LUPUS SCIENCE & MEDICINE™

Impact of glucocorticoids on the incidence of lupus-related major organ damage: a systematic literature review and meta-regression analysis of longitudinal observational studies

Manuel Francisco Ugarte-Gil ,[1,2] Anselm Mak ,[3,4] Joanna Leong,[5] Bhushan Dharmadhikari,[3,6] Nien Yee Kow,[3,4] Cristina Reátegui-Sokolova ,[1,7] Claudia Elera-Fitzcarrald ,[1,2] Cinthia Aranow,[8] Laurent Arnaud ,[9] Anca D Askanase ,[10] Sang-Cheol Bae ,[11,12] Sasha Bernatsky ,[13] Ian N Bruce ,[14,15] Jill Buyon,[16] Nathalie Costedoat-Chalumeau,[17,18,19] Mary Ann Dooley,[20] Paul R Fortin ,[21] Ellen M Ginzler,[22] Dafna D Gladman,[23] John Hanly,[24] Murat Inanc,[25] David Isenberg,[26] Soren Jacobsen,[27] Judith A James,[28,29] Andreas Jönsen,[30] Kenneth Kalunian,[31] Diane L Kamen,[32] Sung Sam Lim ,[33] Eric Morand ,[34] Marta Mosca,[35] Christine Peschken,[36] Bernardo A Pons-Estel ,[37] Anisur Rahman,[26] Rosalind Ramsey-Goldman,[38] John Reynolds,[39,40] Juanita Romero-Diaz,[41] Guillermo Ruiz-Irastorza ,[42] Jorge Sánchez-Guerrero,[43,44] Elisabet Svenungsson ,[45] Murray Urowitz ,[23] Evelyne Vinet ,[46] Ronald F van Vollenhoven ,[47] Alexandre Voskuyl,[48] Daniel J Wallace ,[49,50] Michelle A Petri ,[51] Susan Manzi ,[52] Ann Elaine Clarke,[53] Mike Cheung,[54] Vernon Farewell,[55] Graciela S. Alarcon[56,57]

To cite: Ugarte-Gil MF, Mak A, Leong J, *et al*. Impact of glucocorticoids on the incidence of lupus-related major organ damage: a systematic literature review and meta-regression analysis of longitudinal observational studies. *Lupus Science & Medicine* 2021;**8**:e000590. doi:10.1136/lupus-2021-000590

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/lupus-2021-000590).

MFU-G and AM are joint first authors.
MC, VF and GSA are joint senior authors.

Received 21 September 2021
Accepted 24 November 2021

For numbered affiliations see end of article.

Correspondence to
Dr Manuel Francisco Ugarte-Gil; mugarte@cientifica.edu.pe

ABSTRACT

Objective In systemic lupus erythematosus (SLE), disease activity and glucocorticoid (GC) exposure are known to contribute to irreversible organ damage. We aimed to examine the association between GC exposure and organ damage occurrence.

Methods We conducted a literature search (PubMed (Medline), Embase and Cochrane January 1966–October 2021). We identified original longitudinal observational studies reporting GC exposure as the proportion of users and/or GC use with dose information as well as the occurrence of new major organ damage as defined in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. Meta-regression analyses were performed. Reviews, case-reports and studies with <5 years of follow-up, <50 patients, different outcomes and special populations were excluded.

Results We selected 49 articles including 16 224 patients, 14 755 (90.9%) female with a mean age and disease duration of 35.1 years and of 37.1 months. The mean follow-up time was 104.9 months. For individual damage items, the average daily GC dose was associated with the occurrence of overall cardiovascular events and with osteoporosis with fractures. A higher average cumulative dose adjusted (or not)/number of follow-up years and a higher proportion of patients on GC were associated with the occurrence of osteonecrosis.

Conclusions We confirm associations of GC use with three specific damage items. In treating patients with SLE, our aim should be to maximise the efficacy of GC and to minimise their harms.

Key messages

What is already known about this subject?

► Exposure to glucocorticoid (GC) has been recognised as contributing to damage occurrence in patients with lupus; however, this association has been reported in different ways, leading to inconsistent conclusions.

What does this study add?

► This study examines the information available in the literature from lupus cohorts/studies and confirms the association between GC exposure and osteonecrosis, cardiovascular events and osteoporosis with fractures.

How might this impact on clinical practice or future developments?

► Physicians should use GC judiciously to maximise their efficacy and minimise their harms.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, relapsing-remitting inflammatory autoimmune disease with multisystemic manifestations.[1] Inflammation due to active SLE, if not promptly and adequately treated, leads to irreversible tissue or organ damage that negatively impacts survival and health-related quality of life.[2–5] While the overall survival of patients with SLE has gradually improved over the past four decades, organ damage, particularly that of the renal and neuropsychiatric systems, has been shown to limit further improvement of the short-term and long-term survival rates of patients with SLE.[6] Therefore, clinicians and scientists are actively pursuing factors that lead to organ damage in patients with SLE and devising strategies to mitigate them.

While uncontrolled SLE disease activity potentially leads to eventual tissue and organ damage, pharmacological treatment of SLE can also be contributory.[6] Among various drugs that are used in patients with SLE, clinicians have long recognised that glucocorticoids (GC), while often clinically beneficial, can induce damage, particularly in the ocular, cerebrovascular, cardiovascular and musculoskeletal systems.[7–11] Nevertheless, the different impacts of several modes of GC exposure including its daily and cumulative doses, as well as the mere presence of GC exposure on major organ damage in patients with SLE have not been fully addressed. The differences in study populations and chronological periods, research designs and methodologies used, duration of disease and study observation as well as the different ways of expressing GC exposure (daily, cumulative, oral vs parenteral) have led to inconsistent conclusions.[7 9 12]

In this study, we sought to examine the data published in the past 55 years by evaluating all longitudinal observational studies published between 1 January 1966 and 18 October 2021. Our initial aim was to conduct a meta-analysis of estimated effects of GC on damage using the relevant literature but that was not feasible due to the relatively small number of studies that supported such analysis (*vide infra*). Thus, a systematic literature review and meta-regression analyses of the association between GC exposure and the occurrence of major SLE-related organ damage were conducted. Damage was defined as *per* the Systemic Lupus International Collaborating Clinic/American College of Rheumatology Damage Index (SDI) or the corresponding terms prior to the availability of this instrument. Among the items included in the SDI, we evaluated overall damage as well as those items more probably related to GC as previously described: cataracts, cerebrovascular accidents (CVA), myocardial infarction (MI), overall cardiovascular events (CVE) including angina and coronary artery bypass graft, avascular/osteonecrosis and osteoporosis with fractures.

METHODS

Literature search and data entry

This systematic literature review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines; the protocol has not been registered;[13] online supplemental material 1 corresponds to the PRISMA checklist. The search was conducted on PubMed (Medline), Embase and Cochrane (from 1 January 1966 to 18 October 2021) for original longitudinal observational research articles that reported GC (glucocorticoids is the MESH term) exposure in terms of (i) proportion of GC users in the cohort and/or (ii) GC use with dose information, as well as the occurrence of major organ damage reported as incidence as defined in the SDI. The following keywords 'overall damage', 'cataracts', 'cerebrovascular', 'stroke', 'cardiovascular', 'angina', 'myocardial infarction', 'coronary artery bypass', 'avascular necrosis', 'osteonecrosis', 'osteoporosis' or 'fractures' were used in respective combinations with the keyword 'lupus' (see online supplemental material 2). Articles excluded were those with a sample size smaller than 50, with an observation duration less than 60 months, and others not describing the proportion of patients with SLE who were exposed to GC and/or without definite elaboration of the dose and/or duration of GC exposure. Studies in which the disease started in childhood, those with selected populations based on organ involvement (eg, only patients with lupus nephritis, for example) or based on presence or absence of a specific damage item (eg, osteonecrosis or stroke) and others in which damage was not examined, either globally or for any of its individual components, were also excluded. For studies conducted using the same cohort/population, the most recent one, or the one that provided more detailed data on GC use was chosen. However, if the same cohort/population reported different outcomes in different articles, the relevant article was included for each outcome. Also, if two articles from the same cohort reported the SDI, and one of them reported one specific SDI domain and another domain was reported in the other article, only the most recent or the one that provide more detailed data on GC was included for the SDI analysis, but each of them was retained for the analysis of the specific domain item that they reported. Similarly, if the same cohort/population reported GC use in different ways in different articles, both articles were used but in separate analyses of the different GC use variable.

Disease duration was defined as the time that elapsed from the diagnosis of SLE to entry into the cohort whereas duration of follow-up was the time elapsing from entry into the cohort, to the time the analyses were conducted.

The literature search was conducted by two independent teams; the first one was constituted by MUG, GSA, CEF and CRS and the second one by AM, JWYL, NYK and BD. Both teams extracted the data in an electronic database in the form of an Excel spreadsheet. MUG and NYK collected the extracted data, checked for the accuracy of the data inputted and returned potentially problematic data to their respective literature searchers for verification. Subsequently, each team convened to resolve potential duplications, questions related to specific publications and conflicts of data extraction before finalising the dataset. Then, the data from both teams were again reviewed and collated by MUG's team. These data were then used for the various analyses. Figure 1 depicts the

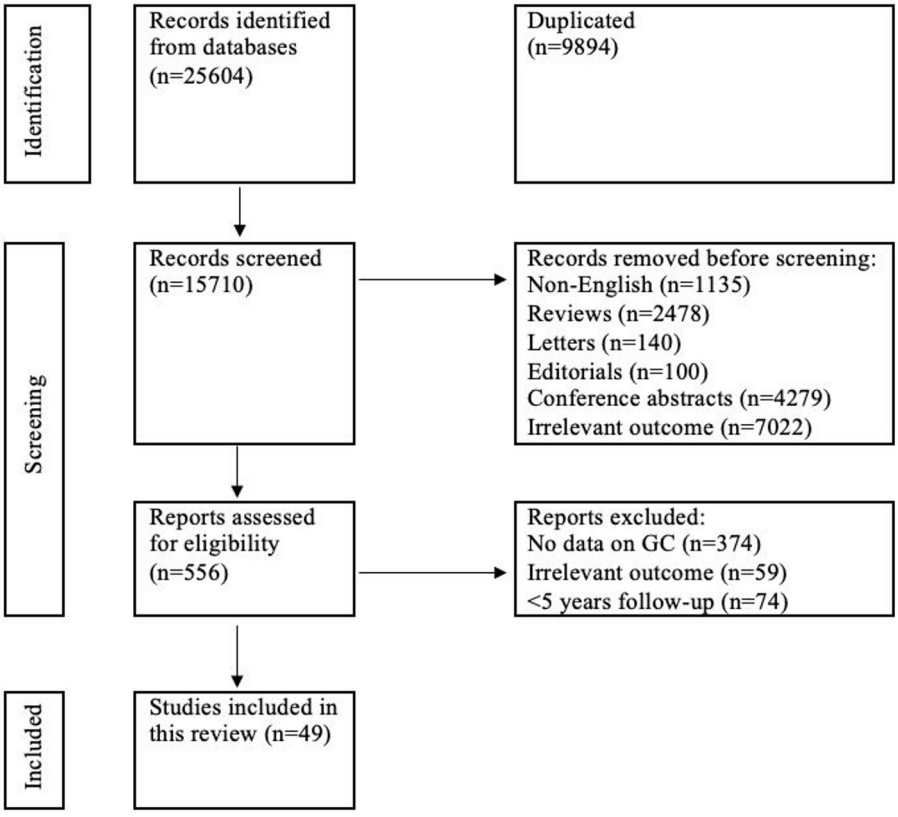

Figure 1 Identification of studies via databases and registries. GC, glucocorticoids.

steps taken in the selection of the articles included in these analyses according to the PRISMA guidelines.[13]

Evaluation of the quality of the studies

Following the PRISMA guidelines, the quality of the studies identified for this meta-regression analysis was assessed. To this end, the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, a tool specifically developed to assess the quality of observational studies was used. The scoring system covers three major domains: (1) selection of cohorts (maximum 4 points), (2) comparability of cohorts (maximum 2 points) and (3) ascertainment of either the exposure or the outcome of interest (maximum 3 points). The resulting score ranges from 0 to 9 with a higher score representing a better methodological quality. While there is no validated cut-off value to discern between studies of good or poor quality, studies with a score of ≥7 are arbitrarily considered high quality.[14] This grading was not used to either include or exclude a given study.

Statistical methods

The outcomes examined were the different types of damage including: (1) difference in average SDI scores between the beginning and the end of follow-up, (2) cataracts, (3) CVA, (4) MI, (4) overall CVE, (6) avascular necrosis/osteonecrosis and (7) osteoporosis and fractures (both had to be present). The rate of change in overall damage, as measured by the SDI, has been modelled with the rate scaled to represent *the rate of increase per 100 patient years*. Other damage rates have been scaled to represent rates in units of *patients developing damage per 100 patient years*. The analyses have been based on a random effects meta-regression model[15] with the logarithm of the rate of damage as the outcome variable and with treatment related variables and variables defining other cohort characteristics as explanatory variables.

Restricted maximum likelihood estimation of this regression model was implemented in the R package 'metafor', as described by Viechtbauer *et al*.[16] Further details on the methodology are provided in online supplemental material 3.

The treatment-related variables that have been extracted from the publications, when possible, are the following: (1) proportion of patients using GC, (2) average daily oral GC as prednisone/prednisone equivalent (PDN)) dose across patients (mg), (3) average cumulative GC as PDN dose across patients (per 10 g); (4) average cumulative GC as PDN dose across patients per year of follow-up (g) and (5) proportion of patients using parenteral GC (as methylprednisolone). Additional variables examined include: (1) year of publication, (2) average age at diagnosis, (3) average age at cohort entry and (4) average disease duration at cohort entry. For studies in which more than one group of patients was studied, each group was examined independently; this applied to 5 of the 49 selected articles[17–21] so that 54 cohorts are available for analysis.

Table 1 Data availability for overall and specific damage items

Outcome	Number of studies	Follow-up duration	GC, number	PDN, daily dose, mg	PDN, cumulative dose, g	Par. GC (methylprednisolone), number
SDI differences	29	29	24	10	16	3
Cataracts	17	17	14	5	10	3
CVA	15	15	12	2	4	3
MI	16	16	13	4	6	3
Overall CVE	18	18	17	6	9	3
Osteonecrosis	22	22	17	8	12	8
Osteoporosis and fractures	16	16	12	5	11	3

CVA, cerebrovascular accident; CVE, cardiovascular event; GC, glucocorticoids; MI, myocardial infarction; Par, parenteral; PDN, prednisone; SDI, SLICC Damage Index.

Pooled estimates of the rates of different types of damage from a simple meta-analysis model will be presented along with I^2 values which assess relative heterogeneity and an absolute measure of heterogeneity, τ^2.[22] Corresponding 'forest plots' associated with these estimates, including the estimates from the set of studies used for the meta-analysis, are provided as online supplemental material 4; 95% CI are also shown. From meta-regression models, transformed regression coefficients representing relative risk estimates along with 95% CI and significance levels are presented and R^2 values representing the estimated amount of heterogeneity explained were also calculated, although these should be interpreted cautiously with small sample sizes. Detailed plots of the log rates of damage vs the various potential moderators for the different damage types are provided in online supplemental material 5.

RESULTS

Out of 15 710 publications screened, 15 661 were excluded leaving 49 articles which involved 16 224 patients with SLE, 147 555 (90.9%) female and 1469 (9.1%) male, selected for these analyses (see figure 1 and online supplemental material 6 for details on the articles included (n=49) and the reasons for excluding the others (n=15 661)). Five of the 49 studies included were published prior to 2000, 10 between 2000 and 2009, 23 between 2010 and 2019 and 11 between 2020 and 2021. At study entry, patients included had a mean (SD) age of 35.1 (7.4) years and a mean disease duration of 37.1 (41.6) months; their mean follow-up time was 104.9 (49.4) months,[9 17–21 23–65] each mean calculated as a weighted average of cohort averages. Seventeen out of the 49 studies had a high quality (at least seven points in the NOS). The cohorts available provided data for one or more of the outcomes examined as noted in table 1. In this table, a summary of the amount of data available for the different types of damage is presented; the number of cohorts providing information on damage varies from 15 to 29.

Rates of damage

Table 2 presents overall estimates of the rates of damage and associated I^2 relative heterogeneity measures. As might be expected, there is evidence of substantial heterogeneity in these rates of damage accrual across studies (from 80.1% for MI to 99.2% for overall damage) given the variation in cohort characteristics. Absolute heterogeneity estimates varied from 0.30 for CVA to 0.64 for osteoporosis with fractures. The estimated rate for changes

Table 2 Estimated overall rates of observed damage

Outcome	Number of studies included	Rate* (95% CI)	I^2 (Percentage)	τ^2
Changes in SDI scores	29	9.89 (7.59 to 12.88)	99.2	0.50
Cataracts	17	0.95 (0.65 to 1.40)	91.5	0.51
CVA	15	0.53 (0.38 to 0.73)	85.1	0.30
MI	16	0.40 (0.27 to 0.59)	80.1	0.41
Overall CVE	18	1.09 (0.75 to 1.59)	92.5	0.55
Osteonecrosis	22	1.14 (0.82 to 1.60)	92.0	0.51
Osteoporosis and fractures	16	0.78 (0.50 to 1.22)	92.1	0.64

*Rate is patients developing damage per 100 patient years except for change in SDI which is rate of SDI change per 100 patient years.
CVA, cerebrovascular accident; CVE, cardiovascular events; I^2, heterogeneity; MI, myocardial infarction; SDI, SLICC Damage Index; τ^2, absolute heterogeneity.

Table 3 Univariate meta-regression results

Outcome	GC, proportion*	PDN, daily dose, mg	PDN, cumulative dose, 10 g	PDN, cumulative dose/year of follow-up, g	Par. GC (methylprednisolone), proportion
Changes in SDI Scores	0.81 (0.61 to 1.09) (0.161, 0%)	0.99 (0.92 to 1.07) (0.827, 0%)	0.90 (0.73 to 1.11) (0.316, 0.61%)	0.99 (0.86 to 1.13) (0.840, 0%)	0.76 (0.47 to 1.22) (0.258, 6.4%)
Cataracts	1.04 (0.88 to 1.23) (0.645, 0%)	1.03 (0.76 to 1.40) (0.846, 0%)	0.90 (0.57 to 1.43) (0.659, 0%)	0.96 (0.60 to 1.55) (0.880, 0%)	0.81 (0.29 to 2.29) (0.697, 0%)
CVA	1.38 (0.97 to 1.98) (0.075, 22.4%)		0.92 (0.63 to 1.34) (0.662, 0%)	0.81 (0.31 to 2.10) (0.666, 0%)	1.21 (0.60 to 2.42) (0.597, 0%)
MI	1.19 (0.84 to 1.69) (0.337, .8%)	0.92 (0.76 to 1.12) (0.411, 0%)	1.13 (0.32 to 3.97) (0.848, 0%)	0.44 (0.14 to 1.41) (0.167, 33.6%)	1.50 (0.43 to 5.24) (0.525, 0%)
Overall CVE	0.86 (0.70 to 1.07) (0.175, 19.1%)	**1.12** **(1.02 to 1.24)** **(0.019, 100%)**	1.43 (0.77 to 2.67) (0.258, 0%)	1.23 (0.93 to 1.62) (0.148, 0.7%)	0.86 (0.52 to 1.44) (0.573, 0%)
Osteonecrosis	**1.24** **(1.02 to 1.51)** **(0.033, 11.5%)**	1.141.12 (0.97 to 1.34) (0.118, 0%)	**1.67** **(1.22 to 2.29)** **(0.002, 49.3%)**	**1.23** **(1.12 to 1.34)** **(<0.001, 100.0%)**	1.71 (0.96 to 3.03) (0.066, 37.9%)
Osteoporosis and fractures	1.09 (0.82 to 1.44) (0.556, 0%)	**1.21** **(1.11 to 1.33)** **(<0.001, 86.7%)**	1.10 (0.63 to 1.89) (0.743, 0%)	1.33 (0.86 to 2.06) (0.197, 4.9%)	1.05 (0.74 to 1.50) (0.770, 0%)

Relative risks, confidence intervals (.) and p values plus R^2 values (…) for variables with information from three or more studies are presented. Potentially significant effects are bolded for a positive relationship (more drug, more damage) and they are in italics for a negative relationship (lower value, more damage).
*Analysed as log odds of proportion.
CVA, cerebrovascular accident; CVE, cardiovascular events; GC, glucocorticoids; MI, myocardial infarction; PDN, prednisone; SDI, SLICC Damage Index.

in the SDI scores per 100 patient years was 9.89 (95% CI 7.59 to 12.88), corresponding to an expected change for one patient in 1 year of 0.0989. For the development of specific damage (yes/no) per 100 patient years, the range of rates was from 0.40 (0.27 to 0.59) for MI to 1.14 (95% CI 0.82 to 1.60) for osteoporosis, corresponding to 0.40% and 1.14% of patients developing damage in a 1-year period.

The forest plots associated with these analyses are provided as online supplemental material 4.

Damage and treatment variables

Table 3 presents estimated relative risks associated with treatment related variables in univariate meta-regression models. Plots associated with these analyses are provided in online supplemental material 5. There are no demonstrable relationships between the use of GC and the occurrence of overall damage. When examining the different specific damage items, support for such association was found for CVE and the daily dose of PDN (mg/day) (1.12 (95% CI 1.02 to 1.24), p=0.019), based on six cohorts with virtually all the heterogeneity in rates explained. Osteonecrosis was demonstrably associated with the proportion of patients receiving GC (1.24 (95% CI 1.02 to 1.51, p=0.03)), based on 17 cohorts explaining 11.5% of the heterogeneity, and with the cumulative PDN dose, adjusted (g/year) or not (per 10 g increase) for the number of years of follow-up (1.67 (95% CI 1.22 to 2.29), p=0.002 and 1.23 (95% CI 1.12 to 1.34), p<0.001), based on 12 cohorts and explaining 49.3% and 100.0% of heterogeneity, respectively. Osteoporosis with fractures was associated with the daily dose of prednisone (mg/day) (1.21 (95% CI 1.11 to 1.33, p<0.001), based on five studies and explaining 86.7% of the heterogeneity although largely based on one small study with a high rate and high average dose.[61] A similar relationship was seen for the adjusted cumulative dose although, even with 11 studies, the estimated relationship was not significant.

Damage and other variables

Univariate meta-regression results for the additional potential moderating variables such as year of study, age at diagnosis and age at entry into the cohort are presented in table 4 with associated plots in online supplementary material 5. Of interest, the accrual of overall damage seems to decrease from the earlier publications to the most recent ones with comparable effects estimated for cataracts, CVA and MI, the latter being highly significant and cataracts and CVA not achieving 5% significance. In addition, age at cohort entry seems to play an important role in increasing the occurrence of CVE. As well, a later average age at diagnosis is associated with a higher rate

Table 4 Additional univariate meta-regression results

Outcome	Year of publication	Cohort, number	Average age at diagnosis (years)	Cohort, number	Age at entry (years)	Cohort, number	Disease duration at entry (months)	Cohort, number
SDI difference	*0.96 (0.92 to 1.00) (0.037, 10.2%)*	29	1.01 (0.99 to 1.04) (0.3351, 0%)	27	1.01 (0.99 to 1.04) (0.404, 0%)	28	1.00 (0.99 to 1.01) (0.972, 0%)	27
Cataracts	0.95 (0.88 to 1.02) (0.162, 2.3%)	17	**1.05 (1.00 to 1.09) (0.028, 22.0%)**	16	**1.04 (1.01 to 1.08) (0.023, 19.3%)**	17	1.01 (0.99 to 1.02) (0.372, 0%)	16
CVA	0.96 (0.92 to 1.00) (0.052, 22.6%)	15	1.02 (0.95 to 1.09) (0.555, 0%)	13	1.00 (0.95 to 1.05) (0.941, 0%)	15	1.00 (0.99 to 1.01) (0.356,0%)	13
MI	*0.95 (0.91 to 0.99) (0.018, 37.4%)*	16	**1.08 (1.04 to 1.13) (<0.001, 71.8%)**	14	**1.06 (1.00 to 1.12) (0.035, 30.3%)**	15	0.99 (0.98, 1.00) (0.175, 18.6%)	14
Overall CVE	0.99 (0.95 to 1.05) (0.831, 0%)	18	**1.06 (1.01 to 1.13) (0.031, 36.4%)**	15	**1.08 (1.04 to 1.12) (<0.001, 61.7%)**	17	1.01 (0.99 to 1.03) (0.081, 14.7%)	15
Osteonecrosis	1.00 (0.96 to 1.04) (0.93, 1.0%)	22	0.93 (0.86 to 1.00) (0.063, 9.7%)	21	0.97 (0.89 to 1.05) (0.41, 4,0%)	22	1.01 (1.00 to 1.02) (0.115, 3.1%)	21
Osteoporosis and fractures	1.00 (0.90 to 1.11) (0.97, 1.0%)	16	1.05 (0.99 to 1.12) (0.112, 14.0%)	16	**1.06 (1.01 to 1.12) (0.016, 36.0%)**	16	**1.02 (1.01 to 1.03) (0.003, 49.9%)**	16

Relative risks, CI (,) and p values plus R^2 values (…) for variables with information from three or more studies. Potentially significant effects are bolded for a positive relationship (higher value, more damage) and in italics for a negative relationship (lower value, more damage).

of CVE but this is heavily influenced by one study with a very high age at diagnosis.[32] Longer disease duration was found to be associated with osteoporosis with fractures, but this is largely the result of having one study with a high rate of damage and high average disease duration.[61] Other significant relationships in table 4 associated with age at diagnosis and age at entry are largely due to one or two cohorts with very much older ages. This can be visualised in online supplemental material 5 where explanatory variable plots are displayed. If cohorts with age at diagnosis or age at entry greater than 50 are excluded from the respective analyses, then no significant relationships are maintained except for the age at cohort entry relationship with CVE already mentioned.

As expected, the majority of patients in the cohorts were female and the limited variation in the proportion of females was not demonstrably associated with any measure of damage except osteoporosis with fractures which was highly significant based largely on one study[61] and, to some extent, cataracts with this relationship of lower rates in females generating a p value of 0.06 based on 17 studies. Plots related to the proportion of females are also included in online supplemental material 5.

Relationships between damage and GC related variables were unaltered by adjustment for other variables in selected multivariate analyses when sufficient data were available (results not shown).

Sensitivity analysis

Ten of the 49 articles, bolded in online supplemental material 6, in which the data for the intake of GC were only recorded at the baseline visit but not over time were removed, and the same analyses redone. The assumption for the primary analysis presented earlier is that the patients were taking a similar amount of GC over their follow-up, which may or may not have been the case. Nevertheless, there were, overall, no marked differences observed in comparison with the analysis in which all 49 articles were included (data not shown) except that the suggestive relationship between CVA and proportion of GC use entirely disappears (RR=0.96, 95% CI (0.62 to 1.49)) with the removal of three studies, two of which had a very low rate of damage and low rate of GC use.

DISCUSSION

In this comprehensive systematic literature review and meta-regression analysis, we have confirmed associations of the use of GC with the occurrence of damage in patients with SLE. This applies to overall CVE, osteonecrosis and osteoporosis and fractures but not to overall damage. For CVE, it was with the average daily PDN dose; for osteonecrosis, it was with the proportion of patients on GC, and with the average cumulative adjusted or unadjusted PDN dose/years of follow-up and for osteoporosis with fractures, it was with the average daily PDN dose. It is also noteworthy that in the most recent publications included in these analyses, less damage seems to have been accrued as compared with the older studies; that was the case for overall damage and MI. This has also been reported in the Toronto cohort, with a reduction of CVE from 11% (in patients followed from 1975 to 1992 to 3.8% in those followed from 1999 to 2016).[12] Whether this is due to the inclusion of patients with less severe

disease, better overall control of the inflammatory disease process or cardiovascular risk factors or a decrease in the use of GC is not readily apparent from the data reviewed. Younger age seems to protect against the occurrence of osteoporosis with fractures, whereas longer disease duration seems to favour their occurrence. In terms of gender, women seem to experience osteoporosis with fractures more frequently than men; however, as noted, this seems to be driven primarily by one study and thus the finding should be interpreted with caution.

Our findings are concordant with the clinical experience of those treating lupus patients as well as with the literature on the subject. The Hopkins Cohort, for example, has shown a higher cumulative average GC dose to be associated with damage accrual.[66] A higher cumulative dose of GC was also associated with a higher risk of cataracts and osteoporosis with fractures, even after adjusting for possible confounders.[7] Similarly, in an Australian study, Apostolopoulos *et al* reported that a higher dose of GC was associated with an increase of GC-related and non GC-related damage.[67] The independence of GC effects on damage accrual is supported by a large multicentre Asia Pacific cohort study which revealed strong associations between GC use and damage accrual in SLE, after adjustment for disease activity and, importantly, in a subgroup without evidence of active disease.[68] In two other case-control studies comparing patients with and without osteonecrosis, osteonecrosis was associated with the use and/or dose of GC.[69 70] These supporting articles were not included in our analysis because they did not fulfil our inclusion criteria; the Hopkins cohort reported the risk of damage as a function of the cumulative dose of PDN (dividing their patients into five groups) but did not provide the information for the entire group of patients;[66] the report from the Asia Pacific cohort had a median follow-up of 2.2 years[66] and the last two articles were case-control studies comparing patients with and without osteonecrosis and were excluded because they evaluated only selected populations.[69 70] It is also noteworthy that no association was found between damage accrual, more specifically osteonecrosis, and the use of intravenous methylprednisolone. Although this was based on few studies, it is also consistent with the results observed in the Hopkins[66] and Cruces cohorts.[17 25]

Our study has limitations. First, we need to consider that given the limited data available (only 49 studies in total and between two and 29 studies per outcome) and the potential for chance results due to multiple comparisons, the numerical results presented should be viewed with caution and not be overinterpreted. Second, it is also relevant to point out that the meta-regression methodology used is essentially an association study based on group (ie, cohort) characteristics. This contrasts to the methodologically more rigorous investigation of associations based on individual (ie, patient) characteristics, which is more common in meta-analyses and would be expected to provide more definitive conclusions. Group association studies are generally felt to be at risk of the so-called 'ecological' fallacy arising when other factors are associated with both the outcome (ie, damage) and the group characteristic used in the analysis (ie, GC use).[71] This is basically a type of confounding. For example, although not examined in this study, ethnicity might influence the rate of damage and (through, for example, different healthcare systems) the extent of GC treatment. This limitation arose because, after carefully reviewing the available literature, there were a small number of articles meeting our criteria for selection and the variability in, and sparsity of, the recording of GC use. Also, in a meta-regression, each cohort essentially provides only one data point for each analysis and thus its power is limited in any event. Third, an attempt was also made to develop a standardised GC variable as a single explanatory variable and thus increase the sample size, but that did not lead to any substantial increase in power. Fourth, there may also be some question about the suitability of the use of the cumulative GC dose variable in a study of rates as this is influenced by the length of follow-up time. This was the reason for including the cumulative dose per year variable. Fifth, we realise that the use of GC reflects disease activity which by itself may lead to damage. However, due to the lack of information about disease activity in many of the original studies included in this meta-regression, we have not been able to adjust for it in our analysis. Sixth, while some degree of overlap for patients from the same cohorts was possible, this is unlikely given that we have included only one article per outcome or per method of reporting GC use.

To conclude, in this comprehensive meta-regression analysis of longitudinal cohort studies, in spite of their limited number and considerable heterogeneity, we confirm associations of the use of GC with damage. This applies to CVE, osteonecrosis and osteoporosis with fractures. Our study highlights the difficulties in conducting such analyses[42] and suggests that the relationship between GC and damage is quite complex. Our aim should be to judiciously use GC to maximise their efficacy and minimise their harms.

Author affiliations
[1]Rheumatology, Hospital Nacional Guillermo Almenara Irigoyen, Lima, Peru
[2]Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistémicas, Universidad Cientifica del Sur, Lima, Peru
[3]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4]Division of Rheumatology, University Medicine Cluster, National University Health System, Singapore
[5]Department of Medicine, Changi General Hospital, Singapore
[6]Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[7]Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, LimaPeru
[8]Feinstein Institute for Medical Research, Manhasset, New York, USA
[9]Service de Rhumatologie, Centre National de Reference des Maladies Autoimmunes et Systemique Rares (CRMR RESO), INSERM UMR-S 1109, Université de Strasbourg, Strasbourg, France
[10]Lupus Center, Columbia University Medical Center, New York, New York, USA
[11]Rheumatology, Hanyang University Seoul Hospital, Seoul, South Korea
[12]Hanyang University Institute for Rheumatology Research, Seoul, South Korea

[13]Divisions of Rheumatology and Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Québec, Canada
[14]Centre for Epidemiology Versus Arthritis, Faculty of Biology Medicine and Health, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, UK
[15]NIHR Manchester Musculoskeletal Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[16]Grossman School of Medicine, New York University, New York, New York, USA
[17]Internal Medicine Department, Centre de référence maladies auto-immunes et systémiques rares d'île de France, Hopital Cochin, Paris, France
[18]Université Paris Descartes-Sorbonne, Paris, France
[19]INSERM U 1153, Center for Epidemiology and Statistics, Paris, France
[20]Thurston Arthritis Research Centre, University of North Carolina System, Chapel Hill, North Carolina, USA
[21]Division of Rheumatology, Department of Medicine, CHU du Québec - Université Laval, Quebec City, Quebec, Canada
[22]Medicine, SUNY Downstate Medical Center, Brooklyn, New York, USA
[23]Schroeder Arthritis Institute, Krembil Research Institute, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada
[24]Division of Rheumatology, Department of Medicine and Department of Pathology, Queen Elizabeth II Science Centre & Dalhousie University, Halifax, Nova Scotia, Canada
[25]Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey
[26]Centre for Rheumatology, Department of Medicine, University College London, London, UK
[27]Copenhagen Lupus and Vasculitis Clinic, 4242, Rigshospitalet, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[28]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA
[29]University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[30]Department of Clinical Sciences Lund, Rheumatology, Lund University, Lund, Sweden
[31]School of Medicine, University of California at San Diego, La Jolla, California, USA
[32]Medical University of South Carolina, Charleston, South Carolina, USA
[33]Department of Medicine, Division of Rheumatology, Emory University, Atlanta, Georgia, USA
[34]Faculty of Medicine, Nursing and Health, Monash University, Clayton, Victoria, Australia
[35]Rheumatology Unit, University of Pisa, Pisa, Toscana, Italy
[36]University of Manitoba, Winnipeg, Manitoba, Canada
[37]Rheumatology, Grupo Oroño-Centro Regional de Enfermedades Autoinmunes y Reumáticas (GO-CREAR), Sanatorio Parque S.A, Rosario, Santa Fe, Argentina
[38]Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA
[39]Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[40]City Hospital, Sandwell and West Birmingham NHS Trust, Birmingham, UK
[41]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[42]Autoimmune Diseases Research Unit, BioCruces Bizkaia Health Research Institute, University of the Basque Country, Barakaldo, Spain
[43]University of Toronto, Toronto, Ontario, Canada
[44]Division of Rheumatology, Department of Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada
[45]Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet/ Karolinska University Hospital, Stockholm, Sweden
[46]Faculty of Medicine, Division of Rheumatology, McGill University, Montreal, Quebec, Canada
[47]Department of Rheumatology and Clinical Immunology, University Medical Centres, Amsterdam, The Netherlands
[48]Department of Rheumatology and Clinical Immunology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Noord-Holland, The Netherlands
[49]Rheumatology, Cedars-Sinai Medical Center, West Hollywood, California, USA
[50]David Geffen School of Medicine Center, University of California, Los Angeles, Los Angeles, California, USA
[51]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[52]Lupus Center of Excellence, Allegheny Health Network, Pittsburgh, Pennsylvania, USA
[53]Division of Rheumatology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[54]Department of Psychology, Faculty of Arts and Social Sciences, National University of Singapore, Singapore
[55]MRC Biostatistics Unit, University of Cambridge, Cambridge, UK
[56]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA
[57]Department of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru

Twitter Manuel Francisco Ugarte-Gil @mugartegil, Laurent Arnaud @lupusreference, Ian N Bruce @Lupusdoc, Paul R Fortin @prfortin, Sung Sam Lim @lupusdoclim, Eric Morand @ericfmorand, Anisur Rahman @anisurrahman60, Ronald F van Vollenhoven @ronfvv and Susan Manzi @SueManzi

Contributors All authors were involved in drafting or revising this article critically for important intellectual content and have approved the final version to be published. MFU-G, VF and GA have full access to all of the data from the study and take responsibility for their integrity and the accuracy of the analyses performed. VF an GA are the guarantors

Funding This work was partially supported by a grant to the SLICC group from the Lupus Foundation of America, Inc.

Competing interests JB and RFvV are Editors-in-Chief of Lupus Science & Medicine.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Not applicable.

ORCID iDs
Manuel Francisco Ugarte-Gil http://orcid.org/0000-0003-1728-1999
Anselm Mak http://orcid.org/0000-0002-4688-7829
Cristina Reátegui-Sokolova http://orcid.org/0000-0003-3421-2717
Claudia Elera-Fitzcarrald http://orcid.org/0000-0001-7271-2523
Laurent Arnaud http://orcid.org/0000-0002-8077-8394
Anca D Askanase http://orcid.org/0000-0003-4597-5023
Sang-Cheol Bae http://orcid.org/0000-0003-4658-1093
Sasha Bernatsky http://orcid.org/0000-0002-9515-2802
Ian N Bruce http://orcid.org/0000-0003-3047-500X
Paul R Fortin http://orcid.org/0000-0002-7278-2596
Sung Sam Lim http://orcid.org/0000-0003-2361-0787
Eric Morand http://orcid.org/0000-0002-9507-3338
Bernardo A Pons-Estel http://orcid.org/0000-0003-2518-0266
Guillermo Ruiz-Irastorza http://orcid.org/0000-0001-7788-1043
Elisabet Svenungsson http://orcid.org/0000-0003-3396-3244
Murray Urowitz http://orcid.org/0000-0001-7506-9166
Evelyne Vinet http://orcid.org/0000-0001-7727-5879
Ronald F van Vollenhoven http://orcid.org/0000-0001-6438-8663
Daniel J Wallace http://orcid.org/0000-0002-2502-1372
Michelle A Petri http://orcid.org/0000-0003-1441-5373
Susan Manzi http://orcid.org/0000-0002-0803-6150

REFERENCES

1 Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med* 2008;358:929–39.
2 Groot N, Shaikhani D, Teng YKO, *et al*. Long-Term clinical outcomes in a cohort of adults with childhood-onset systemic lupus erythematosus. *Arthritis Rheumatol* 2019;71:290–301.
3 Mak A, Cheung MW-L, Chiew HJ, *et al*. Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. *Semin Arthritis Rheum* 2012;41:830–9.
4 Bruce IN, O'Keeffe AG, Farewell V, *et al*. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the systemic lupus international collaborating clinics (SLICC) inception cohort. *Ann Rheum Dis* 2015;74:1706–13.
5 Doria A, Rinaldi S, Ermani M, *et al*. Health-Related quality of life in Italian patients with systemic lupus erythematosus. II. Role of clinical, immunological and psychological determinants. *Rheumatology* 2004;43:1580–6.
6 Mak A, Isenberg DA, Lau C-S. Global trends, potential mechanisms and early detection of organ damage in SLE. *Nat Rev Rheumatol* 2013;9:301–10.
7 Davidson JE, Fu Q, Rao S, *et al*. Quantifying the burden of steroid-related damage in SLE in the Hopkins lupus cohort. *Lupus Sci Med* 2018;5:e000237.
8 Kasturi S, Sammaritano LR. Corticosteroids in lupus. *Rheum Dis Clin North Am* 2016;42:viii:47–62.
9 Zonana-Nacach A, Barr SG, Magder LS, *et al*. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801–8.
10 Watson P, Brennan A, Birch H, *et al*. An integrated extrapolation of long-term outcomes in systemic lupus erythematosus: analysis and simulation of the Hopkins lupus cohort. *Rheumatology* 2015;54:623–32.
11 Kuan WP, Li EK, Tam L-S. Lupus organ damage: what is damaged in Asian patients? *Lupus* 2010;19:1436–41.
12 Urowitz MB, Su J, Gladman DD. Atherosclerotic vascular events in systemic lupus erythematosus: an evolving story. *J Rheumatol* 2020;47:66–71.
13 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
14 Wells G, Shea B, O'connell D, *et al*. The Newcastle–Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
15 DerSimonian R, Laird N. Meta-Analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
16 Viechtbauer W. Conducting Meta-Analyses in *R* with the metafor Package. *J Stat Softw* 2010;36:1–48.
17 Ruiz-Arruza I, Lozano J, Cabezas-Rodriguez I, *et al*. Restrictive use of oral glucocorticoids in systemic lupus erythematosus and prevention of damage without worsening long-term disease control: an observational study. *Arthritis Care Res* 2018;70:582–91.
18 Sheane BJ, Gladman DD, Su J, *et al*. Disease outcomes in Glucocorticosteroid-Naive patients with systemic lupus erythematosus. *Arthritis Care Res* 2017;69:252–6.
19 Aljohani R, Gladman DD, Su J, *et al*. Comparison of systemic lupus erythematosus (SLE) patients managed early after diagnosis in specialty versus community care clinics. *Clin Rheumatol* 2017;36:1773–8.
20 Aljohani R, Gladman DD, Su J, *et al*. Disease evolution in late-onset and early-onset systemic lupus erythematosus. *Lupus* 2017;26:1190–6.
21 Appenzeller S, Pereira DA, Costallat LTL. Greater accrual damage in late-onset systemic lupus erythematosus: a long-term follow-up study. *Lupus* 2008;17:1023–8.
22 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
23 Cervera R, Khamashta MA, Font J, *et al*. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine* 2003;82:299–308.
24 Guarize J, Appenzeller S, Costallat LTL. Skin damage occurs early in systemic lupus erythematosus and independently of disease duration in Brazilian patients. *Rheumatol Int* 2007;27:483–7.
25 Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, *et al*. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. *Rheumatology* 2014;53:1470–6.
26 Tarr T, Papp G, Nagy N, *et al*. Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens disease outcome in systemic lupus erythematosus. *Clin Rheumatol* 2017;36:327–33.
27 Bertoli AM, Vilá LM, Alarcón GS, *et al*. Factors associated with arterial vascular events in profile: a multiethnic lupus cohort. *Lupus* 2009;18:958–65.
28 Mok CC, Lau CS, Wong RW. Neuropsychiatric manifestations and their clinical associations in southern Chinese patients with systemic lupus erythematosus. *J Rheumatol* 2001;28:766–71.
29 Mok CC, Tse SM, Chan KL, *et al*. Effect of the metabolic syndrome on organ damage and mortality in patients with systemic lupus erythematosus: a longitudinal analysis. *Clin Exp Rheumatol* 2018;36:389–95.
30 Ibañez D, Gladman DD, Urowitz MB. Adjusted mean systemic lupus erythematosus disease activity Index-2K is a predictor of outcome in SLE. *J Rheumatol* 2005;32:824–7.
31 Sugano N, Ohzono K, Masuhara K, *et al*. Prognostication of osteonecrosis of the femoral head in patients with systemic lupus erythematosus by magnetic resonance imaging. *Clin Orthop Relat Res* 1994;305:190–9.
32 Bartels CM, Buhr KA, Goldberg JW, *et al*. Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. *J Rheumatol* 2014;41:680–7.
33 Prasad R, Ibañez D, Gladman D, *et al*. Anti-dsDNA and anti-Sm antibodies do not predict damage in systemic lupus erythematosus. *Lupus* 2006;15:285–91.
34 Yee C-S, Su L, Toescu V, *et al*. Birmingham SLE cohort: outcomes of a large inception cohort followed for up to 21 years. *Rheumatology* 2015;54:836–43.
35 Legge A, Kirkland S, Rockwood K, *et al*. Prediction of damage Accrual in systemic lupus erythematosus using the systemic lupus international collaborating clinics frailty index. *Arthritis Rheumatol* 2020;72:658–66.
36 Urowitz MB, Gladman DD, Ibañez D, *et al*. Effect of disease activity on organ damage progression in systemic lupus erythematosus: University of Toronto lupus clinic cohort. *J Rheumatol* 2021;48:67–73.
37 Segura BT, Bernstein BS, McDonnell T, *et al*. Damage accrual and mortality over long-term follow-up in 300 patients with systemic lupus erythematosus in a multi-ethnic British cohort. *Rheumatology* 2020;59:524–33.
38 Gladman DD, Urowitz MB, Rahman P, *et al*. Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol* 2003;30:1955–9.
39 Manzi S, Meilahn EN, Rairie JE, *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;145:408–15.
40 Kwon HH, Bang SY, Won S, *et al*. Synergistic effect of cumulative corticosteroid dose and immunosuppressants on avascular necrosis in patients with systemic lupus erythematosus. *Lupus* 2018;27:1644–51.
41 Nossent JC. SLICC/ACR damage index in Afro-Caribbean patients with systemic lupus erythematosus: changes in and relationship to disease activity, corticosteroid therapy, and prognosis. *J Rheumatol* 1998;25:654–9.
42 Swaak AJ, van den Brink HG, Smeenk RJ, *et al*. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. *Rheumatology* 1999;38:953–8.
43 Cassano G, Roverano S, Paira S, *et al*. Accrual of organ damage over time in Argentine patients with systemic lupus erythematosus: a multi-centre study. *Clin Rheumatol* 2007;26:2017–22.
44 Hammad M, Eissa M, Fathi S. Possible risk factors associated with greater damage in systemic lupus erythematosus patients: an Egyptian multicenter study. *Lupus* 2016;25:1019–27.
45 Furie RA, Wallace DJ, Aranow C, *et al*. Long-Term safety and efficacy of belimumab in patients with systemic lupus erythematosus: a continuation of a Seventy-Six-Week phase III parent study in the United States. *Arthritis Rheumatol* 2018;70:868–77.
46 Shaharir SS, Chua SH, Mohd R, *et al*. Risk factors for symptomatic avascular necrosis (AVN) in a multi-ethnic systemic lupus erythematosus (SLE) cohort. *PLoS One* 2021;16:e0248845.
47 Nikfar M, Malek Mahdavi A, Khabbazi A, *et al*. Long-Term remission in patients with systemic lupus erythematosus. *Int J Clin Pract* 2021;75:e13909.
48 Garelick D, Pinto SM, Farinha F, *et al*. Fracture risk in systemic lupus erythematosus patients over 28 years. *Rheumatology* 2021;60:2765–72.
49 Hanly JG, Li Q, Su L, *et al*. Cerebrovascular events in systemic lupus erythematosus: results from an international inception cohort study. *Arthritis Care Res* 2018;70:1478–87.
50 Sharma C, Raymond W, Eilertsen G, *et al*. Association of achieving lupus low disease activity state fifty percent of the time with both reduced damage Accrual and mortality in patients with systemic lupus erythematosus. *Arthritis Care Res* 2020;72:447–51.

51 Tselios K, Gladman DD, Su J, *et al*. Impact of the new American College of Cardiology/American heart association definition of hypertension on atherosclerotic vascular events in systemic lupus erythematosus. *Ann Rheum Dis* 2020;79:612–7.
52 Doğan I, Kalyoncu U, Kiliç L, *et al*. Avascular necrosis less frequently found in systemic lupus erythematosus patients with the use of alternate day corticosteroid. *Turk J Med Sci* 2020;50:219–24.
53 Shaharir SS, Hussein H, Rajalingham S, *et al*. Damage in the multiethnic Malaysian systemic lupus erythematosus (SLE) cohort: comparison with other cohorts worldwide. *PLoS One* 2016;11:e0166270.
54 Urowitz MB, Gladman DD, Ibañez D, *et al*. Evolution of disease burden over five years in a multicenter inception systemic lupus erythematosus cohort. *Arthritis Care Res* 2012;64:132–7.
55 Cardoso CRL, Signorelli FV, Papi JAS, *et al*. Initial and accrued damage as predictors of mortality in Brazilian patients with systemic lupus erythematosus: a cohort study. *Lupus* 2008;17:1042–8.
56 Tselios K, Gladman DD, Touma Z, *et al*. Disease course patterns in systemic lupus erythematosus. *Lupus* 2019;28:114–22.
57 Signorini V, Tani C, Elefante E, *et al*. How do systemic lupus erythematosus patients with very-long disease duration present? analysis of a monocentric cohort. *Lupus* 2021;30:439–47.
58 Cozen L, Wallace DJ. Avascular necrosis in systemic lupus erythematosus: clinical associations and a 47-year perspective. *Am J Orthop* 1998;27:352–4.
59 Kao AH, Lertratanakul A, Elliott JR, *et al*. Relation of carotid intima-media thickness and plaque with incident cardiovascular events in women with systemic lupus erythematosus. *Am J Cardiol* 2013;112:1025–32.
60 Tselios K, Gladman DD, Su J, *et al*. Evolution of risk factors for atherosclerotic cardiovascular events in systemic lupus erythematosus: a longterm prospective study. *J Rheumatol* 2017;44:1841–9.
61 García-Carrasco M, Mendoza-Pinto C, León-Vázquez MdelaL, *et al*. Incidence of vertebral fractures in women with systemic lupus erythematosus after 8 years of follow-up. *Calcif Tissue Int* 2017;101:291–9.
62 Carli L, Tani C, Spera V, *et al*. Risk factors for osteoporosis and fragility fractures in patients with systemic lupus erythematosus. *Lupus Sci Med* 2016;3:e000098.
63 Chen S, Cai Q, Xu Y, *et al*. Associations between glucocorticoids, antiphospholipid antibodies and femur head necrosis in patients with SLE: a directed acyclic graph-based multicentre study. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211002677.
64 Al Sawah S, Zhang X, Zhu B, *et al*. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins lupus cohort. *Lupus Sci Med* 2015;2:e000066.
65 Lima K, Legge A, Hanly JG, *et al*. Association of the systemic lupus international collaborating clinics frailty index and damage Accrual in long standing systemic lupus erythematosus. *Arthritis Care Res* 2021. doi:10.1002/acr.24798. [Epub ahead of print: 30 Sep 2021].
66 Thamer M, Hernán MA, Zhang Y, *et al*. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009;36:560–4.
67 Apostolopoulos D, Kandane-Rathnayake R, Raghunath S, *et al*. Independent association of glucocorticoids with damage accrual in SLE. *Lupus Sci Med* 2016;3:e000157.
68 Apostolopoulos D, Kandane-Rathnayake R, Louthrenoo W, *et al*. Factors associated with damage accrual in patients with systemic lupus erythematosus with no clinical or serological disease activity: a multicentre cohort study. *The Lancet Rheumatology* 2020;2:e24–30.
69 Tse SM, Mok CC. Time trend and risk factors of avascular bone necrosis in patients with systemic lupus erythematosus. *Lupus* 2017;26:715–22.
70 Gladman DD, Urowitz MB, Chaudhry-Ahluwalia V, *et al*. Predictive factors for symptomatic osteonecrosis in patients with systemic lupus erythematosus. *J Rheumatol* 2001;28:761–5.
71 Morgenstern H. Uses of ecologic analysis in epidemiologic research. *Am J Public Health* 1982;72:1336–44.