Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis

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Abstract

Background: Systemic lupus erythematosus (SLE) patients are at high risk for depression and anxiety. However, the estimated prevalence of these disorders varies substantially between studies. This systematic review aimed to establish pooled prevalence levels of depression and anxiety among adult SLE patients.

Methods: We systematically reviewed databases including PubMed, Embase, PsycINFO, and the Cochrane database library from their inception to August 2016. Studies presenting data on depression and/or anxiety in adult SLE patients and having a sample size of at least 60 patients were included. A random-effect meta-analysis was conducted on all eligible data.

Results: A total of 59 identified studies matched the inclusion criteria, reporting on a total of 10828 adult SLE patients. Thirty five and thirteen methods of defining depression and anxiety were reported, respectively. Meta-analyses revealed that the prevalence of major depression and anxiety were 24% (95% CI, 16%-31%, I^2 = 95.2%) and 37% (95% CI, 12%-63%, I^2 = 98.3%) according to clinical interviews. Prevalence estimates of depression were 30% (95% CI, 22%-38%, I^2 = 91.6%) for the Hospital Anxiety and Depression Scale with thresholds of 8 and 39% (95% CI, 29%-49%, I^2 = 88.2%) for the 21-Item Beck Depression Inventory with thresholds of 14, respectively. The main influence on depression prevalence was the publication years of the studies. In addition, the corresponding pooled prevalence was 40% (95% CI, 30%-49%, I^2 = 93.0%) for anxiety according to the Hospital Anxiety and Depression Scale with a cutoff of 8 or more.

Conclusions: The prevalence of depression and anxiety was high in adult SLE patients. It indicated that rheumatologists should screen for depression and anxiety in their patients, and referred them to mental health providers in order to identify effective strategies for preventing and treating depression and anxiety among adult SLE patients.

Keywords: Depression, Anxiety, Meta-analysis, Systematic review

Background

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune, connective-tissue disorder with frequent psychological comorbidities, of which depression and anxiety are two common manifestations [1, 2]. It has been reported that there were 2 times higher prevalence of depression in SLE patients compared to the general population [3]. In addition, previous study has reported that the anxiety disorders were twice as prevalent among SLE patients as compared to the controls [4]. Depression and anxiety often have profound impacts on SLE patients’ health and well-being including increased incidence of cardiovascular diseases [5], myocardial infarction [6], suicidal ideation [7], physical disability [8], decreased quality of life [9, 10], and a higher risk of premature mortality [11]. Therefore, depression and anxiety may be useful targets for interventions aimed at improving subjective health and quality of life in individuals with SLE. However, current epidemiological evidence found that the prevalence of depression and/or anxiety...
in SLE patients ranged widely from 2% to 91.7% in different studies [12, 13]. This vast inter-study difference was previously attributed to multiple factors, including study quality, unclear definition of depression or anxiety, diverse screening strategies used across studies [14]. Reliable estimates of depression and anxiety prevalence are important for informing efforts to prevent, treat, and identify causes of depression and anxiety among SLE patients. Recent meta-analyses have estimated the overall prevalence of depression and/or anxiety in rheumatoid arthritis and osteoarthritis patients [14, 15]. There has only been one previous systematic review of psychiatric symptoms in SLE [16]; however, no systematic review was conducted to quantify the prevalence of depression and anxiety in SLE using meta-analysis techniques. Our goal was to address this limitation. The objectives of this systematic review were (i) to establish pooled prevalence levels of depression and anxiety among adult SLE patients; (ii) to provide a summary of the methods used to define depression and anxiety in SLE; and (iii) to explore the impacts of study characteristics on prevalence estimates.

**Methods**

This systematic review was conducted within the Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [17] and followed a predetermined registered protocol (PROSPERO: CRD42016044125).

**Search strategy**

A systematic review of published literature in scientific journals that reported on the prevalence of depression and/or anxiety among SLE patients was conducted by two independent reviewers using the following databases from their inception to August 2016: PubMed, Embase, PsycINFO, and the Cochrane database library. The computer-based searches combined terms related to SLE patients and study design with those related to depression or anxiety (see Additional file 1). We conducted citation chasing search strategy with all reference lists of included articles and relevant review papers were considered to identify potentially omitted articles. Finally, we corresponded with the authors for further information if we encountered articles just provided the mean and standard deviation of the depression and/or anxiety assessment scale.

**Inclusion and exclusion criteria**

Studies were included if they met the following criteria: (i) cross-sectional design, baseline cross-sectional data from a longitudinal study or baseline cross-sectional data from a trial, before group allocation; (ii) used validated methods (clinical interviews or self-report instruments) to assess depression or anxiety; and (iii) the sample size was no less than 60.

Case reports, review articles, animal studies, studies investigating neuropsychiatric syndromes, studies in languages other than English and papers not dealing with SLE patients were excluded. For this meta-analysis, studies using pediatrics sample or screening tools without stating the cut-off thresholds used to detect depression or anxiety were also excluded. Table 2 and Table 3 presented a full list of the eligible methods of detecting depression and anxiety, alongside the numbers of articles utilizing each method and the number of participants assessed.

**Data extraction and quality assessment**

Two researchers read the relative studies independently by the titles and abstracts to exclude the references which did not meet the inclusion criteria. Then, they read full texts in the remaining studies as mentioned above, and determined whether these references included were final studies or not. When multiple publications spanned the years of longitudinal studies, baseline prevalence levels were reported. The following information was independently extracted from each article by other two trained investigators using a standardized form: year, country, mean disease duration, percentage of female participants, sample size, average age of participants, criteria for detection of depression and anxiety, and reported prevalence of depression and/or anxiety. If we encountered multiple publications from the same cohort, we used the data from the most recent or the paper reporting data from the largest number of participants. The methodological quality of each study included in the present meta-analysis was assessed using a modified version of the Newcastle-Ottawa Scale [18]. Studies were judged to be at low risk of bias (≥3 points) or high risk of bias (<3 points). Any disagreements in data extraction and quality assessment were resolved through discussion between the two reviewers or adjudication with a third reviewer.

**Outcome measures**

The outcomes were major/minor depression and affective/dysthymic/adjustment/anxiety disorder diagnosed with a structured clinical assessment [e.g., Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or International Classification of Diseases (ICD)-10] or depression and/or anxiety assessed with validated assessment tools [e.g., the Hospital Anxiety and Depression Scale (HADS), the Centre for Epidemiologic Studies Depression Scale (CES-D)] (see Additional file 2).

**Statistical analyses**

Because random-effects models tended to provide wider confidence intervals (CI) and were preferable in the
presence of between-study heterogeneity, we used a random-effects meta-analysis to pool studies reporting the prevalence of depression and/or anxiety in SLE patients [19]. Between-study heterogeneity was assessed by the I^2 with thresholds of ≥25%, ≥50% and ≥75% indicating low, moderate and high heterogeneity, respectively [20]. The influence of individual study on the overall prevalence estimate was explored by serially excluding each study in sensitivity analyses. Wherever possible, subgroup analyses were planned by overall study quality, sample size, country of origin and publication year, if there was more than one study in the subgroup. Pearson's and Spearman's correlation analyses were used to assess the association between variables and prevalence of depression and anxiety in people with SLE. Funnel plots and Egger's test were combined to explore the potential publication bias in this meta-analysis [21, 22]. Statistical analyses were performed with STATA version 12.0. Statistical tests were 2-sided and used a significance threshold of P<0.05.

**Results**

**Search results**

Fig. 1 provided the details of the study selection process. The initial search identified a total of 3347 potentially relevant articles. After removal of duplicates, titles and then abstracts were screened for potential eligibility. From this, 121 were considered in the full-text review, of which 59 articles met the inclusion criteria, and a full reference list was presented in Additional file 3. Inter-rater reliability of reviewers regarding study relevancy was high (Kappa = 0.87).

**Study characteristics**

A summary of the included study characteristics was shown in Table 1. A total of 59 identified studies matched the inclusion criteria, reporting on a total of 10828 adult SLE patients. Twenty took place in North America, 18 in Asia, 12 in Europe, 6 in South America, 1 in Oceania, and 1 in Africa. The median of mean ages was 39 years (range, 30.0-50.1), and the median percentage of females represented in the sample was 93%.
| Study ID          | Country        | Disease duration, mean ± SD/median range | Women, % | Sample size | Age, mean ± SD/median (range), years | Criteria for detection of anxiety (cutoff) | Anxiety prevalence, % | Criteria for detection of depression (cutoff) | Depression prevalence, % | NOS |
|------------------|----------------|------------------------------------------|----------|-------------|--------------------------------------|-------------------------------------------|------------------------|-----------------------------------------------|----------------------------|-----|
| Abdul-Sattar 2015 | Egypt          | 10.0 ± 4.6 years                         | 95%      | 80          | 309 ± 11.7                           | CES-D (>16.7)                            | 43.75                  |                                |                             | 2   |
| Appenzeller 2009  | Brazil         | 64.5 ± 48.5 months                      | 94.6%    | 167         | 32.1 ± 11.0                          | 21 Item-BDI (≥10)                         | 20.9                   |                                |                             | 2   |
| Bachen 2009       | USA            | 15.4 ± 9.7 years                         | 100%     | 326         | 47.9 ± 11.3                          | DSM-IV                                   | 64                     |                                |                             | 2   |
| Bogdanovic 2015   | Serbia         | 6.8 ± 2.9 years                          | 100%     | 60          | 43.4 ± 12.8                          | 21 Item-BDI (≥16/≥20/≥30)                | 91.7/70/3.3            |                                |                             | 2   |
| Calderon 2014     | Chile          | Median: 32.0 (0–243.0) months           | 100%     | 82          | Median: 36.0 (17.0–64.0)             | HADS (≥8)                                | 37                     |                                |                             | 2   |
| Cho 2014          | South Korea    | NS                                       | 90.1%    | 201         | 41.3 ± 13.2                          | CES-D (≥16)                              | 39.3                   |                                |                             | 3   |
| Chin 1998         | Malaysia       | 4.1 ± 3.5 years                          | 95%      | 79          | 31.1 ± 9.1                           | ICD-9 and DSM-III                        | 76                     |                                |                             | 2   |
| Da Costa 2005     | Canada         | 13.8 ± 10.1 years                        | 100%     | 100         | 45.4 ± 14.0                          | CES-D (≥16)                              | 31                     |                                |                             | 3   |
| Doria 2004        | Italy          | 9.9 ± 6.3 years                          | 87.3%    | 126         | 389 ± 11.9                           | HAS (≥6/≥15)                             | 746/27                 |                                |                             | 2   |
| Duvdevany 2011    | Israel         | 11.4 ± 9.1 years                         | 88%      | 100         | 370 ± 11.8                           | HADS (≥8)                                | 20                     |                                |                             | 2   |
| García-Carrasco   | Mexico         | 106.5 ± 85.5 months                      | 100%     | 106         | 405 ± 12.0                           | CES-D (≥16)                              | 38.8                   |                                |                             | 2   |
| García-Carrasco 2013 | Mexico         | 10.5 ± 7.4 years                        | 100%     | 105         | 436 ± 11.3                           | CES-D (≥16)                              | 33                     |                                |                             | 2   |
| Greco 2009        | USA            | 16.3 ± 7.0 years                         | 100%     | 161         | 501 ± 10.0                           | CES-D (≥16)                              | 27                     |                                |                             | 2   |
| Hanly 2015        | Canada         | 5.6 ± 4.8 years                          | 88.9%    | 1827        | 35.1 ± 13.3                          | DSM-IV                                  | 12.7                   |                                |                             | 4   |
| Harrison 2006     | USA            | 15.3 ± 3.2 years                         | 100%     | 93          | 433 ± 13.7                           | CES-D (≥27)                              | 16.1                   |                                |                             | 2   |
| Huang 2007        | China          | 7.5 ± 6.9 years                          | 91.5%    | 129         | 374 ± 10.7                           | HADS (≥8)                                | 32                     |                                |                             | 2   |
| Menon 2002        | Canada         | NS                                       | NS       | 103         | NS                                    | 21 Item-BDI (≥17)                        | 39.8                   |                                |                             | 1   |
| Jarpa 2011        | Chile          | Median: 5.0 (0.1–40.0) years             | 90.8%    | 87          | Median: 39.0 (16.0–27.0)             | DSM-IV                                  | 18.1                   |                                |                             | 3   |
| Julian 2011       | USA            | 15.8 ± 9.3 years                         | 93%      | 150         | 488 ± 12.3                           | ICD-10 and DSM-IV                        | 84.9                   |                                |                             | 2   |
| Jung 2015         | Korea          | 6.8 ± 4.4 years                          | 93%      | 100         | 40.6 ± 10.3                           | 21 Item-BDI (≥21)                        | 13                     |                                |                             | 2   |
| Katz 2011         | USA            | 13.6 ± 8.5 years                         | 100%     | 716         | 48.1 ± 12.6                           | CES-D (≥24)                              | 25                     |                                |                             | 3   |
| Karol 2013        | USA            | NS                                       | 93%      | 127         | 38.1 ± 12.3                           | 21 Item-BDI (≥18)                        | 41.7                   |                                |                             | 2   |
| Karimifar 2013    | Iran           | 4.1 ± 0.5 years                          | 80%      | 100         | 34.8 ± 10.9                           | 21 Item-BDI (≥14)                        | 60                     |                                |                             | 2   |
| Kheirandish 2015   | Iran           | 9.0 ± 7.7 years                          | 92.2%    | 166         | 33.1 ± 11.1                           | Cattell questionnaire (≥221)              | 84.9                   |                                |                             | 2   |
| Study Year | Country | Age Range | Gender | Sample Size | Depressive Symptom Measure | Depression Diagnosis |
|-----------|---------|-----------|--------|-------------|----------------------------|---------------------|
| Kotsis 2014 | Greece | 13.2 ± 9.1 years | 84% | 75 | 44.1 ± 13.3 | PHQ-9 (≥10) | 29.3 |
| Kim 2015 | USA | 12.0 ± 8.0 years | 93% | 89 | 39.0 ± 15.0 | CES-D (≥16) | 63 |
| Lapteva 2006 | USA | 13.8 ± 10.2 years | 75% | 60 | 41.0 ± 13.0 | DSM-IV | Major depressive disorder: 16.6 |
| Lisitsyna 2014 | NS | 134.9 ± 8.8 months | 85.6% | 180 | 34.6 ± 0.93 | ICD-10 | Major depressive disorder: 24.4, dysthymic disorder: 25.6, adjustment disorders: 18.9 |
| Mak 2011 | Singapore | 54.9 ± 70.7 months | 88% | 60 | 40.5 ± 12.9 | HADS (≥8) | 22 |
| Maneeton 2013 | Thailand | 6.1 ± 4.8 years | 98% | 62 | 31.8 ± 9.0 | HAS (≥14) | 37.1 |
| Mirbagheri 2016 | Iran | 8.3 ± 3.8 years | 100% | 77 | 36.5 ± 10.1 | HADS (≥8) | 71.4 |
| Monaghan 2007 | Australia | 10.2 ± 8.7 years | 97% | 60 | 44.4 ± 12.2 | HADS (≥8) | 44 |
| Montero-López 2016 | Spain | 0.2 ± 0.7 years | 100% | 97 | 38.6 ± 9.3 | SCL-90-R | 41 |
| Nery 2008 | Brazil | 9.8 ± 6.5 years | 100% | 71 | 34.8 ± 10.1 | SCID for DSM-IV | 465 |
| Neville 2014 | Canada | 10.2 ± 9.5 years | 92.4% | 612 | 46.8 ± 10.7 | SCID for DSM-IV | Major depressive disorder: 40.8 |
| Palagini 2014 | Italy | 15.0 ± 8.0 years | 100% | 81 | 43.6 ± 11.2 | SAS (>44) | 173 |
| Panopalis 2010 | USA | 13.8 ± 8.9 years | 91% | 807 | 47.6 ± 13.1 | CES-D (≥16) | 385 |
| Pettersson 2015 | Sweden | Median: 120 years | 92% | 305 | Median: 48 | HADS (≥8) | 34 |
| Postal 2016 | Brazil | Median: 9.0 (0–33.0) years | 96.7% | 153 | Median: 30.0 (10.0–62.0) | 21 Item-BDI (≥14/≥20/≥29) | 45.7/30.7/18.9 |
| Radhakrishan 2011 | India | NS | 100% | 100 | 18-60 | SCID for DSM-IV | 51 |
| Roebuck-Spencer 2006 | USA | 13.8 ± 10.2 years | 80% | 60 | 41.3 ± 12.8 | 21 Item-BDI (≥14) | 20 |
| Segal 2012 | USA | 12.0 ± 2.3 years | 93% | 71 | 41.7 ± 1.5 | CES-D (≥16) | 39 |
| Sehlo 2013 | Saudi Arabia | 6.9 ± 4.2 years | 100% | 80 | 34.8 ± 11.2 | SCID for DSM-IV | Major depressive disorder: 11.25 |
| Sfikakis 1998 | Greece | 7.8 ± 6.4 years | 91.5% | 71 | 37.9 ± 13.0 | HAS (>17) | 239 |
| Shakeri 2015 | Iran | NS | 92.5% | 160 | 43.0 ± 6.2 | 21 Item-BDI (≥20/≥21/≥26) | 81.2/51.9/18.1 |
| Shen 2015 | China | NS | 91.2% | 156 | 32.9 ± 10.2 | Zung SAS (≥250) | 2051 |
| Skare 2014 | Brazil | 8.2 ± 6.9 years | 93% | 100 | 39.2 ± 12.5 | 21 Item-BDI (≥19/≥20/≥26) | 21/2 |
| Shortill 1995 | England | 11.0 ± 7.1 years | 95% | 80 | 41.0 ± 11.2 | HADS (≥8) | 39 |
| Stoll 2001 | Switzerland | 11.4 ± 9.0 years | 90% | 60 | 44.5 ± 15.4 | HADS (≥8) | 22 |
| Tam 2008 | China | 9.7 years | 95.9% | 291 | 42.0 ± 12.0 | HADS (≥8) | 409 |
| Tay 2015 | Singapore | 72.3 ± 81.1 months | 86.4% | 110 | 38.7 ± 12.6 | HADS (≥8) | 409 |
| Study          | Country   | Median Age          | Prevalence | Duration | HADS ≥ 8 | HADS ≥ 13 | HADS ≥ 17 | BDI ≥ 14 | BDI ≥ 16 | BDI ≥ 21 | Anxiety Scale | Depression Scale |
|---------------|-----------|---------------------|------------|----------|----------|-----------|-----------|----------|----------|----------|---------------|------------------|
| Tench 2000    | England   | Median: 36.0 (12.0–79.5) months | 100%        | 120      | Median: 38.0 (32.0–45.0) | 60         | 37        | 23.8     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| Tjensvoll 2010 | Norway   | 12.3 ± 8.6 years | 87%        | 63       | 43.4 ± 13.3 | 21 Item-BDI (≥13) | 21 Item-BDI (≥14) | 40.7     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| Utset 2014    | USA       | Median: 9 years    | 95%        | 344      | >18      | CES-D (≥10) | CES-D (≥17) | 54.5     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| van Exel 2013 | Netherlands | 7.8 ± 7.0 years | 88.2%      | 102      | 444 ± 12.5 | 21 Item-BDI (≥14) | 21 Item-BDI (≥14) | 40.7     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| Vina 2015     | USA       | 143.2 ± 117.8 months | 93%        | 343      | 44.4 ± 12.9 | CES-D (≥17) | CES-D (≥17) | 54.5     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| Weder-Cisneros 2004 | USA       | Mean: 97.0 (6–348) months | 91.4%      | 81       | 31.2 ± 9.7 | 21 Item-BDI (≥14) | 21 Item-BDI (≥14) | 40.7     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| Xie 2012      | China     | Median: 1.3 years  | 93.7%      | 285      | 34.0 ± 13.0 | 21 Item-BDI (≥14) | 21 Item-BDI (≥14) | 54.5     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |
| Zakeri 2012   | Iran      | NS                  | 90.5%      | 71       | >18      | 21 Item-BDI (≥14) | 21 Item-BDI (≥14) | 54.5     | 27       | 47.2     | 59.3/40.7/19.3   | 60/9.4           |

NS: not stated; CES-D: Centre for Epidemiological Studies Depression Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; DSM-III/IV: Diagnostic and Statistical Manual of Mental Disorders, Third/Fourth Edition; HADS: Hospital Anxiety and Depression Scale; ICD: International Classification of Diseases; HAS: the Hamilton Anxiety Scale; HDS: the Hamilton Depression Scale; PHQ: Patient Health Questionnaire; SCID: Structured Clinical Interview for Diagnostic and Statistical Manual; SCL-90-R: Symptoms Checklist-90-Revised; Zung SAS: Zung Self-rating Anxiety Scale; Zung SDS: Zung Self-rating Depression Scale.
(range, 75%–100%). In addition, the median number of participants per study was 100 (range, 60–1827), and the median of mean disease duration was 9 years (range, 0.22–16.3). Depression was defined in 35 different ways (Table 2). Seventeen studies assessed for depression using the 21 Item-Beck Depression Inventory (BDI), with sixteen different thresholds were presented in the articles. Thirteen articles used the CES-D; six different cut-off points were presented, and the most commonly used being 16. Twelve used the HADS with a cutoff of 8 or more, and 6 used other screening tools. Ten studies assessed for major depression using diagnostic criteria.

**Table 2**: Methods of detecting depression and summary of prevalence and heterogeneity findings

| Tool                | Definition/cutoff | No. of studies | No. of participants | Prevalence, % (95% CI) | Heterogeneity I², % |
|---------------------|-------------------|----------------|---------------------|------------------------|---------------------|
| DSM and/or ICD      |                   |                |                     |                        |                     |
| Major depressive disorder | 10               | 2960           | 24 (16, 31)         | 95.2                   |                     |
| Dysthymic disorder  | 6                 | 922            | 12 (5, 18)          | 93.4                   |                     |
| Adjustment disorder | 2                 | 280            | 20 (15, 24)         | 0.0                    |                     |
| Minor depression    | 1                 | 150            | 6 (2, 10)           | -                      |                     |
| HADS                | ≥8                | 12             | 1474               | 30 (22, 38)            | 91.6                |
| CES-D               | >10               | 1              | 344                | 55 (49, 60)            | -                   |
|                     | ≥16               | 8              | 1640               | 38 (32, 44)            | 81.3                |
|                     | >16.7             | 1              | 80                 | 44 (33, 55)            | -                   |
|                     | ≥17               | 1              | 343                | 47 (42, 52)            | -                   |
|                     | ≥24               | 1              | 716                | 25 (22, 28)            | -                   |
|                     | >27               | 1              | 93                 | 16 (9, 24)             | -                   |
| 21 Item-BDI         | ≥5                | 2              | 451                | 61 (56, 66)            | 17.7                |
|                     | ≥10               | 1              | 167                | 21 (15, 27)            | -                   |
|                     | ≥11               | 1              | 81                 | 35 (24, 45)            | -                   |
|                     | ≥13               | 1              | 63                 | 24 (13, 34)            | -                   |
|                     | ≥14               | 6              | 781                | 39 (29, 49)            | 88.2                |
|                     | ≥16               | 2              | 131                | 76 (45, 107)           | 95.4                |
|                     | ≥17               | 1              | 103                | 40 (30, 49)            | -                   |
|                     | ≥18               | 1              | 127                | 42 (33, 50)            | -                   |
|                     | ≥19               | 1              | 100                | 21 (13, 29)            | -                   |
|                     | ≥20               | 2              | 213                | 50 (12, 89)            | 96.8                |
|                     | ≥21               | 3              | 545                | 34 (2, 65)             | 98.8                |
|                     | ≥29               | 1              | 153                | 19 (13, 25)            | -                   |
|                     | ≥30               | 3              | 326                | 5 (0, 9)               | 72.1                |
|                     | ≥31               | 1              | 160                | 39 (31, 46)            | -                   |
|                     | ≥32               | 1              | 71                 | 9 (3, 16)              | -                   |
|                     | >40               | 1              | 160                | 21 (14, 27)            | -                   |
| HDS                 | ≥8                | 1              | 126                | 41 (32, 49)            | -                   |
|                     | ≥11               | 1              | 62                 | 45 (33, 58)            | -                   |
|                     | ≥16               | 1              | 126                | 2 (0, 5)               | -                   |
|                     | >17               | 1              | 71                 | 20 (10, 29)            | -                   |
| PHQ-9               | ≥10               | 1              | 75                 | 29 (19, 40)            | -                   |
| PHQ-2               | ≥3                | 1              | 612                | 28 (25, 23)            | -                   |
| SCL-90-R            | 1                 | 97              | 5 (1, 10)          | -                      |                     |
| Zung SDS            | ≥53               | 1              | 156                | 33 (26, 41)            | -                   |

*DSM* Diagnostic and Statistical Manual of Mental Disorders, *ICD* International Classification of Diseases, *HADS* Hospital Anxiety and Depression Scale, *CES-D* Centre for Epidemiological Studies Depression Scale, *BDI* Beck Depression Inventory, *HDS* Hamilton Depression Scale, *PHQ* Patient Health Questionnaire, *SCL-90-R* Symptoms Checklist-90-Revised, *Zung SDS* Zung Self-rating Depression Scale
(DSM or ICD). The most commonly used screening questionnaire to assess anxiety was the HADS, with 10 studies using this screening tool with thresholds of 8. The methods employed to assess depression and anxiety and the frequency of their use were presented in Table 2 and Table 3. When evaluated by Newcastle-Ottawa quality assessment criteria, out of 5 possible points, 2 studies received 5 points, 7 received 4 points, 13 received 3 points, 36 received 2 points, and 1 received 1 point. The details of the assessment of individual studies were shown in Additional file 4.

Prevalence of depression among SLE patients
Prevalence estimates of depression ranged from 2% to 91.7% in individual studies (Table 1). Table 2 indicated the summary of meta-analyses and heterogeneity assessments. Meta-analyses revealed the prevalence of major depressive disorder to be 24% (95% CI, 16%–31%) according to the DSM and/or ICD diagnostic criteria, with high heterogeneity (I² = 95.2%). Prevalence estimates of depression were 30% (95% CI, 22%–38%, I² = 91.6%) for the HADS with thresholds of 8 and 38% (95% CI, 32%–44%, I² = 81.3%) for the CES-D with thresholds of 16, respectively. Prevalence of depression according to the 21 Item-BDI with a cutoff of 14 or more was 39% (95% CI, 29%–49%), with high heterogeneity (I² = 88.2%) (Fig. 2).

Prevalence of anxiety among SLE patients
Prevalence of anxiety alone ranged between 4% and 85% in individual studies (Table 1). Table 3 presented the summary of meta-analyses and heterogeneity assessments. Meta-analyses pooled the prevalence of anxiety to be 40% (95% CI, 30%–49%, I² = 93.0%) and 37% (95% CI, 12%–63%, I² = 98.3%) according to the HADS with thresholds of 8 and the DSM and/or ICD diagnostic criteria, respectively (Fig. 3).

Sensitivity and subgroup analyses
Table 4 suggested depression and anxiety prevalence estimates according to each sensitivity and subgroup analysis, in comparison with the primary analysis. Sensitivity analyses revealed that the exclusion of studies with less sample representativeness tended to decrease dysthymic disorder prevalence estimates according to DSM and/or ICD. The removal of studies with less comparable respondent and non-respondent comparability tended to increase depression prevalence estimates according to the HADS with a cutoff of 8 or more. According to DSM and/or ICD, anxiety prevalence estimates had a trend to decrease by exclusion of studies only using female sample. The subgroup analyses were conducted according to sample size, overall quality, publication year, and country of origin. The results showed that studies with sample size <200 had higher anxiety estimates [43% (95% CI, 31%–55%) vs 28% (95% CI, 16%–40%)] according to the HADS with a cutoff of 8 or more. When evaluated by Newcastle-Ottawa criteria, studies with lower total overall quality scores yielded higher dysthymic disorder estimates [18% (95% CI, 6%–29%) vs 3% (95% CI, 2%–25%)] according to DSM and/or ICD. In contrast with clinical interviews (DSM and/or ICD), more recent publications tended to yield higher depression and anxiety prevalence estimates according to self-report instruments. The subgroup analyses for country of origin showed no clear patterns. There was no particular trend or pattern in any other sensitivity analyses or subgroup analyses.

Table 3 Methods of detecting anxiety and summary of prevalence and heterogeneity findings

| Tool                          | Definition/cutoff | No. of studies | No. of participants | Prevalence, % (95% CI) | Heterogeneity I², % |
|-------------------------------|-------------------|----------------|---------------------|------------------------|---------------------|
| DSM and/or ICD for anxiety disorder | 28                | 5              | 663                 | 37 (12, 63)             | 98.3                |
| HADS                          | ≥8                | 10             | 1332                | 40 (30, 49)             | 93.0                |
| 21 Item-BAI                   | ≥8                | 2              | 313                 | 71 (51, 91)             | 94                  |
|                               | ≥16               | 2              | 313                 | 48 (39, 56)             | 59.2                |
|                               | ≥26               | 2              | 313                 | 18 (14, 22)             | 0                   |
| HAS                           | ≥6                | 1              | 126                 | 75 (67, 82)             | -                   |
|                               | ≥14               | 1              | 62                  | 37 (25, 49)             | -                   |
|                               | ≥15               | 1              | 126                 | 27 (19, 35)             | -                   |
|                               | >17               | 1              | 71                  | 24 (14, 34)             | -                   |
| Cattell questionnaire         | ≥21               | 1              | 166                 | 85 (79, 90)             | -                   |
| SCL-90-R                      | 1                 | 1              | 97                  | 4 (0, 8)                | -                   |
| Zung SAS                      | ≥44               | 1              | 81                  | 17 (9, 26)              | -                   |
|                               | ≥250              | 1              | 156                 | 21 (14, 27)             | -                   |

DSM Diagnostic and Statistical Manual of Mental Disorders, ICD International Classification of Diseases, HADS Hospital Anxiety and Depression Scale, BAI Beck Anxiety Inventory, HAS Hamilton Anxiety Scale, SCL-90-R Symptoms Checklist-90-Revised, Zung SAS Zung Self-rating Anxiety Scale
Associated study variables
We used Pearson’s and Spearmen’s correlation analyses to assess the association between variables including mean/medium disease duration, proportion of female participants, mean/medium age, representativeness, sample size, comparability, overall quality, country of origin, publication year, and the prevalence of depression and anxiety. Table 5 indicated that more recent publications was significantly associated with increased depression prevalence ($r = 0.26$, $P = 0.04$). No study characteristics presented a significant association with anxiety prevalence estimate.

Assessment of publication bias
Assessment of publication bias indicated significant publication bias, according to the Egger’s test, in studies reporting depression according to HADS with thresholds of 8 and CES-D with a cutoff of 16 or more [Egger: bias = 0.81 (95% CI: 0.04, 1.58), $P = 0.04$, and Egger: bias = 2.79 (95% CI: 0.61, 4.97), $P = 0.02$, respectively]. There was no significant evidence of publication bias in any other analyses (see Additional file 5).

Discussion
This systematic review and meta-analysis of 59 studies involving 10828 adult SLE patients demonstrated that a few studies using gold standard clinical interviews (DSM and/or ICD) reported that major depression and anxiety were presented in 24% and 37% among SLE patients, respectively. The majority of studies using screening tools found that significant depression were presented in 30% using the HADS a cutoff of 8 or more and 39% using

![Fig. 2 Prevalence of depressive disorder in SLE](https://example.com/fig2.png)
the 21 Item-BDI with thresholds of 14. This study also found that more recent publications was significantly associated with increased depression prevalence among SLE patients. Furthermore, the prevalence of anxiety was 40% according to the HADS with thresholds of 8. These prevalence estimates are significantly higher than those observed in the general population [23, 24] and other rheumatic and connective tissue diseases [15, 25, 26]. Furthermore, these findings demonstrated that SLE patients tended to have a higher prevalence of anxiety than depression, which was in line with previous studies [27, 28]. Such discrepancy could be explained by the differences in time frames when these studies were performed, disease characteristics, social and cultural contexts of the lupus patients and tools used for assessing depression or anxiety. Because the development of depression and/or anxiety could result in increased incidence of cardiovascular diseases [5], decreased quality of life [9, 10], and a higher risk of premature mortality [11] among SLE patients, these findings highlighted an important issue in health education for this population.

Neuropsychiatric (NP) disorders appeared in about 70% of the patients diagnosed with SLE [29]. Previous meta-analyses have assessed the prevalence of the 19 NP syndromes defined by the American College of Rheumatology (ACR) in 1999 among SLE patients [30]. However, there were a wide variety of neurologic and psychiatric manifestations of SLE, which extended beyond those identified in the 1999 ACR classification criteria for SLE [31]. Several attempts have been made to devise a classification of NP-SLE manifestations because there were controversies regarding the inclusion of mood disorders in the 1999 ACR NP-SLE criteria [31, 32]. That’s why we excluded the studies investigating neuropsychiatric syndromes among SLE patients in this meta-analysis.

Although studies varied widely in terms of quality, our sensitivity analyses suggested that depression and/or anxiety prevalence estimates (except dysthymic disorder estimates) were reasonably stable. Variation in study sample size contributed importantly to the observed heterogeneity in the data. Studies with sample size <200 had higher anxiety estimates according to the HADS with thresholds of 8. Furthermore, studies with lower total overall quality scores yielded higher dysthymic disorder estimates according to DSM and/or ICD. Country, publication year, age, and gender also contributed to the heterogeneity between studies.

In this meta-analysis, many methods were used for data extraction and synthesis. The gold standard method was diagnostic interviews using DSM or ICD criteria, which were often time consuming and expensive. Therefore, it was not ideal for examining patients in a busy hospital environment [33]. Alternatively, self-report screening tools might be used, because they were quick

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**Fig. 3 Prevalence of anxiety in SLE**

| Study ID | ES (95% CI) | Weight |
|----------|-------------|--------|
| HADS (98) | - | - |
| Dzordov 2011 | 0.20 (0.12, 0.28) | 6.75 |
| Hoare 2007 | 0.32 (0.24, 0.40) | 6.73 |
| Mok 2011 | 0.58 (0.36, 0.80) | 6.37 |
| Mehallah 2016 | 0.71 (0.51, 0.91) | 6.57 |
| Monganjan 2007 | 0.44 (0.31, 0.57) | 6.34 |
| Peterson 2015 | 0.54 (0.39, 0.69) | 6.90 |
| Shortall 1995 | 0.39 (0.28, 0.50) | 6.52 |
| Taz 2008 | 0.22 (0.17, 0.27) | 6.93 |
| Tey 2015 | 0.41 (0.32, 0.50) | 6.65 |
| Tosh 2000 | 0.60 (0.41, 0.89) | 6.68 |
| Subtotal (I-squared = 93.0%, p = 0.000) | 0.60 (0.30, 0.89) | 66.45 |
| DSM and/or ICD for anxiety disorder | - | - |
| Bachen 2009 | 0.64 (0.59, 0.69) | 6.91 |
| Chin 1995 | 0.08 (0.02, 0.13) | 6.87 |
| Jarsa 2011 | 0.18 (0.10, 0.26) | 6.73 |
| Stor 2008 | 0.47 (0.35, 0.58) | 6.44 |
| Radzubrahman 2011 | 0.51 (0.41, 0.61) | 6.00 |
| Subtotal (I-squared = 98.3%, p = 0.000) | 0.57 (0.12, 0.85) | 33.35 |
| Overall (I-squared = 96.1%, p = 0.000) | 0.29 (0.29, 0.49) | 100.00 |

NOTE: Weights are from random effects analysis
### Table 4 Impact of study characteristics on prevalence estimates for depression and anxiety in SLE: sensitivity and subgroup analyses

| Depression definition (cutoff) | Major depressive disorder (DSM and/or KID) | Dysthymic disorder (DSM and/or KID) | HADS (≥28) | CES-D (≥16) | 21 Item-BDI (≥1) | 21 Item-BDI (≥21) | 21 Item-BDI (≥30) | Anxiety definition (cutoff) | Anxiety disorder (DSM and/or ICD) |
|--------------------------------|------------------------------------------|-----------------------------------|------------|-------------|-----------------|-----------------|-----------------|--------------------------|--------------------------------|
| **Primary analysis**          | 24 (16, 31)                              | 12 (5, 18)                       | 30 (22, 38) | 38 (32, 44) | 39 (29, 49)     | 34 (2, 65)      | 5 (0, 9)        | 40 (30, 49)               | 37 (12, 63)                   |
|                               | *I² = 95.2%*                              | *I² = 93.4%*                     | *I² = 91.6%| *I² = 81.3% | *I² = 88.2%     | *I² = 98.8%     | *I² = 72.1%     | *I² = 93.0%*             | *I² = 98.3%*                   |
| 10 studies                    | 6 studies                                 | 12 studies                       | 1474 patients | 8 studies | 1640 patients | 781 patients | 546 patients | 1332 patients            | 10 studies                     |
| 2960 patients                 | 922 patients                              |                                   |             |             |                 |                 |                 |                           | 663 patients                   |
| **Sensitivity analyses**      |                                          |                                   |             |             |                 |                 |                 |                           |                                |
| Excluding studies with less  | 24 (6, 42)                               | 3 (2, 5)                         | 29 (15, 44) | -           | 36 (27, 45)     | -               | -               | 21 (8, 55)                |                                  |
| sample representativeness    | *I² = 98.2%*                              | *I² = 0%                         | *I² = 82.7% |             | *I² = 72.4%     |                 | -               | *I² = 90.1%*             |                                  |
| 3 studies                    | 2 studies                                 | 3 studies                        | 220 patients | 3 studies | 468 patients |                 | -               | 2 studies                 | 160 patients                   |
| 2303 patients                | 476 patients                              |                                   |             |             |                 |                 | -               | 3 studies                 | 482 patients                   |
| Excluding studies with less  | -                                        | -                                | 45 (37, 54) | 44 (29, 59) | 39 (29, 49)     | 34 (2, 65)      | 5 (–2, 12)      | 33 (27, 39)               |                                  |
| comparable respondent and    |                                          |                                   | *I² = 68.1%| *I² = 91.9%| *I² = 88.2%     | *I² = 98.8%     | *I² = 85.9%     | *I² = 79.4%*             |                                  |
| non-respondent comparability |                                          |                                   | 3 studies  | 482 patients | 3 studies       | 488 patients   | 266 patients    | 2 studies                 | 76.3%                         |
| Excluding studies only using  | 16 (11, 21)                              | 16 (4, 28)                      | 27 (17, 36) | 44 (35, 54) | 39 (29, 49)     | 34 (2, 65)      | 5 (–2, 12)      | 33 (27, 39)               |                                  |
| female sample                | *I² = 79.8%*                              | *I² = 93.0%                      | *I² = 92.9%| *I² = 85.6% | *I² = 88.2%     | *I² = 98.8%     | *I² = 85.9%     | *I² = 79.4%*             |                                  |
| 6 studies                    | 4 studies                                 | 9 studies                        | 1168 patients | 8 studies | 781 patients | 546 patients | 266 patients | 1135 patients            |                                  |
| 2383 patients                | 496 patients                              |                                   |             |             |                 |                 |                 |                           |                                |
| **Subgroup analyses**         |                                          |                                   |             |             |                 |                 |                 |                           |                                |
| **Sample size**              |                                          |                                   |             |             |                 |                 |                 |                           |                                |
| <200                          | 22 (14, 31)                              | 14 (5, 23)                       | 29 (22, 36) | 38 (28, 48) | 39 (25, 52)     | 41 (–14, 96)    | 5 (0, 9)        | 43 (31, 55)               |                                  |
|                               | *I² = 90.5%*                              | *I² = 93.3%                      | *I² = 81.1%| *I² = 86.3% | *I² = 90.5%     | *I² = 99.2%     | *I² = 72.1%     | *I² = 91.8%*             |                                  |
| 8 studies                    | 5 studies                                 | 10 studies                       | 878 patients | 6 studies | 1008 patients | 496 patients | 260 patients | 8 studies                |                                  |
| 807 patients                 | 596 patients                              |                                   |             |             |                 |                 |                 | 443 patients             | 337 patients                   |
| ≥200                          | 27 (2, 57)                               | -                                | 35 (2, 67)  | 39 (36, 42) | 39 (25, 52)     | 41 (–14, 96)    | 5 (0, 9)        | 43 (31, 55)               |                                  |
|                               | *I² = 99.1%*                              |                                   | *I² = 98.0%| *I² = 0.0%  | *I² = 90.5%     | *I² = 99.2%     | *I² = 72.1%     | *I² = 91.8%*             |                                  |
| 2 studies                    | 2 studies                                 | -                                | 596 patients | 632 patients | 632 patients    |                 | -               | 2 studies                | 596 patients                   |
| 2153 patients                | -                                        |                                   |             |             |                 |                 | -               | 2 studies                |                                |
| **Overall quality**          |                                          |                                   |             |             |                 |                 |                 |                           |                                |
| <3 points (low quality)      | 23 (13, 34)                              | 18 (6, 29)                       | 26 (18, 33) | 34 (28, 40) | 42 (21, 63)     | 41 (–14, 96)    | 5 (0, 9)        | 42 (32, 52)               |                                  |
|                               | *I² = 91.8%*                              | *I² = 93.2%                      | *I² = 77.5%| *I² = 45.5% | *I² = 93.8%     | *I² = 99.2%     | *I² = 72.1%     | *I² = 82.5%*             |                                  |
| 7 studies                    | 4 studies                                 | 6 studies                        | 581 patients | 443 patients | 313 patients    | 260 patients    | 326 patients    | 499 patients             |                                  |
| 657 patients                 | 446 patients                              |                                   |             |             |                 |                 |                 | 337 patients             |                                |
| ≥3 points (high quality)     | 26 (6, 42)                               | 3 (2, 5)                         | 34 (20, 48) | 42 (33, 52) | 36 (27, 45)     | -               | -               | 38 (23, 53)               |                                  |
|                               | *I² = 98.2%*                              | *I² = 0%                         | *I² = 95.0%| *I² = 87.9% | *I² = 72.4%     |                 |                 | *I² = 95.5%*             |                                  |
| 3 studies                    | 2 studies                                 | 6 studies                        | 893 patients | 468 patients | 468 patients    |                 | -               | 5 studies                | 833 patients                   |
| 2303 patients                | 476 patients                              |                                   |             |             |                 |                 | -               |                           |                                |
Table 4  Impact of study characteristics on prevalence estimates for depression and anxiety in SLE: sensitivity and subgroup analyses (Continued)

| Publication year | 1990s | 2000s | 2010- |
|------------------|-------|-------|-------|
|                  |       |       |       |
| 1990s            |       |       |       |
|                  | -     | 33 (17, 50) | -     |
|                  |       | 25 (17, 33) | 28 (23, 34) |
|                  |       | 30 (10, 51) | -     |
|                  |       | 39 (22, 57) | 56 (39, 73) |
| Country of origin |       |       |       |
| North America    |       |       |       |
|                  | 22 (8, 37) | 3 (2, 5) | 26 (18, 34) |
|                  | 22 (8, 37) | 3 (2, 5) | 26 (18, 34) |
|                  |        |       |       |
| Asia             |       |       |       |
|                  | 21 (0, 41) | 21 (−3, 44) | 21 (0, 41) |
|                  | 21 (0, 41) | 21 (−3, 44) | 21 (0, 41) |
|                  | 21 (0, 41) | 21 (−3, 44) | 21 (0, 41) |
| Europe           |       |       |       |
|                  | 31 (12, 50) | -     | 33 (17, 49) |
|                  | 31 (12, 50) | -     | 33 (17, 49) |
|                  | 31 (12, 50) | -     | 33 (17, 49) |
| South America    |       |       |       |
|                  | 31 (12, 50) | -     | 33 (17, 49) |
|                  | 31 (12, 50) | -     | 33 (17, 49) |
|                  | 31 (12, 50) | -     | 33 (17, 49) |

The first line in each set of data is percentage prevalence (95% CI).

DSM Diagnostic and Statistical Manual of Mental Disorders, ICD International Classification of Diseases, HADS Hospital Anxiety and Depression Scale, CES-D Centre for Epidemiological Studies Depression Scale, BDI Beck Depression Inventory
and easy to complete and cheaper to use than diagnostic interviews. However, prevalence estimates using screening tools were often overestimated, because such tools tended to prioritize sensitivity over specificity [33]. Furthermore, there have not been validation studies to determine the best cut-point for screening tools in SLE patients, and several cut-off scores on self-report tools were often used in many studies. It indicated that the rheumatologists should always report prevalence at conventional cut-points, and screen for depression and anxiety among SLE patients according to the social and cultural contexts of the rheumatologists and SLE patients in clinical practice.

There are, however, additional important shortcomings in the evidence on prevalence of depression in SLE that need to be addressed. First, a substantial amount of the heterogeneity among the studies remained unexplained by the variables examined. Unexamined factors, such as gender, age, disease duration, might contribute to the risk for depression and/or anxiety symptom among SLE patients. Second, the data were derived from studies that used different designs and involved different groups of patients (e.g., from different countries), which might result in heterogeneity among the studies. Third, we did not look for healthy subjects in each study reporting the prevalence of depression or anxiety in SLE patients, which should be addressed in future research.

Conclusions
The prevalence of depression and anxiety was high in adult SLE patients. It indicated that rheumatologists should screen for depression and anxiety in their patients, and they should refer them to mental health providers in order to identify effective strategies for preventing and treating depression and anxiety among SLE patients.

Table 5 Pearson’s and Spearmen’s correlation between study characteristics and prevalence estimates

| Study characteristic | Depression prevalence estimate | Anxiety prevalence estimate |
|----------------------|-------------------------------|---------------------------|
|                      | No. of studies | \( r \) | \( P \) | No. of studies | \( r \) | \( P \) |
| Female, %            | 59 | 0.03 | 0.84 | 24 | 0.07 | 0.76 |
| Mean/medium age, year| 55 | -0.13 | 0.35 | 23 | -0.18 | 0.94 |
| Mean/medium disease duration, year | 53 | -0.07 | 0.64 | 21 | 0.24 | 0.29 |
| Representativeness   | 59 | 0.03 | 0.85 | 24 | 0.08 | 0.70 |
| Sample size          | 59 | 0.12 | 0.38 | 24 | 0.01 | 0.97 |
| Comparability        | 59 | 0.24 | 0.07 | 24 | -0.11 | 0.61 |
| Overall quality      | 59 | 0.13 | 0.33 | 24 | -0.10 | 0.64 |
| Country of origin    | 59 | 0.01 | 0.92 | 24 | -0.10 | 0.63 |
| Publication year     | 59 | 0.26* | 0.04 | 24 | -0.04 | 0.84 |

*Significant at a \( P <0.05 \) level

Additional files

- **Additional file 1:** Search Terms. (DOCX 10 kb)
- **Additional file 2:** Summaries of symptom thresholds required for diagnosis of depression/anxiety. (DOCX 19 kb)
- **Additional file 3:** The list of 59 studies included in the meta-analysis. (DOCX 19 kb)
- **Additional file 4:** Quality Assessment. (DOCX 19 kb)
- **Additional file 5:** Assessment of Publication Bias. (DOCX 56 kb)

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Availability of data and materials
The majority of data generated or analyzed during this study are included in this published article (and its Additional files). Remaining data not published here are available from the corresponding author on reasonable request.

Authors’ contributions
LZ and TF searched and checked the databases according to the inclusion and exclusion criteria, extracted the data and assessed their quality. LZ analyzed the data and wrote the draft of the paper. RY, QZ and BS gave advice on meta-analysis methodology and revised the paper. All authors contributed to reviewing or revising the paper. BS is the guarantor of this work and had full access to all the data in the study and takes responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final manuscript.

Competing interests
The authors declared that they have no competing interests.

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Not applicable.
Ethics approval and consent to participate

Ethical approval and consent to participate are not required for this review.

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