……

……

……..…… ☐ Δ.ξ./Δ.α.

2.8. Σας έχει πει ποτέ γιατρός ότι πάσχετε από κάποια από τις παρακάτω ασθένειες;

	ΟΧΙ	**ΝΑΙ**	**Πάθηση / Έτος Εμφάνισης**
1. Καρδιοπάθεια			
2. Νευρολογικό πρόβλημα			
3. Κακοήθεια			
4. Πάθηση στα νεφρά			
5. Πάθηση πνευμόνων			
6. Ηπατοπάθεια			
7. Πρόβλημα με τη χολή			
8. Έλκος ή άλλο πρόβλημα στο στομάχι			
9. Ενδοκρινολογικό πρόβλημα			
10. Διαταραχές πήξης του αίματος			
11. Φυματίωση			
12. Λοίμωξη HIV			
13. Λοιμώξεις του ουροποιητικού συστήματος			
14. Δερματοπάθεια			
15. Στίγμα μεσογειακής αναιμίας			
16. Άλλο, καθορίστε:			

2.9 Είχατε ποτέ περάσει κάποια από τις παρακάτω λοιμώδεις ασθένειες;

☐ Ιλαρά ☐ Παρωτίτιδα ☐ Ερυθρά ☐ Ανεμευλογία ☐ Λοιμώδη Μονοπυρήνωση

☐ Δ.ξ./Δ.α.

2.10 Είχατε ποτέ ψυχολογική επιβάρυνση (ώστε λ.χ να ζητήσετε βοήθεια από κάποιον ειδικό;)

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 2.11)***

2.11.1 Αν ναι, ποιο ακριβώς πρόβλημα αντιμετωπίζετε και από πότε;

☐ Άγχος (……..) ☐ Κατάθλιψη (……..) ☐ Ψύχωση (σχιζοφρένεια) (……..)

☐ Μανιοκατάθλιψη-Διπολική διαταραχή (……..) ☐ Νευρογενής ανορεξία-Βουλιμία (……..)

☐ Εξάρτηση από το αλκοόλ (……..) ☐ Εξάρτηση από ναρκωτικές ουσίες (……..)

☐ Ειχα αποπειραθεί να κάνω κακό στον εαυτό μου (……..)

☐ Άλλο: καθορίστε…… (……..) ☐ Δ.ξ./Δ.α.

2.11.2 Έχετε συμβουλευθεί κάποιο ψυχολόγο ή ψυχίατρο;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.11.3 Αν παίρνετε φάρμακα για το συγκεκριμένο πρόβλημα ή νόσο , πείτε μας την ονομασία του φαρμάκου και τη δοσολογία του για κάθε μία από τις ασθένειες

……
……
……..…… ☐ Δ.ξ./Δ.α.

2.12 Έχετε υποβληθεί ποτέ σε χειρουργική επέμβαση;…. ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι περιγράψτε Ετος/ Επέμβαση ……../……..……

……../……..…… ……../……..……

ΠΡΟΛΗΠΤΙΚΕΣ ΕΞΕΤΑΣΕΙΣ **<u>Τώρα θα μιλήσουμε για ορισμένα θέματα πρόληψης</u>**

2.13.1 Έχετε κάνει εμβόλιο για τη γρίπη κατά την διάρκεια του τελευταίου χρόνου?

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.13.2 Έχετε κάνει εμβόλιο για τον πνευμονιόκοκκο κατά την διάρκεια της τελευταίας πενταετίας ?

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.13.3 Έχετε κάνει κάποιο άλλο εμβόλιο κατά την διάρκεια της ασθένειας σας?

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. Εάν ΝΑΙ, Τύπος εμβολίου / ημ/νια (μήνας, έτος)

……../…… ……../……

……../…… ……../……

2.13.4 Έχετε κάνει κάποιο από τα παρακάτω εμβόλια ?

☐ Ιλαράς-Παρωτίτιδας-Ερυθράς ☐ Διφθερίτιδα-Κοκκύτη-Τετάνου ☐ Πολιομυελίτιδας

☐ Ηπατίτιδας Α ☐ Ηπατίτιδας Β ☐ Δ.ξ./Δ.α.

2.13.5 Για πάνω από 50 ετών,

Έχετε κάνει προληπτικά κολονοσκόπηση; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.13.6 Χρησιμοποιείτε ηλιοπροστατευτικά μέτρα (αντηλιακή, καπέλο κτλ) κατά τη διάρκεια της νόσου σας; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Για γυναίκες, επίσης (επί ενδείξεων):

2.14 Έχετε κάνει τεστ Παπανικολάου, κατά τη διάρκεια των τελευταίων 2 ετών;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

2.15 Έχετε κάνει μαστογραφία, κατά τη διάρκεια του τελευταίου χρόνου

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

<u>ΕΝΟΤΗΤΑ 3</u> **(Για άρενες μόνο τις ερωτήσεις 3.1-3.3)**

3. 1 Πόσα παιδιά έχετε;……

3.2 Ποιες χρονιές γεννήθηκαν τα παιδιά σας;……..……..

3.3 Αντιμετωπίζει κάποιο παιδί σας πρόβλημα υγείας; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι ποιο……..……

<u>Τώρα θα θέλαμε μερικά στοιχεία σχετικά με το μαιευτικό ή γυναικολογικό σας ιστορικό;</u>

3.4 Στις εγκυμοσύνη (ες) σας αντιμετωπίσατε κάποιο πρόβλημα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

3.4.1 Αν ναι περιγράψτε, ☐ Διαβήτης κυήσεως ☐ Υπέρταση/προεκλαμψία

☐ Πρόωρος τοκετός ☐ Άλλο……..

3.4.2 Στην περίοδο της λοχείας αντιμετωπίσατε κάποιο πρόβλημα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

3.4.3 Το παιδί/παιδιά σας είχαν κάποιο πρόβλημα όταν γεννήθηκαν λ.χ χαμηλό βάρος γέννησης

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

3.5 Είχατε ποτέ κάποια αποβολή; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

3.5.1 Αν ναι πόσες και σε ποιο τρίμηνο της κύησης συνέβη η καθεμία

☐ Πρώτο τρίμηνο (…….) ☐ Δεύτερο τρίμηνο (…….) ☐ Δ.ξ./Δ.α.

3.6 Είχατε/έχετε προβλήματα με την περίοδο σας; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

3.6.1 Σε ποια ηλικία ξεκίνησε η περίοδος; …….

3.6.2 Αυτή τη στιγμή, είστε σε

☐ Εμμηνορυσιακή περίοδο ☐ Προεμμηνοπαυσιακή περίοδο ☐ Εμμηνόπαυση

3.6.2.1 Αν σε εμμηνόπαυση Σε ποια ηλικία σταμάτησε η περίοδος;…….

3.6.3 Είχατε/έχετε κάποιο γυναικολογικό προβλημα; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

3.6.3.1 Αν ναι περιγράψτε ……

……..

<u>ΕΝΟΤΗΤΑ 4-ΙΣΤΟΡΙΚΟ ΝΟΣΟΥ</u> ***<u>Τώρα θα συζητήσουμε για θέματα γύρω από την ρευματολογική νόσο</u>***

4. 1 Ποιά είναι η κύρια διάγνωση της ασθένειάς σας;……

4.2 Σας έχει πει ποτέ γιατρός ότι πάσχετε και από δεύτερο/επικαλυπτόμενο Ρευματολογικό / αυτοάνοσο νόσημα; Αν ναι ποιο;

	ΟΧΙ	**ΝΑΙ**		**ΟΧΙ**	**ΝΑΙ**
1. Σύνδρομο Sjogren			9. Σακχαρώδης Διαβήτης τύπου Ι		
2. Ρευματοειδής αρθρίτιδα			10. Σκλήρυνση κατά πλάκας		
3. Αντιφωσφολιπιδικό Σύνδρομο			11.Αυτοάνοση ηπατίτιδα		
4. Σκληρόδερμα			12. Πρωτοπαθή χολική κίρρωση		
5. Σπονδυλαρθοπάθεια			13. Κοιλιοκάκη		
6. Δερματομυοσίτιδα			14. Πρωτοπαθή σκληρυντική αγγειίτιδα		
7. Δερματομυοσίτιδα			15. Ατροφική γαστρίτιδα		
8. Φλεγμονώδεις νόσοι του εντέρου (ελκώδης κολίτιδα-νόσος Crohn)			16. Αντιφωσφολιπιδικό Σύνδρομο		
Άλλο, καθορίστε:					

4.3 Πότε διαγνώστηκε η ασθένεια σας; Μήνας / Έτος (……/…….) ☐ Δ.ξ./Δ.α.

4.3.1 Ποιος ιατρός διέγνωσε την ασθένειά σας/ σε ποιο νοσοκομείο/ιατρείο διαγνωστήκατε;

……

4.4. Για πόσο καιρό είχατε συμπτώματα πριν διαγνωστείτε;

☐ 1-5 μήνες ☐ 6-12 μήνες ☐ πάνω από χρόνο ☐ πάνω από 2 χρόνια ☐ Δ.ξ./Δ.α.

4.5. Ποια ήταν τα αρχικά σας συμπτώματα;

……

……

…… ☐ Δ.ξ./Δ.α.

4.6. Από την αρχή της ασθένεια σας μέχρι σήμερα είχατε κάποιο από τα παρακάτω;

1. πυρετό ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. απώλεια βάρους ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. ανορεξία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. λεμφαδενοπάθεια ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
5. εύκολη κόπωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.7 Από την αρχή της ασθένεια σας μέχρι σήμερα είχατε δερματολογικές εκδηλώσεις;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.7.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Φωτοευαισθησία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Εξάνθημα πεταλούδας ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Τριχόπτωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Άφθες ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
5. Άλλη εκδήλωση από το δέρμα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

   (παρακαλώ περιγράψτε)……

4.8. Από την αρχή της ασθένεια σας μέχρι σήμερα είχατε συμπτώματα από τις αρθρώσεις σας;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.8.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Αρθρίτιδα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Μυαλγίες ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Ινομυαλγία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Τενοντίτιδα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
5. Άλλη εκδήλωση από το μυοσκελετικό ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

   (παρακαλώ περιγράψτε)……

4.9. Από την αρχή της ασθένεια σας μέχρι σήμερα είχατε νευρολογικά συμπτώματα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.9.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Εγκεφαλικό Επεισόδιο ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Νευροπάθεια ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Επιληψία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Διαταραχές στη μνήμη σας; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
5. Άλλη εκδήλωση από το νευρικό ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

   (παρακαλώ περιγράψτε)……

Επί ενδείξεων, Mini-Cog Test

A. Θα σας πω τρεις λέξεις και θα σας ρωτήσω μετά αν τις θυμάστε λ.χ κόκκινο-βελούδο-εκκλησία

B. Ζωγραφίστε ένα ρολόι, που να δείχνει 11 και δέκα

Αν το Mini-Cog θετικό, Moca Test και <u>Εξέταση για γνωστική δυσλειτουργία (AD8)</u>

4.9.2. Από την αρχή της ασθένεια σας μέχρι σήμερα είχατε ψυχολογικά/ψυχιατρικά συμπτώματα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.9.2.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Κατάθλιψη** ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Αγχώδη διαταραχή*** ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Άλλη εκδήλωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(παρακαλώ περιγράψτε)……..……

Depression screening

Κατά τη διάρκεια των 2 τελευταίων εβδομάδων είχατε;

Μικρό ενδιαφέρον ή ευχαρίστηση κάνοντας πράγματα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Νιώθετε πεσμένος,θλιμμένος ή χωρίς ελπίδα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

***** Εάν 2 ερωτήσεις θετικές, <u>εκτίμηση για διαταραχή συναισθήματος (PHQ9)</u>***

Anxiety disorder screening

****** <u>Εξέταση για διαταραχή άγχους (GAD-7)]</u>***

4.10. Είχατε ποτέ, <u>στη διάρκεια της ασθένειά σας</u> οφθαλμιατρικά προβλήματα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.10.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Καταρράκτη ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Ξηροφθαλμία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Διαταραχές στον αμφιβληστροειδή ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Γλαύκωμα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
5. Άλλη εκδήλωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(παρακαλώ περιγράψτε)……

4.11. Είχατε ποτέ, στη διάρκεια της ασθένειά σας προβλήματα από το πεπτικό σας σύστημα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.11.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Δυσπεψία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Πεπτικό έλκος ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Χρόνια διάρροια (> 6 εβδομάδες) ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Άλλη εκδήλωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(παρακαλώ περιγράψτε)……

4.12. Στη διάρκεια της νόσου σας αναπτύξατε κάποιο πρόβλημα από την καρδιά ή τα αγγεία σας;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.12.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Περικαρδίτιδα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Στηθάγχη ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Έμφραγμα μυοκαρδίου ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Αρρυθμία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

5. Βαλβιδοπάθεια ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

6. Εν τω βάθει φλεβική θρόμβωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

7. Άλλη εκδήλωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(παρακαλώ περιγράψτε)……

4.13. Υποφέρατε από κάποια συμπτώματα από το αναπνευστικό στη διάρκεια της νόσου σας;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.13.1 Αν ναι, παρουσιάσατε κάτι από τα παρακάτω ;

1. Πλευρίτιδα ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Αναπνευστικές λοιμώξεις ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Άλλη εκδήλωση ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(παρακαλώ περιγράψτε)……

4.15 Είχατε κατά τη διάρκεια της ασθένεια σας κάποιο πρόβλημα με τα νεφρά σας;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. **Αν ναι περιγράψτε**……

4.15.2 Χρειάστηκε ποτέ να κάνετε βιοψία νεφρού; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι πότε……..

4.16 Σας είχε αναφέρει ποτέ ο γιατρός σας να έχετε ;

1. Χαμηλά λευκά ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
2. Χαμηλά αιμοπετάλια ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
3. Χαμηλό αιματοκρίτη / αναιμία ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.
4. Άλλο ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(παρακαλώ περιγράψτε)……

4.17 Σας παρακολουθεί κάποιος ιατρός για κάποιο από τα παραπάνω προβλήματα εκτός του ρευματολόγου σας; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι περιγράψτε: ειδικότητα/νοσοκομείο ……

4.18 Παίρνετε κάποια άλλη θεραπεία εκτός από τα ρευματολογικά σας φάρμακα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

4.19. Από τη στιγμή που διαγνωστήκατε χρειάστηκε να νοσηλευτείτε σε νοσοκομείο;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. ***(εάν όχι πηγαίνετε στην ερώτηση 4.20)***

Νοσηλείες	Χρονικό Διάστημα		Κύρια Αιτία

4.20. Ποια φάρμακα λαμβάνετε τώρα για το λύκο;

Ονομασία φαρμάκου	Δοσολογία	Χρόνος Έναρξης

4.20.1 Ποια φάρμακα έχετε λάβει στο παρελθόν για το λύκο;

Ονομασία φαρμάκου	Δοσολογία	Χρόνικο Διάστημα

4.20.2 Είχατε ποτέ κάποια παρενέργεια από κάποιο φάρμακο; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι περιγράψτε……..

ΚΟΡΤΙΚΟΣΤΕΡΟΕΙΔΗ

4.20.3 Έχετε λάβει κορτιζόνη στα πλαίσια της θεραπείας σας ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι σε ποια δοσολογία και για ποιο διάστημα……

4.20.4 Λαμβάνετε τώρα κορτιζόνη και σε ποια δοσολογία; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

δοσολογία:……..

4.20.5 Είχατε κάποια παρενέργεια που αφορούσε την κορτιζόνη; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

Αν ναι, σε ποιο διάστημα της ασθένειάς σας συνέβει……

4.21. Έχετε κάνει μέχρι σήμερα κάποια βιοψία στα πλαίσια της διερεύνησης του νοσήματος σας;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α. Αν ναι, περιγράψτε……

4.22. Χρειάστηκε ποτέ να κάνετε κάποια άλλη απεικόνιση (αξονική, μαγνητική τομογραφία κτλ) στα πλαίσια του νοσήματος σας; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

(Αν όχι προχωρήστε στο επόμενο κεφάλαιο)

ΕΝΟΤΗΤΑ 5 Ερωτήσεις διαλογής για την επίδραση περιβαλλοντικών παραγόντων

5.1 Καπνίζετε; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

5.1.2 Αν ναι, από πότε και πόσα πακέτα ……(υπολογισμός p/y)

5.2 Χρησιμοποιείτε/χρησιμοποιούσατε καλυντικά; ☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

5.3 Χρησιμοποιούσατε/χρησιμοποιείτε φυτοφάρμακα;

☐ Ναι ☐ Όχι ☐ Δ.ξ./Δ.α.

-END OF QUESTIONNAIRE-

2. ACR-1997/SLICC-2012 CLASSIFICATION CRITERIA

Criteria	***ACR criteria* (1997 update)**	***SLICC criteria* (2012)**
Skin	Malar rash. Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds	Acute cutaneous lupus (lupus malar rash [do not count if malar discoid], bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash), or subcute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring)
	Discoid rash. Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occur in older lesions	Chronic cutaneous lupus (classic discoid rash: localized or generalized, hypertrophic [verrucous] lupus, lupus panniculitis [profundus], mucosal lupus, lupus erythematosus tumidus, chillblains lupus, discoid lupus/lichen planus overlap
	Photosensitivity. Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation	Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
Ulcers	Oral or nasopharyngeal ulceration	Oral or nasal ulcers
Synovitis	Non-erosive arthritis involving ≥2 peripheral joints, characterized by tenderness, swelling or effusion	Inflammatory synovitis in ≥2 joints: characterized by swelling or effusion, or tenderness and ≥30 minutes of morning stiffness
Serositis	Any of: Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion Pericarditis: documented by ECG or rub or evidence of pericardial effusion	Serositis: any of Typical pleurisy lasting >1 day, or pleural effusions, or pleural rub Typical pericardial pain (pain with recumbency improved by sitting forward) for >1 day, or pericardial effusion, or pericardial rub, or pericarditis by electrocardiography
Renal disorder	Any of: Persistent proteinuria >0.5 g per day or >3+ if quantitation is not performed Cellular casts: red cell, haemoglobin, granular tubular, or mixed	Any of: Urine protein/creatinine (or 24 hr urine protein) representing ≥500 mg of protein/24 hr, or red blood cell casts
Neurological disorder	Any of: Seizures: in the absence of offending drugs or known metabolic derangements Psychosis: in the absence of offending drugs or known metabolic derangements	Any of: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)

Haematologic disorder	Any of: Haemolytic anemia with reticulocytosis Lymphopenia: <1500/mm^3 Thrombocytopenia: <100,000/mm^3	Haemolytic anaemia Leukopenia (<4000/mm^3 at least once), or lymphopenia (<1000/mm^3 at least once) Thrombocytopenia (<100,000/mm^3) at least once
Immunologic disorder	Any of: Anti-DNA: antibody to native DNA in abnormal titer Anti-Sm: presence of antibody to Sm nuclear antigen Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) a positive test result for SLE anticoagulant, or (3) a false positive serologic test for syphilis known to be positive for ≥6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test	Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range) Anti-Sm Antiphospholipid antibody, lupus anticoagulant, false-positive test for syphilis, anticardiolipin (at least twice normal or medium-high titer), or anti-b2 glycoprotein 1 Low complement: low C3, or low C4, or low CH50 Direct Coombs test *in the absence of haemolytic anaemia*
Antinuclear antibody	Abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced SLE" syndrome	ANA above laboratory reference range
Diagnosis of SLE	At least 4 out of 11 criteria	Either the biopsy-proven lupus nephritis in the presence of ANA or anti-dsDNA as a "stand alone" criterion, OR four criteria with at least one of the clinical and one of the immunologic/ANA criteria

3. SLE SEVERITY INDEX (Bertsias et al. unpublished data)

Σημειώστε ποιες από τις παρακάτω εκδηλώσεις (κυκλώστε την καθεμία συγκεκριμένη εκδήλωση) έχει εμφανίσει ο ασθενής και το έτος εμφάνισης.

Συνολική γνώμη ιατρού: ☐ ήπια νόσος ☐ μέτρια σοβαρή νόσος ☐ σοβαρή νόσος

	Έτος	**Βαθμός**
Συστηματικές εκδηλώσεις		
4. Πυρετός >38°C, ή απώλεια βάρους >10%, ή λεμφαδενοπάθεια ενδο-κοιλιακή/θωρακική		1
Βλεννογόνοι – δέρμα		
5. Εξάνθημα λύκου/δερματική αγγειΐτιδα σε 9–18% επιφάνειας σώματος [Ε.Σ.] (με/χωρίς ήπια εξέλκωση ή γάγγραινα), ή υποδερματίτιδα <9% Ε.Σ., ή αγγειοοίδημα χωρίς προσβολή αεραγωγών		1
6. Εξάνθημα λύκου/δερματική αγγειΐτιδα σε >18% Ε.Σ. με εκτεταμένη εξέλκωση ή γάγγραινα, ή υποδερματίτιδα >9% Ε.Σ., ή αγγειοοίδημα με προσβολή αεραγωγών		2
7. Εκτεταμένη τριχόπτωση με συνοδό φλεγμονή του δέρματος κεφαλής		1
Γαστρεντερικό		
8. Μέτρια ασκιτική συλλογή, ή μετρίως σοβαρή εντεροπάθεια ή σύνδρομο δυσαπορρόφησης ή παγκρεατίτιδα, ή ηπατίτιδα με tot-Bil <2.5 mg/dl & κ.φ. χρόνοι πήξης		1
9. Μεγάλη ασκιτική συλλογή με σημεία οξείας κοιλίας, ή σοβαρή εντεροπάθεια ή δυσαπορρόφηση, ή παγκρεατική ανεπάρκεια, ή ηπατίτιδα με ηπατική ανεπάρκεια, ή μεσεντέρια αγγειΐτιδα		2
Αναπνευστικό		
10. Μέτρια πλευριτική συλλογή (χωρίς υποξαιμία), ή μέτρια διάμεση πνευμονοπάθεια (απεικονιστικά) χωρίς διαταραχή ανταλλαγής αερίων, ή πνευμονική υπέρταση με mPAP <55 mmHg & στάδιο NYHA I-II, ή κυψελιδίτιδα/πνευμονίτιδα		1
11. Σοβαρή πλευριτική συλλογή με υποξαιμία, ή εκτεταμένη διάμεση πνευμονοπάθεια με διαταραχή ανταλλαγής αερίων, ή πνευμονική υπέρταση με mPAP >55 mmHg & NYHA III-IV, ή κυψ. αιμορραγία		2
Μυοσκελετικό		
12. Πολυαρθρίτιδα με περιορισμό κινητικότητας ή προσβολή μεγάλης άρθρωσης, ή μυοσίτιδα με έκπτωση μυϊκής ισχύς έως 4/5		1
13. Μυοσίτιδα με μυϊκή ισχύ <4/5 ή/και προσβολή μυών διαφράγματος, αυχένα-κεφαλής, φάρυγγα		2

Αιματολογικό	
14. Λευκοπενία 1000-2500/μl, ή ουδετεροπενία 500-1000/μl, ή λεμφοπενία 500-1000/μl, ή θρομβοπενία 20-50$\times 10^3$/μl, ή αναιμία με αιμοσφαιρίνη 8-10 g/dl	1
15. Λευκοπενία <1000/μl, ή ουδετεροπενία <500/μl, ή λεμφοπενία <500/μl, ή θρομβοπενία <20$\times 10^3$/μl, ή αναιμία με αιμοσφαιρίνη <8 g/dl, ή Θρομβωτική θρομβοπενική πορφύρα (TTP/TTP-like)	2
Οφθαλμολογικό	
16. Μετρίως σοβαρή κερατίτιδα ή πρόσθια ραγοειδίτιδα ή σκληρίτιδα/επισκληρίτιδα	1
17. Οπίσθια ραγοειδίτιδα, ή οπτική νευρίτιδα, ή πρόσθια ισχαιμική οπτική νευροπάθεια, ή σοβαρή κερατίτιδα ή πρόσθια ραγοειδίτιδα ή σκληρίτιδα/επισκληρίτιδα	2
Καρδιαγγειακό	
18. Μέτρια/μεγάλη περικαρδιακή συλλογή, ή μυοκαρδίτιδα, ή μη-λοιμώδης ενδοκαρδίτιδα <u>χωρίς</u> αιμοδυναμική αστάθεια ή καρδιακή ανεπάρκεια ή δυσλειτουργία βαλβίδων ή αρρυθμία	1
19. Μεγάλη περικαρδιακή συλλογή, ή μυοκαρδίτιδα, ή μη-λοιμώδης ενδοκαρδίτιδα <u>με</u> αιμοδυναμική αστάθεια ή καρδιακή ανεπάρκεια ή δυσλειτουργία βαλβίδων ή αρρυθμία, ή αορτίτιδα, ή αγγειίτιδα στεφανιαίων αρτηριών	2
Νευρολογικό	
20. Νευρολογική συνδρομή με ήπιο/μέτριο νευρολογικό έλλειμμα, ή μετρίως σοβαρή ψυχιατρική εκδήλωση, ή άσηπτη μηνιγγίτιδα, ή παροδικό ισχαιμικό αγγειακό επεισόδιο	1
21. Αγγειίτιδα ΚΝΣ, ή μυελοπάθεια, ή καθέξην επιληπτικές κρίσεις/status epilepticus, ή νευρολογική συνδρομή με μέτριο/σοβαρό νευρολογικό έλλειμμα, ή σοβαρή ψυχιατρική εκδήλωση	2
Νεφρικό	
22. Νεφρίτιδα class II ή class V με πρωτεϊνουρία <3 g/24-hr και φυσιολογική νεφρική λειτουργία	1
23. Νεφρίτιδα class III/IV ή μικτή V+III/IV, ή με πρωτεϊνουρία ≥3 g/24-hr, ή με επηρεασμένη νεφρική λειτουργία (αύξηση κρεατινίνης ορού ≥30%), ή νεφρική νόσος τελικού σταδίου	2
Χρήση ανοσοκατασταλτικής αγωγής	
24. Αζαθειοπρίνη, μυκοφαινολικό, belimumab	1
25. Κυκλοφωσφαμίδη, rituximab	2

4. ACR/SLICC DAMAGE SCORE

Systemic Lupus International Collaborating Clincs/American College of Rheumatology (SLICC/ACR) Damage Index. Score

Ocular (either eye, by clinical assessment) 0,1
Any cataract ever 0,1
Retinal change or optic atrophy Neuropsychiatric 0,1
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR major psychosis 0,1
Seizures requiring therapy for 6 months 0,1,2
Cerebrovascular accident ever (score 2 if >1) 0,1
Cranial or peripheral neuropathy (excluding optic) 0,1
Transverse myelitis Renal 0,1
Estimated or measured glomerular filtration rate < 50% 0,1
Proteinuria > 3.5g/24h or 3
OR End-stage renal disease (regardless of dialysis or transplantation) Pulmonary 0,1 Pulmonary hypertension (right ventricular prominence, or loud P2) 0,1
Pulmonary fibrosis (physical and radiograph) 0,1 Shrinking lung (radiograph) 0,1
Pleural fibrosis (radiograph) 0,1
Pulmonary infarction (radiograph) Cardiovascular 0,1
Angina OR coronary artery bypass 0,1,2
Myocardial infarction ever (score 2 if > 1) 0,1
Cardiomyopathy (ventricular dysfunction) 0,1
Valvular disease (diastolic murmur or systolic murmur > 3/6) 0,1
Pericarditis for 6 months, OR pericardectomy Peripheral vascular 0,1
Claudication for 6 months 0,1
Minor tissue loss (pulp space) 0,1,2
Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if > 1 site) 0,1
Venous thrombosis with swelling, ulceration, OR venous stasis Gastrointestinal 0,1,2 Infarction or resection of bowel below duodenum, spleen, liver or gallbladder ever, for any cause (score 2 if > 1 site) 0,1
Mesenteric insufficiency 0,1
Chronic peritonitis 0,1 Stricture OR upper gastrointestinal tract surgery ever 0,1
Chronic pancreatitis
Musculoskeletal 0,1
Muscle atrophy or weakness 0,1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis) 0,1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) 0,1,2 Avascular necrosis (score 2 if > 1) 0,1
Osteomyelitis 0,1
Tendon rupture Skin 0,1
Scarring chronic alopecia 0,1

Extensive scarring of panniculum other than scalp and pulp space 0,1
Skin ulceration (excluding thrombosis for > 6 months) 0,1
Premature gonadal failure 0,1
Diabetes (regardless of treatment) 0,1,2
Malignancy (exclude dysplasia) (score 2 if >1 site)

Adapted from Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996; 39:363-9

5. SELENA-SLEDAI 2K ACTIVITY INDEX

SLEDAI-2K (30 DAYS)
DATA COLLECTION SHEET

Study No.:_____ Patient Name:_____ Visit Date: _____ _____ _____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days)

Weight	SCORE	Descriptor	Definition
8	☐	Seizure	Recent onset, exclude metabolic, infections, or drug causes.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	☐	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	☐	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	☐	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exlcude arteriosclerosis.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	≥2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary casts	Heme-granular or red blood cell casts.
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause.
4	☐	Proteinuria	>0.5 gram/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	Rash	Inflammatory type rash.
2	☐	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	☐	Mucosal ulcers	Oral or nasal ulcerations.
2	☐	Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening.
2	☐	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	☐	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	☐	Fever	>38° C. Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets/× 10^9/L, exclude drug causes.
1	☐	Leukopenia	<3000 white blood cells/× 10^9/L, exclude drug causes.

6. Charlson Comorbidity Index Score

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

7. ACR NPSLE NOMENCLATURE

Neuropsychiatric syndromes in SLE as defined by the ACR research committee

Central	*Peripheral*
Aseptic meningitis	Guillain Barré syndrome
Cerebrovascular disease	Autonomic neuropathy
Demyelinating syndrome	Mononeuropathy
Headache	Myasthenia gravis
Movement disorder	Cranial neuropathy
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

8. PATIENT EVALUATION SHEET

ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ
ΝΟΣΟΚΟΜΕΙΟ ΗΡΑΚΛΕΙΟΥ

ΚΛΙΝΙΚΗ ΡΕΥΜΑΤΟΛΟΓΙΑΣ - ΚΛΙΝΙΚΗΣ ΑΝΟΣΟΛΟΓΙΑΣ ΚΑΙ ΑΛΛΕΡΓΙΟΛΟΓΙΑΣ

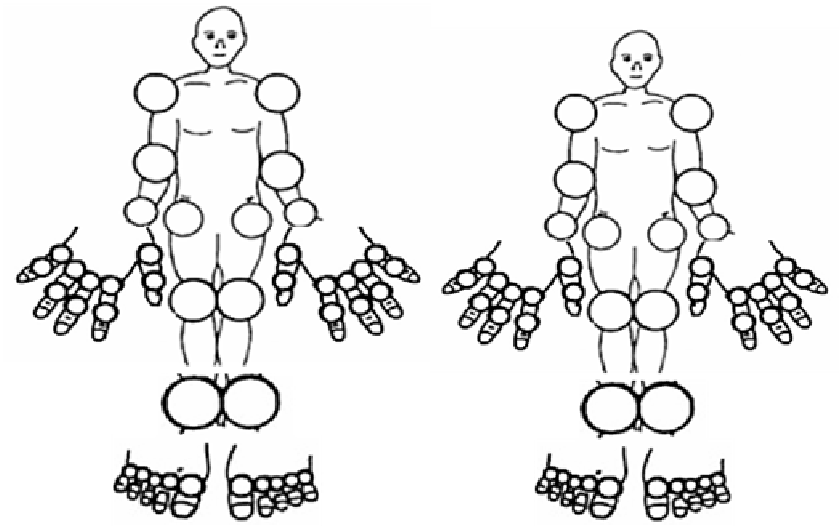
ΟΝΟΜΑΤΕΠΩΝΥΜΟ **ΤΗΛΕΦΩΝΟ:** **Ημερομηνία: ___/___/___**

ΔΙΑΓΝΩΣΕΙΣ **ΗΛΙΚΙΑ:** **ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΓΩΓΗ**

ΥΠΟΚΕΙΜΕΝΙΚΑ

ΑΝΤΙΚΕΙΜΕΝΙΚΑ **ΠΑΡΑΚΛΙΝΙΚΕΣ ΕΞΕΤΑΣΕΙΣ**

ΕΚΤΙΜΗΣΗ – ΘΕΡΑΠΕΥΤΙΚΕΣ ΑΛΛΑΓΕΣ – ΠΡΟΓΡΑΜΑΤΙΣΜΟΣ



ΕΠΩΔΥΝΕΣ ΑΡΘΡΩΣΕΙΣ
(αριθμός: _____)

ΔΙΟΓΚΩΜΕΝΕΣ ΑΡΘΡΩΣΕΙΣ
(αριθμός: _____)

ΣΦΑΙΡΙΚΗ ΕΚΤΙΜΗΣΗ ΙΑΤΡΟΥ

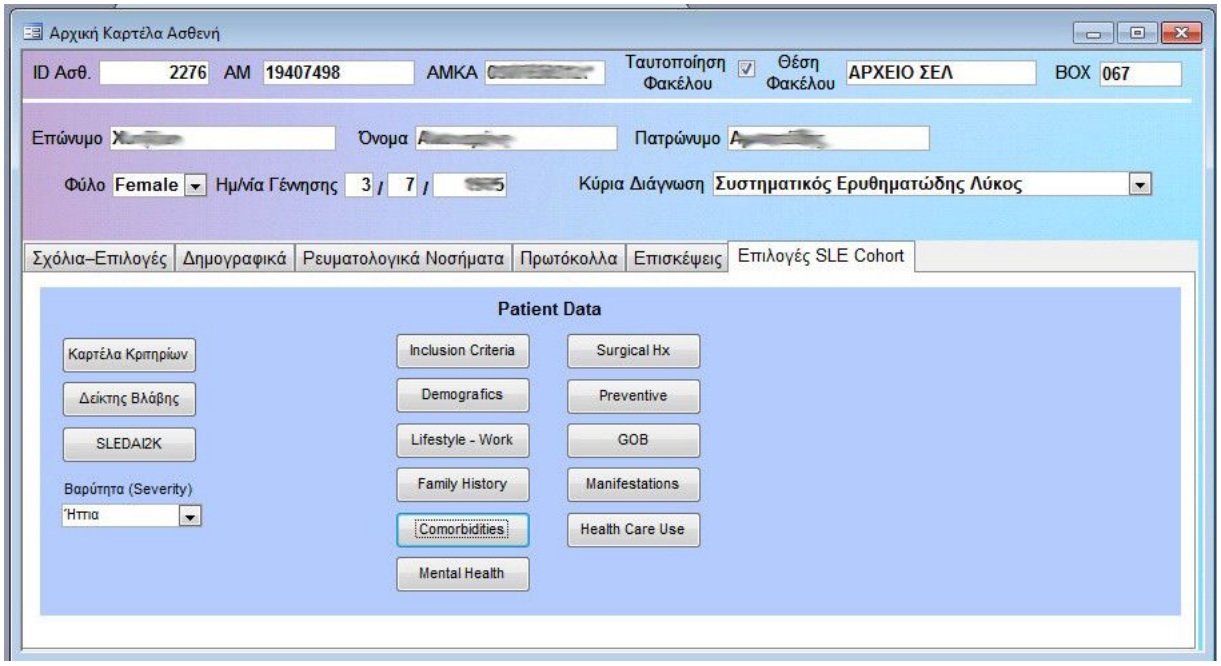
0 (ύφεση) 1 (ήπια) 2 (μέτρια) 3 (σοβαρή)

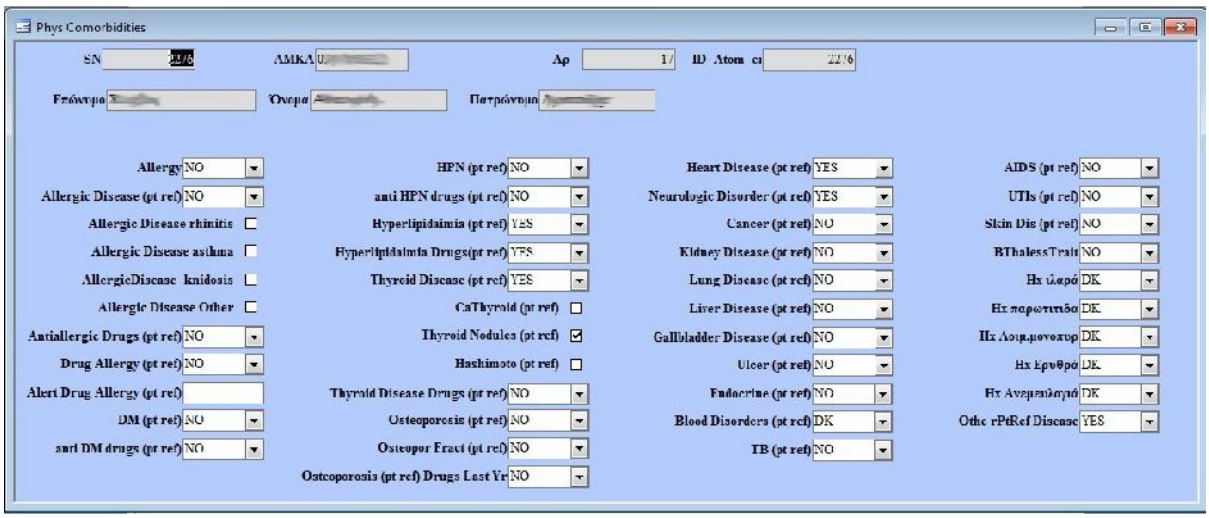
ΚΛΙΜΑΚΑ ΠΟΝΟΥ ΑΣΘΕΝΗ

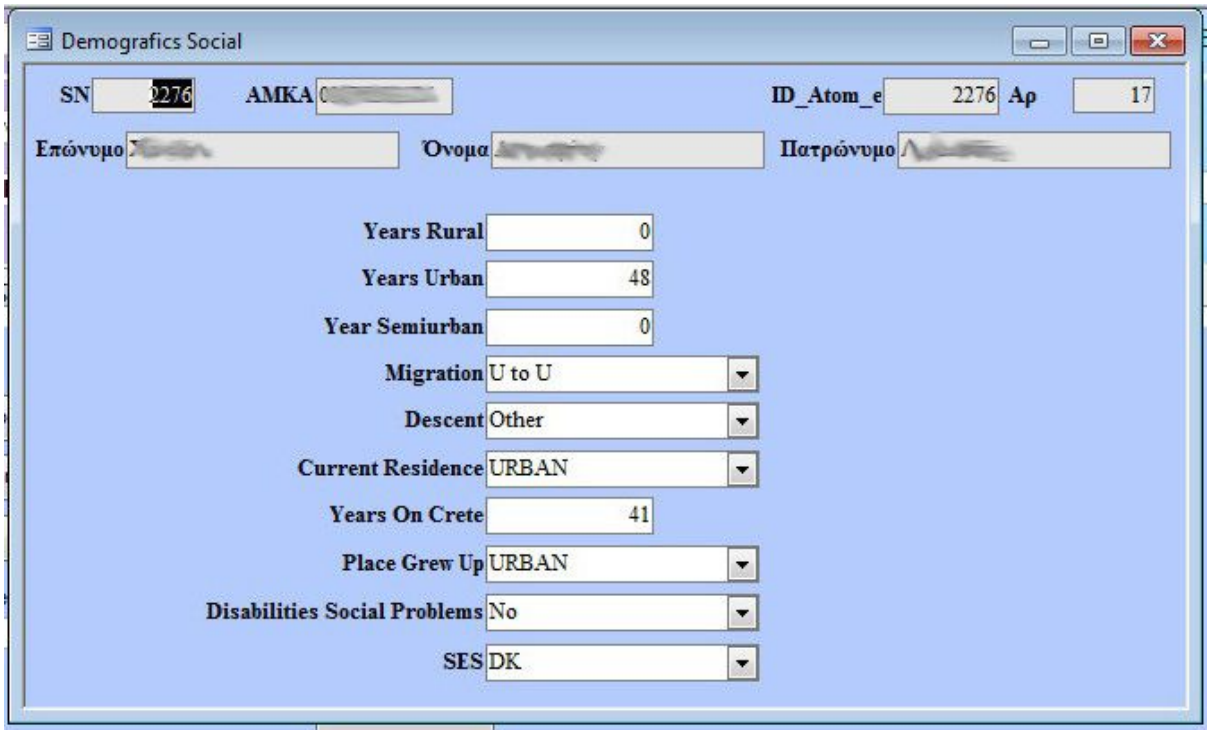
0 1 2 3 4 5 6 7 8 9 10

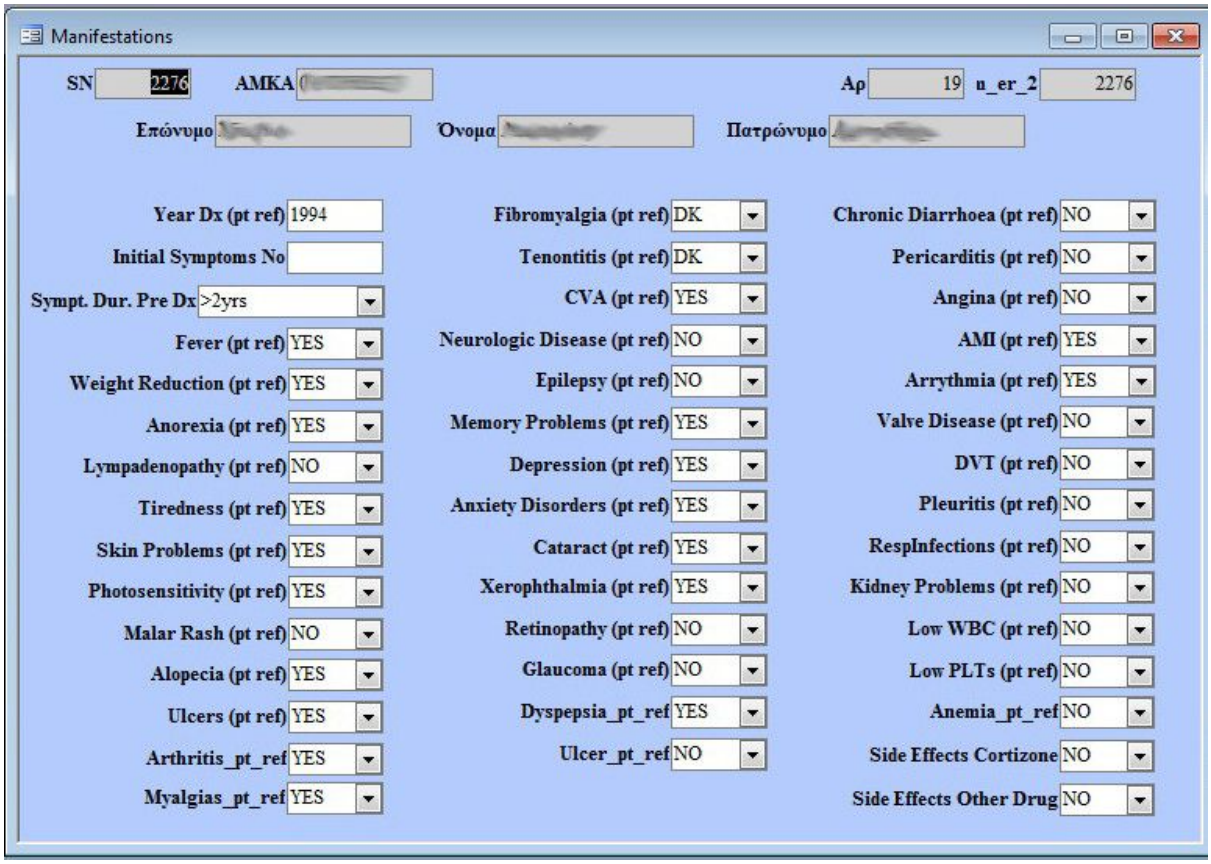
Ημερομηνία επανεκτίμησης:

9. DATA BASE SNAPSHOTS






Demografics Social
SN 2276
AMKA
ID_Atom_e 2276
Αρ 17
Επώνυμο
Όνομα
Πατρώνυμο
Years Rural 0
Years Urban 48
Year Semiurban 0
Migration U to U
Descent Other
Current Residence URBAN
Years On Crete 41
Place Grew Up URBAN
Disabilities Social Problems No
SES DK


Manifestations
SN 2276
AMKA
Αρ 19
n_er_2 2276
Επώνυμο
Όνομα
Πατρώνυμο
Year Dx (pt ref) 1994
Initial Symptoms No
Sympt. Dur. Pre Dx >2yrs
Fever (pt ref) YES
Weight Reduction (pt ref) YES
Anorexia (pt ref) YES
Lympadenopathy (pt ref) NO
Tiredness (pt ref) YES
Skin Problems (pt ref) YES
Photosensitivity (pt ref) YES
Malar Rash (pt ref) NO
Alopecia (pt ref) YES
Ulcers (pt ref) YES
Arthritis_pt_ref YES
Myalgias_pt_ref YES
Fibromyalgia (pt ref) DK
Tenontitis (pt ref) DK
CVA (pt ref) YES
Neurologic Disease (pt ref) NO
Epilepsy (pt ref) NO
Memory Problems (pt ref) YES
Depression (pt ref) YES
Anxiety Disorders (pt ref) YES
Cataract (pt ref) YES
Xerophthalmia (pt ref) YES
Retinopathy (pt ref) NO
Glaucoma (pt ref) NO
Dyspepsia_pt_ref YES
Ulcer_pt_ref NO
Chronic Diarrhoea (pt ref) NO
Pericarditis (pt ref) NO
Angina (pt ref) NO
AMI (pt ref) YES
Arrythmia (pt ref) YES
Valve Disease (pt ref) NO
DVT (pt ref) NO
Pleuritis (pt ref) NO
RespInfections (pt ref) NO
Kidney Problems (pt ref) NO
Low WBC (pt ref) NO
Low PLTs (pt ref) NO
Anemia_pt_ref NO
Side Effects Cortizone NO
Side Effects Other Drug NO

PUBLICATIONS-CONFERENCE PROCCEDINGS

I. Journal Publications and Conference Proceedings

1. **I.Gergianaki,** Antonios Fanouriakis, Argyro Repa, Michalis Tzanakakis, Christina Adamichou, Alexandra Pompieri, Giorgis Spyrou, Antonios Bertsias, Eleni Kabouraki, Ioannis Tzanakis, Leda Chatzi, Prodromos Sidiropoulos, Dimitrios T. Boumpas, George Bertsias Epidemiology and Burden of Systemic Lupus Erythematosus in a Southern European population: Data from the Community-Based Lupus Registry of Crete, Ann Rheum Dis 2017;0:1–9. doi:10.1136/annrheumdis-2017-211206

2. **Irini Gergianaki,** Antonios Fanouriakis, Christina Adamichou, Giorgis Spyrou, Prodromos Sidiropoulos, Dimitrios T. Boumpas, George Bertsias: Twice increased risk of Systemic Lupus Erythematosus (SLE) in urban than rural environment., Madrid Spain, EULAR 2017, DOI:10.13140/RG.2.2.10717.41447

3. **Irini Gergianaki,** Antonios Fanouriakis, Christina Adamichou, Giorgis Spyrou, Prodromos Sidiropoulos, Dimitrios Boumpas, George Bertsias: The impact of classifying SLE patients with the SLICC-2012 versus the ACR-1997 classification criteria: Data from the community-based Cretan Lupus Registry Madrid Spain, EULAR 2017, DOI:10.13140/RG.2.2.22880.89603

4. **Γεργιανάκη Ε**., Φανουριάκης Α., Ρέπα Α. και συν. Σταθεροποίηση στην τάση επίπτωσης ΣΕΛ, νεφρίτιδας και νευροψυχιατρικού λύκου και ηπιότερη νόσος στην κοινότητα: Δεδομένα αρχείο ΣΕΛ «Λητώ» 1999-2013, 25ο Πανελλήνιο Ρευματολογικό Συνέδριο 2016 Αθήνα

5. **Γεργιανάκη Ε., Φανουριάκης Α., Τζανάκης Ι. και συν. Διπλάσιος Σχετικός Κίνδυνος Εμφάνισης ΣΕΛ στο Αστικό σε σχέση με το Αγροτικό Περιβάλλον. Προκαταρκτικά αποτελέσματα από το Αρχείο ΣΕΛ "Λητώ"Κρήτη** 25ο Πανελλήνιο Ρευματολογικό Συνέδριο 2016 Αθήνα

6. **Gergianaki I,** A. Repa, M. Tzanakakis, A. Fanouriakis, C. Adamichou, A. Pompieri, G. Spyrou, E. Kabouraki, M. Mamoulaki, I. Tzanakis, L. Chatzi: THE CRETAN LUPUS REGISTRY "LETO": INCIDENCE AND PREVALENCE OVER A 15-YEAR PERIOD, CLINICAL FEATURES AND ENVIRONMENTAL FACTORS IN A HOMOGENEOUS, SOUTHERN-EUROPEAN POPULATION. 10th Lupus Meeting, Venice; 10/2016

7. **Gergianaki I**, A. Fanouriakis, A. Repa, A. Pompieri, E. Kabouraki, G. Spyrou, M. Tzanakakis, I. Kallitsakis, M. Mamoulaki, P. Katzakis, L. Chatzi, P. Sidiropoulos, D. Boumpas, G. Bertsias: AB1119 The Cretan Lupus Registry "Leto": Prevalence, Clinical Features and Environmental Factors in a Genetically Homogenous, Mixed Urban and Rural, South European Population:. Annals of the Rheumatic Diseases 06/2015; 74(Suppl 2):1275.1-1275., DOI:10.1136/annrheumdis-2015-eular.5086

8. M Tzanakakis, **Gergianaki I,** D Xydakis, A Papadaki, G Perysinaki, X Petra, E Maragaki, S Stratakis, R Poulidaki, K Perakis, E Vardaki, S Stratigis, K. Stylianou, L Nakopoulou, X Gakiopoulou, F Sotsiou, A Fanouriakis, G Bertsias, E Ntaountaki, G Parasiris, A Papadogiannakis, G Tzanakis, D Boumpas, P Sidiropoulos, E Dafnis: Biopsy-proven Lupus Nephritis in a Southern European Genetically Homogenous Population. 9th European Lupus Meeting, Athens; 04/2014

9. Kampouraki et. Al LUPUS PATIENTS' NEEDS AND PERSPECTIVES IN SOUTHEASTERN EUROPE: DATA FROM THE CRETAN LUPUS COHORT "LETO" 9th European Lupus Meeting, Athens; 04/2014

10. Rapsomaki et al. Mapping and utilization of health care services from patients with newly diagnosed systemic lupus erythematosus 9th European Lupus Meeting, Athens; 04/2014

11. Γεργιανάκη Ι. Φανουριάκης Α. Πομπιέρη Α. και συν. Μελέτη Επιπολασμού, κλινικών χαρακτηριστικών και περιβαλλοντικών παραγόντων κινδύνου του Συστηματικού Ερυθηματώδους Λύκου στην Κρήτη: το Αρχείο «Λητώ» 24ο Συνέδριο Ρευματολογίας, Αθήνα 2014

II. Journal Publications/Conference Proceedings which have used clinical data from Cretan Registry and Biobanking DataBase (10)

1. G. Bertsias, E. Karampli, P. Sidiropoulos, **I. Gergianaki,** A. Drosos, L. Sakkas, A. Garyfallos, A. Tzioufas, D. Vassilopoulos, C. Tsalapaki, P. Sfikakis, S. Panopoulos, K. Athanasakis, A. Perna, D. Psomali, J. Kyriopoulos, D.T. Boumpas: Clinical and financial burden of active lupus in Greece: A nationwide study. Lupus 04/2016; 25(12)., DOI:10.1177/0961203316642310

2. Fanouriakis Antonis, **Gergianaki Irini,** Sidiropoulos Prodromos, Bertsias George, Boumpas Dimitrios: Evolving Concepts in Systemic Lupus Erythematosus. The Israel Medical Association journal: IMAJ 12/2016; 18(12).

3. Evangelos C Karademas, Georgia Ktistaki, Georgia Dimitraki, Emmanouil Papastefanakis, Vasileios Mastorodemos, Argyro Repa, **Irini Gergianaki,** George Bertsias, Prodromos Sidiropoulos, Panagiotis Simos: Patient and partner dispositional optimism as a long-term predictor of illness representations in autoimmune diseases. Journal of Health Psychology 03/2016;, DOI:10.1177/1359105316633287

4. Evangelos C Karademas, Georgia Ktistaki, Georgia Dimitraki, Emmanouil Papastefanakis, Nikolaos Kougkas, Antonios Fanouriakis, **Irini Gergianaki,** George Bertsias, Prodromos Sidiropoulos, Panagiotis Simos: Adaptation to an Autoimmune Disorder: Does Mental Flexibility Impact Illness-related Self-regulation?. Psychology & Health 08/2015; 31(3):1-29., DOI:10.1080/08870446.2015.1083568

5. A. Seretis, A. Zampoulaki, C. Choulaki, **I. Gergianaki,** P. Sidiropoulos, D. Boumpas, G. Bertsias: A6.34 The role of the costimulatory receptor herpes virus entry mediator (HVEM) in B-cell activation and differentiation. implications for SLE pathogenesis. Annals of the Rheumatic Diseases 02/2015; 74(Suppl 1):A69-A70., DOI:10.1136/annrheumdis-2015-207259.160

6. A. Seretis, A. Zampoulaki, **I. Gergianaki,** P. Sidiropoulos, D. Boumpas: Enter PHENOTYPICAL CHARACTERISATION OF THE OUTCOME OF HVEM-MEDIATED CO-STIMULATION OF B CELLS. A POTENTIAL MECHANISM INVOLVED IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). 10th Lupus Meeting, Venice Italy; 10/2016

7. G. Bertsias, N. Panousis, **I. Gergiannaki,** M. Tektonidou, M. Trachana, A. Banos, A. Fanouriakis, C. Pamfil, E. Dermitzakis, D. Boumpas: MOLECULAR CHARACTERIZATION OF SLE BY RNA-SEQ: IDENTIFICATION OF GENES AND EXPRESSION-QUANTITATIVE TRAIT LOCI CONTRIBUTING TO PATHOGENESIS, SEVERITY AND TISSUE SUSCEPTIBILITYMOLECULAR CHARACTERIZATION OF SLE BY RNA-SEQ: IDENTIFICATION OF GENES AND EXPRESSION-QUANTITATIVE TRAIT LOCI CONTRIBUTING TO PATHOGENESIS, SEVERITY AND TISSUE SUSCEPTIBILITY. 10th Lupus Meeting, Venice, Italy; 10/2016

8. A. Fanouriakis**, I. Gergianaki,** C. Adamichou, P. Sidiropoulos, T. Karageorgas, P. Katsibri, G. Spyrou, G. Bertsias, D. Boumpas: LUPUS IN THE COMMUNITY VERSUS REFERRAL CENTRES: DISEASE PHENOTYPE AND SEVERITY AND IMPLICATIONS FOR CLINICAL CARE AND RHEUMATOLOGY TRAINING. 10th Lupus Meeting; 10/2016

9. Gkirtzimanaki K, Kabrani E, **Gergianaki I,** Bertsias G, Boumpas D, Verginis P.: IFNa INDUCED DIFFERENTIATION AND MATURATION OF SLE MONOCYTES ARE SUBJECTED TO AUTOPHAGIC CONTROL. 9th European Lupus Meeting; 04/2014

10. Frangou E.A, Kambas K, **Gergianaki I,** Karagiorgas F, Karabela, Bertsias G, Boumpas D: AUTOPHAGY-MEDIATED TISSUE FACTOR RELEASE IN LUPUS NEUTROPHIL EXTRACELLULAR TRAPS MAY ACTIVATE THE COAGULATION CASCADE AND CONTRIBUTE TO MICROVASCULAR INJURY. 9th European Lupus Meeting, Athens; 04/2014