Association between organ damage and mortality in systemic lupus erythematosus: a systematic review and meta-analysis

Irene B Murimi-Worstell,1,2 Dora H Lin,3 Henk Nab,4 Hong J Kan,5 Oluwadamilola Onasanya,2,6 Jonothan C Tierce,1,2 Xia Wang,7 Barnabas Desta,7 G Caleb Alexander,1,2,8 Edward R Hammond7

ABSTRACT

Objective At least half of patients with systemic lupus erythematosus (SLE) develop organ damage as a consequence of autoimmune disease or long-term therapeutic steroid use. This study synthesises evidence on the association between organ damage and mortality in patients with SLE.

Design Systematic review and meta-analysis.

Methods Electronic searches were performed in PubMed, Embase, Cochrane Library and Latin American and Caribbean Health Sciences Literature for observational (cohort, case-control and cross-sectional) studies published between January 2000 and February 2017. Included studies reported HRs or ORs on the association between organ damage (measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score) and mortality. Study quality was assessed using the modified Newcastle-Ottawa assessment. Pooled HRs were obtained using the DerSimonian and Laird random-effects model. Heterogeneity was assessed using the Cochrane Q (Q) and I² statistics.

Results The search yielded 10 420 articles, from which 21 longitudinal studies were selected. Most studies (85%) were of high quality. For 10 studies evaluating organ damage (SDI) as a continuous variable and reporting HR as a measure of association, a 1-unit increase in SDI was associated with increased mortality; pooled HR was 1.34 (95% CI: 1.24 to 1.44, p<0.001; Q p=0.027, I²=52.1%). Exclusion of one potential outlying study reduced heterogeneity with minimal impact on pooled HR (1.33 (95% CI: 1.25 to 1.42), p<0.001, Q p=0.087, I²=42.0%). The 11 remaining studies, although they could not be aggregated because of their varying patient populations and analyses, consistently demonstrated that greater SDI was associated with increased mortality.

Conclusions Organ damage in SLE is consistently associated with increased mortality across studies from various countries. Modifying the disease course with effective therapies and steroid-sparing regimens may reduce organ damage, improve outcomes and decrease mortality for patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with a reported prevalence of 20 to 150 cases per 100 000 persons.1 SLE is a chronic and debilitating disease characterised by flares, progressive end organ damage2 and increased mortality.3 SLE affects multiple organ systems,4 including the kidneys, the skin, and

Strengths and limitations of this study

► We report a systematic review with meta-analysis of high-quality studies across four continents that demonstrates a consistent association between systemic lupus erythematosus (SLE)-related organ damage and increased mortality.

► To our knowledge, this is the first meta-analysis informed by a systematic literature review investigating the association between organ damage, assessed by SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index), and mortality in patients with SLE.

► A meta-analysis was performed on 10 of 21 identified studies because of variations in methods used across studies; however, we observed consistency in the association between organ damage and mortality across multiple study design types with varying analytical methods.

► Although our search strategy was limited to studies published between 2000 and 2017, it is unlikely that inclusion of studies published after 2017 would change the observed result significantly, because of the consistency of the association between organ damage and mortality informed by the long patient follow-up periods of the studies analysed.

► Statistical evidence of study heterogeneity was identified, potentially attributable to the few studies included in the meta-analysis; however, exclusion of a potential outlying study reduced between-study heterogeneity to moderate, with minimal impact on the pooled association between organ damage and mortality.
the cardiovascular, musculoskeletal and central nervous systems. Approximately half of all patients with SLE will have some form of organ damage within 10 years of their diagnosis.

Furthermore, patients with SLE experience a higher rate of mortality and earlier mortality than the general population.

SLE mortality is an important outcome to patients and providers and may be affected by accumulation of SLE-related organ damage. Organ damage potentially occurs through different mechanisms. Hyperactive B cells are known to increase the formation and deposition of autoantibodies and immune complexes, which induce inflammatory tissue damage in the microvasculature. In addition, long-term corticosteroid use is associated with an increased risk for the accumulation of organ damage, such as osteoporosis and cardiovascular disease. Despite well-recognized adverse effects, corticosteroids are still widely used, in part because there is no optimal treatment for SLE.

Published literature suggests that the extent of accumulated organ damage in patients with SLE is associated with poorer health outcomes, including decreased physical functioning, reduced health-related quality of life and increased mortality. Although there have been studies that report mortality in patients with SLE and organ damage, the extent to which organ damage is associated with increased mortality is unknown. We sought to aggregate available evidence on the association between organ damage, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), and mortality in SLE, and risk of mortality through systematic review and meta-analysis.

METHODS AND ANALYSIS
This systematic literature review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines. Methods of the inclusion criteria and analysis were specified in advance and documented in a study protocol, which underwent internal organisational review and approval prior to study initiation.

Literature search and screen
A systematic literature search of PubMed, Embase, Cochrane Library and Latin American and Caribbean Health Sciences Literature was performed to identify studies published between January 2000 and February 2017 that evaluated the association between organ damage (measured by SDI) and mortality, and the association between organ damage and health-related quality of life, in adults with SLE. This report presents findings on the association between organ damage and mortality. Results regarding the association between organ damage and health-related quality of life have been presented separately.

Search terms were chosen based on relevant free text keywords and Medical Subject Headings or Emtree-controlled vocabulary related to SLE and mortality. Details of the search terms for each database are provided in online supplementary appendix 1. Handsearching and citation review of relevant studies were conducted but did not identify additional studies that were not captured by the electronic database search.

Inclusion criteria included observational and case-control studies, cross-sectional studies and systematic reviews. Exclusion criteria included the following: non-English language articles, study designs that did not report original, population-level measures of association and studies of patients <18 years of age. Case series, case reports and studies with limited populations that are not generalisable were also excluded. Full inclusion/exclusion criteria are provided in online supplementary appendix 2. Clarivate Analytics EndNote X7 was used to organise the study titles and abstracts downloaded from the databases. One reviewer screened article titles and abstracts for selection according to inclusion and exclusion criteria. After article selection was complete, a panel of three investigators, working independently, re-examined 20% of the included articles to validate the quality of the initial selection process. Once validated, a full-text screening was conducted by two reviewers working independently to obtain the final set of articles.

Data extraction
Data extraction was performed by two independent reviewers, and discordances were adjudicated by a third independent reviewer. Data extraction forms were created for capturing study characteristics and outcomes reported in the identified studies, including characteristics such as the study country, organ damage, baseline SDI scores and duration of follow-up, which would inform interpretation of the associations of interest. Study quality was assessed using the modified Newcastle-Ottawa quality assessment scale.

Data synthesis and meta-analysis
The primary quantitative analyses focused on longitudinal cohort studies that assessed the risk of mortality per unit change in SDI. Pooled HRs were obtained using the DerSimonian and Laird random-effects model. A narrative evidence synthesis approach was used for studies that evaluated organ damage as binary based on varying SDI cut-points (SDI=0 vs >0; SDI≤2 vs >2; SDI≤3 vs ≥3 or SDI≤5 vs ≥5) and that also reported varying measures of association, ORs and HRs. Heterogeneity was assessed across studies using the Cochrane $Q$ and $I^2$ statistics, with consideration given to clinical judgement. Cochrane $Q$ tests with $P$ values <0.10 suggest statistically significant heterogeneity, whereas cut-offs of 25%, 50% and 75% on the $I^2$ statistic are routinely used to demarcate low, medium and high levels of heterogeneity, respectively. Sensitivity
analyses were performed to assess the effect of studies with outlying effect estimates. A funnel plot of included studies that reported HRs was visually inspected and Egger’s test was used to quantify publication bias, where p<0.05 was considered statistically significant.

Patient and public involvement
Neither patients nor the public were involved in the design and conduct of the study. Dissemination of our findings, however, targets a wide audience including patients and members of the public and those who read peer-reviewed publications.

RESULTS
Characteristics of included studies
The combined literature search for mortality and health-related quality of life outcomes yielded 10 420 articles. We identified 1127 articles for full-text review. A total of 21 longitudinal cohort studies were selected that evaluated the association between organ damage and mortality in patients with SLE (figure 1).

Table 1 summarises key characteristics of these 21 identified studies (more detailed study characteristics are provided in online supplementary appendix 3). A total of 20 studies were identified that examine the association between organ damage and quality of life; these findings will be published separately.

The selected studies varied by sample size (ranging from 105 to 1241 patients), geographical location, duration of follow-up and methods by which the association between organ damage measured by SDI and mortality was evaluated.

Five studies reported on populations from North America; the remaining 16 reported on populations from Asia, Europe or South America. In 11 of the 21 studies, the mean or median reported age of participants (at either study enrolment, SLE onset or SLE diagnosis) was between 30 and 40 years; six studies contained study groups (eg, patients with late-onset SLE) with a mean or median age >40 years, and four contained study groups with mean age <30 years. The populations studied were predominantly female (78% to 97%). The follow-up periods varied across studies—the shortest mean and median follow-up periods were 1.7 years and 3.3 years, respectively. The longest mean and median follow-up periods were 36 years and 26 years, respectively.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Last year of data collection</th>
<th>Sample size</th>
<th>Follow-up duration (years), mean (median) [SD or range]</th>
<th>Baseline SDI, mean (median) [SD or range]</th>
<th>Associations between organ damage (SDI) and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Estimator (95% CI)* Reference group Covariates†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mok et al 2003</td>
<td>aSLE: 213</td>
<td>Max 13</td>
<td>Year 1</td>
<td>aSLE: 0.4 [0.7]</td>
<td>HR 3.65 (1.32 to 8.76)</td>
</tr>
<tr>
<td></td>
<td>LSLE: 22</td>
<td></td>
<td></td>
<td>LSLE: 1.0 [1,1]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All: 285</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-point SDI increase in Year 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernández et al 2006</td>
<td>AA: 221</td>
<td>Max 12</td>
<td>Baseline, by race</td>
<td>OR 1.19 (1.02 to 1.39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: 176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H-PR: 103</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H-T: 117</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernández et al 2006</td>
<td>AA: 221</td>
<td>Max 12</td>
<td>Baseline, by race</td>
<td>OR 1.19 (1.02 to 1.39)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: 176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H-PR: 103</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>H-T: 117</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hitchon, Peschken 2001</td>
<td>C: 240</td>
<td>NS</td>
<td>At diagnosis</td>
<td>RR 1.7 (0.8 to 3.7)§</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AO: 22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FN: 68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All: 330</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urowsitz et al 2005</td>
<td>All: 1241</td>
<td>[9–36]</td>
<td></td>
<td>HR 1.24 (1.14 to 1.35)‡‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>I: 36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>II: 27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>III: 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV: 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardoso et al 2007</td>
<td>Alive: 86</td>
<td>(6.3)</td>
<td></td>
<td>Baseline HR 1.34 (1.14 to 1.58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died: 19</td>
<td>[0.3–7.0]</td>
<td></td>
<td>Study end HR 1.35 (1.16 to 1.57)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All: 105</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.32 (1.09 to 1.60)‡‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jönsen et al 2007</td>
<td>MLC: 499</td>
<td>[1–50]</td>
<td></td>
<td>MLC HR 1.20 (0.97 to 1.48)§</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LLC: 170</td>
<td></td>
<td></td>
<td>LLC HR 1.40 (1.19 to 1.64)§</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All: 669</td>
<td></td>
<td></td>
<td>All HR 1.48 (1.37 to 1.60)§‡‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kang et al 2007</td>
<td>1010</td>
<td>Max 11</td>
<td></td>
<td>OR 19.7 (5.3 to 72.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez et al 2007</td>
<td>NS</td>
<td>350</td>
<td></td>
<td>HR 1.70 (p=0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gafter-Gvili et al 2010</td>
<td>143</td>
<td>9.4 [3.3, 1–19]</td>
<td></td>
<td>HR 1.28 (1.08 to 1.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telles et al 2009</td>
<td>179</td>
<td>(3.3)</td>
<td></td>
<td>HR 1.40 (1.08 to 1.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruce et al 2012</td>
<td>671</td>
<td>NS</td>
<td></td>
<td>HR 1.46 (1.18 to 1.81)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joo et al 2012</td>
<td>979</td>
<td>7.2 [4.3, 0–15]</td>
<td></td>
<td>HR 1.2 (1.0 to 1.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manger et al 1999</td>
<td>338</td>
<td>(5.4)</td>
<td></td>
<td>RR 7.7 (3.3 to 18.6) maize</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
Assessment of study quality

Most studies (85%) analysed were of high quality as measured using the Newcastle-Ottawa Scale (online supplementary appendix 4).13–21 23 24 26–30 32 All 21 studies scored high regarding selection of patients who were representative of the population of adults with SLE in each country. All studies relied on secure clinical records to determine SLE diagnoses and extent of organ damage. Study quality differed with regard to analysis and follow-up cohort retention. Analyses were rated as adequate in 15 studies that adjusted for age and at least one other factor related to mortality;13 15 16 18–21 23 24 26–30 32 the remaining studies either were not age adjusted (three studies),14 17 31 were only adjusted for age (two studies);5 25 or had no description of adjustment (one study).22 In eight studies, less than 20% of the cohort was lost to follow-up,5 13 17 19 20 24–26 30 and nine studies lost more than 20% to follow-up.5 15 19 21–23 27–29 31
Mortality in patients with SLE

In all of the studies reviewed, standardised mortality ratios (SMRs) or survival rates were reported for patients with SLE. Four studies reported SMRs for patients with SLE relative to the general population within a specific country (online supplementary appendix 5). The SMRs reported ranged from 2.4 over a 12-year period in a Swedish cohort, 2.9 in a Korean cohort over a 5-year period and 2.4 and 2.7 over 5-year and 10-year periods, respectively, in a German cohort. Urowitz et al reported on a cohort of Canadian patients with SLE and estimated a 36-year overall SMR of 4.5 in patients with SLE compared with the general population. When this study population was stratified into cohorts based on time of study entry, the reported SMRs varied widely: the 1970 to 1979 and 1996 to 2005 entry cohorts had 10-year SMRs of 12.6 and 3.5, respectively.

Eight studies reported survival rates; six studies reported 5-year survival rates (range: 87% to 99%, in populations/subpopulations from Germany, China, the USA, South Korea and Hungary), and two studies reported 4-year and 12-year survival rates of 95% (Latin America) and 80% (Sweden), respectively.

Organ damage and mortality

Table 1 summarises the key findings of the 21 included studies regarding organ damage and mortality (full data shown in online supplementary appendix 5). Baseline mean SDI scores ranged from 0.1 to 1.0 (SD range: 0.6 to 1.5). Across studies, SDI was evaluated as a continuous variable or binary category to assess the association between organ damage and mortality; SDI was evaluated as a continuous variable in 14 studies and as a binary category (comparing risk of mortality at various SDI score cutoffs) in eight studies. One study evaluated SDI both as a continuous variable and a binary category (table 1).

Meta-analysis of organ damage and mortality

SDI evaluated as a continuous variable

Fourteen studies evaluated SDI as a continuous predictor of mortality. Of these, 10 performed time-to-event analyses and reported the risk of death per 1-unit increase in SDI. These represent the group of studies that were pooled for meta-analysis. Figure 2 is a forest plot of HRs across the 10 studies included in the meta-analysis. Findings from meta-analysis suggest a 34% increased risk of death for each 1-point increase in SDI score (pooled HR 1.34, 95% CI: 1.24 to 1.44, p<0.001; Cochrane Q p=0.027, I²=52.1%).

To account for study heterogeneity, the data were analysed excluding Mok et al which evaluated 213 Chinese patients over the course of 13 years and reported a notably greater risk of mortality per 1-unit SDI increase than other studies (HR 3.65, 95% CI: 1.52 to 8.76, p=0.004). The exclusion of the Mok et al study reduced heterogeneity to moderate (Cochrane Q p=0.087, I²=42.0%) but had minimal impact on pooled HR (pooled HR of mortality for a 1-unit increase in SDI=1.33 (95% CI: 1.25 to 1.42, p<0.001), figure 2).

A funnel plot representing HR of organ damage and mortality in patients with SLE was used to evaluate population bias (online supplementary appendix 6). Visual inspection of the funnel plot (excluding Mok et al) identified marginal asymmetry, suggesting publication bias, whereas an Egger’s test did not suggest publication bias (p>0.05). These findings should be interpreted with consideration given the few studies included in the meta-analysis.

In addition to the studies summarised above in the meta-analysis, three studies that evaluated SDI as a continuous variable reported ORs for a 1-point increase in SDI; these ORs were 1.19 (95% CI: 1.02 to 1.39, p=0.031), 1.70 (95% CI: 0.80 to 3.70, p=0.054) and 19.70 (95% CI: 5.30 to 72.50, p<0.001) (figure 3). The largest likelihood of mortality observed suggests approximately 20-fold increased odds of mortality for a 1-point increase in organ damage, among 1010 patients evaluated in South Korea.

SDI evaluated as binary categories

Of eight analyses that evaluated SDI as binary categories, two assessed the odds of death associated with any organ damage compared with no organ damage (SDI=0 vs SDI≥1), and four studies, compared the risk of mortality by various SDI categories (SDI<2 vs SDI≥2; SDI<3 vs SDI≥3 or SDI<5 vs SDI≥5) (figure 3). Pons-Estel et al studied 1214 patients from Latin America (including 537 mestizo, 507 white and 152 African-Latin American patients) who had been diagnosed with SLE within the previous 2 years. Over a median follow-up period of 20 months, Pons-Estel et al reported increased odds of death associated with any organ damage, SDI≥1 vs SDI=0, in patients with SLE (OR 2.8, 95% CI: 1.2 to 6.4). In Spain, Martínez-Barrio et al studied 276 patients with adult-onset SLE and 77 patients with late-onset
SLE over a mean 26-year follow-up period and reported significantly increased odds of death associated with any organ damage, SDI=0 vs SDI>0 (OR 12, 95% CI: 1.6 to 92, p=0.01). Other studies reported the odds of death associated with having an SDI≥2 vs SDI<2 (208 patients from Sweden; HR 3.80, 95% CI: 1.30 to 16.40, p=0.01),30 SDI≥3 vs SDI<3 (105 patients from Brazil; HR 4.74, 95% CI: 1.55 to 14.51, p=0.006)24 or SDI≥5 vs SDI<5 (357 patients from Hungary; HR 55.12, 95% CI: 19.15 to 158.63, p<0.001).17 In the study by Becker-Merok and Nosseen18 from Norway (n=158), the authors reported a positive association between greater organ damage and increased mortality risk (SDI≥2 vs SDI<1, HR 1.44, 95% CI: 0.67 to 3.09, p=0.42), although this was not statistically significant.

Two studies identified that additional organ damage accrued during study follow-up was significantly associated with increased risk of mortality.21 24 In the study by Cardoso et al24 including 105 patients from Brazil, any increase in SDI during follow-up was associated with a significant increase in risk of mortality compared with no change in SDI (HR 5.1, 95% CI: 1.99 to 13.03, p=0.001).24 Similarly, in 338 patients in Germany, Manger et al36 found nearly eightfold increase in mortality with organ damage accrual (ASDI≥2 vs ASDI<2 from the first to the third year of follow-up; relative risk 7.7, 95% CI: 3.3 to 18.6, p<0.0001).

Danila et al29 evaluated the association between specific organ damage and mortality in a multi-ethnic cohort of 635 patients from the USA. This analysis identified significantly greater risk of earlier death for patients with SLE who had renal damage compared with those without renal damage (HR 1.65, 95% CI: 1.03 to 2.66, p=0.05). There was, however, no significant association between cardiovascular damage and earlier death (HR 1.55, 95% CI: 0.94 to 2.56, p=0.05).29

## Discussion

In this meta-analysis of 10 studies from four continents that evaluated the risk of death among individuals with SLE who had organ damage, we identified that each 1-unit increase in SDI was associated with a 34% increased risk of death. We also identified an increased risk and consistent association between increasing organ damage and greater mortality in all 21 articles that were retained for this systematic review. The increased risk of death associated with organ damage was present across studies from various countries and different patient populations, as well as across studies that used varying epidemiological and statistical methods. It is notable that the association between incremental organ damage and mortality was largely consistent, despite the differences in healthcare delivery systems and life expectancy across countries. The magnitude of the estimated associations between organ damage and mortality varied and may be attributable to differences in how SDI was modelled (eg, as a continuous variable or binary category), the thresholds of SDI used for analysis, and the choice of covariates accounted for when multivariable analyses were performed.

From 1950 to 2000, the 10-year survival rate in patients with SLE has improved from 63% to 91%,37 and it is postulated that improvements in patient management are responsible for these gains in survival. Despite such positive achievements, it is clear that further gains are needed. Optimising treatment to obtain good control of SLE disease is important for reducing organ damage and mortality risk. For treatment of patients with SLE, the Treat to Target (T2T)/SLE international task force has outlined several overarching principles, including optimising disease control, minimising comorbidities, reducing drug toxicities to enable long-term survival, preventing organ damage and enhancing health-related quality of life.38

The T2T task force highlighted the importance of minimising glucocorticoid dosages and eliminating them entirely, if possible. As with other rheumatological diseases, studies of patients with SLE have shown that greater systemic steroid dosage is associated with increasing damage to multiple body systems.8 New treatments for SLE that would allow steroid sparing would be clinically important for reducing organ damage and improving outcomes for patients.

To our knowledge, this is the first meta-analysis informed by a systematic literature review to quantitatively synthesise published literature on SLE-related organ damage measured by SDI and its association with mortality. We observed some heterogeneity in the studies included in these meta-analyses. However, sensitivity analyses demonstrated that exclusion of one study,26
which reported a notably greater HR than other studies, reduced heterogeneity with minimal impact on pooled HR. The search criteria excluded studies published in languages other than English, which may represent a bias in reporting; however, there is limited evidence to suggest language bias with this approach. Morrison et al conducted a comprehensive literature review and found no evidence of systematic bias from the use of language restrictions in systematic review-based meta-analyses. Because our search strategy was restricted to the inclusion of publications identified between 2000 and 2017, if there are relevant studies published after 2017, they are not included in this analysis. This is a limitation of our work; however, because of the consistency of our findings across a large number of studies and geographical regions, and long patient follow-up periods for included studies ranging from a few years to 50 years, it is unlikely that studies published after 2017, or in languages other than English, would significantly affect the observed association between organ damage and mortality. An update on the available evidence in the next few years would allow an expanded assessment of the effect of newer treatments on organ damage and how this may be associated with mortality in patients with SLE. In the current study, we were unable to summarise across all identified studies using meta-analytic methods because of variations in methods used across studies. Ten of 21 studies were combined in meta-analysis and the remaining 11 studies were summarised qualitatively. The consistency of the results across multiple study design types and varying methods of analyses corroborates our overall conclusions.

A previous qualitative review, based on studies prior to 2012, supports our findings. A systematic review by Sutton et al included five studies examining the association between organ damage and risk of death in patients with SLE. All five studies confirmed a positive association between higher SDI scores and mortality. For example, one study included in the Sutton meta-analysis found a significantly higher 10-year mortality rate (25%) in patients with early damage (SDI ≥ 1 at enrolment) than in patients with no early damage (7.3%, p<0.001). Biological therapy has recently become available for the treatment of SLE. However, none of the studies we evaluated examined how specific drugs may mediate the association between organ damage and mortality, perhaps because of the relatively short period since biologics were introduced for SLE. Thus, future studies assessing the impact of various SLE therapies, including steroids and biologic treatment, on organ damage and consequent mortality will be needed.

CONCLUSIONS
Organ damage in patients with SLE is consistently associated with increased mortality across studies from around the world that evaluated different patient populations using various study methods. Novel therapies that are potentially disease modifying and steroid sparing could reduce organ damage, improve overall outcomes and decrease mortality for patients with SLE.

Author affiliations
1Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
2Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
3Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Champaign, Illinois, USA
4Inflammation & Autoimmunity, AstraZeneca, Cambridge, UK
5Center for Population Health IF, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
6Department of Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA
7BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, Maryland, USA
8Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Acknowledgements
Medical writing and editing support was provided by Bryony Jones, PhD, and Ellen Stoltzfus, PhD, of JK Associates, Inc, in accordance with Good Publication Practice (GPP3) guidelines (http://www.icmnp.org/gpp3).

Contributors
IBMW, DHL, HN, HJK, JCT, WX, BD, GCA and ERH were involved in the conception and design of the review. IBMW and DHL developed the search strategy and performed study selection. IBMW, DHL and OO extracted data from included studies. IBMW, DHL, HN, HJK, OJ, JCT, WX, BD, GCA and ERH were involved in the data analysis. All authors (IBMW, DHL, HN, HJK, OO, JCT, WX, BD, GCA and ERH) were involved in the interpretation and discussion of results. All authors drafted the manuscript, contributed to the drafting of the review and/or revised it critically for important intellectual content. All authors approved the final version of the article. All authors had access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. ERH is the guarantor.

Funding
AstraZeneca provided funding for this systematic review and the medical writing support.

Competing interests
All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work. HN was an employee of AstraZeneca when this work was performed. HJK is a shareholder of GlaxoSmithKline. WX, BD and ERH are employees of AstraZeneca. GCA is Chair of the FDA’s Peripheral and Central Nervous System Advisory Committee, has served as a paid advisor to IQVIA, serves on the advisory board of MassRx Innovations, is a member of OptumRx’s National P&T Committee and holds equity in Monument Analytics, a healthcare consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies.

Patient consent for publication
Not required.

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. No additional data available.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES