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REVIEW ARTICLE

Exploring the Association Between Systemic Lupus Erythematosus and High-Density Lipoproteins: A Systematic Review and Meta-Analysis

Julián Pérez-Ocampo,[1] Natalia A. Taborda,[2] Lina M. Yassin,[2] Luis Felipe Higuita-Gutiérrez,[1,3] and Juan C. Hernandez[1,4]

Objective. Systemic lupus erythematosus (SLE) is an autoimmune disease with inflammation as a critical feature. Recently, high-density lipoprotein cholesterol (HDLc) have been evidenced to have anti-inflammatory effects, suggesting a potential link between HDL and SLE that needs to be thoroughly studied. The aim was to explore the association between SLE and HDLc through a systematic review with meta-analysis.

Methods. A systematic review with meta-analysis was conducted to assess mean differences in HDL levels between patients with SLE and healthy controls. Both qualitative and quantitative syntheses were performed, including an assessment of heterogeneity using I^2, a publication bias evaluation, a methodologic quality assessment, and a forest plot under a random effects model. Subgroup analyses were conducted based on disease activity and the report of corticosteroid dosage.

Results. A total of 53 studies were included in the qualitative synthesis, and 35 studies were included in the quantitative synthesis, comprising 3,002 patients with SLE and 2,123 healthy controls. Mean HDL levels were found to be lower in patients with SLE as follows: in the meta-analysis including all articles −6.55 (95% confidence interval [CI] −8.77 to −4.33); in patients with mild disease activity −5.46 (95% CI −8.26 to −2.65); in patients with moderate or severe disease activity −9.42 (95% CI −15.49 to −3.34); in patients using corticosteroids −5.32 (95% CI −10.35 to −0.29); and in studies with excellent methodologic quality −8.71 (95% CI −12.38 to −5.03).

Conclusion. HDL levels appear to be quantitatively altered in patients with SLE, suggesting a potential contribution to immune dysregulation, highlighting the importance of HDL in autoimmune diseases.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can affect almost any tissue or organ, causing a wide range of clinical manifestations, from skin rashes to compromised organ functionality. Although anyone can develop SLE, premenopausal women are the most affected because of a complex epigenetic association involving gene inheritance and environmental interactions.[1] Consequently, cellular and humoral immunity dysregulation, with a particular chronic inflammation follows.[2] The disease burden worsens as the lack of immune control expands, leading to additional complications in other systems' homeostasis. Cardiovascular and renal complications are the most studied and well-described complications in patients with SLE.[3]

The epidemiology of SLE is complex because of the heterogeneity of patients and nonuniform definitions of the disease.[4] Recent studies show significant differences in the prevalence and incidence rates, with specific-region prevalence rates ranging

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[1]Julián Pérez-Ocampo, MSc, Luis Felipe Higuita-Gutiérrez, Msc, Phd, Juan C. Hernandez, PhD: Infettare, Facultad de Medicina, Universidad Cooperativa de Colombia, Medellín, Colombia; [2]Natalia A. Taborda, MSc, PhD, Lina M. Yassin, MSc, PhD: Grupo de Investigaciones Biomédicas Uniremington, Programa de Medicina, Facultad de Ciencias de la Salud, Corporación Universitaria Remington, Medellín, Colombia; [3]Luis Felipe Higuita-Gutiérrez, MSc, PhD: Escuela de microbiología, Universidad de Antioquia UdeA, Medellin, Colombia; [4]Juan C. Hernandez, PhD: Grupo Inmunovirología, Facultad de Medicina (UdeA), Universidad de Antioquia UdeA, Medellín, Colombia.

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Address correspondence via email to Juan C. Hernandez, PhD, at juankhernandez@gmail.com.

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from 13 to 7,713 per 100,000 individuals and incidence rates ranging from 1.4 to 49 per 100,000 person-years.[4,5]

Diagnosing and managing SLE remain challenging for clinicians, particularly in the early stages of the disease. The heterogeneity of clinical manifestations and unpredictable flares make clinical evaluation highly dependent on the clinician's expertise.[6] Consequently, diagnostic delays and mismanagement negatively affect the patient's prognosis. Efforts have been made to create a standardized definition of SLE, including developing indexes to aid in classification, definition, and disease activity assessment. The SLE Disease Activity Index (SLEDAI) was introduced in 1985 as a validated index for a global measure of disease activity for clinical decisions, which was developed by expert rheumatologists with rigorous methodologic approaches.[7] Nevertheless, high-density lipoprotein (HDL) assessment is not part of these index descriptors, even though HDL is commonly studied in patients with SLE because of their higher cardiovascular risk. Studies to understand the immunologic role of HDL in chronic inflammatory disorders such as SLE deserve more attention.

HDLs are plasma proteins that transport lipids in the circulation system, primarily from tissues to the liver,[8] also known as lipid reverse transport. HDLs have a complex structure consisting of various particles that vary in size and lipid composition. Their main components are cholesterol, both esterified and free; phospholipids; and several apolipoproteins, such as ApoA1, ApoA-II, ApoA-IV, ApoC, ApoE, ApoJ, and ApoM.[9] Additionally, HDLs contain enzymes that play a role in their maturation and cholesterol reverse transport, including lecithin–cholesterol acyltransferase, lipoprotein lipase, and cholesteryl ester transfer protein.[10] Other enzymes, such as paraoxonase 1 (PON1), are also associated with HDL and contribute to their antioxidant and anti-inflammatory activities.[11]

Interest in HDL and its potential in immunologic regulation has been increasing recently. Although HDL was traditionally viewed as a cardiovascular risk estimator, a growing body of evidence now supports the notion that HDL plays a significant role in immunity. Several functions and mechanisms of HDL in immunologic regulation have been described.[12–16]

Furthermore, it is necessary to assess HDL while considering other patient characteristics that might influence the functionality of these proteins, and thus contribute to inflammation. In this regard, it is fundamental to consider HDL and SLEDAI, because several studies have associated higher SLEDAI scores with increased inflammation.[17–26] Moreover, medication use could also potentially alter the quantity or functionality of HDL, particularly when using corticosteroids. This effect has been observed in certain rheumatic diseases in which prolonged corticosteroid therapy has been shown to reduce HDL cholesterol (HDLc) levels.[27,28]

In this sense, SLE is an autoimmune disease with an exacerbated inflammatory response involved in its progression and clinical manifestations. Recent studies have highlighted HDL involvement in immunity and anti-inflammatory effects, establishing a clear link between HDL's immunomodulatory effects and immune alterations in SLE. Although a common dyslipoproteinemia has been established in patients with SLE for whom low-density lipoprotein cholesterol levels are higher and HDLc levels are lower when compared with those of healthy controls, previous studies have not been able to highlight a common HDL behavior in these patients under different focuses, such as SLEDAI score or therapy schemes, and even though many studies have had an interest in determining HDLc levels as a biomarker for disease activity in SLE. These results are usually heterogeneous or nonexistent when segregated according to SLEDAI or therapy use, whereas some studies show significantly lower HDLc levels on patients with SLE compared with those of healthy donors[19,29,30]; others studies contrast with these results,[31–33] leading to an inconclusive interpretation of these relationships. An explanation could be that most studies are analytical and observational and thus require a wide number of patients and healthy controls to achieve precise and solid conclusions.

By conducting a meta-analysis, data can be pooled and analyzed from multiple studies to obtain a comprehensive overview of the relationship between HDL and SLE. It will help to establish the association's consistency and strength of low HDL levels in patients with SLE. Furthermore, a meta-analysis could identify potential sources of heterogeneity and explore subgroups within the SLE population that may be particularly susceptible to low HDL levels. For example, disease duration, disease activity, medication use, and comorbidities may influence HDL levels in patients with SLE. Understanding these factors can aid in risk stratification and personalized management of patients with SLE. Meta-analyzing HDL data can also highlight gaps in knowledge and guide future research by identifying areas for which further investigation is needed. Considering this, a systematic review with a meta-analysis provides a more robust estimation of aftermath and statistical power than individual studies. By combining data from multiple studies, a larger sample size can be achieved, increasing the precision and generalizability of the findings, which is particularly important in diseases with low prevalence and high diversity, such as SLE. A meta-analysis can enhance the statistical power to detect meaningful associations between HDL and SLE, mainly when individual studies have limited sample sizes and inconsistent results. This systematic review and meta-analysis aimed to explore, through a quantitative and qualitative description, the association between SLE and HDL and how this could hypothetically alter the immunomodulatory capabilities of HDL.

PATIENTS AND METHODS

Orientation of search. A population exposure comparator outcome question framework was established as follows: The population included adult patients between 18 and 70 years old of both sexes with SLE. The exposure was SLE. The comparison was healthy donors. The outcome was HDLc levels. After this process, a research question was proposed: what is the

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difference between HDLc levels in patients with SLE and healthy controls?

Search strategies. A systematic search was conducted in PubMed, ScienceDirect, Scielo, LILACS, Scopus, and Google Scholar following the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines to perform the meta-analysis. All articles published under the statement systemic lupus erythematosus and high density lipoprotein using the Medical Subject Headings (MESH) terms "Systemic lupus erythematosus" AND "High density lipoprotein" OR "HDL," "SLE" AND "High density lipoprotein" OR "HDL," and "Lupus" AND "High density lipoprotein" OR "HDL" were searched. In all databases and search engines, excluding Scopus and Google Scholar, all articles containing these terms in the title, keywords, or abstract were included. For Google Scholar and Scopus, a title filter containing MESH words was applied for the included papers. Some of the search algorithms were (systemic lupus erythematosus [Title/Abstract]) AND (High density lipoprotein [Title/Abstract] OR HDL [Title/Abstract]), title, abstract, and keywords (systemic lupus erythematosus) AND ([high density lipoprotein]) OR [HDL]).

Review process. All records previously included in the searches were loaded in Zotero open source software version 6.0.20, and duplicates were removed. The remaining articles' abstracts were screened to apply the following inclusion criteria: (1) the study assessed HDLc in patients with SLE and healthy controls, (2) the study determined SLEDAI or immunologic markers in patients with SLE, (3) the paper was an original research article, (4) the study was analytical, and (5) the article was in English or Spanish. After this, papers that fulfilled these inclusion criteria were full-text read and the following exclusion criteria were applied: (1) studies that did not report HDLc levels as mean with SD, (2) studies that did not report the SLEDAI score, (3) studies that were conducted in nonhumans, (4) studies that assessed fewer than 10 patients with SLE, and (5) studies of patients with SLE with HIV, cancer, pregnancy, or familial dyslipidemia were also excluded.

Data extraction. With the articles included, the qualitative synthesis was done with the following variables: year of publication, publisher journal's country, objective, methodology, gender proportion, SLE sample size, healthy control sample size, SLE and control's HDLc mean value, SLEDAI score for patients with SLE, main finding, and principal author's country. The quantitative synthesis was also conducted with the HDLc means and their respective SDs.

Information search and election were done by two researchers independently, and then inconsistencies were resolved either by consensus or reference from a third party. The data extracted from the studies were consigned to a database built in Microsoft Excel; the reproducibility of this stage was tested and corroborated by a kappa coefficient of 1 for qualitative variables and intraclass correlation coefficient of 1 for the quantitative variables.

Evaluation of methodologic quality. For this section, the Joanna Briggs Institute checklist[34] for case-control studies was applied for every included article. The criteria evaluated were SLE and control comparability aside from the HDLc levels, controls and patients with SLE adequate pairing (sex and age), adequate identification and definition of patients with SLE and healthy controls, proper determination of SLE in the patient's group, evaluation and control of confounding factors in study design and information analysis, appropriate assessment of HDLc and interest variables in patients with SLE and controls (including the correct preanalytical and analytical conditions for samples, such as blood sample collection after 8h–12h fasting, sera stored at −80°C until the measurements and use of validated analytical methods were conducted), and suitability of statistical analyses.

Information analysis. In the qualitative synthesis, the variables were described as absolute frequencies. In the quantitative synthesis, a meta-analysis was conducted using the mean values of HDLc, establishing the meta-analysis as a global mean difference. Heterogeneity was assessed by the I^2 statistic and Galbraith plot. As heterogeneity was present, we used a random effects model to conduct the analysis. Additionally, publication bias was evaluated by funnel plot.

Furthermore, we executed additional subgrouped meta-analyses to check whether our results would change when analyzing under different groupings of the studies' patients. The first grouped meta-analyses were done to evaluate the SLEDAI relationship to HDLc levels. For this effect, we considered a SLEDAI score of 5 or less as mild or no disease activity, a score between 6 and 12 as moderate disease activity, and scores higher than 12 as severe disease activity. To define these thresholds, we adapted the definitions from the research of Bombardier et al[35] and Gladman et al[7] according to the reported values of SLEDAI we found across the studies we meta-analyzed.

The other grouped meta-analyses were performed to inquire how the use of medication could influence HDLc levels. To this end, we investigated if the studies reported segregated HDLc levels in patients with SLE according to the pharmacological treatment they had at the time of the study. Only two articles did this differential analysis,[27,36] but every study reported medication usage, especially corticosteroids, so, to meta-analyze these data, we included studies in which the corticosteroid dosage was reported.

Finally, the last subgrouped meta-analysis was conducted to see if the methodologic quality of studies would influence HDLc levels. This way we only included studies with an adequate

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number of healthy controls and correct pairing to patients with SLE for the meta-analysis.

RESULTS

We found 1,238 articles in the screening process using six different databases. After duplicate removal, 386 articles were classified as follows: 284 original articles (preclinical studies or observational studies), 5 case reports, 56 reviews, 3 systematic reviews, 27 clinical trials, 4 book sections, and 7 others (documents, websites, articles corrections, or protocols). After that, 51 articles were excluded because of being published in languages other than English or Spanish or because they had restricted access. Of these 233 original articles, 19 were preclinical studies, and so they were also excluded. The remaining 214 studies were full-text read and assessed under the inclusion criteria. Finally, 53 records were included in the systematic review,[17–19,21,23,25,27,29–33,36–76] and 35 of these were included in the meta-analysis.[29,31,33,36–39,41,43–45,49,50,52–54,56–59,61,63,64,66,71,73,75] These search results are outlined in Figure 1.

Characteristics of studies evaluated. A total of 4,709 patients with SLE, along with 3,549 healthy controls were included in the 53 studies that fulfilled all inclusion criteria. All studies included were analytical observational studies. Only one research study was a longitudinal cohort prospective study. The other 52 were cross-sectional studies. The sample size range for patients with SLE was 9 to 250 patients, and for controls was from 9 to 223 patients. Two studies did not specify the HDLc measurement on either patients with SLE or controls.[47,48] The mean values for HDLc for patients with SLE across all studies ranged from 29.58 to 69.6 mg/dL and for controls from 42.8 to 73.47 mg/dL. The studies were conducted between 1993 and 2022. The countries where studies were conducted are highlighted in Figure 2.

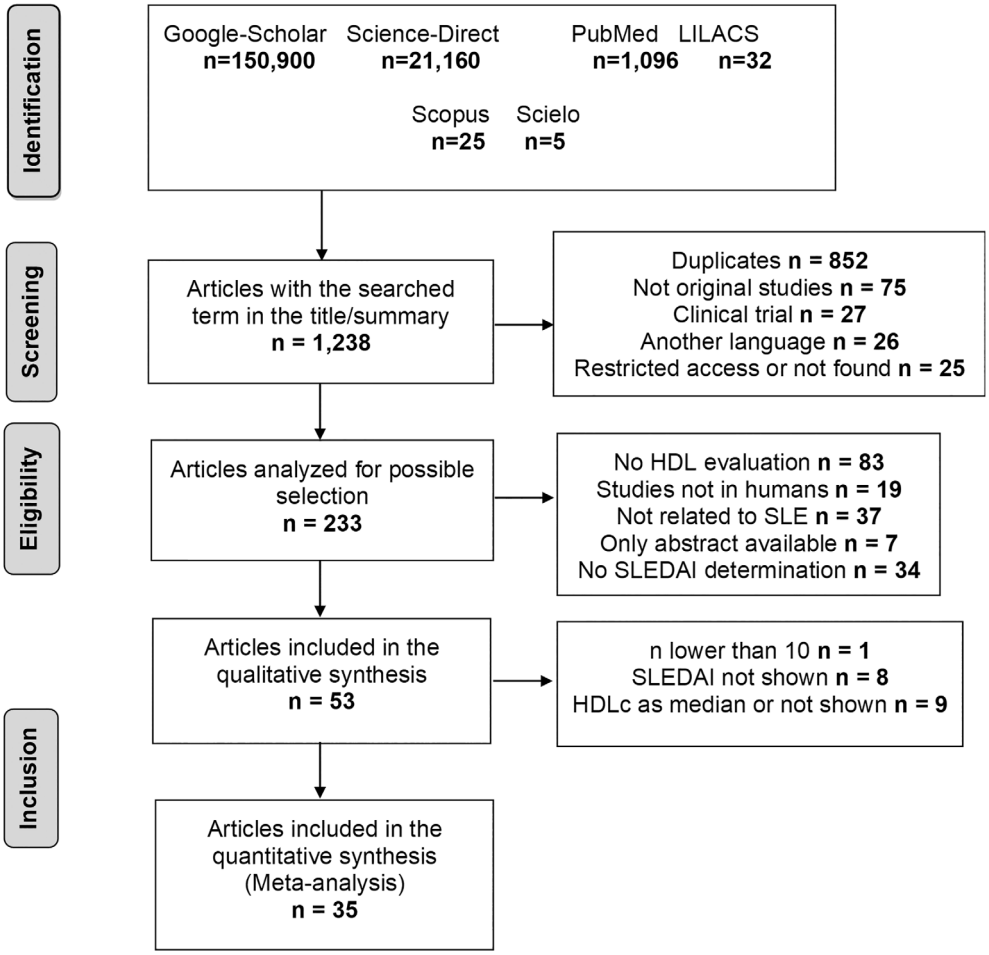

Figure 1. Search flowchart and selection of studies. The identification phase corresponds to the raw searches of Medical Subject Headings terms without any filter in the six databases consulted. The screening, eligibility, and inclusion phases comprised searches of Medical Subject Headings terms with filters, depuration of duplicates, and application of inclusion and exclusion criteria. HDL, high-density lipoprotein; HDLc, high-density lipoprotein cholesterol; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

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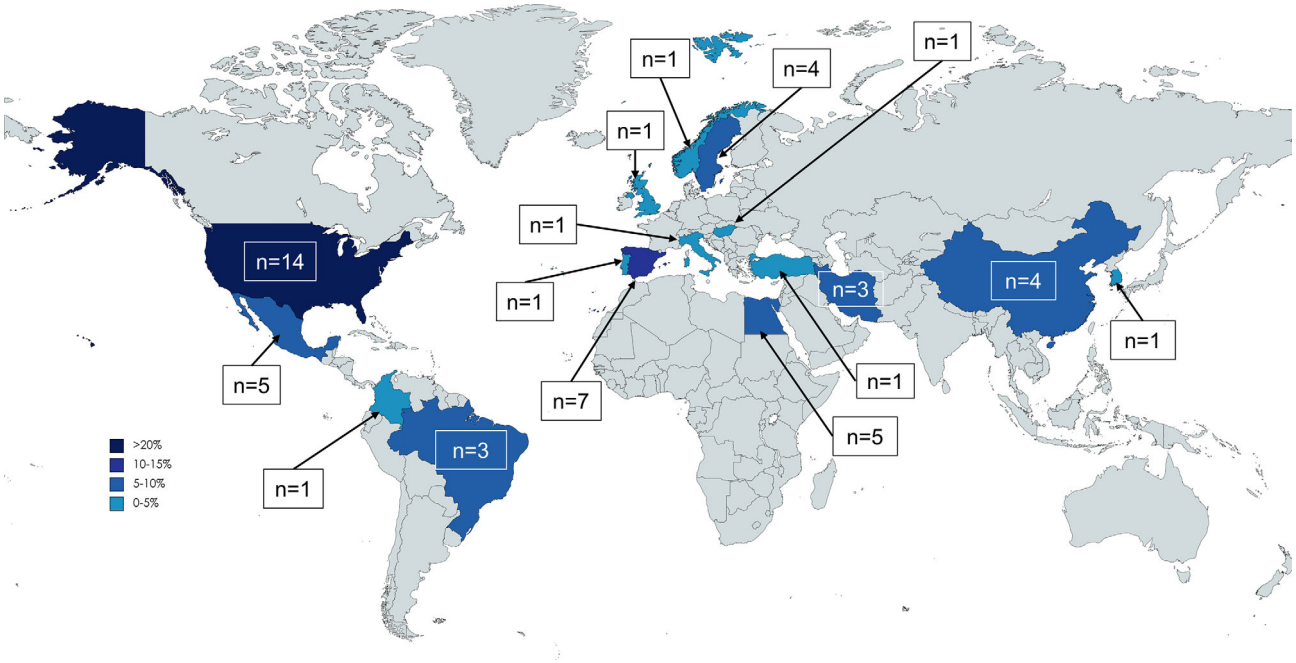

Figure 2. Studies meta-analyzed according to their country of origin. Geographic distribution of the 53 studies included in the systematic review. The colors represent the number of studies.

Of the 53 studies, 35 were included in the meta-analysis (Table 1), and 3,002 patients with SLE were studied. Not surprisingly, 2,762 (92%) of them were women. The same scenario happened with the healthy controls, where 2,123 were assessed and 1,760 (82.90%) were women. To highlight, the mean HDLc levels reported in the 35 studies without any statistics treatment showed a lower value in patients with SLE (50.96 mg/dL) than in healthy controls (55.88 mg/dL).

Methodologic quality of studies meta-analyzed. In the methodologic quality evaluation (Table 2), of the eight criteria applied, 8 studies[23,29,41,44,59,64,67,68] fulfilled all of them, 18 satisfied seven criteria,[27,31,36,37,43,45,49,50,52–54,56–58,61,71,73,75] and the rest of the investigations attained at least five of the criteria. The criteria that were less fulfilled were the ones related to the adequate pairing of patients with SLE and healthy controls (they had considerably fewer controls than patients with SLE, so an adequate individual pairing could not be achieved) and the ones related to the assessment of outcomes (as a handful studies did not specify if samples were collected and conserved under correct preanalytical conditions, such as adequate fasting time before blood collection or sera storage at –80°C until analyzed, or did not mention the analytical methods used for measurements).

Aspects considered of HDLc levels in included studies. The HDLc dimension was heterogeneous according to the Galbraith distribution graphic (Supplementary Figure 1) and analytical methods. Publication bias was absent in the funnel plot drawing (Supplementary Figure 2). The distribution of HDLc levels varied across all studies, with a global difference mean of –6.51 (95% confidence interval [CI] –9.14 to –3.88) under a random effects model (Supplementary Figure 3). In most of the studies, HDLc levels were lower in patients with SLE; in none of them were these levels significantly higher in the SLE population. We inquired whether this heterogeneity could be assessed by different subgrouped meta-analyses; for this, we grouped studies as stated in the information analysis section of this manuscript.

Characteristics of HDLc levels in patients with SLE with mild or inactive disease. This subgrouped meta-analysis included 26 studies,[23,27,29,31,36–39,41,43–45,52–54,58,61,63–69,71] as described in Table 1. Heterogeneity was observed (Figure 3), and there was no publication bias (Figure 4). The distribution of HDLc levels also favored lower levels in the SLE population. Interestingly, the global difference mean was lower than the previous meta-analyses with a mean value of –5.46 (95% CI –8,26 to –2,65) (Figure 3).

Characteristics of HDLc levels in patients with SLE with moderate or severe disease activity. For this meta-analysis, nine articles were analyzed.[33,49,50,56,57,70,73–75] Again, heterogeneity was present and publication bias was absent (Figures 5 and 6). The HDLc levels were remarkedly lower in the SLE population, with a surprising global difference mean of –9.42 (95% CI –15.49 to –3.34) (Figure 5), significantly higher than the previous analysis, suggesting a stronger relationship between lower HDLc levels and higher disease activity.

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Table 1. Description of the studies' populations included in the meta-analysis*

Study first author	Publication year	SLE sample size, n	Sex, F/M, n	SLE HDLc, mg/dL	Control sample size, n	Sex, F/M, n	Control HDLc, mg/dL	SLEDAI score
Gaál K	2016	51	44/7	48.72 ± 18.17	49	41/8	66.12 ± 17.4	4 (2–6)
Smith C	2014	40	36/4	52 ± 18.5	20	18/2	57.5 ± 28.0	3 (6)
Rezaieyazdi Z	2021	60	55/5	45.00 ± 9.00	30	26/4	43.00 ± 5.00	4.5 (2–12)
McMahon M	2006	154	154/0	56.3 ± 18.7	72	72/0	51.8 ± 14.9	4.5 ± 5.3
López P	2020	109	103/6	61.50 ± 17.42	33	31/2	63.94 ± 13.90	2.6 ± 2.76
Bahrehmand F	2013	109	87/22	42.1 ± 21.1	103	82/21	42.7 ± 11	21 ± 12.2
Sánchez-Pérez H	2020	195	185/10	63 ± 21	223	155/68	63 ± 17	2 (0–5)
Lilleby V	2007	68	51/17	46.4 ± 11.6	68	51/17	61.87 ± 15.47	2.9 ± 2
Santos M	2010	100	100/0	56.5 ± 16	102	NS	62.2 ± 16	2 (0–4)
López P	2017	198	188/10	61.51 ± 17.23	100	93/7	62.00 ± 13.89	2.9 ± 3.31
Zhou B	2020	71	71/0	32.09 ± 13.06	71	71/0	60.32 ± 16.26	12.87 ± 2.81
Sari RA	2002	24	22/2	33.2 ± 9.7	26	22/4	46 ± 8.3	43 ± 7
Lourdudoss C	2018	109	95/14	69.6 ± 58	106	96/10	65.73 ± 23.2	2 (0–6)
McMahon M	2014	210	210/0	57.3 ± 17.9	100	100/0	60.8 ± 15.3	3.5 ± 4
McMahon M	2011	250	250/0	56.3 ± 16.8	122	122/0	58.3 ± 15.6	3.9 ± 4
Ammirati E	2014	50	43/7	54 ± 13	50	43/7	63 ± 13	3 ± 2
Abd-Elmawla M	2018	65	58/7	46.4 ± 3.4	35	28/7	49.1 ± 2.5	23.5 ± 1.4
Soep J	2004	33	30/3	40.6 ± 13	30	24/6	50.7 ± 12	8 ± 8
Rodríguez M	2019	78	72/6	63.36 ± 15.48	38	38/0	69.10 ± 15.72	4 ± 2
Asanuma Y	2003	65	59/6	47.3 ± 16.5	69	58/11	48.9 ± 16.2	3.9 ± 3.6
Purmalek M	2019	64	56/8	54.1 ± 16	30	29/1	66.9 ± 16	3.8 ± 3
Ajeganova S	2021	99	86/13	61.87 ± 19.33	109	99/10	65.73 ± 23.2	3 (1–5.30)
Park J	2016	35	34/1	21.7 ± 9.3	15	13/2	46.2 ± 9.3	4.26 ± 4.24
Borba E	2000	10	10/0	41.0 ± 9.3	10	10/0	53.5 ± 9.2	0
Marsillach J	2015	54	54/0	58.7 ± 18.2	25	25/0	64.8 ± 16.1	2 ± 2
Borba E	2001	60	60/0	40.21 ± 10.44	30	30/0	54.13 ± 14.31	4 (2–6)
Asanuma Y	2006	74	67/7	47 ± 16.0	85	77/8	49.3 ± 15.7	3.6 ± 3.5
Li Z	2019	98	98/0	46.4 ± 15.47	108	108/0	54.13 ± 11.6	2.5 ± 4
López P	2020	197	186/11	61.51 ± 17.23	99	92/7	61.60 ± 13.80	2.92 ± 3.22
Yassin L	2011	38	NS	43 ± 17	29	NS	61 ± 6	12 ± 9
Valdivielso P	2008	26	25/1	46 ± 20	21	20/1	53 ± 17	5.58 ± 8.60
Parra S	2019	69	69/0	65.73 ± 15.47	34	34/0	59.55 ± 15.47	0
Rezaieyazdi Z	2020	59	54/5	44.7 ± 9.3	31	27/4	47.13 ± 8.2	7.9 ± 7.3
Badawi A	2017	30	NS	39.3 ± 14.9	20	NS	49.7 ± 6.5	8.7 ± 3.3
El-Hady A	2019	50	50/0	50.3 ± 5.1	25	25/0	51.5 ± 7.3	25.2 ± 9.5
Total	–	3,002	2,762/240	x̄: 50.96	2,123	1,760/363	x̄: 55.88	x̄: 6.92

*HDLc values are reported as mean ± SD and SLEDAI score as mean ± SD or median (interquartile range).
F, female; HDLc, high-density lipoprotein cholesterol; M, male; NS, not specified; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Table 2. Quality evaluation of the studies meta-analyzed*

Criterium	% compliance
Appropriate cases and controls comparability	100
Clear identification and definition of cases and controls	91
Adequate case-control pairing (sex and age)	46
Proper determination of SLE in the patients' group	94
Clear identification of confounding factors	97
Proper control of confounding factors	97
Fitting measurement of outcomes (HDLc) in both groups	65
Suitability of statistical analyses	91

*In the first column are the criteria established according to the Joanna Briggs Institute's checklist for case-control studies. In the second column are the percentage of articles that fulfilled each criterium.
HDLc, high-density lipoprotein cholesterol; SLE, systemic lupus erythematosus.

Characteristics of HDLc levels in patients with SLE in studies that reported corticosteroid dosage. This subgrouped meta-analysis comprised 10 studies.[31,54,59,62,63,68,70,73,75,76] Heterogeneity was observed (Figure 7), and publication bias was absent. The disposal of HDLc levels favored lower levels in the SLE group, with a global difference mean of –5.32 (95% CI –10.35 to –0.29) (Figure 7).

Characteristics of HDLc levels in studies with good methodologic quality. For this meta-analysis, 17 articles were analyzed.[23,27,29,30,32,33,41,43,44,49,50,52,57,59,61,68] Heterogeneity was observed (Figure 8) and publication bias was not (Supplementary Figure 4). Interestingly, the HDLc levels were significant lower in the SLE population, with a global difference mean of –8.71 (95% CI –12.38 to –5.03)

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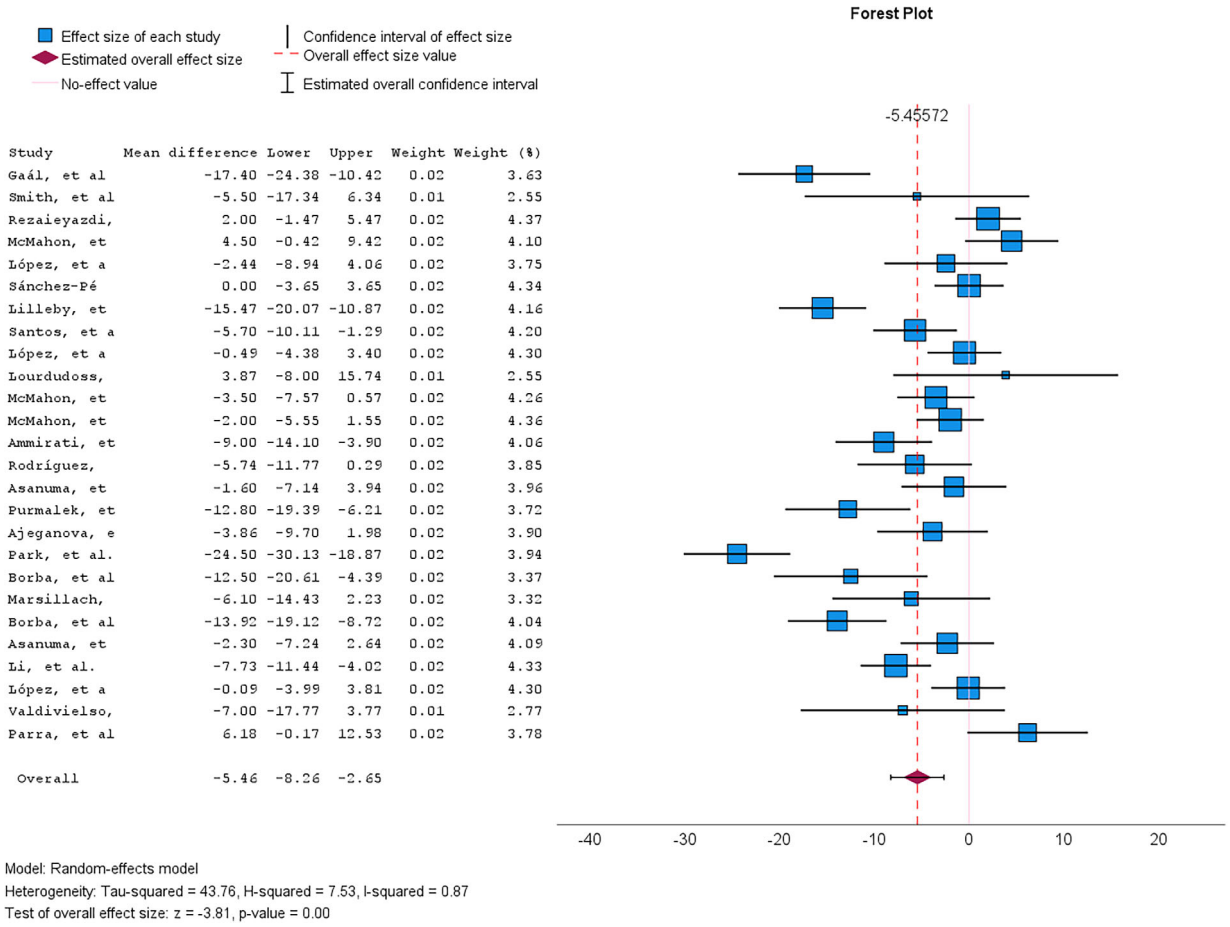

Figure 3. Random effects model meta-analysis of the 26 studies that had a mean Systemic Lupus Erythematosus (SLE) Disease Activity Index score of ≤5. The first group comprises patients with SLE and the second healthy controls; therefore, scores <0 indicate favorability toward lower high-density lipoprotein cholesterol (HDLc) levels in patients with SLE and values >0 favor higher HDLc levels in healthy controls. Data that intercept with 0 indicate that these study results showed no statistically significant differences between patients with SLE and healthy controls in HDLc levels. Heterogeneity results are shown in the lower left corner by the analytical methods.

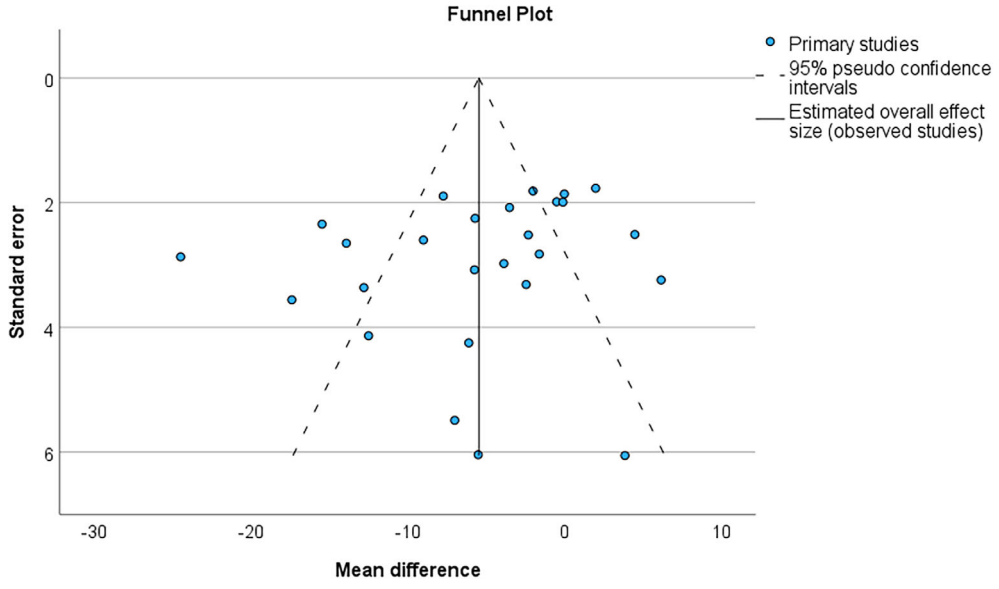

Figure 4. Publication bias analysis by funnel plot of studies with a mean Systemic Lupus Erythematosus Disease Activity Index score of ≤5.

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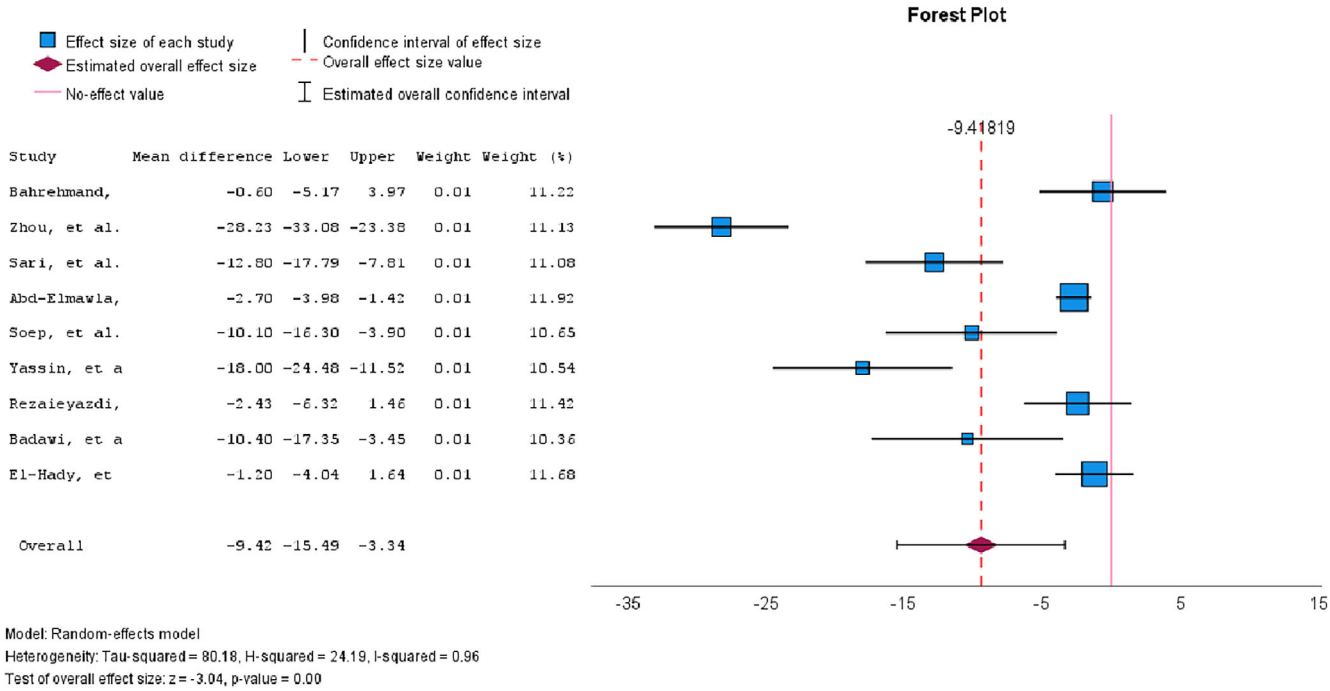

Figure 5. Random effects model meta-analysis in studies with a mean Systemic Lupus Erythematosus Disease Activity Index score of ≥6. The first group comprises patients with SLE and the second healthy controls.

(Figure 8). As with the previous analysis about higher disease activity, this global difference mean was significantly higher than in the the other analyses, implying that an adequate pairing is further evidence of the fact of lower HDLc levels in patients with SLE when compared with those of healthy controls.

DISCUSSION

The relationship between HDL levels and SLE severity has been analyzed in different studies but with contradictory results that have not allowed a clear association to be established. This systematic review aimed to explore the association between

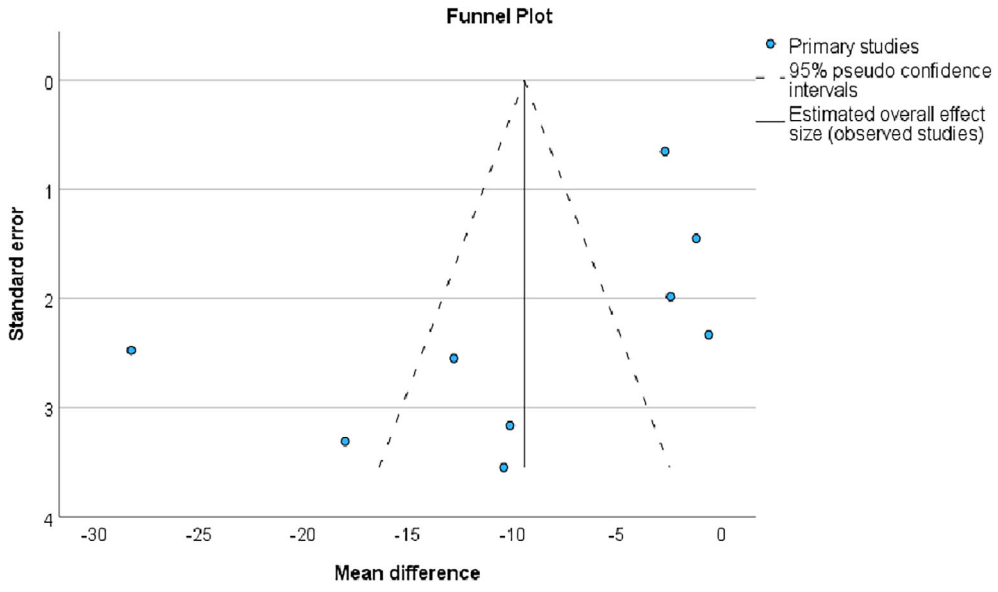

Figure 6. Publication bias analysis by funnel plot of studies with a mean Systemic Lupus Erythematosus Disease Activity Index score of ≥6.

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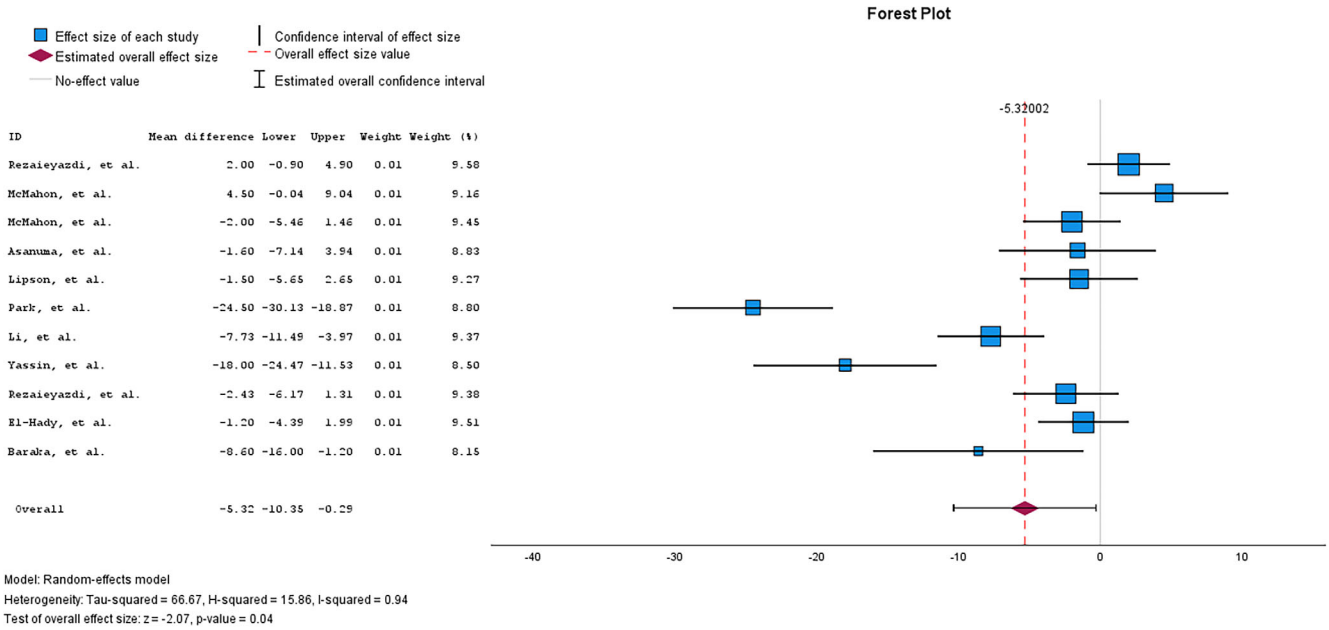

Figure 7. Random effects model meta-analysis in studies that reported corticosteroid dosage. The first group comprises patients with systemic lupus erythematosus and the second healthy controls.

SLE and HDLc in the context of the immunomodulatory capabilities of HDL through a systematic review with meta-analysis. For this reason, we included disease activity as a main component of this study. The results of this study confirm an alteration in HDL levels in patients with SLE compared with healthy individuals, with significantly lower levels of HDLc observed in these rheumatologic patients and with a significant role in disease activity. These findings were further assessed by conducting separate

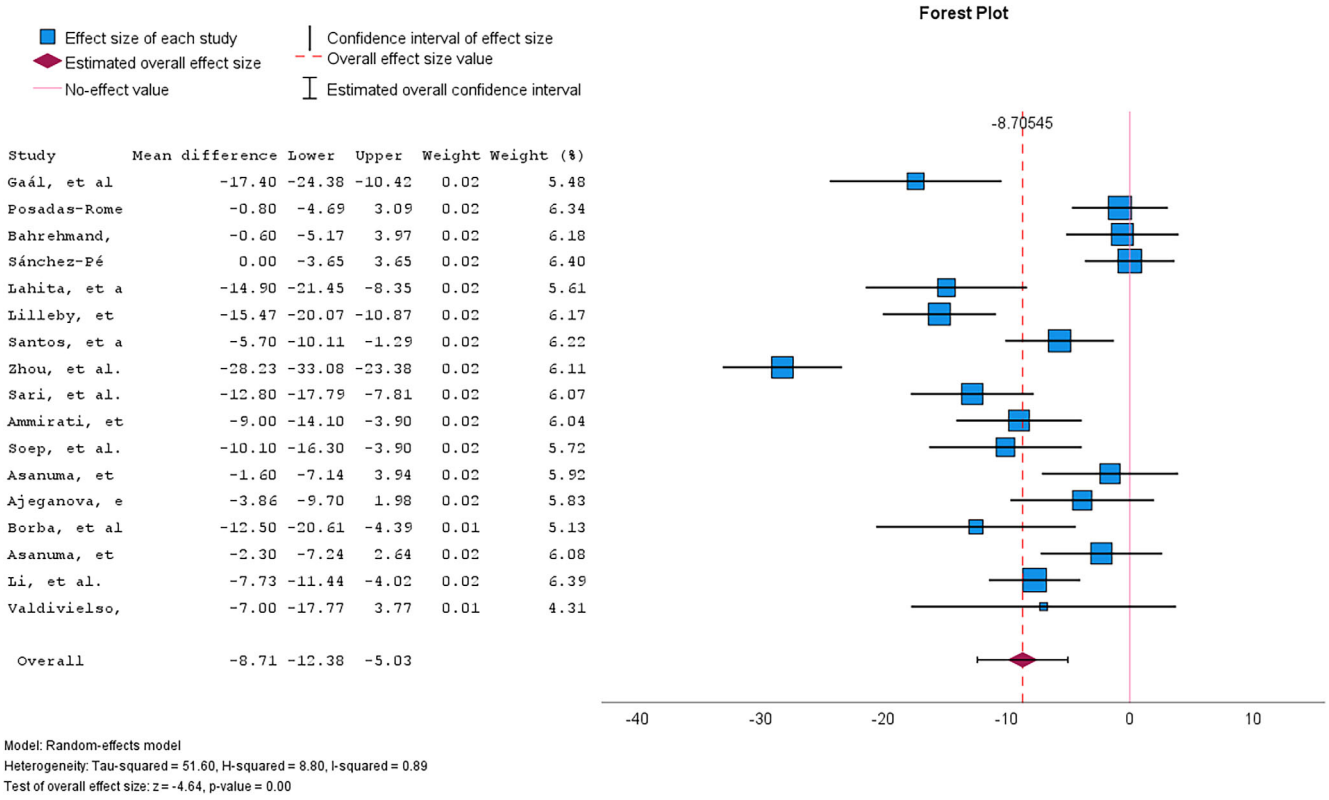

Figure 8. Random effects model meta-analysis in studies with good methodologic quality. The first group comprises patients with systemic lupus erythematosus and the second healthy controls.

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meta-analyses for different clusters of patients with SLE. Interestingly, each of these individual meta-analyses consistently revealed lower HDLc levels in the SLE population.

The grouped analyses also indicated an inverse relationship between disease activity classified by the SLEDAI-2K score and HDLc levels. This observation aligns with expectations, as higher SLEDAI scores can correlate with inflammation, which, in turn, may lead to decreased HDLc levels.[20] However, caution must be taken when interpreting this relationship because SLEDAI indexes usually incorporate clinical descriptors that may not necessarily be directly related to inflammation and, thus, lower HDLc levels. Nonetheless, it is noteworthy that the patients with SLE with moderate or severe disease activity exhibited the highest difference in global mean HDLc levels when compared with those of the controls. Recent studies, both experimental and theoretical, have emphasized the decrease of HDL levels in different inflammatory contexts, such as rheumatoid arthritis, psoriasis, and SLE.[77–79] Recent reviews by Nazir et al[80] and Parra et al[81] have highlighted how alterations in the quantitative and functional aspects of HDL are associated with disease activity in SLE through a variety of mechanisms, including enzyme behavior modification, such as decreases in PON1 activity, enhanced cholesteryl ester transfer protein activity, and activation of remodeling enzymes. Moreover, autoantibodies against HDL and its structural components, especially ApoA1, can further decrease HDL levels and impair their functions in these rheumatologic patients. Although these studies show a correlation between disease activity and HDL levels and functionality, there is a notable absence of research that delves into how the stages of disease activity can modify these lipoproteins within SLE populations and to what degree.

Another interesting finding was a lower HDLc in patients with SLE in the studies that reported corticosteroid dosage. Our analysis compared healthy controls and patients with SLE because this was the available information published. A more suitable study would involve comparing patients receiving treatment with those not receiving treatment to investigate the influence of corticosteroids on HDL levels. Nevertheless, we conducted this analysis because high-dose extended prednisone treatment was the most commonly used among these patients. Following this, lower HDLc levels were expected because previous reports on the use of these medications show lower HDLc levels in patients with SLE.[27,28,82] However, other reports indicate increased HDLc levels with the use of this drug.[73] This reveals a limited scope in this relationship, whereas other immunologic, environmental, and genetic factors, which require further investigation, could explain some of the contrasted levels reported in the literature.

Regarding the methodologic quality of studies, it is not surprising that patients with SLE had remarkably lower HDLc levels in good-quality studies. This just reaffirms the known dyslipoproteinemia observed in patients with SLE when compared with adequately age-sex matched healthy controls.

Possible biologic explanations of our results would undoubtedly include immunologic factors because studies by Lahita et al and Batuca et al have described the presence of autoantibodies against various structural components of these lipoproteins.[30,83] However, it is important to consider that other factors, such as lifestyle, therapeutic regimens, comorbidities, and genetic predisposition, can also contribute to modifying HDLc levels.[18,26,33,84]

Understanding how HDL contributes to SLE disease progression and prognosis is still limited. Initial investigations have primarily focused on HDL alterations as biomarkers. Notably, the studies by McMahon et al[38,85] have established a foundation by introducing the concept of pro-inflammatory HDL (piHDL), which plays a crucial role in SLE chronic inflammation.

Subsequent research has explored the role of piHDL in various SLE populations[24,85–87] and has revealed that HDL in these patients does not exert anti-inflammatory effects. Instead, they promote inflammation and lipid oxidation. This switch in immunomodulation is likely influenced by autoantibodies targeting HDL-associated enzymes, such as PON1[45] or lipoprotein lipase.[88] PON1 is a lactonase associated with HDL that increases HDL binding to macrophages, thereby promoting cholesterol efflux from these cells and reducing foam cell formation. At the same time, PON1 protects against LDL oxidization by macrophages.[89] It has been shown that liver-secreted PON1 can decrease the oxidation of apolipoprotein H in the bloodstream.[90] This apolipoprotein H, also known as β2-glycoprotein I, is a lipid-binding anticoagulant. When oxidized, it becomes a primary antiphospholipid antibodies target. Notably, the production of antiphospholipid antibodies precedes the onset of SLE in mice models and humans patients.[91,92] Although this study did not specifically focus on piHDL, it is important to acknowledge that these altered lipoproteins are part of and may contribute to some extent to the HDLc levels in the SLE population.

Additional studies have highlighted further alterations in HDL among those with SLE, including differences in HDL size and fraction composition, which contribute to impaired anti-inflammatory modulation.[42] It is well established that a quantitative reduction of HDL also affects immunomodulation by HDL.[22,25]

Moreover, it is important to acknowledge the significant interaction between altered HDL and immune cells as a crucial event in the dynamics of the HDL-SLE relationship. Our study observed statistically significant lower levels of HDLc in patients with SLE compared with those of healthy controls. However, it is noteworthy that, in some studies, HDLc levels in the SLE population were similar to those of healthy controls. Nevertheless, it is important to consider that normal HDLc levels do not necessarily indicate proper functional HDL in those with SLE.

The functional aspect of HDL in patients with SLE is as important as its quantitative assessment. HDL can bind to endotoxin and other bacterial products, reducing recognition by monocytes and macrophages, decreasing cytokine release, and providing protection in inflammatory conditions.[9] Similarly,

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HDL can modulate the expression of long pentraxin 3, which regulates complement activation and facilitates pathogen recognition by phagocytes.[13] In addition, during atherosclerosis, HDL also plays a role in modulating dendritic cells (DCs) and impaired migration of DCs. By restoring DC migration, plaque inflammation and size can be reduced by promoting the clearance of dead cells.[12,15]

Lipid raft modification is another mechanism associated with HDL immune modulation. Lipid rafts are cell membrane microdomains enriched with cholesterol, packed saturated glycosphingolipids, and sphingomyelin.[16] These are thought to play an important role in cellular functions such as signaling and cytokine secretion.[93,94] HDL and ApoA1 can modulate the cholesterol content within lipid rafts through transporters ABCA1 and ABCG1. This modulation promotes cholesterol efflux from the lipid rafts, ultimately reducing their signaling functions in the case of Toll-like receptors and other cell receptors related to inflammation.[9,12,16,95] Considering these immunologic mechanisms, any alteration in the function or quantity of HDL could impair these processes, leading to changes in the clinical progression of the disease.

The findings of this theoretical research strongly support the fact that HDL is altered in individuals with SLE and relates to disease activity, which could be a consequence of the widely documented immune-metabolic alterations described in these patients. Considering this, we emphasize the crucial significance of assessing HDL in its multiple dimensions in SLE.

The observed heterogeneity in the meta-analysis is likely to be attributed to differences in clinical features and study populations rather than publication bias or chance. All the included studies followed a similar analytical observational study design, which is appropriate for comparing HDLc levels between groups. Most of the studies clearly defined and differentiated the SLE and healthy control populations, adhered to adequate preanalytical conditions for sera samples, and used validated methodologies or clinical laboratory settings to measure HDLc. Therefore, although methodologic factors contributing to heterogeneity might exist, they are unlikely to contribute significantly to the heterogeneity observed.

Publication bias was assessed, and all studies with significant and nonsignificant results were included, further supporting the notion that heterogeneity arises from population-based differences rather than publication bias. Additionally, excluding studies with very small sample sizes ($n < 10$) minimized the potential impact of chance findings. Most of the included studies had sample sizes double or higher than the minimum sample size requirement, reducing the influence of chance on the observed heterogeneity. Therefore, any potential heterogeneity arising from chance would be minimal and insignificant.

In this way, heterogeneity caused by study population differences may be the most feasible source of this variance in our study and can have two implications. Firstly, this population-based variation may introduce confounding factors unrelated to SLE that could alter HDLc levels. Secondly, this heterogeneity reflects the diversity of those with SLE in different populations and the need for a broader scope that applies to a more comprehensive range of individuals when studying HDL dynamics in SLE.

It is important to emphasize the necessity of conducting analytical observational studies in individuals with SLE. Given the inherent diversity of this disease, a larger number of study participants would increase the precision and accuracy of the results and analyses. By including a more extensive and diverse range of participants, we can enhance our understanding of the relationship between SLE and HDL and provide more reliable and generalizable findings.

We have obtained statistically significant evidence supporting the fact of HDL alterations in the SLE population compared with healthy donors. Furthermore, we examined these changes in patients with SLE in relation to their SLEDAI score, revealing an intriguing relationship. This relationship highlights that higher SLEDAI values are associated with decreased HDLc levels, which offers an interesting scope for exploring the interaction between disease activity and HDLc, extending beyond inflammation. We also identified a direct proportionality behavior regarding corticosteroid use and HDL levels, which further confirms the lipid profile alterations related to the use of these medications in SLE. These findings provide a solid basis for emphasizing the importance of studying HDL in autoimmune diseases like SLE, because these alterations may play a role in immune dysregulation in these patients. Because of the limitations of our study, such as the focus solely on HDLc levels and the exclusion of other variables, such as lifestyles and other comorbidities that may contribute to HDL functional alterations, further research considering additional dimensions of HDL function and exploring the underlying mechanisms is warranted to enhance our understanding of the relationship between HDL and SLE pathogenesis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Pérez-Ocampo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Pérez-Ocampo, Taborda, Higuita-Gutiérrez, Hernandez.

Acquisition of data. Pérez-Ocampo, Taborda, Higuita-Gutiérrez, Hernandez.

Analysis and interpretation of data. Taborda, Yassin, Higuita-Gutiérrez, Hernandez.

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