RESEARCH ARTICLE

The relation between, metabolic syndrome and quality of life in patients with Systemic Lupus Erythematosus

Domenico Paolo Emanuele Margiotta*, Fabio Basta, Giulio Dolcini, Veronica Batani, Luca Navarini, Antonella Afeltra

Unit of Allergology, Clinical Immunology and Rheumatology, Università Campus Bio-Medico di Roma, Rome, Italy

* d.margiotta@unicampus.it

Abstract

Introduction
Systemic Lupus Erythematosus (SLE) is associated to an increased prevalence of Metabolic Syndrome (MeS) and to a reduction of Quality of Life (QoL). The aim of this study is to evaluate the association between MeS and QoL in SLE.

Methods
SLE patients were consecutively enrolled in a cross sectional study. MeS was defined according to IFD definition. Therapy with glucocorticoids (GC) and antimalarial was analyzed as cumulative years of exposure. We used a cut off of 7.5 mg of prednisone to define high daily dose of GC. QoL was quantified using SF-36. We used BDI and HAM-H to assess symptoms of mood disorders. Fatigue was evaluated using Facit-Fatigue, physical activity using IPAQ, sleep quality using PSQI and alexithymia using TAS-20.

Results
We enrolled 100 SLE patients. MeS prevalence was 34%. Patients with MeS presented reduced scores in SF-36 MCS and PCS compared to patients without MeS (p 0.03 and p 0.004). BDI and HAM-H score were significantly higher in patients meeting MeS criteria compared to subjects without MeS (p 0.004, p 0.02). These results were confirmed after adjustment for confounders. Compared to patients without MeS, those with MeS presented higher age, lower education level, higher recent SELENA-SLEDAI, higher number of flares, increased SDI, longer cumulative exposure to high dose GC and shorter duration of antimalarial therapy. In the multiple logistic regression model, the variable associated to the Odds Ratio of having MeS were: the average of recent SELENA-SLEDAI (OR 1.15 p 0.04), the years of exposure to high dose of GC (OR 1.18 p 0.004), the years of exposure to antimalarials (OR 0.82 p 0.03) and the BDI score (OR 1.1 p 0.005).

Conclusion
A modern management of SLE should not miss to take all the possible measures to ensure an adequate QoL to SLE patients, with particular attention to those affected by MeS.
Introduction

Metabolic Syndrome (MeS) is a cluster of cardiovascular diseases (CVDs) risk factors in which insulin-resistance (IR) and visceral adiposity play a pivotal role. In the last decade, several definitions of MeS have been proposed. The most widely used MeS definitions are the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) [1] and the International Diabetes Federation (IDF) ones [2].

All definitions include a measure of visceral obesity such as waist circumference, measures of dyslipidemia including raised triglycerides and low high-density lipoprotein (HDL) cholesterol, measures of IR usually expressed by fasting plasma glucose (FPG) and arterial hypertension.

Epidemiological studies clearly demonstrated that MeS is not just the sum of CVDs risk factors, but is an independent CVDs risk factor [3]. A recent meta-analysis including nearly 1 million individuals showed that the MetS was associated with almost twice the relative risk of CVDs prevalence and mortality and a 1.6 relative risk of all-cause mortality [4]. In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes [5]. The clustering of CVD risk factors that typifies the metabolic syndrome is now considered to be the driving force for a CVD epidemic.

In general population, a poor Health Related Quality of Life (HRQoL), especially in physical domain, has been described in patients with MeS [6–10]. Ford et al. compared HRQoL in patients with and without MeS in a cross-sectional analysis of 1859 subjects from the National Health and Nutrition Examination Survey, demonstrating that patients with the metabolic syndrome were more likely to have fair or poor health, mentally unhealthy days and activity limitation days [7].

Moreover, MeS seems to be associated to depression and chronic fatigue, both factors tightly connected to HRQoL [11, 12].

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease with a possible involvement of all organs and systems, with an extremely wide spectrum of clinical manifestations. The immune-pathogenesis of SLE is complex and involves both innate and adaptive immunity. SLE therapy varies according to clinical manifestations and is based on the use of glucocorticoids, synthetic antimalarials, immunosuppressants and, recently, biological drugs (in particular, directed against B-lymphocytes) [13, 14]. Crescent literature data clearly demonstrated an increased CVDs prevalence and mortality in SLE, due to accelerated atherosclerosis [15–17]. SLE patients present higher prevalence of insulin-resistance and MeS compared to age and sex matched healthy controls [18–24]. According to available studies, in SLE patients, MeS seems to be related to traditional CVDs risk factors, age, disease duration, low complement levels, renal involvement and glucocorticoid therapy [20–24]. Data from the Systemic Lupus International Collaborating Clinics (SLICC) Registry for Atherosclerosis inception cohort, concerning 1494 recently diagnosed SLE, demonstrated that MeS was present at enrollment visit in 16% of patients suggesting that lupus-related inflammatory factors could facilitate insulin-resistance and MeS development. In the same study, factors associated to MeS in multivariate analysis were renal lupus, higher corticosteroid doses, Korean and Hispanic ethnicity [25]. In a longitudinal analysis of patients enrolled in SLICC registry, in addition to the factors already highlighted, presence of organ damage according to SLICC damage index and higher disease activity were independently associated with MeS over the first 2 years of follow-up [26].

Despite the improvement in SLE prognosis in the last decades, patients are still burdened by poor quality of life, often associated to pain, depression and fatigue, all common lupus manifestations [25].
The aim of this study was to compare QoL in SLE patients with and without MeS, after adjustment for possible confounders. Furthermore, secondary objective of this study was evaluate, in a multivariable model, if MeS could be a factor related to QoL in SLE.

Methods

Study population

Patients affected by SLE according to SLICC classification criteria [27] were consecutively enrolled at University Campus Bio-Medico outpatient clinic between January 2015 and December 2015. Patients were enrolled from the inception cohort of our Lupus Clinic. All patients enrolled were continuously followed in our Lupus Clinic from diagnosis until the enrollment in this study. The opportunity to take part in the study was orally proposed during outpatient outreach visits. Exclusion criteria for SLE patients were: recent pregnancy (<2 years before enrollment), active malignancy, end-stage lupus nephritis, treatment with Belimumab in the last two years, previous diagnosis of mood disorders or ongoing therapy for mood disorders.

Sample size calculation

For sample size calculation and power analysis we considered data concerning QoL in general population with and without MeS [8]. Setting a significance level of 0.05 (alpha), power at 80% (beta), an Effect size of 0.9, according to data on general population, and a proportion of subject exposed at 0.3 (considering MeS prevalence in SLE), we estimated a total group size of 46 patients including 14 patients affected by MeS. Sample size calculation and power analysis were performed using SAS University Edition, SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA.

Ethical considerations

Ethics committee of Università Campus Bio-Medico di Roma approved the study, which complied with the Declaration of Helsinki. All the study participants provided signed an informed consent prior to enrolment.

Evaluation of metabolic parameters and CV risk factors

Clinical history, history of diabetes mellitus, dyslipidemia or hypertension, familiar or personal CVD history were assessed. Waist circumference, Waist/Hip ratio, body mass index (BMI), resting arterial blood pressure were recorded. In every patients enrolled fasting blood samples was analyzed for metabolic parameters as total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein cholesterol (HDL) cholesterol, triglycerides, fasting glucose, C-reactive protein (CRP) using diagnostic commercial kits. Metabolic Syndrome was defined according to IFD criteria [2].

Evaluation of SLE disease features, disease activity and damage accrual

Disease activity was defined using Safety of Estrogens in Lupus Erythematosus National Assessment disease activity index (SELENA-SLEDAI) [28, 29]. We calculated actual SELENA-SLEDAI and mean SELENA-SLEDAI of the last 12 months. Disease flares were assessed by SELENA-SLEDAI Flares Index (SFI) [30]. According to SFI, disease flares were classified in mild-moderate or severe. Disease damage was calculated using SLICC damage index (SDI) [31]. We evaluated the cumulative duration of exposure to glucocorticoids and to...
antimalarials, expressed in years. We used a cut off of 7.5 mg of prednisone or equivalents to define high daily dose glucocorticoid regimens, according to the evidences that link this cut off dose to an increased risk of damage accrual, in particular on cardio-metabolic damages [32]. According to this cut-off, we further evaluated the cumulative exposure to high dose glucocorticoids.

Evaluation of QoL, mood disorders, fatigue, sleep quality, physical activity

To assess HRQoL we used Italian version of Medical Outcomes Study (MOS) 36-Items Short-Form Healthy Survey (SF-36) [33]. Fatigue was evaluated by Italian version of The Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue [34]. Depressive symptoms was quantified by the Beck Depression inventory (BDI version II) [35] and anxiety symptoms were evaluated by Hamilton Anxiety rating scale (HAM-H) [36]. Subjects were classified according to BDI cut-offs: BDI<13 no depression; BDI 14–19, mild depression; BDI 20–28 moderate depression; BDI 29–63 severe depression [37]. Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) and expressed according to categorical IPAQ total score: 1, patient inactive; 2 patient minimally active; 3 patient active according to Health Enhancing Physical Activity (HEPA) standards [38]. We also evaluated sleep quality by the Pittsburgh Sleep Quality Index (PSQI) [39]. Alexithymia construct was evaluated by Toronto Alexithymia Scale (TAS-20) [40].

Statistical analysis

The two-tailed Student t-test or One-Way ANOVA was used to compare means when normal distribution was observed in a Kolmogorov-Smirnov test. When normality was not observed, the non-parametric Mann-Whitney test was used to compare medians. In order to take into account the impact on analyzed variable of possible confounders such as age, sex, education level and alexithymia, we compared the last square mean values (LS mean) of the analyzed variable in patients with and without MeS using a multiple mixed regression model (SAS PROC MIXED). The mixed models allowed us to compare LS means in an unbalanced design (the proportion of patients without MeS was significantly greater that subjects without MeS) and to compare variable with difference variance. SF-36 summary components MCS and PCS values were stratified in quartiles.

A generalized linear regression model (SAS PROC GENMOD) with multinomial distribution of dependent variable and cumulative logit link function was built to analyze the variables associated to MCS and PCS quartile (odds ratio to be in upper quartiles of MCS or PCS values vs lower one).

We used a generalized linear model (SAS PROC GENMOD) with binomial distribution of dependent variable (presence of MeS, yes or no) and logit link function to create a univariable and then a multivariable logistic regression model. Significance level adopted was two tailed p<0.05. All statistical analyses were performed with SAS University Edition, SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA.

Results

SLE disease features

We enrolled 100 SLE patients, 6 male and 94 female. In Table 1 were reported demographic and SLE disease feature of enrolled sample.
Metabolic Syndrome prevalence and parameters

Results regarding MeS parameters and the other CVDs risk factors in SLE patients were summarized in Table 2. MeS prevalence in our SLE sample was 34%. The prevalence of MeS components was: obesity in 46% of patients, raised triglycerides in 23% and reduced HDL cholesterol in 26%, raised blood pressure in 45% of patients, impaired fasting glucose in 11% of patients.
Quality of life in SLE patients with and without MeS

Considering SF-36 summary measures, SLE patients with MeS presented lower scores in both Mental Component Summary (MCS) and in Physical Component Summary (PCS) compared to SLE patients without MeS. Mean values of MCS in patients with MeS and without MeS were 45.2±25.0 vs 56.1±21.1 respectively (p 0.03). Mean PCS score in patients with MeS compared to patients without MeS were 39.7±19.7 vs 52.5±21.5 respectively (p 0.004). We reported in Table 3 the mean values of MCS and PCS adjusted for confounders.

We reported in Table 3 the mean values of Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health Perception (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and General Mental Health (MH) in subjects with and without MeS.

SLE disease features and QoL related factors in patients with and without MeS

Significant differences were not found in disease duration and cumulative exposure to glucocorticoids (GC) among SLE patients with and without MeS diagnosis. Compared to patients without MeS, SLE patients with MeS diagnosis presented an higher age, elevated mean recent SLEDAI score (expressed as an average of the last year disease activity), higher number of organ damage (SDI), higher number of disease flares, and a greater exposure to high doses of GC (daily GC doses ≥ 7.5 mg of prednisone or equivalents. Moreover, we found a lower cumulative exposure to antimalarials in patients with MeS compared to patients without MeS. SLE patients with MeS presented a significantly raised score of depressive symptoms (BDI) and anxiety symptoms (HAM-H). These results were confirmed in last square means comparison using mixed regression models adjusted for age, education levels and alexithymia score (TAS). Moreover, we found a reduced score of physical activity (IPAQ) in patients with MeS. Significant differences were not found in fatigue, sleep disorders score and alexithymia score among SLE patients with and without MeS diagnosis. We reported detailed results in Table 4.

A greater proportion of patients with MeS were seropositive (low complement levels and/or anti-dsDNA positivity), presented low complement levels and presented active renal disease (almost renal BILAG C). 21 of 34 patients with MeS (67.6%) presented low education level
(primary or lower secondary school). Conversely, 45 of 66 patients without MeS (68.2%) presented education levels almost equal to upper secondary school (Table 5).

**Variables associated to SF-36 summary components**

A multinomial logistic regression model was used to analyze variables associated to the odds ratio to be in the upper quartiles of MCS and PCS values distribution. The lowest quartile of MCS and PCS values were used as reference. In the univariable analysis, the variables that reduce the odds ratio of being in the upper quartile of MCS were higher education level, the average of recent SLEDAI values, the diagnosis of MeS, the BDI and HAM-H scores, the PSQI score, the TAS-20 score and to be physically inactive. The variable associated to odds ration below 1 of being in the upper quartile of PCS were the same as observed for MCS, plus age, female sex, cumulative years of exposure to high dose GC, the SDI score and the number of recent disease flares. MeS was significantly associated to a reduced odds ratio to be in the upper quartile of MCS and PCS also in multivariable models, after adjustment for demographic and disease related variables. Nevertheless, the significant association between MeS and the odds ratio of being in the upper MCS and PCS quartile was lost when the model was adjusted for BDI score, PSQI score, TAS-20 score and the state of physical inactivity. The detailed results were reported in Table 6.

**SLE-related variables, QoL-related variables and probability of MeS**

In Table 7 we reported the results of univariable and multivariable logistic regression having as depend binary variable the diagnosis of MeS. In the final model, we found that the increase of

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**Table 3. Least-squares means of SF-36 components in patients with and without MeS.**

| Parameter | Class | Mean (SE) Model I | p>| Mean (SE) Model II | p>| Mean (SE) Model III | p>|
|---|---|---|---|---|---|---|
| MCS | MeS- | 56.1 (2.6) | 0.03 | 58.9 (4.9) | 0.01 | 58.3 (4.6) | 0.03 |
| | MeS+ | 45.2 (4.3) | | 46.8 (6.0) | | 46.8 (5.6) | |
| PCS | MeS- | 52.5 (2.6) | 0.004 | 62.3 (4.8) | 0.01 | 61.9 (4.6) | 0.008 |
| | MeS+ | 39.7 (3.4) | | 50.0 (5.6) | | 48.7 (5.2) | |
| PF | MeS- | 63.4 (2.9) | 0.01 | 74.0 (5.6) | 0.02 | 72.3 (5.6) | 0.08 |
| | MeS+ | 49.1 (4.5) | | 60.6 (6.9) | | 61.2 (6.8) | |
| RP | MeS- | 49.5 (4.0) | 0.02 | 61.6 (7.8) | 0.02 | 60.8 (7.7) | 0.06 |
| | MeS+ | 32.9 (5.5) | | 44.3 (9.2) | | 44.9 (8.9) | |
| BP | MeS- | 54.7 (3.3) | 0.003 | 64.1 (5.7) | 0.02 | 64.5 (5.6) | 0.003 |
| | MeS+ | 40.2 (3.4) | | 51.6 (6.2) | | 46.9 (5.7) | |
| GH | MeS- | 42.5 (2.1) | 0.13 | 48.9 (3.9) | 0.14 | 48.6 (3.9) | 0.15 |
| | MeS+ | 36.8 (3.1) | | 42.9 (4.9) | | 42.3 (4.7) | |
| VT | MeS- | 49.3 (2.3) | 0.24 | 55.9 (4.5) | 0.20 | 55.4 (4.4) | 0.07 |
| | MeS+ | 43.3 (4.5) | | 49.1 (6.2) | | 45.8 (5.7) | |
| SF | MeS- | 56.9 (2.9) | 0.018 | 60.5 (5.6) | 0.02 | 58.9 (5.3) | 0.06 |
| | MeS+ | 43.7 (4.6) | | 46.6 (6.8) | | 47.3 (6.6) | |
| RE | MeS- | 58.8 (4.6) | 0.04 | 60.0 (8.3) | 0.02 | 60.6 (8.4) | 0.02 |
| | MeS+ | 43.0 (6.3) | | 40.8 (9.4) | | 40.1 (9.6) | |
| MH | MeS- | 59.4 (2.5) | 0.09 | 62.1 (4.9) | 0.04 | 60.1 (4.7) | 0.30 |
| | MeS+ | 50.9 (4.4) | | 51.9 (5.7) | | 54.6 (5.7) | |

Model I: unadjusted. Model II adjusted for sex, age, education level and TAS. Model III: adjusted for disease duration, mean average of last year SELENA SLEDA, last SDI, years of cumulative exposure to high dose GH and years of exposure to antimalarials, education level, TAS. Abbreviations: SE, standard error. MeS+, patients with MeS. MeS-, patients without MeS.

https://doi.org/10.1371/journal.pone.0187645.t003
years of exposure to high doses of glucocorticoids, the average of recent disease activity (mean SLEDAI of the last year) and the increase in the score of depressive symptoms (BDI) are positively associated to the probability of having MeS. Conversely, the increase of years of exposure to antimalarials reduced the probability of having MeS.

Table 4. Least-squares means of SLE-related variables and QoL-related variables in patients with and without MeS.

| Parameter                       | Class   | Mean (SE) Model I | p>t | Mean (SE) Model II | p>t | Mean (SE) Model III | p>t |
|---------------------------------|---------|------------------|-----|--------------------|-----|---------------------|-----|
| **Disease related parameters**  |         |                  |     |                    |     |                     |     |
| Age, years                      | MeS-    | 44.7 (1.8)       | 0.003 | 47.6 (3.0)         | 0.003* |                     |     |
|                                 | MeS+    | 52.9 (2.0)       |       | 55.7 (3.2)         |       |                     |     |
| Disease Duration, years         | MeS-    | 9.2 (0.8)        | 0.2  | 9.5 (1.5)          | 0.47** |                     |     |
|                                 | MeS+    | 11.2 (1.4)       |       | 10.7 (1.9)         |       |                     |     |
| Actual SLEDAI                   | MeS-    | 2.9 (0.4)        | <0.0001 | 2.3 (0.8)       | 0.001** |                     |     |
|                                 | MeS+    | 7.6 (0.9)        |       | 5.6 (1.1)          |       |                     |     |
| Number of flares, last year     | MeS-    | 0.29 (0.09)      | 0.01  | 0.16 (0.17)        | 0.012** |                     |     |
|                                 | MeS+    | 0.79 (0.19)      |       | 0.7 (0.25)         |       |                     |     |
| Actual SDI                      | MeS-    | 0.36 (0.09)      | <0.0001 | 0.3 (0.2)     | 0.0005** |                     |     |
|                                 | MeS+    | 1.12 (0.1)       |       | 0.9 (0.2)          |       |                     |     |
| Cumulative exposure to GC, years| MeS-    | 7.1 (1.5)        | 0.09  | 6.9 (1.5)          | 0.17** |                     |     |
|                                 | MeS+    | 10.0 (0.8)       |       | 9.4 (2.1)          |       |                     |     |
| Cumulative exposure to GCs, %   | MeS-    | 0.75 (0.04)      | 0.051  | 0.7 (0.07)        | 0.012** |                     |     |
|                                 | MeS+    | 0.88 (0.04)      |       | 0.9 (0.08)         |       |                     |     |
| Cumulative exposure to hd GC, years | MeS-    | 2.4 (0.6)       | 0.001  | 3.1 (1.1)         | 0.001** |                     |     |
|                                 | MeS+    | 6.4 (1.0)        |       | 7.6 (1.5)          |       |                     |     |
| Cumulative exposure to hd GC, % | MeS-    | 0.24 (0.04)      | <0.0001 | 0.25 (0.07) | <0.0001** |                     |     |
|                                 | MeS+    | 0.69 (0.05)      |       | 0.76 (0.09)        |       |                     |     |
| Cumulative exposure to antimalarial, years | MeS-    | 5.7 (0.5)       | 0.023  | 5.2 (0.9)         | 0.01** |                     |     |
|                                 | MeS+    | 3.8 (0.6)        |       | 2.8 (1.1)          |       |                     |     |
| Cumulative exposure to antimalarial, % | MeS-    | 0.74 (0.04)      | <0.0001 | 0.63 (0.07) | <0.0001** |                     |     |
|                                 | MeS+    | 0.41 (0.06)      |       | 0.29 (0.09)        |       |                     |     |
| **QoL related parameters**      |         |                  |     |                    |     |                     |     |
| BDI score                       | MeS-    | 9.1 (0.9)        | 0.004  | 6.9 (1.6)         | 0.01  | 6.9 (1.6)          | 0.02 |
|                                 | MeS+    | 15.5 (1.9)       |       | 12.9 (2.5)        |       | 12.1 (1.6)         |       |
| HAM score                       | MeS-    | 11.9 (1.0)       | 0.02  | 10.3 (1.8)        | 0.03  | 9.4 (1.9)          | 0.01 |
|                                 | MeS+    | 17.7 (2.1)       |       | 15.5 (2.7)        |       | 15.6 (2.7)         |       |
| IPAQ score                      | MeS-    | 2.3 (0.1)        | 0.001  | 2.5 (0.2)         | 0.01  |                     |     |
|                                 | MeS+    | 1.6 (0.1)        |       | 1.9 (0.2)         |       |                     |     |
| Fatig-Fatigue score             | MeS-    | 34.6 (1.2)       | 0.12  | 38.4 (2.2)        | 0.38  | 38.7 (2.3)        | 0.44 |
|                                 | MeS+    | 30.7 (2.1)       |       | 36.1 (3.0)        |       | 36.5 (2.3)        |       |
| PSQI score                      | MeS-    | 6.5 (0.5)        | 0.12  | 6.7 (0.8)         | 0.22  |                     |     |
|                                 | MeS+    | 8.1 (0.9)        |       | 8.1 (1.2)         |       |                     |     |
| TAS-20 score                    | MeS-    | 48.6 (1.9)       | 0.44  | 50.3 (3.4)        | 0.75  |                     |     |
|                                 | MeS+    | 51.4 (3.1)       |       | 51.6 (4.6)        |       |                     |     |

Model I: unadjusted. Model II adjusted for sex, age, education level and TAS. Model III: adjusted for disease duration, mean average of last year SELENA SLEDA, last SDI, years of cumulative exposure to high dose GC and years of exposure to antimalarials, education levels and TAS.

*Model II adjusted for sex.

**Model II adjusted for sex, age. Legend: SE, standard error. MeS+, patients with MeS. MeS-, patients without MeS. GC, glucocorticoids. hd GC, high doses of glucocorticoids (daily dose ≥ 7.5 mg of prednisone or equivalents). %, exposure time expressed as percentage of disease duration.

https://doi.org/10.1371/journal.pone.0187645.t004
Approximately one in three patients enrolled in this study had a diagnosis of MeS according to IFD criteria. This finding is in agreement with the prevalence of MeS described in the scientific literature, considering the variability due to different classification criteria used [20–26]. The high MeS prevalence we have observed in our sample is a consequence of the cross sectional design of this study, allowing the enrollment of patients with a wide range of disease duration, disease activity and therapy exposure, in particular glucocorticoids. Considering these aspects, we underline that the mean age of patients enrolled was about 47 years old and the mean disease duration was about 10 years. Moreover, we observed that the mean proportion of disease duration spent with high doses of glucocorticoids (defined as daily dose \( \geq 7.5 \) mg of prednisone or equivalents) was about 40%.

As previously reported [24–26], we found that, compared with patients without MeS, SLE patients with MeS diagnosis presented older age, higher disease activity, an increased number of recent disease flare and an higher score of organ damage. As demonstrated in general population, also SLE patients with MeS seem to present a low education levels [9].

The first finding of this study was that patients with diagnosis of MeS presented an impoverishment of QoL both in physical and mental summary components of SF-36. We applied a mixed regression model to compare the last square means of SF-36 parameters between subjects with and without MeS, allowing the adjustment for factors with considerable impact on physical and mental health perception as age, sex, education levels. We also decided to include in the models the alexithymia score with the aim of considering also the possible effects on SF-36 results of the impairment of the emotion perception / expression [42].

We evaluated QoL using SF-36 instrument, allowing us to analyze the single QoL components. After adjustment for age, sex, education level and alexithymia, we found a reduction in all individual SF-36 score in patients with MeS, with the exception of vitality and global health. We further evaluated the results of vitality score using Facit-fatigue index. In analogy with

### Table 5. Analysis categorical variable SLE-related and QoL–related in patients with and without MeS.

| Factor                        | MeS- (N 66) | MeS+ (N 34) | P   |
|-------------------------------|------------|------------|-----|
| **Sex, N (%)**                |            |            |     |
| Male                          | 4 (6.1)    | 2 (5.9)    | 0.97|
| Female                        | 62 (93.9)  | 32 (94.1)  |     |
| **SLE related factors**       |            |            |     |
| Seropositive, N (%)           | 34 (51.5)  | 26 (76.5)  | 0.01|
| Low complement levels, N (%)  | 29 (43.9)  | 23 (67.6)  | 0.02|
| Neuro-Psychiatric disease, N (%) | 11 (16.7)  | 16 (47.1)  | 0.001|
| Active Renal disease, N (%)   | 3 (4.5)    | 8 (23.5)   | 0.004|
| **QoL related factors**       |            |            |     |
| Education level               |            |            |     |
| None                          | 0 (0)      | 0 (0)      | 0.03|
| Primary education             | 0 (0)      | 2 (5.9)    |     |
| Lower Secondary education     | 21 (31.8)  | 21 (61.7)  |     |
| Upper Secondary education     | 26 (39.4)  | 8 (23.6)   |     |
| University degree or upper education levels | 19 (28.8) | 3 (8.8)    |     |
| Physically inactive (IPAQ = 1) | 14 (21.2)  | 19 (55.8)  | 0.001|

Legend. Seropositive: ANA (Anti-nuclear antibodies) positivity + anti-dsDNA positivity and/or ipo-complement.

https://doi.org/10.1371/journal.pone.0187645.t005
Table 6. Multinomial regression model (dependent variable: quartiles of MCS and PCS values; upper quartile vs lower quartiles). Analysis of variables associated to MCS and PCS in SLE.

| Independent Variable | Dependent Variable (multinomial distribution: upper quartile vs others) | Univariable | Multivariable Model I | Multivariable Model II |
|-----------------------|---------------------------------------------------------------|-------------|------------------------|------------------------|
|                       |                                                               | OR (95% CI) | p                      | OR (95% CI)            | p          |
| Age, years            | MCS                                                           | 0.98 (0.96--1.01) | 0.19                   | 0.97 (0.94/0.99)      | 0.02       |
|                       | PCS                                                           | 0.97 (0.94--0.99) | 0.02                   | 0.97 (0.94/1.02)      | 0.14       |
| Education Level       | MCS                                                           | 0.41 (0.19--0.8) | 0.02                   | 0.25 (0.11/0.57)      | 0.0008     |
|                       | PCS                                                           | 0.76 (0.37--1.53) | 0.44                   | 0.39 (0.16/0.98)      | 0.04       |
|                       |                                                               |             |                        |                       |            |
|                       | Sex (female vs male)                                          | 0.70 (0.16/3.1) | 0.64                   | 0.41 (0.05/3.63)      | 0.45       |
|                       |                                                               |             |                        |                       |            |
|                       | Disease Duration, years                                       | 1.01 (0.97/1.07) | 0.54                   | 0.94 (0.86/1.03)      | 0.17       |
|                       |                                                               |             |                        |                       |            |
|                       | Low complement (yes vs no)                                    | 1.09 (0.54/2.19) | 0.81                   | 0.94 (0.86/1.03)      | 0.17       |
|                       |                                                               |             |                        |                       |            |
|                       | Anti-phospholipid syndrome (yes vs no)                        | 1.42 (0.60/3.38) | 0.42                   | 0.89 (0.80/1.02)      | 0.05       |
|                       |                                                               |             |                        |                       |            |
|                       | Cumulative exposure to hd GC, years                           | 0.96 (0.89/1.03) | 0.23                   | 0.94 (0.86/1.03)      | 0.17       |
|                       |                                                               |             |                        |                       |            |
|                       | Cumulative exposure to antimalarials, years                   | 1.05 (0.96/1.14) | 0.26                   | 0.89 (0.81/1.09)      | 0.53       |
|                       |                                                               |             |                        |                       |            |
| Mean SLEDAI last year |                                                               | 0.90 (0.82/0.99) | 0.03                   | 0.89 (0.81/0.99)      | 0.04       |
|                       |                                                               |             |                        |                       |            |
| Actual SDI            |                                                               | 0.87 (0.79/0.96) | 0.006                  | 0.90 (0.79/1.02)      | 0.09       |
|                       |                                                               |             |                        |                       |            |
|                       | Number of disease flares last year                            | 0.95 (0.57/1.26) | 0.42                   | 0.95 (0.52/1.61)      | 0.75       |
|                       |                                                               |             |                        |                       |            |
|                       | Physically inactive (IPAQ = 1) (yes vs no)                    | 0.40 (0.18/0.90) | 0.03                   | 0.41 (0.14/1.22)      | 0.11       |

(Continued)
what we observed for vitally, patients with and without MeS did not differ for fatigue level. This result was confirmed after correction for age, sex, education level and alexithymia score. We do not have an explanation that the MeS has no impact on the fatigue in our cohort of SLE patients. In SLE patients, fatigue was reported to be strongly associated to mood disorders and, in several study, to sleep quality and stress, while the relation of fatigue with disease activity and damage was controversial [43]. In general population, the impact of MeS on fatigue is still poorly explored [12]. None of the available study on SLE patients reported a relation between fatigue and MeS or MeS components, such as obesity. We propose to investigate this aspect in the prospective extension of this study.

Since we observed an increase of disease activity, damage index and exposure to therapy in SLE patients with MeS compared to those without MeS, we decided to adjust SF-36 components also for average of recent SLEDAI, SDI score, cumulative years of high dose GC therapy and antimalarial therapy. Summary component of SF-36 were reduced in MeS also after controlling for SLE disease feature. However, considering the individual SF-36 component after control for SLE disease feature, only bodily pain and role emotional remained significantly different between patients with and without MeS.

To deepen the impact of MeS on QoL of SLE patients, we built a multinomial logistic regression model having as dependent variable the MCS or PCS quartiles. As extensively reviewed elsewhere [43], we found that age, the average of recent disease activity, the organ damage score and the number of recent flares reduced the probability of have high values of PCS. Moreover, we observed that the odds ratio of been in the upper PCS quartile was reduced by the years of cumulative exposure to high dose GC. In accordance with what has already

### Table 6. (Continued)

| Independent Variable | Dependent Variable (multinomial distribution: upper quartile vs others) | Univariable | Multivariable Model I | Multivariable Model II |
|----------------------|--------------------------------------------------|-------------|-----------------------|-----------------------|
|                      | OR (95% CI) p                                    | OR (95% CI) p | OR (95% CI) p         |
| BDI score            | MCS                                              | 0.85 (0.80/0.90) <0.0001 | 0.89 (0.82/0.97) 0.009 |
|                      | PCS                                              | 0.83 (0.78/0.88) <0.0001 | 0.87 (0.79/0.95) 0.004 |
| HAM score            | MCS                                              | 0.86 (0.81/0.90) <0.0001 |             |
|                      | PCS                                              | 0.84 (0.79/0.89) <0.0001 |             |
| PSQI                 | MCS                                              | 0.85 (0.77/0.94) 0.001  | 0.99 (0.87/1.14) 0.95 |
|                      | PCS                                              | 0.80 (0.72/0.89) <0.0001 | 0.94 (0.81/1.09) 0.42 |
| TAS-20 score         | MCS                                              | 0.95 (0.93/0.97) <0.0001 | 0.97 (0.93/1.00) 0.08 |
|                      | PCS                                              | 0.97 (0.94/0.99) 0.005  | 1.02 (0.99/1.07) 0.19 |
| Metabolic Syndrome   | MCS                                              | 0.42 (0.19/0.90) 0.03   | 0.62 (0.22/1.73) 0.36 |
|                      | PCS                                              | 0.30 (0.14/0.66) 0.003  | 0.56 (0.18/1.70) 0.30 |

Multivariable Model I: adjusted for demographic and SLE disease variables (only variables with significant results in univariable analysis were included).
Multivariable Model II: adjusted for Model I variables + QoL related variables (depressive symptoms, alexithymia, physical activity)

https://doi.org/10.1371/journal.pone.0187645.t006
been described, the distribution of MCS values is more arduous to describe with a statistical model. Interestingly, we observed that higher education levels reduced the probability of having better QoL, both in mental and physical components. This phenomenon has already been described in middle-aged women of general population [44]. As previously reported, in our analysis, the distribution of MCS and PCS values was strongly associated with the severity of symptoms of mood disorders, the sleep quality score, the physical activity and the score of alexithymia construct [43]. In our analysis, MeS was inversely related to the probability of being in the higher MCS and PCS quartiles even adjusted for demographic and disease features as age, education level, average of recent SLEDAI, cumulative exposure to high dose GC. This significant association of MeS and QoL was lost when the model was enriched with QoL related variables evaluating mood disorder symptoms, sleep quality, physical activity and alexithymia. This observation suggests that much of the MeS impact on QoL may be mediated by mood disorders and, to a lesser extent, by poor physical activity.

We evaluated the extent of symptoms of mood disorders in our SLE sample. In particular, we explored depressive and anxiety symptoms. According to our findings, SLE patients meeting MeS criteria are burdened by depressive and anxiety symptoms more seriously than patients without MeS. The scores evaluating the extent of manifestations related to mood disorders remain high in MeS also after control for confounders as age, sex, education levels and alexithymia. The relation of mood disorders with MeS and MeS components, in particular obesity, was widely demonstrated. A recent meta-analysis on 29 cross-sectional studies and 11 cohort studies suggested that it could exist a bidirectional association of MeS and depression.

Table 7. Multiple logistic regression analysis investigating the effects of SLE-related parameters and QoL-related parameters on MeS.

| Variable                                      | Univariable Logistic Regression | Multivariable Logistic Regression |
|-----------------------------------------------|---------------------------------|-----------------------------------|
| Event: having MeS diagnosis                  |                                 |                                   |
| Variable                                      | OR (95% CI)                     | p                                 | OR (95% CI)                     | p     |
| Age, years                                    | 1.04 (1.01/1.08)                | 0.07                              |                                 |       |
| Education Level (>upper secondary vs ≤lower secondary) | 0.3 (0.1/0.7)                  | 0.005                             |                                 |       |
| Sex (male vs female)                          | 0.97 (0.17/5.57)                | 0.9                               |                                 |       |
| Disease Duration, years                       | 1.04 (0.98/1.1)                 | 0.2                               |                                 |       |
| Low complement (yes vs no)                    | 2.7 (1.1/6.3)                   | 0.02                              |                                 |       |
| Anti-phospholipid syndrome (yes vs no)        | 2.7 (1.1/7.2)                   | 0.04                              |                                 |       |
| Active Lupus Nephritis (yes vs no)            | 6.1 (1.6/26.3)                  | 0.009                             |                                 |       |
| Cumulative exposure to hd GC, years           | 1.2 (1.1/1.3)                   | 0.002                             | 1.18 (1.06/1.3)                 | 0.004 |
| Cumulative exposure to antimalarials, years   | 0.8 (0.7/0.9)                   | 0.03                              | 0.82 (0.68/0.98)                | 0.03  |
| Mean SLEDAI last year                         | 1.2 (1.1/1.4)                   | 0.0003                            | 1.15 (1.0/1.3)                  | 0.04  |
| Actual SDI                                    | 2.8 (1.6/4.9)                   | 0.0003                            |                                 |       |
| Number of disease flares last year            | 1.9 (1.1/3.1)                   | 0.01                              |                                 |       |
| Physically inactive (IPAQ = 1) (yes vs no)    | 4.4 (1.7/10.9)                  | 0.002                             |                                 |       |
| BDI score                                     | 1.1 (1.03/1.15)                 | 0.002                             | 1.1 (1.03/1.17)                 | 0.005 |
| HAM score                                     | 1.06 (1.02/1.11)                | 0.009                             |                                 |       |
| FACIT Fatigue score                           | 0.97 (0.9/1.01)                 | 0.1                               |                                 |       |
| TAS score                                     | 1.01 (0.9/1.04)                 | 0.4                               |                                 |       |
| PCS score                                     | 0.97 (0.94/0.99)                | 0.007                             |                                 |       |
| MCS score                                     | 0.98 (0.96/0.99)                | 0.03                              |                                 |       |
Several cross sectional studies and a meta-analysis on 15 cohort studies seem demonstrate a reciprocal link between depression and obesity. The conclusion of the meta-analysis was that obesity could increase the risk of depression, and depression was found to be predictive of developing obesity [45]. The pathophysiological basis of these relation between MeS with reduced QoL remain to be elucidated in SLE patients as well as in general population. Several explanations have been proposed. Firstly, the MeS is often accompanied by CVDs and type 2 diabetes, as end-organ damage, consequences of MeS. Both of these conditions are associated with a reduced QoL [46, 47]. Moreover, both MeS and obesity are characterized by the activation of several inflammatory pathways, including cytokines as Interleukin-6, Tumor Necrosis Factor-alpha, Interleukin-1 and adipokines as leptin, adiponectin and resistin [13, 48, 49]. These inflammatory mediators have been demonstrated to be involved in depression and anxiety [50]. Another possible pathophysiological mechanism could involve the hypothalamic-pituitary-adrenal axis (HPA axis). In particular, insulin-resistance and weight gain, both associated to MeS, lead to HPA-axis dysregulation [51]. An implication of HPA-axis dysregulation in depression has been widely demonstrated [52]. Indeed, it needs to be considered also the role of psychological distress related to being overweight. Body image alteration and satisfaction in obese patients could be a potential mediator of the relationship between obesity and psychological distress [53]. Finally, we must consider the role of reduced physical activity in lowering the QoL in patients with MeS as well as in obese subjects [54, 55]. In SLE patients, Pinto et al recently reported a reduced QoL in all SF-36 domains in a cross section study on 21 physically inactive patients [56]. We found that a larger proportion of SLE patients with MeS are physically inactive according to IPAQ score, while patients without MeS are frequently physically active and sometimes meet HEPA criteria for adequate physical activity [38].

To further evaluate the relation between MeS and QoL related factors, we build a logistic regression model using as predicted event the diagnosis of MeS. As we expected, several SLE related factor increase the odds ratio of MeS in SLE patients, such as the low complement status, the diagnosis of anti-phospholipid syndrome, the presence of active lupus nephritis, the average values of recent disease activity expressed by SELENA-SLEDAI, the number of disease flares in the last year and the time of exposure to high doses of glucocorticoids. Furthermore, our results underline the positive impact on MeS odds ratio of QoL related variables such as to be physically inactive, the values of the BDI and HAM-H scores and the values of SF-36 summary physical and mental components. In the final multivariable models, we found that the odds ratio of MeS in our SLE sample was associated to the SELENA-SLEDAI score, to the extent of depressive symptoms and to the duration of exposure to high doses of glucocorticoids. Interestingly, the length of therapy with antimalarials seems to exert a protective role on the probability of having MeS, according to our results.

We observed that the extent of antimalarial therapy could reduce the odds ratio of MeS. We recently demonstrated that hydroxychloroquine assumed for more than five years protects against the first cardiovascular event in a large retrospective lupus cohort [57]. Beside the well-known effects on SLE disease, as the reduction of flares risk, the steroid sparing effect, the reduction of organ damage accrual and the prevention of the thrombotic effects of anti-phospholipid antibodies [58, 59], a crescent body of evidences supports the beneficial impacts of antimalarial on cardio-metabolic diseases including diabetes mellitus and dyslipidemia. The biological mechanism of these positive effects has not yet been clarified but may include alterations in insulin metabolism and signaling through cellular receptors [60].

Our study presents several limitations. First of all, the cross sectional design of the study does not allow to analyze a causative relation between MeS, QoL and related factors. Moreover, the sample size, and consequently the number of patients with diagnosis of MeS, reduces the possibility to include other variables in the final multivariable regression model. Moreover, the
sample size limits the possibility of stratifying the analysis according to therapy exposure. One of the strengths of our work is the evaluation of multiple dimensions related to QoL (mood disorders, fatigue, sleep quality, alexithymia). Another one is the use of mixed models for comparing the values of SF36, which has allowed to consider possible confounders.

In conclusion, according to our findings, MeS seems to be associated with an impoverishment of QoL in SLE patients, both in mental and physical components. Moreover, SLE patients with MeS presented an increased amount of symptoms of mood disorders and are often physically inactive.

MeS is associated to a reduction of the probability of having values of MCS and PCS in their upper quartiles of distribution, even after adjustment for confounders regarding demographic and SLE disease features. Conversely, when we add to the model the scores of the mood disorders symptoms, sleep quality, physical activity and alexithymia, MeS losses its significant impact on MCS and PCS values. This observation underlines the central role of mood disorders and physical activity in the impact of MeS on QoL measures.

The factors mainly associated to the presence of MeS in SLE were the recent disease activity, the duration of exposure to high dose glucocorticoids and the severity of depression, while the length of therapy with antimalarials seems to except a protective action.

Overall, these evidences underline the need to maximize the control of disease activity, minimizing as much as possible the use of high doses of glucocorticoids and potentially using antimalarials in all SLE patients, in order to manage the cardio-metabolic risk. Alongside these aspects, we have to increase our awareness of the need to properly manage mood disorders in these patients. In particular, it seems necessary to put in place all pharmacological and non-pharmacological measures to try to improve the quality of life in lupus patients with MeS.

Author Contributions
Conceptualization: Domenico Paolo Emanuele Margiotta, Fabio Basta, Antonella Afeltra.
Data curation: Domenico Paolo Emanuele Margiotta, Fabio Basta, Giulio Dolcini, Veronica Batani.
Formal analysis: Domenico Paolo Emanuele Margiotta.
Methodology: Domenico Paolo Emanuele Margiotta, Fabio Basta.
Supervision: Domenico Paolo Emanuele Margiotta.
Validation: Domenico Paolo Emanuele Margiotta.
Writing – original draft: Domenico Paolo Emanuele Margiotta.
Writing – review & editing: Domenico Paolo Emanuele Margiotta, Luca Navarini, Antonella Afeltra.

References
1. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285(19):2486–97. PMID: 11368702.
2. Alberti KG, Zimmet P, Shaw J, Group IDFETFC. The metabolic syndrome—a new worldwide definition. Lancet (London, England). 2005; 366(9491):1059–62. https://doi.org/10.1016/S0140-6736(05)67402-8 PMID: 16182882.
3. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care. 2001; 24(4):683–9. PMID: 11315831.
4. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol. 2010; 56(14):1113–32. https://doi.org/10.1016/j.jacc.2010.05.034 PMID: 20863953.

5. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care. 2004; 27(11):2676–81. PMID: 15505004.

6. Amiri P, Dehirm T, Hosseinipanah F, Barzin M, Hashemnia M, Montazeri A, et al. Diagnostic values of different definitions of metabolic syndrome to detect poor health status in Iranian adults without diabetes. Diabet Med. 2014; 31(7):854–61. https://doi.org/10.1111/dme.12443 PMID: 24654736.

7. Ford ES, Li C. Metabolic syndrome and health-related quality of life among U.S. adults. Ann Epidemiol. 2008; 18(3):165–71. https://doi.org/10.1016/j.annepidem.2007.10.009 PMID: 18280918.

8. Lee YJ, Woo SY, Ahn JH, Cho S, Kim SR. Health-related quality of life in adults with metabolic syndrome: the Korea national health and nutrition examination survey, 2007–2008. Annals of nutrition & metabolism. 2012; 61(4):275–80. https://doi.org/10.1159/000341494 PMID: 23208156.

9. Lidfeldt J, Nyberg P, Samsioe G, Schersten B, Agardh CD. Socio-demographic and psychosocial factors are associated with features of the metabolic syndrome. The Women’s Health in the Lund Area (WHILA) study. Diabetes Obes Metab. 2003; 5(2):106–12. PMID: 12630935.

10. Park SS, Yoon YS, Oh SW. Health-related quality of life in metabolic syndrome: The Korea National Health and Nutrition Examination Survey 2005. Diabetes Res Clin Pract. 2011; 91(3):381–8. https://doi.org/10.1016/j.diabres.2010.11.010 PMID: 21134699.

11. Pan A, Keum N, Okereke OI, Sun Q, Kivimaki M, Rubin RR, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care. 2012; 35(5):1171–80. https://doi.org/10.2337/dc11-2055 PMID: 22517938; PubMed Central PMCID: PMCPMC3193421.

12. Maloney EM, Boneva RS, Lin JM, Reeves WC. Chronic fatigue syndrome is associated with metabolic syndrome: results from a case-control study in Georgia. Metabolism. 2010; 59(9):1351–7. https://doi.org/10.1016/j.metabol.2009.12.019 PMID: 20102774.

13. Margiotta D, Navarini L, Vadacca M, Basta F, Lo Vullo M, Pignataro F, et al. Relationship between leptin and regulatory T cells in systemic lupus erythematosus: preliminary results. European review for medical and pharmacological sciences. 2016; 20(4):636–41. Epub 2016/03/10. PMID: 26957264.

14. Paley MA, Strand V, Kim AH. From mechanism to therapies in systemic lupus erythematosus. Curr Opin Rheumatol. 2017; 29(2):178–86. Epub 2017/01/25. https://doi.org/10.1097/BOR.0000000000000309 PMID: 28118202.

15. Bruce IN, Urowitz MB, Gladman DD, Ibañez D, Steiner G. Risk factors for coronary heart disease in women with systemic lupus erythematosus: the Toronto Risk Factor Study. Arthritis Rheum. 2003; 48(11):3159–67. https://doi.org/10.1002/art.11296 PMID: 14613278.

16. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr., Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol. 1997; 145(5):408–15. PMID: 9048514.

17. Urowitz MB, Ibañez D, Gladman DD. Atherosclerotic vascular events in a single large lupus cohort: prevalence and risk factors. J Rheumatol. 2007; 34(1):70–5. PMID: 17117488.

18. El Magadmi M, Ahmad Y, Turkie W, Yates AP, Sheikin N, Bernstein RM, et al. Hyperinsulinemia, insulin resistance, and circulating oxidized low density lipoprotein in women with systemic lupus erythematosus. J Rheumatol. 2006; 33(1):50–6. Epub 2006/01/06. PMID: 16395749.

19. Sada KE, Yamasaki Y, Maruyama M, Hashemnia M, Montazeri A, et al. Diagnostic values of different definitions of metabolic syndrome to detect poor health status in Iranian adults without diabetes. Diabet Med. 2014; 31(7):854–61. https://doi.org/10.1111/dme.12443 PMID: 24654736.

20. Azevedo GD, Gadelha RG, Vilar MJ. Metabolic syndrome in systemic lupus erythematosus: lower prevalence in Brazil than in the USA. Ann Rheum Dis. 66. England2007. p. 1542. https://doi.org/10.1136/ard.2007.074583 PMID: 17934082.

21. Chung CP, Avalos I, Oeser A, Gebretsadik T, Shintani A, Raggi P, et al. High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis. 2007; 66(2):208–14. Epub 2006/08/12. https://doi.org/10.1136/ard.2006.054973 PMID: 16901956; PubMed Central PMCID: PMCPMC1798504.

22. Parker B, Ahmad Y, Sheilmerdine J, Edlin H, Yates AP, Teh LS, et al. An analysis of the metabolic syndrome phenotype in systemic lupus erythematosus. Lupus. 2011; 20(14):1459–65. Epub 2011/09/07. https://doi.org/10.1177/0961203311416695 PMID: 21893561.

23. Telles R, Lanna C, Ferreira G, Ribeiro A. Metabolic syndrome in patients with systemic lupus erythematosus: association with traditional risk factors for coronary heart disease and lupus characteristics.
Lupus. 2010; 19(7):803–9. Epub 2010/02/02. https://doi.org/10.1177/0961203309359781 PMID: 20118159.

24. Vadacca M, Margiotta D, Rigon A, Cacciapaglia F, Coppolo G, Amoroso A, et al. Adipokines and systemic lupus erythematosus: relationship with metabolic and cardiovascular disease risk factors. J Rheumatol. 2009; 36(2):295–7. https://doi.org/10.3899/jrheum.080503 PMID: 19132788.

25. Parker B, Urowitz MB, Gladman DD, Lunt M, Bae SC, Sanchez-Guerrero J, et al. Clinical associations of the metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis. 2013; 72(8):1308–14. Epub 2012/09/05. https://doi.org/10.1136/annrheumdis-2012-202106 PMID: 22945501; PubMed Central PMCID: PMCPMC3711497.

26. Parker B, Urowitz MB, Gladman DD, Lunt M, Donn R, Bae SC, et al. Impact of early disease factors on metabolic syndrome in systemic lupus erythematosus: data from an international inception cohort. Ann Rheum Dis. 2015; 74(8):1530–6. Epub 2014/04/03. https://doi.org/10.1136/annrheumdis-2013-203933 PMID: 24692585; PubMed Central PMCID: PMCPMC4515988.

27. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012; 64(8):2677–86. https://doi.org/10.1002/art.34473 PMID: 22553077; PubMed Central PMCID: PMCPMC3409311.

28. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 1992; 35(6):630–40. PMID: 15995520.

29. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005; 353(24):2550–8. https://doi.org/10.1056/NEJMoa051135 PMID: 16354891.

30. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Annals of internal medicine. 2005; 142(12 Pt 1):953–62. PMID: 15968009.

31. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, 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(3):363–9. PMID: 8607884.

32. Ruiz-Arruzaz I, Ugarte A, Cabezas-Rodriguez I, Medina JA, Moran MA, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2014; 53(8):1470–6. https://doi.org/10.1093/rheumatology/keu148 PMID: 24681836.

33. Apolone G, Mosconi P. The Italian SF-36 Health Survey: translation, validation and norming. J Clin Epidemiol. 1998; 51(11):1025–36. PMID: 9817120.

34. Webster K, Cellia D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003; 1:79. https://doi.org/10.1186/1477-7525-1-79 PMID: 14678568; PubMed Central PMCID: PMCPMC317391.

35. Sacco R, Santangelo G, Stamenova S, Bisceco A, Bonavita S, Lavorgna L, et al. Psychometric properties and validity of Beck Depression Inventory II in multiple sclerosis. Eur J Neurol. 2016; 23(4):744–50. https://doi.org/10.1111/ene.12932 PMID: 26782789.

36. Panchari P, Picardi A, Pasquini M, Gaetano P, Biondi M. Psychopathological dimensions of depression: a factor study of the 17-item Hamilton depression rating scale in unipolar depressed outpatients. J Affect Disord. 2002; 68(1-2):41–7. PMID: 11869781.

37. Smarr CB, Hsu CL, Byrne AJ, Miller SD, Bryce PJ. Antigen-fixed leukocytes tolerate Th2 responses in mouse models of allergy. J Immunol. 2011; 187(10):5090–8. https://doi.org/10.4049/jimmunol.1100608 PMID: 21976774; PubMed Central PMCID: PMCPMC3208064.

38. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003; 35(8):1381–95. https://doi.org/10.1249/12.000000000000078924.61453.FB PMID: 12900694.

39. Curcio G, Tempesta D, Scarlata S, Marzano C, Moroni F, Rossini PM, et al. Validity of the Italian version of the Pittsburgh Sleep Quality Index (PSQI). Neurol Sci. 2013; 34(4):511–9. https://doi.org/10.1007/s10072-012-1085-y PMID: 22526760.

40. Bressi C, Taylor G, Parker J, Bressi S, Brambilla V, Aguglia E, et al. Cross validation of the factor structure of the 20-item Toronto Alexithymia Scale: an Italian multicenter study. Journal of psychosomatic research. 1996; 41(6):551–9. Epub 1996/12/01. PMID: 9032718.

41. Symmons DP, Coppock JS, Bacon PA, Bresnihan B, Isenberg DA, Maddison P, et al. Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. Members of the British Isles Lupus Assessment Group (BILAG). Q J Med. 1988; 69(259):927–37. PMID: 3271396.
42. Vadacca M, Bruni R, Terminio N, Sambataro G, Margiotta D, Serino FM, et al. Alexithymia, mood states and pain experience in systemic lupus erythematosus and rheumatoid arthritis. Clin Rheumatol. 2014; 33(10):1443–50. https://doi.org/10.1007/s10067-014-2593-3 PMID: 24718486.

43. Schmeding A, Schneider M. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. Best Pract Res Clin Rheumatol. 2013; 27(3):363–75. https://doi.org/10.1016/j.berh.2013.07.009 PMID: 24238693.

44. Regidor E, Barrio G, de la Fuente L, Domingo A, Rodríguez C, Alonso J. Association between educational level and health related quality of life in Spanish adults. J Epidemiol Community Health. 1999; 53(2):75–82. PMID: 10396467; PubMed Central PMCID: PMCPMC1756832.

45. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Archives of general psychiatry. 2010; 67(3):220–9. Epub 2010/03/03. https://doi.org/10.1001/archgenpsychiatry.2010.2 PMID: 20194822.

46. Coffey JT, Brandle M, Zhou H, Marriott D, Burke R, Tabaei BP, et al. Valuing health-related quality of life in diabetes. Diabetes Care. 2002; 25(12):2238–43. PMID: 12453967.

47. Lalande L, O’Connor A, Joseph L, Grover SA, Canadian Collaborative Cardiac Assessment G. Health-related quality of life in cardiac patients with dyslipidemia and hypertension. Qual Life Res. 2004; 13(4):793–804. https://doi.org/10.1023/B:QURE.0000021695.26201.a0 PMID: 15129889.

48. Vadacca M, Margiotta DP, Navarini L, Afeltra A. Leptin in immuno-rheumatologic diseases. Cell Mol Immunol. 2011; 8(3):203–12. Epub 2011/03/14. https://doi.org/10.1038/cmi.2010.75 PMID: 21399656; PubMed Central PMCID: PMCPMC4012876.

49. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. Gastroenterology. 2007; 132(6):2169–80. https://doi.org/10.1053/j.gastro.2007.03.059 PMID: 17498510.

50. Milaneschi Y, Corsi AM, Penninx BW, Bandinelli S, Guralnik JM, Ferrucci L. Interleukin-1 receptor antagonist and incident depressive symptoms over 6 years in older persons: the InCHIANT I study. Biol Psychiatry. 2009; 65(11):973–8. Epub 2008/12/25. https://doi.org/10.1016/j.biopsych.2008.11.011 PMID: 19111279; PubMed Central PMCID: PMCPMC2682634.

51. Pasquali R, Vicennati V. Activity of the hypothalamic-pituitary-adrenal axis in different obesity phenotypes. Int J Obes Relat Metab Disord. 2000; 24 Suppl 2:S47–9. PMID: 10997608.

52. Belanoff J, Kalehzan M, Sund B, Fleming Ficek SK, Schatzberg AF. Cortisol activity and cognitive changes in psychotic major depression. Am J Psychiatry. 2001; 158(10):1612–6. https://doi.org/10.1176/appi.ajp.158.10.1612 PMID: 11578992.

53. Friedman KE, Reichmann SK, Costanzo PR, Musante GJ. Body image partially mediates the relationship between obesity and psychological distress. Obesity research. 2002; 10(1):33–41. Epub 2002/01/12. https://doi.org/10.1038/oby.2002.5 PMID: 11786599.

54. Heath GW, Brown DW. Recommended levels of physical activity and health-related quality of life among overweight and obese adults in the United States, 2005. J Phys Act Health. 2009; 6(4):403–11. PMID: 19842453.

55. Balboa-Castillo T, León-Muñoz LM, Graciani A, Rodríguez-Artalejo F, Guallar-Castillón P. Longitudinal association of physical activity and sedentary behavior during leisure time with health-related quality of life in community-dwelling older adults. Health Qual Life Outcomes. 2011; 9:47. Epub 2011/06/27. https://doi.org/10.1186/1477-7525-9-47 PMID: 21708011; PubMed Central PMCID: PMCPMC3142200.

56. Pinto AJ, Miyake CN, Benatti FB, Silva CA, Sallum AM, Borba E, et al. Reduced Aerobic Capacity and Quality of Life in Physically Inactive Patients With Systemic Lupus Erythematosus With Mild or Inactive Disease. Arthritis Care Res (Hoboken). 2016; 68(12):1780–6. Epub 2016/10/28. https://doi.org/10.1002/acr.22905 PMID: 27058995.

57. Fasano S, Margiotta DP, Navarini L, Pierro L, Pantano I, Riccardi A, et al. Primary prevention of cardiovascular disease in patients with systemic lupus erythematosus: case series and literature review. Lupus. 2017;691203317722847. https://doi.org/10.1177/0961203317722847 PMID: 28786786.

58. Ponticelli C, Moroni G. Hydroxychloroquine in systemic lupus erythematosus (SLE). Expert opinion on drug safety. 2017; 16(3):411–9. Epub 2016/12/09. https://doi.org/10.1080/14740338.2017.1269168 PMID: 27927040.

59. Tang C, Godfrey T, Stawell R, Nikpour M. Hydroxychloroquine in lupus: emerging evidence supporting multiple beneficial effects. Internal medicine journal. 2012; 42(9):968–76. Epub 2012/07/26. https://doi.org/10.1111/j.1445-5994.2012.02886.x PMID: 22927853.

60. Hage MP, Al-Badri MR, Azar ST. A favorable effect of hydroxychloroquine on glucose and lipid metabolism beyond its anti-inflammatory role. Therapeutic advances in endocrinology and metabolism. 2014; 5(4):77–85. Epub 2014/10/25. https://doi.org/10.1177/204218814547204 PMID: 25343023; PubMed Central PMCID: PMCPMC4206615.