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Impact of sex disparities on the clinical manifestations in patients with systemic lupus erythematosus

A systematic review and meta-analysis

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune multiorgan disorder of unknown etiology. It affects both men and women, but with different disease manifestations of differing disease severity and in varying proportion, with a female predominance of approximately 90%. There have been numerous studies addressing this issue, especially its implications in relation to optimal sex-tailored treatment and improvement of survival rate; however, further research is warranted. A meta-analysis of studies was performed to compare the impact of sex on the clinical outcomes of SLE in different populations.

Methods: A literature search of the MEDLINE/PubMed and EMBASE databases (until January 2016) was conducted to identify relevant articles. Clinical manifestations reported in these patients were considered as endpoints for this meta-analysis. Two independent reviewers determined eligibility criteria. A fixed-effect model has been used where a small heterogeneity was observed, or else, a random-effect model has been used among the studies. Odd ratio (OR) with 95% confidence interval (Cl) was used to express the pooled effect on dichotomous variables, and the pooled analyses were performed with RevMan 5.3.

Results: Sixteen studies consisting of a total of 11,934 SLE patients (10,331 females and 1603 males) have been included in this meta-analysis. The average female-to-male ratio of all the included studies is around 9.3:1. Several statistically significant differences were found: alopecia, photosensitivity, and oral ulcers were significantly higher in female patients (OR 0.36, 95% CI 0.29–0.46, P < 0.00001; OR 0.72, 95% CI 0.63–0.83, P < 0.00001; and OR 0.70, 95% CI 0.60–0.82, P < 0.00001, respectively). Malar rash was significantly higher in female patients (OR 0.68, 95% CI 0.53–0.88, P = 0.003), and arthritis was significantly lower in male patients (OR 0.72, 95% CI 1.25–1.84, P < 0.00001). However, serositis and pleurisies were significantly higher in female patients (OR 1.52, 95% CI 1.25–1.84 P < 0.00001; and OR 1.26, 95% CI 1.07–1.48, P = 0.006, respectively). Renal involvement was higher in male patients (OR 1.51, 95% CI 1.31–1.75, P < 0.00001).

Conclusion: The results of this meta-analysis suggest that alopecia, photosensitivity, oral ulcers, arthritis, malar rash, lupus anticoagulant level, and low level of C3 were significantly higher in female lupus patients, whereas renal involvement, serositis and pleurisies, thrombocytopenia, and anti-double stranded deoxyribonucleic acid level were predominant in male patients.

Abbreviations: ANAs = antinuclear antibodies, Anti-dsDNA = anti-double stranded deoxyribonucleic acid, OR = odd ratio, SLE = systemic lupus erythematosus.

Keywords: clinical manifestations, meta-analysis, sex differences, systemic lupus erythematosus

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown etiology involving multiple organ systems. It occurs after the loss of self-tolerance of the immune system, which leads to the development of autoantibodies against nuclear antigens, immune complex formation, inflammation, and eventually permanent organ injury. It affects predominantly women, primarily during the reproductive age, with a lower ratio seen before puberty and a decline later in life. The incidence of SLE varies according to the characteristics of each population, such as patients' age, sex, and ethnicity. Sex differences may influence the clinical and serological expression, therapy, and outcome. Epidemiologic studies report the occurrence of SLE varies among different countries and different ethnic groups.^[1,2] These differences suggest that besides hormonal and genetic susceptibility, geographic and environmental factors are also implicated in the development of this connective tissue disease.^[1,2] Whereas SLE is more common in women than in men, male patients are thought to have more severe disease than females.^[3] Over 5-year follow-up, Stefanidou et al^[4] found that male sex might be a poor factor in SLE prognosis.

The objectives of this study were to conduct a systemic literature review and meta-analysis of studies that directly compared the difference in clinical outcomes between male and female lupus patients in various population groups.

2. Methods

2.1. Data sources and search strategy

Medline and EMBASE were searched for studies comparing the clinical manifestations in male and female SLE patients by typing the words/phrases "systemic lupus erythematosus and gender differences." To further enhance this search, the abbreviations "SLE" and the words "sex disparities" have also been used. Reference lists were also searched for relevant titles. Official Web sites of certain journals such as "Medicine" have also been searched for relevant articles.

2.2. Study selection

2.2.1. Inclusion and exclusion criteria. Studies were included if:

- (a) They compared the clinical manifestations in male and female SLE patients.
- (b) Their data were available for comparison (including data for both the experimental and control groups).
- (c) Full text articles were available.

Studies were excluded if:

- (a) They were case studies, letter to editors, or review articles.
- (b) Clinical manifestations were not reported as their endpoints.
- (c) Full text articles were not available.
- (d) Duplicates.

2.3. Outcomes

Outcomes analyzed in this meta-analysis included the following:

- (1) Clinical manifestations of the
 - (a) Cardiovascular system

- (b) Respiratory system
- (c) Renal system
- (d) Connective tissues system
- (e) Hematological system
- (f) Dermatological system
- (g) Neurological system
- (2) Manifestations of certain organ systems according to the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index:
 - (a) Cardiovascular: pericarditis
 - (b) Lungs: pleurisies
 - (c) Skin: alopecia, malar rash, discoid rash, photosensitivity
 - (d) Blood: hematological involvement, hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
 - (e) Connective tissues: arthritis
 - (f) Neurological: neurological involvement, seizures, psychosis
 - (g) Renal: lupus nephritis

The reported outcomes of the included studies have been represented in Tables 1–4.

2.4. Data extraction and quality assessment

Two authors (KDB and SL) independently reviewed the data and assessed the eligibility and methodological quality of each eligible study. Information regarding type and length of study, location and number of patients, clinical manifestations, and authors' first names were systematically extracted. Disagreements were discussed between the authors, and if the authors could not reach a consensus, disagreements were resolved by the third author (XZ). The bias risk within the studies was assessed with the components recommended by the Cochrane Collaboration.^[18]

2.5. Methodological quality and statistical analysis

Heterogeneity across trials was assessed using the Cochrane Q-statistic ($P \le 0.05$ was considered significant) and I^2 -statistic. I^2 described the percentage of total variation across studies, which is due to heterogeneity rather than chance. A value of 0% indicated no heterogeneity, and larger values indicated increase

Table 1

Demographical and clinical manifestations of male and female lupus patients.

Clinical features	Rash malar (%) M/F	Discoid lupus (%) M/F	Photosensitivity (%) M/F	Oral ulcers (%) M/F	Arthritis (%) M/F	Raynaud phenomenon (%) M/F
Brazil ^[5] (2013)	69.4/84.5	8.3/5.6	75.0/77.1	15.3/23.9	88.9/87.3	
Iran ^[6] (2014)	59/60.3	25.9/13	51.5/57.8	39.3/38.8	61.1/71.7	
South Korea ⁽⁷⁾ (2014)	37.7/41.5	17.0/38.2	13.2/24.3	17.0/20.0	60.4/59.3	20.8/28.1
Spain ^[35] (2014)	26.1/41.7	4.4/5.5	30.4/44.9	8.7/15.8		
Latin America ^[51] (1996)					85/88	28/46
Spain ^[36] (2006)	34.8/51.1	19.6/17.7	32.6/48.3	21.7/33.8	78.3/72.9	47.8/33.1
Central America, Mexico, Puerto Rico ^[8] (2007)	55.6/65.0	19.0/17.8	61.9/67.9	57.1/59.5		
Turkey ^[9] (2013])		13.8/17.3	51.7/71.4	24.1/39.8	62.1/71.9	24.1/48.1
Thailand ^[10] (2007)	45.9/48.6	45.9/31.1	29.7/35.1	32.4/29.7	43.2/40.5	0/12.2
Canada ^[11] (1983)				48/58	94/90	50/58
USA ^[12] (2012]) China ^[13] (2009)	39.7/52.4	24.7/19.8	40.4/55.5	34.0/52.9	70.3/74.4	
China ^[14] (2012) Malaysia ^[15] (2001)	67.2/47.6		17.2/12.4	10.3/14.0	17.2/36.7	13.8/8.3
Spain ^[16] (1992])	23/52	20/3	30/31		60/81	30/28
Tunisia ^[17] (2002)	71/61	8/9,2	41/46	12,5/16	95/90	26/22,5

M/F = male/female.

Table 2

Demographical and clinical manifestations of male and female lupus patients (continued).

Clinical features	Serositis (%) M/F	Pleurisies (%) M/F	Pericarditis (%) M/F	Renal (%) M/F	Neurological (%) M/F	Seizure (%) M/F	Psychosis (%) M/F
Brazil ^[5] (2013)	30.6/26.4	25.0/18.1	11.1/10.9	47.2/36.0	8.3/9.8	1.4/1.6	6.9/8.2
Iran ^[6] (2014)		18.4/15.6	10/8.9	52.7/43		13.8/13	4.2/4.9
South Korea ^[7] (2014)	35.8/27.4			62.3/33.6	13.2/5.9		
Spain ^[35] (2014)	39.1/24.4			43.5/24.4	8.7/3.9		
Latin America ^[51] (1996)		38/36		58/44		12/11	4/8
Spain ^[36] (2006)	45.7/26.2	37.0/20.2	26.1/10.4	26.1/30.6	15.2/5.4		
Central America, Mexico, Puerto Rico ^[8] (2007)	63.5/53.0			63.5/52.1	20.6/14.6	15.9/9.7	7.9/6.8
Turkey ^[9] (2013)	24.1/14.8			69/30.3	27.6/11.8		
Thailand ^[10] (2007)	13.5/4.1	21.6/10.8	10.8/5.4	73.0/67.6	13.5/29.7	8.1/9.5	0/13.5
Canada ^[11] (1983)		72/44	48/38	44/46	18/38		
USA ^[12] (2012)		41.7/44.7	25.0/22.3	34.1/18.9		12.7/9.6	4.5/3.7
China ^[13] (2009)							
China ^[14] (2012)	29.3/27.1			58.6/47.2	20.7/12.0		
Malaysia ^[15] (2001)							
Spain ^[16] (1992)	37/29			40/37	0/12		
Tunisia ^[17] (2002)		20/22	37.5/26.6	66/55	12.5/14		

M/F = male/female.

Table 3	
ematological profile and complement levels of male and female lunus patients	

	Hem (%) M/F	Ane (%) M/F	Leu (%) M/F	Lym (%) M/F	Throm (%) M/F	Low C3 levels (%) M/F	Low C4 level (%) M/F
Brazil ^[5] (2013)	47.2/43.8	5.6/9.0	18.1/18.5	30.6/5.7	15.3/14.5		
Iran ^[6] (2014)		2.9/4.3	28.5/35.8	35.1/33.3	19.2/17.7		
Korea ^[7] (2014)	83.0/86.6	28.8/23.9	24.5/53.2	69.8/77.6	28.8/18.7		
Spain ^[35] (2014)		8.7/8.7	34.8/46.5	69.6/71.7	39.1/16.5	60.9/54.3	69.6/80.3
Latin America ^[51] (1996)		16/11	37/39		21/20		
Spain ^[36] (2006)		13.0/21.1	34.8/51.7	34.8/51.7	10.9/14.8		
Central America, Mexico,	86.9/80.6	4.8/11.5	38.1/40.0	77.8/72.1	23.8/21.3		
Puerto Rico ^[8] (2007)							
Turkey ^[9] (2013)	69/67.2	13.8/6			24.1/17.5	37.9/26.8	31/29.3
Thailand ^[10] (2007)	91.9/91.9	37.8/29.7	81.1/74.3	48.6/41.9	32.4/12.1		
Canada ^[11] (1983)		8/10	46/32				
USA ^[12] (2012)		12.8/10.1	47.4/43.3	49.4/38.8	28.8/19.5	60.3/53.2	47.4/46.9
China ^[13] (2009)						67.2/49.8	
China ^[14] (2012)	37.9/40.2						
Malaysia ^[15] (2001)							
Spain ^[16] (1992)		13/6			23/22		
Tunisia ^[17] (2002)		12.5/6	46/44.6	46/46.5	12.5/16.5		

Ane=hemolytic anemia, Hem=hematological involvement, Leu=leukopenia, Lym=lymphopenia, M/F=male/female, Throm=thrombocytopenia.

Table 4

The autoantibody positivity of male and female lupus patients.

	ANA (%) M/F	Anti-dsDNA (%) M/F	Anti-Sm (%) M/F	Anti-RNP (%) M/F	Anti-SSA (%) M/F	Anti-SSB (%) M/F	LAC (%) M/F	ACL (%) M/F
Brazil ^[5]		45.8/34.2	29.2/21.2	16.7/20.1	33.3/31.5	9.7/6.7	5.5/5.5	4.2/5.9
Iran ^[6]	75.3/79	67.8/71.3						
Korea ^[7]	94.3/99.3							
Spain ^[35]	100/99.2	60.9/60.6	8.7/18.1	8.7/21.3	13.0/31.5	0.0/17.7		34.8/45.7
Latin America ^[51]	100/99	54/37	19/15	25/32	25/26	19/17		
Spain ^[36]		89.1/82.6	6.5/7.9	11.1/11.7	22.2/37.0	15.6/17.0	13.0/10.4	26.1/28.4
Central America,							63.5/52.1	
Mexico, Puerto Rico ^[8]								
Turkey ^[9]								
Thailand ^[10]	100/95.9	66.7/70.8	0.0/33.3	0.0/22.2	0.0/11.1	0.0/0.0		50/33.3
Canada ^[11]	100/98	64/80						
Canada ^[11] USA ^[12]		68.2/61.7	23.5/17.5	29.7/26.4	23.9/29.9	7.7/13.0	41.3/25.3	51.4/48.3
China ^[13]								
China ^[14]	94.8/98.0	25.9/16.8	17.2/8.7	29.3/15.3	46.6/28.4	13.8/8.5		25.9/11.4
Malaysia ^[15]								
Spain ^[16]			24/19	16/18	24/27	12/13		
Tunisia ^[17]	100/91.7	82/73.3	44/59		50/53	25/35		53/56.7

ACL=anticardiolipin, anti-RNP=antiribosomal P protein, LAC=lupus anticoagulant, M/F=male/female, SSA=sjogren syndrome-related antigen A, SSB=sjogren syndrome-related antigen B.

heterogeneity. If I^2 was <50%, fixed-effect model was used. However, if I^2 was >50%, a random-effect model was used. Publication bias was visually estimated by assessing funnel plots. We calculated odd ratios (ORs) and 95% confidence intervals (CIs) for categorical variables. The pooled analyses were performed with RevMan 5.3 software. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

2.6. Ethics

Ethical approval was not necessary as this study is a "Systematic Review and Meta-analysis."

3. Results

3.1. Search results

Study selection, data collection, analysis, and reporting of the results were performed using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.^[19] A total of 560 articles were obtained during the search process. Among them, 396 articles were eliminated because they were either duplicates or they were not related to our topic. The remaining 124 full-text articles were assessed for eligibility. A further 95 articles were eliminated because they were letter to editors, review articles, or case studies. Among the 29 remaining articles, 13 more studies were eliminated because either only their abstract parts were available, or there were no control groups for comparison. After strictly considering the inclusion and exclusion criteria, 16 articles were finally selected for this systematic review and meta-analysis. The study selection including the flow of the process for identifying potentially eligible trials has been represented in Fig. 1. The characteristics of the 16 studies that met the eligibility criteria are displayed in Tables 5 and 6.

3.2. Description of the included studies

The 16 articles included in the meta-analysis incorporated a total of 11934 lupus patients, with 1603 males and 10331 females

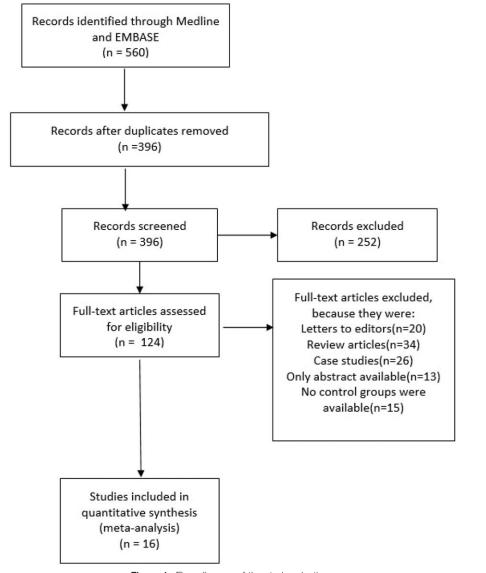




Table c			
General o	haractoristics of the	, included	etudioe

Study	Type of study	Duration of study	Study location	Ethnicity	Ν	F:M
Borba et al ^[5] (2013)	Cohort	2008-2012	Brazil	Caucasian	888	11.3:1
Faezi et al ^[6] (2014)	Retrospective	1976-2011	Iran	Caucasian	2355	10:1
Hwang et al ^[7] (2014)	Retrospective case-control	1994-2010	South Korea	Korean	632	10.1:1
Alonso et al ^[35] (2014)	Retrospective	1987-2006	Spain	Caucasian	150	5.5:1
Molina et al ^[52] (1996)	Cross-sectional	1972-1993	Latin America	Hispanic	1316	11:1
Gomez et al ^[36] (2006)	Prospective	1992-2003	Spain	Caucasian	383	7:1
Andrade et al ^[8] (2007)	Retrospective cohort	2006	Central America,	Hispanic, African American,	618	8.8:1
			Mexico, Puerto Rico	Caucasian		
Pamuk et al ^[9] (2013)	Retrospective	1996-2012	Turkey	Caucasian	428	13.8:1
Mongkoltanatus et al ^[10] (2007)	Retrospective case-control	1992-2005	Thailand	Thai	508	12.2:1
Miller et al ^[11] (1983)	Prospective	1970-1982	Canada	Caucasian	100	1:1
Tan et al ^[12] (2012)	Prospective	2012	USA	African American, Caucasian	1979	11.6:1
Feng et al ^[13] (2009)	Retrospective		China	Chinese	1790	9.2:1
Ding et al ^[14] (2012)	Retrospective	2008-2010	China	Chinese	516	7.98:1
Azizah et al ^[15] (2001)			Malaysia	Malay Chinese Indian	144	10:1
Font et al ^[16] (1992)	Prospective	1980-1990	Spain	Caucasian	261	7.7:1
Othmani et al ^[17] (2002)	Retrospective	1990-1999	Tunisia	Caucasian	295	11.3:1

F:M = female-to-male ratio, N = total number of SLE patients.

from many different locations such as America, Latin America, Spain, China, Malaysia, Iran, Turkey, Korea, Taiwan, Canada, and Brazil. Baseline characteristics of the studies, including sample size, type and duration of study, study location, ethnicity, female-to-male ratio, mean age at time of diagnosis, mean age at disease onset, and length of follow-up are outlined in Tables 5 and 6.

3.3. Results of our analysis

The average female-to-male ratio of all the included studies is around 9.3:1.The forest plots provided pooled OR estimates indicating which clinical features were more common in male patients versus female patients. Results have been summarized in Table 7. The differences in manifestations between male and female patients are shown in Figs. 2–8.

Our analysis, which compared the clinical features between males and females with lupus, showed that alopecia, photosensitivity, and oral ulcers were significantly higher in female patients (OR 0.36, 95% CI 0.29–0.46, P < 0.00001; OR 0.72, 95% CI 0.63–0.83, P < 0.00001; and OR 0.70, 95% CI 0.60–0.82, P < 0.00001, respectively). These results have been represented in Fig. 2.

Arthritis was also significantly lower in male patients (OR 0.72, 95% CI 1.25–1.84, P < 0.00001). However, serositis and pleurisies were significantly higher in male patients (OR 1.52, 95% CI 1.25–1.84, P < 0.0001; and OR 1.26, 95% CI 1.07–1.48, P = 0.006, respectively). Cardiovascular diseases favored females (OR 1.43, 95% CI 0.93–2.19, P = 0.10); however, the result was not statistically significant. These results have been represented in Fig. 3.

Our analysis showed renal involvement also to be significantly lower in female patients (OR 1.51, 95% CI 1.31–1.75, P < 0.00001). Pericarditis, seizure, and psychosis were almost similarly manifested between male and female patients with lupus (OR 1.19, 95% CI 0.97–1.45, P=0.10; OR 1.18, 95% CI 0.92–1.50, P=0.19; and OR 0.76, 95% CI 0.53–1.10, P=0.14, respectively). These results have been represented in Fig. 4.

Table 6

General characteristics of the included studies

	Mean age at di	sease onset, yrs	Mean age at	diagnosis, yrs	Follow-u	o duration
Study	Male	Female	Male	Female	Male	Female
Borba et al ^[5] (2013)	29.9±10.4	29.9±9.5			14.7±8.7 (yrs)	13.8±8.8 (yrs)
Faezi et al ^[6] (2014)	25 ± 11.8	24.5±10.3			6.4 (SD8.3) (yrs)	7.9 (SD10.8) (yrs)
Hwang et al ^[7] (2014)			32.9±13.6	32.6±11.6	58.3±52.2 (mos)	54.2±50.8 (mos
Alonso et al ^[35] (2013)	51.8 ± 21.1	43.2±18.6	52.5 ± 21.4	45.0 ± 19.1	7.5±4.1 (yrs)	7.8±4.6 (yrs)
Molina et al ^[52] (1996)			26	28		
Gomez et al ^[36] (2006)			47.8±16.5	36.6±15.4	11.6±6.7 (yrs)	13.9±10.3 (yrs)
Andrade et al ^[8] (2007)			37 <u>+</u> 14.9	36.5±12.1		
Pamuk et al ^[9] (2013)			40.4 ± 12.3	38.5 ± 13.5	70.5±53.5 (mos)	72.1 ± 67.8 (mos
Mongkoltanatuset al ^[10] (2007)			34.6±14.0	34.4 ± 11.7	26.3 ± 30.3 (mos)	22.9±34.6 (mos
Miller et al ^[11] (1983)			39	37	41 (mos)	48 (mos)
Tan et al ^[12] (2012)					10.2±7.6 (yrs)	11.1±8.5 (yrs)
Feng et al ^[13] (2009)	31 ± 15.9	30.9 ± 11.5				
Ding et al ^[14] (2012)	27.2	28.6				
Azizah et al ^[15] (2001)	30 ± 9	26 ± 10	31 ± 10	27 ± 10	7 ± 4 (yrs)	8±5 (yrs)
Font et al ^[16] (1992)	34	31				
Othmani et al ^[17] (2002)			31.75	30.58		

Table 7

Comparison of clinical manifestations in male and female patients.

More common in male	More common in female	Not significant	Results
	Alopecia		OR 0.36, 95% Cl 0.29–0.46; P<0.00001
	Photosensitivity		OR 0.72, 95% CI 0.63-0.83; P<0.00001
	Oral ulcers		OR 0.70, 95% CI 0.60-0.82; P<0.00001
	Arthritis		OR 0.72, 95% Cl 1.25-1.84; P<0.00001
Serositis			OR 1.52, 95% CI 1.25-1.84; P<0.0001
Pleurisies			OR 1.26, 95% CI 1.07-1.48; P=0.006
		Cardiovascular diseases	OR 1.43, 95% CI 0.93-2.19; P=0.10
Renal involvement			OR 1.51, 95% CI 1.31-1.75; P<0.00001
		Pericarditis	OR 1.19, 95% CI 0.97-1.45; P=0.10
		Seizure	OR 1.18, 95% CI 0.92–1.50; P=0.19
		Psychosis	OR 0.76, 95% CI 0.53-1.10; P=0.14
		Hematological involvement	OR 0.92, 95% CI 0.71-1.19; P=0.52
		Hemolytic anemia	OR 1.03, 95% CI 0.81–1.31; P=0.80
		Lymphopenia	OR 1.13, 95% CI 0.96–1.33; P=0.15
Thrombocytopenia			OR 1.31, 95% CI 1.10-1.56; P=0.002
	Malar rash		OR 0.68, 95% CI 0.53–0.88; P=0.003
		Discoid rash	OR 1.17, 95% CI 0.79–1.73; P=0.43
		Raynaud phenomenon	OR 0.76, 95% CI 0.46-1.24; P=0.27
		Neurological manifestations	OR 1.16, 95% CI 0.80-1.69; P=0.42
	Leukopenia	-	OR 0.80, 95% CI 0.62-1.04; P=0.09
		Anti-Sm antibodies	OR 1.56, 95% CI 0.94–2.59; P=0.09
		Anticardiolipin antibodies	OR 1.26, 95% CI 0.79–2.00; P=0.33
	Lupus anticoagulant	·	OR 1.98, 95% CI 1.53–2.57; P<0.00001
	Low level of C3		OR 1.36, 95% CI 1.06–1.76; P=0.02
		Low C4 level	OR 0.98, 95% CI 0.74–1.31; P=0.91
Anti-dsDNA			OR 1.22, 95% Cl 1.02–1.45; <i>P</i> =0.03
	ANA		OR 0.79, 95% CI 0.59–1.06; P=0.12

ANA=antinuclear antibodies, CI=confidence interval, dsDNA=anti-double stranded deoxyribonucleic acid, OR=odds ratio.

Hematological manifestations, as a whole, were similar between male and female patients with lupus (OR 0.92, 95% CI 0.71–1.19, P=0.52). If analyzed individually, hemolytic anemia and lymphopenia were similar in males and females (OR 1.03, 95% CI 0.81–1.31, P=0.80; and OR 1.13, 95% CI 0.96–1.33, P=0.15, respectively). However, thrombocytopenia was significantly higher in male patients (OR 1.31, 95% CI 1.10–1.56, P=0.002). These results have been represented in Fig. 5.

Since heterogeneity was higher while analyzing certain clinical features, a random-effect model has been used to analyze these features with high heterogeneity. Malar rash was significantly higher in female patients (OR 0.68, 95% CI 0.53–0.88, P= 0.003), whereas discoid rash was higher in male patients (OR 1.17, 95% CI 0.79–1.73, P=0.43). However, the result for discoid rash was not statistically significant. Raynaud phenomenon and neurological manifestations were similar between males and females (OR 0.76, 95% CI 0.46–1.24, P=0.27; and OR 1.16, 95% CI 0.80–1.69, P=0.42, respectively). These results have been shown in Fig. 6.

Leukopenia was higher in female patients; however, the result was not statistically significant (OR 0.80, 95% CI 0.62–1.04, P = 0.09). Anti-Sm antibodies favored female patients (OR 1.56, 95% CI 0.94–2.59, P = 0.09. However, the result was not statistically significant in our study. Anticardiolipin antibodies were also similarly manifested between male and female patients (OR 1.26, 95% CI 0.79–2.00, P = 0.33). These results have been represented in Fig. 7.

Lupus anticoagulant was significantly higher in female patients (OR 1.98, 95% CI 1.53–2.57, P < 0.00001). Low level of C3 was also significantly apparent in females (OR 1.36, 95% CI

1.06–1.76, P=0.02). Low C4 level was similarly observed in males and females (OR 0.98, 95% CI 0.74–1.31, P=0.91). Antidouble stranded deoxyribonucleic acid (dsDNA) was significantly higher in male patients (OR 1.22, 95% CI 1.02–1.45, P= 0.03). Antinuclear antibodies (ANAs) favored male patients; however, the result was not statistically significant (OR 0.79, 95% CI 0.59–1.06, P=0.12). These results have been represented in Fig. 8.

For all of the above analyses, sensitivity analyses yielded consistent results. Based on a visual inspection of the funnel plots, there has been no evidence of publication bias for the included studies that assessed all clinical endpoints in male and female patients with lupus. The funnel plot has been illustrated in Fig. 9.

4. Discussion

This study aimed to show the impact of sex on the clinical manifestations in SLE patients from different population groups. The mean average female-to-male ratio of all the included studies was 9.3:1. This reflects the results of most previous studies, which suggest female predominance in SLE.^[20,21] Several reasons have been brought forward to explain this. One of the main reasons is genetic susceptibility. At least 3 gene variants located on the X chromosome have been shown to be associated with increased risk of developing SLE (Interleukin-1 receptor-associated kinase 1, Methyl CpG binding protein 2, and toll-like receptor 7 [TLR7]). Another possible reason may be related to sex hormones.^[22] It is generally recognized that the male hormone, testosterone, is immunosuppressive, whereas the female hormone, estrogen, stimulates immune response.^[23,24] Lower

	male	s	fema	es		Odds Ratio	Odds Ratio
Study or Subgroup			Events		Weight		
1.1.1 Alopecia	Lionto	. otai	=======	10101	mongint	in 11, 1 1X00, 0070 0	
Canada1983	13	50	28	50	1.8%	0.28 [0.12, 0.64]	
China2009	21	176	376	1614	5.7%	0.45 [0.28, 0.71]	
China2003	10	58	110	458	1.8%	0.66 [0.32, 1.35]	
Malaysia2001	8	12	74	122	0.4%	1.30 [0.37, 4.55]	
Spain2006	3	46	76	317	1.6%	0.22 [0.07, 0.73]	
Thailand2007	5	37	33	74	1.7%	0.19 [0.07, 0.55]	
Tunisia2002	3	24	92	271	1.2%	0.28 [0.08, 0.96]	
USA2012	44	157	1023	1822	10.3%	0.30 [0.21, 0.44]	—
Subtotal (95% CI)		560	1020	4728	24.5%	0.36 [0.29, 0.46]	•
Total events	107		1812				•
Heterogeneity: Chi ² = 10		7 (P =		36%			
Test for overall effect: Z	· · ·	,	<i>,,</i>	0070			
	- 0.00 (1	- 0.00	001)				
1.1.2 Photosensitivity							
Brazil2013	54	72	629	816	2.2%	0.89 [0.51, 1.56]	
Central America2007	39	63	377	555	2.6%	0.77 [0.45, 1.32]	
China2009	22	176	243	1614	3.7%	0.81 [0.51, 1.29]	
China2012	10	58	57	458	0.9%	1.47 [0.70, 3.06]	
Iran2014	123	239	1222	2116	10.6%	0.78 [0.59, 1.01]	
Malaysia2001	7	12	67	122	0.4%	1.15 [0.35, 3.82]	
South Korea2014	7	53	36	150	1.4%	0.48 [0.20, 1.16]	
Spain1992	9	30	71	231	1.0%	0.97 [0.42, 2.21]	
Spain2006	15	46	153	317	2.3%	0.52 [0.27, 1.00]	
Spain2013	39	63	377	555	2.6%	0.77 [0.45, 1.32]	
Thailand2007	11	37	26	74	1.1%	0.78 [0.33, 1.83]	
Tunisia2002	10	24	124	271	1.0%	0.85 [0.36, 1.97]	
Turkey2013	15	29	285	399	1.6%	0.43 [0.20, 0.92]	
USA2012	63	157	1007	1822	8.4%	0.54 [0.39, 0.76]	
Subtotal (95% CI)		1059		9500	40.0%	0.72 [0.63, 0.83]	◆
Total events	424		4674				
Heterogeneity: Chi ² = 12	2.36, df =	13 (P =	: 0.50); l ²	= 0%			
Test for overall effect: Z	= 4.51 (F	P < 0.00	001)				
1.1.3 Oral Ulcers							
Brazil2013	11	72	185	826	2.2%	0.62 [0.32, 1.21]	
Canada1983	24	50	28	50	1.3%	0.73 [0.33, 1.59]	
Central America2007	36	63	330	555	2.5%	0.91 [0.54, 1.54]	
China2009	11	176	232	1614	3.8%	0.40 [0.21, 0.74]	
China2012	6	58	64	458	1.1%	0.71 [0.29, 1.72]	
Iran2014	94	239	820	2116	8.9%	1.02 [0.78, 1.35]	
Malaysia2001	3	12	30	122	0.4%	1.02 [0.26, 4.02]	
South Korea2014	9	53	30	150	1.1%	0.82 [0.36, 1.86]	
Spain2006	10	46	107	317	1.9%	0.55 [0.26, 1.14]	
Spain2013	2	23	20	127	0.5%	0.51 [0.11, 2.35]	
Thailand2007	12	37	22	74	0.9%	1.13 [0.48, 2.65]	
Tunisia2002	3	24	43	271	0.5%	0.76 [0.22, 2.65]	
Turkey2013	7	29	159	399	1.4%	0.48 [0.20, 1.15]	
USA2012	53	157	961	1822	8.9%	0.46 [0.32, 0.64]	
Subtotal (95% CI)		1039		8901	35.5%	0.70 [0.60, 0.82]	•
Total events	281		3031				
Heterogeneity: Chi ² = 20				= 37%			
Test for overall effect: Z	= 4.55 (F	P < 0.00	001)				
Total (95% CI)		2658		23129	100.0%	0.63 [0.57, 0.69]	♦
Total events	812		9517	2		,	
Heterogeneity: $Chi^2 = 7^2$		35 (P =		$ ^2 = 510$	%		
Test for overall effect: Z	· · ·	· ·	,	,. 01			0.01 0.1 1 10 100
Test for subgroup differe			,	2 (P < 0	00001) l²	= 92.6%	Favours [males] Favours [females]
		_0.	-	-		ohotosensitivity, oral u	lleers
			ing		"opooia, j	cholocholinity, of all	

testosterone levels have been observed in male and female patients with SLE. Several studies indicate that testosterone also interacts with the immune system by suppressing both cellular and humoral responses.^[25] Exacerbations of the disease activities of SLE are commonly noted during the premenstrual period,

early pregnancy, and in the puerperium.^[26] This is suggestive of a close relationship between increasing concentrations of plasma estrogen and flare-ups of SLE.^[27] Estrogen seems to play an important role in promoting autoimmune-related immune responses, including the production of cytokines such as Th2

64 47 101 10 146 91 32 18 36 16 16 16 18 109 707 df = 1	Total 72 50 176 58 239 107 12 53 30 46 23 37 29 157 1089	female Events 712 45 1042 168 1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ² 101)	Total 816 50 1614 458 2116 1209 122 150 231 317 127 74 399 1822 9505	Weight 1.5% 0.3% 10.0% 3.6% 13.7% 3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5% 50.0%	Odds Ratio M-H, Fixed, 95% Cl 1.17 [0.54, 2.51] 1.74 [0.39, 7.71] 0.74 [0.54, 1.01] 0.36 [0.18, 0.73] 0.62 [0.47, 0.82] 0.78 [0.45, 1.37] 0.41 [0.10, 1.57] 1.04 [0.55, 1.98] 0.34 [0.15, 0.77] 1.34 [0.64, 2.82] 1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14] 0.72 [0.63, 0.83]	Odds Ratio
64 47 101 10 146 91 32 18 36 16 16 16 18 109 707 df = 1	72 50 176 58 239 107 12 53 30 46 23 37 29 157 1089	712 45 1042 168 1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	816 50 1614 458 2116 1209 122 150 231 317 127 74 399 1822 9505	1.5% 0.3% 10.0% 3.6% 13.7% 3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	$\begin{array}{c} 1.17 \; [0.54,\; 2.51] \\ 1.74 \; [0.39,\; 7.71] \\ 0.74 \; [0.54,\; 1.01] \\ 0.36 \; [0.18,\; 0.73] \\ 0.62 \; [0.47,\; 0.82] \\ 0.78 \; [0.45,\; 1.37] \\ 0.41 \; [0.10,\; 1.57] \\ 1.04 \; [0.55,\; 1.98] \\ 0.34 \; [0.15,\; 0.77] \\ 1.34 \; [0.64,\; 2.82] \\ 1.05 \; [0.40,\; 2.76] \\ 1.12 \; [0.50,\; 2.48] \\ 0.46 \; [0.21,\; 1.02] \\ 0.80 \; [0.56,\; 1.14] \end{array}$	
47 101 146 91 32 18 36 16 16 18 109 707 df = 1	50 176 58 239 107 12 53 30 46 23 37 29 157 1089	45 1042 168 1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	50 1614 458 2116 1209 122 150 231 317 127 74 399 1822 9505	0.3% 10.0% 3.6% 13.7% 3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	$\begin{array}{c} 1.74 \ [0.39, 7.71] \\ 0.74 \ [0.54, 1.01] \\ 0.36 \ [0.18, 0.73] \\ 0.62 \ [0.47, 0.82] \\ 0.78 \ [0.45, 1.37] \\ 0.41 \ [0.10, 1.57] \\ 1.04 \ [0.55, 1.98] \\ 0.34 \ [0.15, 0.77] \\ 1.34 \ [0.64, 2.82] \\ 1.05 \ [0.40, 2.76] \\ 1.12 \ [0.50, 2.48] \\ 0.46 \ [0.21, 1.02] \\ 0.80 \ [0.56, 1.14] \end{array}$	
47 101 146 91 32 18 36 16 16 18 109 707 df = 1	50 176 58 239 107 12 53 30 46 23 37 29 157 1089	45 1042 168 1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	50 1614 458 2116 1209 122 150 231 317 127 74 399 1822 9505	0.3% 10.0% 3.6% 13.7% 3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	$\begin{array}{c} 1.74 \ [0.39, 7.71] \\ 0.74 \ [0.54, 1.01] \\ 0.36 \ [0.18, 0.73] \\ 0.62 \ [0.47, 0.82] \\ 0.78 \ [0.45, 1.37] \\ 0.41 \ [0.10, 1.57] \\ 1.04 \ [0.55, 1.98] \\ 0.34 \ [0.15, 0.77] \\ 1.34 \ [0.64, 2.82] \\ 1.05 \ [0.40, 2.76] \\ 1.12 \ [0.50, 2.48] \\ 0.46 \ [0.21, 1.02] \\ 0.80 \ [0.56, 1.14] \end{array}$	
101 10 146 91 32 18 36 16 16 16 18 109 707 df = 1	176 58 239 107 12 53 30 46 23 37 29 157 1089	1042 168 1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	1614 458 2116 1209 122 150 231 317 127 74 399 1822 9505	$10.0\% \\ 3.6\% \\ 13.7\% \\ 3.0\% \\ 0.8\% \\ 2.1\% \\ 2.0\% \\ 1.5\% \\ 0.9\% \\ 1.3\% \\ 1.8\% \\ 7.5\% \\$	$\begin{array}{c} 0.74 & [0.54, 1.01] \\ 0.36 & [0.18, 0.73] \\ 0.62 & [0.47, 0.82] \\ 0.78 & [0.45, 1.37] \\ 0.41 & [0.10, 1.57] \\ 1.04 & [0.55, 1.98] \\ 0.34 & [0.15, 0.77] \\ 1.34 & [0.64, 2.82] \\ 1.05 & [0.40, 2.76] \\ 1.12 & [0.50, 2.48] \\ 0.46 & [0.21, 1.02] \\ 0.80 & [0.56, 1.14] \end{array}$	
10 146 91 3 2 18 36 16 16 16 18 109 707 df = 1	58 239 107 12 53 30 46 23 37 29 157 1089	168 1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	458 2116 1209 122 231 317 127 74 399 1822 9505	3.6% 13.7% 3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	0.36 [0.18, 0.73] 0.62 [0.47, 0.82] 0.78 [0.45, 1.37] 0.41 [0.10, 1.57] 1.04 [0.55, 1.98] 0.34 [0.15, 1.98] 1.35 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
146 91 32 18 36 16 16 18 109 707 df = 1	239 107 12 53 30 46 23 37 29 157 1089	1517 1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	2116 1209 122 150 231 317 127 74 399 1822 9505	13.7% 3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	0.62 [0.47, 0.82] 0.78 [0.45, 1.37] 0.41 [0.10, 1.57] 1.04 [0.55, 1.98] 0.34 [0.15, 0.77] 1.34 [0.64, 2.82] 1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
91 3 32 18 36 16 16 18 109 707 df = 1	107 12 53 30 46 23 37 29 157 1089	1063 55 89 188 231 87 30 311 1347 6885 0.12); I ²	1209 122 150 231 317 127 74 399 1822 9505	3.0% 0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	0.78 [0.45, 1.37] 0.41 [0.10, 1.57] 1.04 [0.55, 1.98] 0.34 [0.15, 0.77] 1.34 [0.64, 2.82] 1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
3 32 18 36 16 16 18 109 707 df = 1	12 53 30 46 23 37 29 157 1089	55 89 188 231 87 30 311 1347 6885 0.12); I ²	122 150 231 317 127 74 399 1822 9505	0.8% 2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	0.41 [0.10, 1.57] 1.04 [0.55, 1.98] 0.34 [0.15, 0.77] 1.34 [0.64, 2.82] 1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
32 18 36 16 16 18 109 707 df = 1	53 30 46 23 37 29 157 1089	89 188 231 87 30 311 1347 6885 0.12); I ²	150 231 317 127 74 399 1822 9505	2.1% 2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	1.04 (0.55, 1.98) 0.34 (0.15, 0.77) 1.34 (0.64, 2.82) 1.05 (0.40, 2.76) 1.12 (0.50, 2.48) 0.46 (0.21, 1.02) 0.80 (0.56, 1.14)	
18 36 16 18 109 707 df = 1	30 46 23 37 29 157 1089 13 (P = 1	188 231 87 30 311 1347 6885 0.12); I ²	231 317 127 74 399 1822 9505	2.0% 1.5% 0.9% 1.3% 1.8% 7.5%	0.34 [0.15, 0.77] 1.34 [0.64, 2.82] 1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
36 16 18 109 707 df = 1	46 23 37 29 157 1089 13 (P = 1	231 87 30 311 1347 6885 0.12); I ²	317 127 74 399 1822 9505	1.5% 0.9% 1.3% 1.8% 7.5%	1.34 [0.64, 2.82] 1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
16 16 18 109 707 df = 1	23 37 29 157 1089	87 30 311 1347 6885 0.12); I ²	127 74 399 1822 9505	0.9% 1.3% 1.8% 7.5%	1.05 [0.40, 2.76] 1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
16 18 109 707 df = 1	37 29 157 1089 13 (P = 1	30 311 1347 6885 0.12); I ²	74 399 1822 9505	1.3% 1.8% 7.5%	1.12 [0.50, 2.48] 0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
18 109 1 707 df = 1	29 157 1089 13 (P = 1	311 1347 6885 0.12); I ²	399 1822 9505	1.8% 7.5%	0.46 [0.21, 1.02] 0.80 [0.56, 1.14]	
109 707 df = 1	157 1089 13 (P =	1347 6885 0.12); l²	1822 9505	7.5%	0.80 [0.56, 1.14]	
1 707 df = 1	1089 13 (P =	6885 0.12); l²	9505			•
707 df = 1	13 (P =	0.12); l²		50.0%	0.72 [0.63, 0.83]	♥
df = 1		0.12); l²	= 32%			1
		1.	= 32%			
48 (P ·	< 0.000	01)				
22	72	215	816	2.8%	1.23 [0.73, 2.08]	-
40	63	294	555	2.5%	1.54 [0.90, 2.65]	+
38	176	258	1614	4.6%	1.45 [0.99, 2.12]	
17	58	124	458	2.3%	1.12 [0.61, 2.04]	-
19	53	41	150	1.6%	1.49 [0.76, 2.89]	+
11	30	67	231	1.1%		
21	46	83	317	1.3%		
9	23	31	127	0.7%		+
	587					•
			770			
				0.404		
3		21	122	0.3%	1.60 [0.40, 6.43]	
	46	64	317	1.2%	2.32 [1.20, 4.48]	
17			511	1.270	2.02 [1.20, 4.40]	
17 8	46 37	8	74	0.5%	2.28 [0.78, 6.65]	+
8	37 24 157	8	74	0.5%	2.28 [0.78, 6.65]	
8 5	37 24	8 60	74 271	0.5% 0.9%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58]	
8 5 65 262 df = 9	37 24 157 920	8 60 810 2060 .06); I ² =	74 271 1822 8411	0.5% 0.9% 8.6%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23]	
8 5 65 262 df = 9	37 24 157 920 9 (P = 0	8 60 810 2060 .06); I ² =	74 271 1822 8411	0.5% 0.9% 8.6%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23]	
8 5 65 262 df = 9 75 (P =	37 24 157 920 9 (P = 0 = 0.006	8 60 810 2060 .06); I ² =	74 271 1822 8411 45%	0.5% 0.9% 8.6% 28.7%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48]	
8 5 65 262 df = 9 75 (P =	37 24 157 920 9 (P = 0 = 0.006	8 60 810 2060 .06); I ² =	74 271 1822 8411 45% 1209	0.5% 0.9% 8.6% 28.7% 2.9%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48]	
8 5 65 262 df = 9 75 (P = 22 3	$37 \\ 24 \\ 157 \\ 920 \\ 0 (P = 0) \\ = 0.006 \\ 107 \\ 30 \\ 30$	8 60 810 2060 .06); I ² = ;) 193 11	74 271 1822 8411 45% 1209 231	0.5% 0.9% 8.6% 28.7% 2.9% 0.3%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47]	
8 5 65 262 df = 9 75 (P =	$37 \\ 24 \\ 157 \\ 920 \\ 9 (P = 0) \\ = 0.006 \\ 107 \\ 30 \\ 37 \\ 37 \\ 37 \\ 30 \\ 37 \\ 37 \\ $	8 60 810 2060 .06); I ² =	74 271 1822 8411 45% 1209 231 74	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28]	
8 5 65 262 df = 9 75 (P = 22 3 6	$37 \\ 24 \\ 157 \\ 920 \\ 0 (P = 0) \\ = 0.006 \\ 107 \\ 30 \\ 30$	8 60 810 2060 .06); I ² = ;) 193 11 9	74 271 1822 8411 45% 1209 231	0.5% 0.9% 8.6% 28.7% 2.9% 0.3%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47]	
8 5 65 262 df = 9 75 (P = 22 3 6 31 df = 2 (37 24 157 920 9 (P = 0 = 0.006 107 30 37 174	8 60 810 2060 .06); I ² = ;) 193 11	74 271 1822 8411 45% 1209 231 74 1514	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28]	
8 5 65 df = 9 75 (P = 22 3 6 31 df = 2 (63 (P =	$37 \\ 24 \\ 157 \\ 920 \\ 9 (P = 0) \\ = 0.006 \\ 107 \\ 30 \\ 37 \\ 174 \\ (P = 0.8 \\ = 0.10)$	8 60 810 2060 .06); I ² = ;) 193 11 9 213 30); I ² = (74 271 1822 8411 45% 1209 231 74 1514	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6% 3.7%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28] 1.43 [0.93, 2.19]	
8 5 65 262 df = 9 75 (P = 22 3 6 31 df = 2 (63 (P =	$37 \\ 24 \\ 157 \\ 920 \\ 0 (P = 0) \\ 0 = 0.006 \\ 107 \\ 30 \\ 37 \\ 174 \\ (P = 0.8) \\ 0 = 0.006 \\ 0 = 0.00$	8 60 810 2060 .06); I ² = ;) 193 11 9 213 30); I ² = (74 271 1822 8411 45% 1209 231 74 1514	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28]	
8 5 65 262 df = 9 75 (P = 22 3 6 31 if = 2 (63 (P = 23 6 31 15 24 31 22 3 6 31 31 31 31 31 31 31 31 31 31 31 31 31	$37 \\ 24 \\ 157 \\ 920 \\ 0 (P = 0) \\ 0 = 0.006 \\ 107 \\ 30 \\ 37 \\ 174 \\ (P = 0.8 \\ 0 = 0.10) \\ 2770 \\ 0 = 0.00 \\$	8 60 810 2060 .06); l ² = ;) 193 11 9 213 80); l ² = (10333	74 271 1822 8411 45% 1209 231 74 1514 0% 24171	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6% 3.7%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28] 1.43 [0.93, 2.19]	
8 5 65 262 df = 9 75 (P = 22 3 6 31 if = 2 (63 (P = 2 189 31 df = 3	$37 \\ 24 \\ 157 \\ 920 \\ 9 = 0.006 \\ 107 \\ 30 \\ 37 \\ 174 \\ (P = 0.8 \\ = 0.10) \\ 2770 \\ 36 (P < 10) \\ 37 \\ 174 \\ (P = 0.8 \\ 10) \\ 100 $	8 60 810 2060 .06); I ² = ;) 193 11 9 213 30); I ² = (74 271 1822 8411 45% 1209 231 74 1514 0% 24171	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6% 3.7%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28] 1.43 [0.93, 2.19]	
8 5 65 262 df = 9 75 (P = 22 3 6 31 if = 2 (63 (P = 2 189 df = 3 888 (P =	$37 \\ 24 \\ 157 \\ 920 \\ 9 (P = 0) \\ 0 = 0.006 \\ 107 \\ 30 \\ 37 \\ 174 \\ (P = 0.8 \\ = 0.10) \\ 2770 \\ 36 (P < 0) \\ 0 = 0.38) \\ 0 = 0.38 $	$8 \\ 60 \\ 810 \\ 2060 \\ 06); ^{2} = $ $193 \\ 11 \\ 9 \\ 213 \\ 30); ^{2} = ($ $10333 \\ 0.00001]$	74 271 1822 8411 45% 1209 231 74 1514 0% 24171); l ² = 59	0.5% 0.9% 8.6% 28.7% 2.9% 0.3% 0.6% 3.7%	2.28 [0.78, 6.65] 0.93 [0.33, 2.58] 0.88 [0.63, 1.23] 1.26 [1.07, 1.48] 1.36 [0.83, 2.23] 2.22 [0.58, 8.47] 1.40 [0.46, 4.28] 1.43 [0.93, 2.19] 1.04 [0.95, 1.14]	0.01 0.1 [males] Favours [females]
11	38 17 19 11 21 9 5 7 89 5 7 89 5 7 89 6 (P 18 36 26 44 40 3	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

cytokines (e.g., interleukin [IL]-4, IL-6, and IL-10), antibodies, and endogenous autoantigens such as Human endogenous retroviruses (HERV).^[28–30] These HERV proteins seem to be related to autoantibody production, through molecular mimicry between HERV proteins and autoantigens such as ribonucleoprotein antigens, and are reported to be one of the pathogenic

factors of SLE.^[30] Moreover, estrogens bind to and activate estrogen receptors which modulate the expression of many genes. The abnormal expression of estrogen or its receptors may lead to immunological diseases, including SLE. Possible mechanisms suggested for the high female predominance are fetal microchimerism, X chromosome inactivation, and X chromosome

Study or Subgroup	males	s	femal	es		Odds Ratio	Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
1.1.1 Pericarditis							
Brazil2013	8	72	89	816	2.0%	1.02 [0.47, 2.20]	
Canada1983	24	50	19	50	1.5%	1.51 [0.68, 3.34]	+
China2009	14	176	156	1614	4.4%	0.81 [0.46, 1.43]	
ran2014	24	239	188	2116	5.3%	1.14 [0.73, 1.79]	
_atin America1996	15	107	157	1209	3.4%	1.09 [0.62, 1.93]	
Valaysia2001	1	12	6	122	0.2%	1.76 [0.19, 15.95]	
Spain2006	12	46	33	317	1.0%	3.04 [1.43, 6.43]	
Thailand2007	4	37	4	74	0.4%	2.12 [0.50, 9.01]	
JSA2012	39	157	403	1822	7.4%	1.16 [0.80, 1.70]	
Subtotal (95% CI)		896		8140	25.5%	1.19 [0.97, 1.45]	•
Total events	141		1055				
Heterogeneity: Chi ² = 9	.12, df = 8	6 (P = 0	.33); I² =	12%			
est for overall effect: Z	<u>′</u> = 1.66 (P	P = 0.10)				
1.1.2 Renal involveme							
Brazil2013	34	72	294	816	3.9%	1.59 [0.98, 2.58]	
Canada1983	22	50	23	50	2.0%	0.92 [0.42, 2.03]	
China2009	108	176	892	1614	10.5%	1.29 [0.93, 1.77]	† •-
China2012	34	58	216	458	3.1%	1.59 [0.91, 2.76]	<u> </u>
atin America1996	62	107	532	1209	5.6%	1.75 [1.17, 2.62]	
Malaysia2001	9	12	77	122	0.5%	1.75 [0.45, 6.81]	
South Korea2014	33	53	50	150	1.5%	3.30 [1.72, 6.33]	· · · ·
Spain1992	12	30	86	231	1.8%	1.12 [0.52, 2.45]	- <u>+</u>
Spain2006	12	46	97	317	2.8%	0.80 [0.40, 1.61]	
Spain2013	10	23	31	127	0.8%	2.38 [0.95, 5.97]	
Thailand2007	23	37	50	74	2.0%	0.79 [0.35, 1.80]	
Funisia2002	15	24	149	271	1.4%	1.36 [0.58, 3.23]	
Turkey2013	20	29	121	399	0.8%	5.11 [2.26, 11.54]	
JSA2012	78	157	732	1822	9.1%	1.47 [1.06, 2.04]	
Subtotal (95% CI)		874		7660	45.9%	1.51 [1.31, 1.75]	•
Total events	472		3350				
Heterogeneity: Chi ² = 2	4.38. df =	13 (P =	= 0.03); l ²	= 47%			
Test for overall effect: Z							
	,		,				
1.1.3 Seizure							
Brazil2013	1	72	13	816	0.3%	0.87 [0.11, 6.75]	
Central America2007	10	63	54	555	1.4%	1.75 [0.84, 3.64]	
			275	2116	7.5%	1.07 [0.73, 1.58]	+
ran2014	33	239		1209	3.7%	0.85 [0.47, 1.55]	
			169		÷ /v		
_atin America1996	13	107	169 11		0.3%	2.02 [0.39. 10.40]	
₋atin America1996 Malaysia2001		107 12	11	122	0.3% 0.3%	2.02 [0.39, 10.40] 2.11 [0.52, 8.55]	
₋atin America1996 Malaysia2001 Γhailand2007	13 2 3	107 12 37	11 7	122 174	0.3%	2.11 [0.52, 8.55]	
.atin America1996 Malaysia2001 Fhailand2007 JSA2012	13 2	107 12	11	122		2.11 [0.52, 8.55] 1.37 [0.84, 2.25]	
.atin America1996 Malaysia2001 Fhailand2007 JSA2012 Subtotal (95% CI)	13 2 3 20	107 12 37 157	11 7 175	122 174 1822	0.3% 3.8%	2.11 [0.52, 8.55]	•
atin America1996 Malaysia2001 Fhailand2007 JSA2012 Subtotal (95% CI) Fotal events	13 2 3 20 82	107 12 37 157 687	11 7 175 704	122 174 1822 6814	0.3% 3.8%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25]	•
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4	13 2 3 20 82 00, df = 6	107 12 37 157 687	11 7 175 704 .68); I ² = 0	122 174 1822 6814	0.3% 3.8%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25]	•
₋atin America1996 Malaysia2001 Thailand2007 JSA2012	13 2 3 20 82 00, df = 6	107 12 37 157 687	11 7 175 704 .68); I ² = 0	122 174 1822 6814	0.3% 3.8%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25]	•
Latin America1996 Malaysia2001 Fhailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: Z	13 2 3 20 82 00, df = 6	107 12 37 157 687	11 7 175 704 .68); I ² = 0	122 174 1822 6814	0.3% 3.8%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25]	•
Latin America1996 Malaysia2001 Fhailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: Z 1.1.4 Psychosis	13 2 3 20 82 00, df = 6	107 12 37 157 687 6 (P = 0	11 7 175 704 .68); I ² = (122 174 1822 6814	0.3% 3.8% 17.3%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50]	•
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: Z	13 2 3 20 82 00, df = 6	107 12 37 157 687	11 7 175 704 .68); I ² = 0	122 174 1822 6814 0% 816	0.3% 3.8% 17.3%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14]	
Latin America1996 Malaysia2001 Fhailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: Z 1.1.4 Psychosis Brazil2013	13 2 3 20 82 .00, df = 6 Z = 1.30 (P 5 5	107 12 37 157 687 687 6 (P = 0 P = 0.19 72 63	11 7 175 704 .68); I ² = ()) 67 37	122 174 1822 6814 0% 816 555	0.3% 3.8% 17.3% 1.6% 1.1%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America2007 ran2014	13 2 3 20 82 .00, df = 6 Z = 1.30 (P	107 12 37 157 687 6 (P = 0 P = 0.19 72 63 239	11 7 175 .68); I ² = ()) 67 37 103	122 174 1822 6814 0% 816 555 2116	0.3% 3.8% 17.3% 1.6% 1.1% 3.1%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: 2 1.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996	13 2 3 20 82 .00, df = 6 2 = 1.30 (P 5 5 5 10 4	107 12 37 157 687 6 (P = 0 P = 0.19 72 63 239 107	11 7 175 68); l ² = ()) 67 37 103 97	122 174 1822 6814 0% 816 555 2116 1209	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23]	
Latin America1996 Malaysia2001 Fnailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fost for overall effect: 2 I.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001	13 2 3 20 82 2.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1	107 12 37 157 687 687 687 610 72 63 239 107 12	11 7 175 704 .68); l ² = ()) 67 37 103 97 19	122 174 1822 6814 0% 816 555 2116 1209 122	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04]	
atin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: 2 I.1.4 Psychosis Brazil2013 Central America2007 ran2014 .atin America1996 Malaysia2001 Thailand2007	13 2 3 20 82 0.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1 0	107 12 37 157 687 687 69 = 0.19 72 63 239 107 12 37	11 7 175 704 .68); l ² = ()) 67 37 103 97 19 10	122 174 1822 6814 0% 816 555 2116 1209 122 74	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America2007 ran2014	13 2 3 20 82 2.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1	107 12 37 157 687 687 687 610 72 63 239 107 12	11 7 175 704 .68); l ² = ()) 67 37 103 97 19	122 174 1822 6814 0% 816 555 2116 1209 122	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1% 1.6%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Fest for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI)	13 2 3 20 82 .00, df = 6 Z = 1.30 (P 5 5 5 10 4 1 0 7	107 12 37 157 687 6 9 = 0.19 72 63 239 107 12 37 157	11 7 175 668); ² = ()) 67 37 103 97 19 10 67	122 174 1822 6814 0% 816 555 2116 1209 122 74 1822	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Fest for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events	13 2 3 20 82 .00, df = 6 2 = 1.30 (P 5 5 5 10 4 1 0 7 32	$\begin{array}{c} 107 \\ 12 \\ 37 \\ 157 \\ 687 \\ 687 \\ 687 \\ 687 \\ 687 \\ 72 \\ 63 \\ 239 \\ 107 \\ 12 \\ 37 \\ 157 \\ 687 \end{array}$	11 7 175 704 .68); l ² = ()) 67 37 103 97 19 10 67 400	122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1% 1.6%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: 2 I.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 5	13 2 3 20 82 2.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1 0 7 32 0.92, df = 6	107 12 37 157 687 687 687 72 63 239 107 12 37 157 687 5 (P = 0	11 7 175 704 .68); l ² = ()) 67 37 103 97 19 10 67 400 .43); l ² = (122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1% 1.6%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Fest for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events	13 2 3 20 82 2.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1 0 7 32 0.92, df = 6	107 12 37 157 687 687 687 72 63 239 107 12 37 157 687 5 (P = 0	11 7 175 704 .68); l ² = ()) 67 37 103 97 19 10 67 400 .43); l ² = (122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1% 1.6%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: 2 I.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 5	13 2 3 20 82 2.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1 0 7 32 0.92, df = 6	107 12 37 157 687 687 687 72 63 239 107 12 37 157 687 5 (P = 0	11 7 175 704 .68); l ² = ()) 67 37 103 97 19 10 67 400 .43); l ² = (122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714	0.3% 3.8% 17.3% 1.6% 1.1% 3.1% 2.4% 0.5% 1.1% 1.6%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Fest for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5 Fest for overall effect: Z	13 2 3 20 82 .00, df = 6 Z = 1.30 (P 5 5 5 10 4 1 0 7 32 9.92, df = 6 Z = 1.46 (P	$\begin{array}{c} 107\\ 12\\ 37\\ 157\\ 687\\ \end{array}$	11 7 175 704 .68); ² = ()) 67 37 103 97 19 10 67 400 .43); ² = (122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714	0.3% 3.8% 17.3% 1.6% 1.1% 2.4% 0.5% 1.1% 1.6% 11.2%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71] 0.76 [0.53, 1.10]	
Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: Z 1.1.4 Psychosis Brazil2013 Central America2007 ran2014 Latin America1996 Malaysia2001 Thailand2007 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5 Test for overall effect: Z Total (95% CI) Total events	13 2 3 20 82 .00, df = 6 Z = 1.30 (P 5 5 5 10 4 1 0 7 7 2.92, df = 6 Z = 1.46 (P 727	$\begin{array}{c} 107\\ 12\\ 37\\ 157\\ 687\\ \end{array}$	11 7 175 704 .68); l ² = ()) 67 37 103 97 19 10 67 400 67 400 .43); l ² = (122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714 0% 29328	0.3% 3.8% 17.3% 1.6% 1.1% 2.4% 0.5% 1.1% 1.6% 11.2%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71] 0.76 [0.53, 1.10]	
Latin America 1996 Malaysia 2001 Thailand 2007 JSA 2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: Z I.1.4 Psychosis Brazil 2013 Central America 2007 ran 2014 Latin America 1996 Malaysia 2001 Fhailand 2007 JSA 2012 Subtotal (95% CI) Fotal events Heterogeneity: Chi ² = 5 Fest for overall effect: Z Fotal (95% CI) Fotal events Heterogeneity: Chi ² = 5	13 2 3 20 82 2.00, df = 6 2 = 1.30 (P 5 5 5 10 4 1 0 7 32 9.92, df = 6 2 = 1.46 (P 727 3.71, df =	$\begin{array}{c} 107\\ 12\\ 37\\ 157\\ 687\\ \end{array}$	11 7 704 .68); l ² = ()) 67 37 103 97 19 10 67 400 .43); l ² = (.) 5509 = 0.03); l ²	122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714 0% 29328	0.3% 3.8% 17.3% 1.6% 1.1% 2.4% 0.5% 1.1% 1.6% 11.2%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71] 0.76 [0.53, 1.10]	• • • • • • • • • • • • • • • • • • •
atin America 1996 Aalaysia 2001 Thailand 2007 JSA 2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4 Test for overall effect: Z .1.4 Psychosis Brazil 2013 Central America 1996 Aalaysia 2001 Thailand 2007 JSA 2012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5 Test for overall effect: Z Total (95% CI) Total events	13 2 3 20 82 .00, df = 6 Z = 1.30 (P 5 5 10 4 1 0 7 32 .92, df = 6 Z = 1.46 (P 727 3.71, df = Z = 4.92 (P	$\begin{array}{c} 107\\ 12\\ 37\\ 157\\ 687\\ \end{array}$	11 7 704 .68); ² = ()) 67 37 103 97 19 10 67 400 .43); ² = (.) 5509 = 0.03); ²	122 174 1822 6814 0% 816 555 2116 1209 122 74 1822 6714 0% 29328 = 33%	0.3% 3.8% 17.3% 1.6% 1.1% 2.4% 0.5% 1.1% 1.6% 11.2%	2.11 [0.52, 8.55] 1.37 [0.84, 2.25] 1.18 [0.92, 1.50] 0.83 [0.33, 2.14] 1.21 [0.46, 3.19] 0.85 [0.44, 1.66] 0.45 [0.16, 1.23] 0.49 [0.06, 4.04] 0.08 [0.00, 1.44] 1.22 [0.55, 2.71] 0.76 [0.53, 1.10] 1.29 [1.16, 1.42]	

abnormalities.^[31] However, further research is warranted here. Specific mutations of X chromosome genes cause autoimmune syndromes characterized by different degrees of severity.^[32] Scofield et al suggested that the number of X chromosomes is another major cause of sex-specific difference because both the

number of X chromosomes and genetic variants on the X chromosome are related to the risk of development of SLE. Hence, 2 functional X chromosomes, either by sex or by translocation or duplication, seem to confer a greater risk of SLE than 1 X chromosome.^[33] Male patients with Klinefelter

	male		femal			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
1.1.1 Hematological		=0					
Brazil2013	34 54	72 63	357 449	816 555	4.1%	1.15 [0.71, 1.86]	
Central America2007 China2012	54 22	58	449 184	555 458	1.8% 3.5%	1.42 [0.68, 2.96] 0.91 [0.52, 1.60]	
South Korea2014	44	53	130	150	1.6%	0.75 [0.32, 1.77]	
Spain2006	20	46	200	317	3.9%	0.45 [0.24, 0.84]	
Thailand2007	34	37	68	74	0.5%	1.00 [0.24, 4.25]	
Turkey2013	20	29	268	399	1.5%	1.09 [0.48, 2.45]	
Subtotal (95% CI)		358		2769	16.8%	0.92 [0.71, 1.19]	◆
Total events	228		1656				
Heterogeneity: Chi ² = 7				20%			
Test for overall effect: 2	z = 0.64 (F	P = 0.52	2)				
1.1.2 Hemolytic anem	ia						
Brazil2013	1a 4	72	73	816	1.5%	0 60 10 21 1 601	
Central America2007	4	63	63	555	1.6%	0.60 [0.21, 1.69] 0.39 [0.12, 1.28]	
Iran2014	7	239	91	2116	2.4%	0.67 [0.31, 1.47]	
Latin America1996	17	107	133	1209	2.5%	1.53 [0.88, 2.65]	
Malaysia2001	1	12	27	122	0.6%	0.32 [0.04, 2.59]	
South Korea2014	15	53	36	150	1.8%	1.25 [0.62, 2.53]	
Spain1992	4	30	15	231	0.4%	2.22 [0.68, 7.18]	
Spain2006	6	46	67	317	2.0%	0.56 [0.23, 1.38]	
Spain2013	2	23	11	127	0.4%	1.00 [0.21, 4.86]	
Thailand2007	14	37	22	74	1.2%	1.44 [0.63, 3.30]	- •
Turkey2013	4	29	24	399	0.4%	2.50 [0.80, 7.76]	+
USA2012	19	157	178	1822	3.3%	1.27 [0.77, 2.10]	<u>+-</u>
Subtotal (95% CI)		868		7938	18.2%	1.03 [0.81, 1.31]	•
Total events	96		740				
Heterogeneity: Chi ² = 1		,	,.	= 28%			
Test for overall effect: 2	2 = 0.26 (F	² = 0.80))				
1.1.3 thrombocytopen	ia						
Brazil2013	11	72	118	816	2.2%	1.07 [0.55, 2.09]	
Central America2007	15	63	118	555	2.5%	1.16 [0.63, 2.14]	
Iran2014	46	239	374	2116	8.3%	1.11 [0.79, 1.56]	
Latin America1996	22	107	241	1209	4.2%	1.04 [0.64, 1.70]	
Malaysia2001	3	12	27	122	0.5%	1.17 [0.30, 4.64]	
South Korea2014	15	53	28	150	1.4%	1.72 [0.83, 3.55]	
Spain1992	7	30	50	231	1.2%	1.10 [0.45, 2.72]	
Spain2006	5	46	47	317	1.4%	0.70 [0.26, 1.86]	
Spain2013	9	23	21	127	0.5%	3.24 [1.24, 8.47]	
Thailand2007	12	37	9	74	0.5%	3.47 [1.30, 9.23]	
Turkey2013	7	29	70	399	1.0%	1.50 [0.61, 3.64]	
USA2012	45	157 868	353	1822 7938	5.4%	1.67 [1.16, 2.41]	
Subtotal (95% CI)	197	000	1456	1930	29.1%	1.31 [1.10, 1.56]	•
Total events Heterogeneity: Chi ² = 1		11 (P =		= 19%			
Test for overall effect: 2				- 1070			
		5.00	·/				
1.1.4 Lymphopenia							
Brazil2013	22	72	210	816	3.2%	1.27 [0.75, 2.15]	
Central America2007	49	63	400	555	2.4%	1.36 [0.73, 2.53]	
Iran2014	84	239	705	2116	12.5%	1.08 [0.82, 1.44]	
South Korea2014	37	53	116	150	2.5%	0.68 [0.34, 1.36]	
Spain2006	16	46	164	317	3.7%	0.50 [0.26, 0.95]	
Spain2013	16	23	91	127	1.1%	0.90 [0.34, 2.38]	
Thailand2007	18	37	31	74 271	1.4%	1.31 [0.59, 2.90]	
Tunisia2002 USA2012	11	24 157	126	271	1.5%	0.97 [0.42, 2.25] 1.55 [1.12, 2.15]	
Subtotal (95% CI)	77	157 714	698	1822 6248	7.6% 35.9%	1.55 [1.12, 2.15]	↓ [−]
Total events	330		2541	01-10	00.070		▼
Heterogeneity: Chi ² = 1		8 (P =		38%			
Test for overall effect: 2				5070			
		20	'				
Total (95% CI)		2808		24893	100.0%	1.13 [1.02, 1.25]	•
Total events	851		6393				
Heterogeneity: Chi ² = 5				= 29%			0.01 0.1 1 10 100
Test for overall effect: 2			/	(D -	4. 10 -	0.01	Favours [males] Favours [females]
Test for subgroup differ							
	Figur	e 5. ⊦	Iematol	ogical	manifest	ations, hemolytic	anemia, lymphopenia.

syndrome (47,XXY) have similar risk to develop SLE compared with females (46,XX).^[34] It is also possible that women and men have different environmental exposures during their lifetimes, due to occupational or culturally-determined factors, which could be potentially linked to the increased incidence of SLE among women.

The mean age at disease onset and mean age at diagnosis of male and female patients in most of the included studies were comparable, as shown in Table 6. However, our data show a later age of disease onset and diagnosis in the studies from Spain.^[35,36] Several other European studies have reported peak incidences to occur at a later age in both European males and females.^[37–39]

Tendor Tendor Odde Path								
1.11 Mater Teach Canada (1983) 0 0 7 0 1.5% 0.42 (0.25, 0.72) Canada (1983) 0 0 0 0.2% 0.42 (0.25, 0.72) 0.48 (0.25, 2.70) Chinado (1) 14 2.29 1.27% 0.68 (0.24, 2.70) 0.68 (0.24, 2.70) Chinado (1) 14 2.29 1.22 2.42 0.05 (0.71, 2.42) Materyaizaboli 8 12 2.5% 0.58 (0.71, 2.42) Scient (2002) 17 2.43 2.21 0.50 (0.71, 2.42) Scient (2002) 17 2.43 2.21 0.50 (0.11, 0.83) Trainaido200 17 2.43 2.21 0.50 (0.11, 0.83) Trainaido200 17 2.43 2.21 0.50 (0.24, 0.83) Trainaido200 17 2.43 2.21 0.50 (0.11, 0.83) Trainaido200 17 2.43 2.21 0.50 (0.11, 0.83) Trainaido200 12 17 12 0.75 0.50 (0.11, 0.83) Trainaido201 13 12 17 12 0.75 0.50 (0.11, 0.83)		males	5	femal	es		Odds Ratio	Odds Ratio
Back20013 b 7 2 b 8 b 8 c 27% b 0.42 (0.26, 0.72) Central America.2007 3 c 63 300 555 2.7% b 0.48 (0.40, 1.15) Central America.2007 3 c 7 3 c 7 60 1 c 2.25 c 0.28 c 1.44 0.83 c 1.45 c 0.28 c 1.44 c 2.25 c 0.28 c 1.44 0.83 c 1.45 c 0.28 c 1.44 c 0.25 c 0.28 c 0.48 c 0.40 c 0.3 c 0.28 c 0.44 c 0.45 c 0.44 c 0.27 c 0.48 c 0.45 c 0.44 c 0.27 c 0.27 c 0.44 c 0.27 c 0.27 c 0.44 c 0.28 c 0.24 c 0.24 c 0.14 c 0.28 c 0.24 c 0.24 c 0.14 c 0.28 c 0.24 	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
Canada fields 6 0 7 9 0 1.5% 0.24 [0.22, 270] Chinal American Sec. 1 77 8 028 [0.44 0.03] Chinal 2007 7 3 77 8 028 [0.44 0.03] Chinal 2007 7 3 77 8 028 [0.44 0.03] Chinal 2007 8 1 8 0 10 222 1.4% 0.027 [0.25, 3.07] Spain 2007 8 1 8 12 122 1.4% 0.027 [0.25, 3.07] Spain 2007 8 1 8 12 123 1.20% 0.28 [0.11.0.67] Spain 2007 8 1 8 12 123 1.20% 0.28 [0.11.0.7] Spain 2007 8 1 24 10 12 [0.12] Spain 2007 8 1 24 10 20% 1.22 [0.8, 3.69] Total events 4 402 2 2 210 210 3.2% Spain 2013 6 7 2 4 6 15 (P = 0.0000); P = 63% Tast for worth 4 46 2 23 270 271 0 3.2% Spain 2006 2 4 23 0 271 0 1.3% 0.20% 0.24 [0.10.7] Spain 2006 2 4 23 0 271 0 1.3% 0.20% 0.48 [0.30, 0.7] Traileacogone 7 1 7 37 2.3 77 2.5% 1.18 [0.84, 4.23] Table events 4 7 5 100 5 22% 0.24 [0.10.7] Spain 2006 2 4 23 0 271 1.1% 0.20% 0.24 [0.30, 0.7] Traileacogone 7 1 7 37 2.3 77 2.5% 1.10 [0.80, 0.7] Table events 4 7 5 106 5 120 2.2% 0.48 [0.30, 0.7] Table events 4 7 5 106 5 120 2.2% 0.48 [0.30, 0.7] Table events 4 7 5 106 5 120 2.2% 0.48 [0.30, 0.7] Table events 4 7 5 106 5 120 2.2% 0.48 [0.30, 0.7] Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 77% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 1 10 (P = 0.0000; P = 60% Table events 4 7 10 (P = 0.0000; P = 77% Table events 4 7 10 (P = 0.0000; P = 60% Spain 2006 7 4 6 17 317 (P = 1.4	1.1.1 Malar Rash							
Central American2007 35 64 360 555 2.7% 0.85 [0.40, 119] Dima2012 39 68 218 468 2.6% 2.28 [1.27, 40.0 83] Dima2014 141 238 24 648 2.6% 2.28 [1.27, 40.0 83] Dima2014 141 238 162 150 2.5% 0.86 [0.4, 1.59] Spainel 1002 7 8 30 121 231 2.2% 0.86 [0.4, 1.59] Spainel 1002 7 7 30 121 231 2.2% 0.86 [0.4, 1.59] Spainel 1002 7 7 37 28 7 74 2.2% 0.85 [0.4, 1.10 3] Subtration [65% c] 164 40 192 317 2.2% 0.86 [0.4, 1.59] Thailenc2007 17 37 28 37 74 2.2% 0.86 [0.4, 1.10 3] Subtration [65% c] 164 9 162 20% 1.2% 0.86 [0.53, 0.88] Heterogeneity: Tar = 0.12 C.DH = 4.080, d = 13 02 - 0.0000; P = 63% Tarla events 477 500 46 100 2.0% 1.25 [0.53, 0.68] Material 22 2.48 2.5 271 1.1% 0.86 [0.07, 4.63] Spainel 002 7 7 32 87 7127 2.5% 0.46 [0.07, 4.63] Spainel 102 7 7 32 87 7127 2.5% 0.46 [0.07, 4.63] Material 22 2.42 2.57 2.11% 0.46 [0.02, 4.23] Spainel 102 7 7 32 87 7127 2.5% 0.46 [0.07, 4.63] Material 22 2.42 2.57 2.11% 0.46 [0.02, 4.23] Spainel 102 7 7 32 87 7127 2.5% 0.46 [0.07, 4.63] Material 22 3.6% 1.17 (1.10 2, 0.000); P = 63% Tarla events 7 75 300 1622 3.5% 1.130 [0.86, 1.00] Spainel 102 7 7 32 87 7127 2.5% 0.46 [0.07, 4.63] Material 22 3.6% 1.17 (1.10 P 0.0000); P = 63% Tarla events 7 75 300 1622 3.5% 1.130 [0.86, 1.00] Spainel 102 7 7 32 87 7127 2.5% 0.45 [0.02, 4.23] Material 23 1.17 (1.10 P 0.0000); P = 69% Test for overall effect 2 = 0.79 (P = 0.43) 1.12 Database 1.100 1.13 Raymaud Phenomenon China2012 0 8 38 83 64 62 2.4% 1.17 [0.28, 4.01] 1.14 Raymaud Phenomenon China2012 0 13 3 2.27 2.11 1.1% 0.46 [0.26, 1.13] 1.14 Raymaud Phenomenon China2012 0 13 3 2.27 2.11 1.1% 0.46 [0.26, 0.13] 1.15 Dise 3.100 (1.162, 2.10) (P = 0.0000); P = 6.9% Tarla events 8 1136 Heterogeneity: Tar = 0.28. Chi = 31.07, d = 1.10 P = 0.0000; P = 2.5% Tarla events 9 1136 Heterogeneity: Tar = 0.28. Chi = 31.07, d = 1.10 P = 0.0000; P = 2.5% Tarla events 9 1136 Heterogeneity: Tar = 0.28. Chi = 30.07, d = 1.33 P = 0.0000; P = 2.5% Tarla events 9 136 7 150 2.5% 0.50 14, 0.50 0.14, 0.50 0.14, 0.50 0.14, 0.50 0.14	Brazil2013	50	72	689	816	2.7%	0.42 [0.25, 0.72]	
China2019 73 776 825 1414 32% 0.65 (0.40, 0.39) Ima2014 141 239 1275 218 32% 0.65 (0.72, 128) Ima2014 141 239 1275 218 32% 0.65 (0.72, 128) Ima2014 28 12 21 23% 0.25 (0.71, 0.25, 0.71) Spain2026 16 4 41 22 12 22% 0.25 (0.71, 0.72) Spain2026 16 4 41 22 12 22% 0.25 (0.71, 0.72) Spain2026 16 4 41 22 12 22% 0.25 (0.71, 0.72) Spain2026 16 4 41 22 21 22% 0.02 (0.41, 0.81) Spain2026 17 2 24 23 35 122 12% 0.44 (0.16, 1.03) Ima2012 16 2 17 24 23 23 271 12% 0.25 (0.17, 0.73) Ima2020 17 17 37 36 74 22% 0.02 (0.41, 0.81) Ima2020 17 12 24 23 32 71 12% 0.25 (0.11, 0.73) Ima2020 17 12 24 23 32 71 12% 0.25 (0.11, 0.25, 0.17) Ima2020 17 12 24 23 32 71 12% 0.25 (0.11, 0.25, 0.17) Ima2020 17 12 24 23 32 71 12% 0.25 (0.11, 0.25, 0.17) Ima2020 17 12 24 23 271 12% 0.25 (0.11, 0.25, 0.17) Ima2020 17 12 24 23 271 12% 0.25 (0.11, 0.25, 0.17) Ima2020 17 12 24 23 271 12% 0.25 (0.11, 0.25, 0.17) Ima2020 17 12 27 24 23 275 22% 1.13 (0.25, 0.26) Ima2021 3 6 72 46 95 52 22% 1.24 (1.01, 3.26) Ima2021 17 12 2 0.25 (0.11, 0.12) Ima2021 17 12 2 0 77 10 72 50 17 127 12% 12% 125 2.24 Ima2021 17 17 23 77 127 12% 0.15 2.24 Ima2021 17 12 23 77 127 12% 0.16 84 120 Ima2012 13 6 77 120 57 66 120 2.25% 1.17 (0.75 0.170) Imaam:2007 17 73 35 67 120 2.25% 1.17 (0.75 0.40) Imaam:2007 17 73 35 67 120 2.25% 1.17 (0.75 0.40) Imaam:2007 17 73 36 74 127 12% 12% 128 0.22 (0.61, 7.7) Imaam:2013 7 23 74 127 12% 12% 128 0.24 (0.25 0.13) Imaam:2013 7 23 67 127 12% 12% 128 0.22 (0.61, 7.7) Imaam:2014 0.25 (0.11, 37) (1 = 10 (1.9 - 0.000); I = 69% Imaam:2013 7 23 74 27 12% 12% 128 0.22 (0.61, 0.7) Imaam:2014 0.25 (0.11, 37) (1 = 10 (1.9 - 0.000); I = 69% Imaam:2013 7 29 74 0.45 0.25 (0.61, 0.70, 2.1, 1.3] Imaam:2013 7 29 74 0.45 0.25 (0.61, 0.70, 0.1, 1.2) Imaam:2013 7 29 74 0.25 (0.11, 0.00); I = 69% Imaam:2013 7 29 19 0.19% 0.27 (1.13, 0.24 0.25 0.01) Imaam:2017 11 13 14 22 0.7% 0.38 0.16 0.27 (1.14, 0.25 0.1.7) Ima	Canada1983	6	50	7	50	1.5%	0.84 [0.26, 2.70]	
China2012 39 68 218 488 26% 226 [127.4.28] Materyale201 8 12 68 122 1.4% 0.67 (2.2.37) Materyale201 8 12 68 122 1.4% 0.67 (2.2.37) Materyale201 8 12 68 122 1.4% 0.67 (2.2.37) Thainc2007 17 37 18 122 120 50 0.88 [0.11.0.07] Thainc2007 17 37 18 7 4 23 27 120 50 0.88 [0.11.0.07] Thainc2007 17 37 18 7 4 23 27 120 50 0.88 [0.10.37] USA012 0 2 157 943 122 3.1% 0.68 [0.4.1.63] Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Table vents $u^{+} = 0.12, 07 + 0.00, 07 + 0.000; t = 6.3\%$ Spin-2003 7 2 25 77 127 11% 0.48 [0.02, 1.49] Table vents $u^{+} = 0.12, 07 + 0.00, 000; t = 6.3\%$ Spin-2005 9 44 56 137 2.2% 1.13 [0.02, 2.48] Spin-2006 9 44 56 137 2.2% 1.13 [0.02, 2.48] Spin-2006 9 44 56 137 2.2% 1.13 [0.02, 2.48] Spin-2007 17 37 23 74 2.1% 1.18 [0.84, 3.29] Table vents $u^{+} = 0.2, 07 + 0.00, 000; t = 6.0\%$ Spin-2006 9 46 56 137 2.2% 1.13 [0.62, 4.30] Table vents $u^{+} = 0.2, 07 + 0.00, 000; t = 6.0\%$ Table vents $u^{+} = 0.00, 000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000; t = 6.0\%$ Table vents $u^{+} = 0.000; t = 0.000$								
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Spalar2013 6 23 51 227 0.47 Thailar20207 17 37 36 74 2.5% 0.51 (27, 0.97) Thailar20207 17 37 36 74 2.2% 0.50 (0.41, 1.89) USA012 17 24 243 271 1.9% 0.28 (0.10, 2.3) USA012 17 24 243 271 1.9% 0.28 (0.10, 2.3) Teterapping Tat" = 0.12 (DH" = 54.50, df = 13 (P = 0.0009); P = 63% Test for overall effect: Z = 2.94 (P = 0.0013) Tatalar2013 6 72 46 810 2.0% Test for overall effect: Z = 2.94 (P = 0.0013) Tatalar2014 62 239 276 216 3.2% 2.34 (T, 0.30) Tatalar2014 62 239 276 216 3.2% 2.34 (T, 0.30) Tatalar2013 6 72 46 810 2.0% Test for overall effect: Z = 2.94 (P = 0.0013) Tatalar2013 6 72 46 810 2.0% Test for overall effect: Z = 2.94 (P = 0.0003); P = 63% Test for overall effect: Z = 0.29 (P = 0.0004); P = 60% Tatalar2017 17 37 23 74 2.1% Tatalar2017 17 37 25 06 120 2.2% Tatalar2017 17 37 25 06 120 2.0% Tatalar2017 10 3 6 11 50 1.7% Tatalar2017 10 3 6 11 50 1.7% Tatalar2017 10 3 6 11 50 1.7% Tatalar2017 10 3 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7								
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Tunisag202 17 24 24 27 1.5% 0.28 [0.1, 0.7] Subtol (9% C) 17 24 24 23 271 1.5% 0.28 [0.1, 0.7] Subtol (9% C) 17 37 9590 Heterogeneity: Tat ² - 0.12 C) ²⁺ 34 89, d ⁺ 130 \neq 0.0000; P = 63% Test for overall effect 2 - 234 (P = 0.000) 1.12 Disorde Rash Braza2013 6 7 2 46 816 20% 1.52 [0.63, 3.69] Central America2007 20 63 99 555 2.6% 2.14 [1.21, 3.80] Central America2007 1 20 63 57 150 2.2% 0.36 [1.5, 0.7] Spain2016 1 12 17 122 0.7% 0.65 [0.7, 4.6] Spain2016 7 2 46 816 2.2% 1.13 [0.5, 2.48] Spain2013 7 23 57 127 1.9% 0.54 [0.2, 7] Spain2013 7 23 74 2.1% 1.38 [0.84, 4.25] Tunisa2007 17 37 23 74 2.1% 1.38 [0.84, 4.25] Tunisa2007 17 37 23 74 2.1% 1.58 [0.84, 4.25] Tunisa2010 1 1 21 17 122 0.7% 0.65 [0.7, 1.63] Spain2016 7 24 25 27 [0.9] Spain2013 7 23 77 2.74 2.1% 1.58 [0.84, 4.25] Tunisa2007 17 37 23 74 2.1% 1.57 [0.78, 4.00] Lish America1996 30 107 558 1209 2.8% 1.77 [0.78, 4.00] Lish America1996 30 107 558 1209 2.8% 0.66 [0.3, 7] Total events 17 55 7 1005 Spain2013 2 4 21 107 122 1.0% 1.24 [0.25, 6.17] Total events 17 55 7 1005 120 2.0% 0.46 [0.30, 7] Spain2013 2 43 100 2.12 1.1% 1.20 [0.2, 4.27] 1.1.7 Raynaud Phenomenon Tunisa2002 2 1 47 122 1.0% 1.24 [0.25, 6.17] Tunisa2002 2 1 41 15 34 22 100 2.3% 0.67 [0.32, 1.43] South Korea2014 1 1 53 42 150 2.3% 0.67 [0.32, 1.43] South Korea2014 1 1 53 42 105 0.23 2.1% 0.77 [0.78, 4.00] Latin America1996 30 107 558 1209 2.9% 0.46 [0.30, 0.7] Tunisa2002 6 24 61 271 19% 0.54 [0.10, 4.12] Spain103 2 43 100 2.17 2.1% 1.20 [0.2, 1.26] Spain103 2 43 100 2.17 2.1% 1.26 [0.2, 1.26] Subtol (9% C) 419 3385 18.7% 0.76 [0.44, 1.28] Display 2.2001 1 1 2 24 122 0.7% 0.37 [0.13, 1.07] Tunisa2002 1 1 2 24 12 2.0% 0.24 [0.12, 0.5] Spain103 2 2 35 12.7% 0.38 [0.44, 1.55] Tunisa2002 1 1 2 46 177 119% 0.34 [0.40, 1.56] Display 2.000 17 46 177 317 19% 0.32 [0.44, 1.56] Display 2.000 17 46 177 317 19% 0.32 [0.44, 1.56] Display 2.000 17 7 46 177 317 19% 0.32 [0.44, 1.56] Display 2.000 17 7 40 83 2.5% 1.16 [0.50, 1.69] Display 2.000 17 7 40 83 2.5% 1								
USA0012 6.2 167 953 1622 3.1% 0.60 [0.4.3, 0.8] Total events 497 5690 Heterogeneity: Tur ² - 0.12, Ch ² 3.288, df = 13 0 = 0.0009; J = 6.3%, Test for vorall effect Z = 2.94 (P = 0.000); J = 6.3%, Test for vorall effect Z = 2.94 (P = 0.000); J = 6.3%, Test for vorall effect Z = 2.94 (P = 0.000); J = 6.3%, Test for vorall effect Z = 0.20 (Z = 0.000); J = 0.000; J =								
Subtack (95% CI) 1040 events 407 5090 Heterogenety: Tat" = 0.12, CDF = 3.48, df = 13 (P = 0.0008); P = 63% Test for overall effect Z = 2.44 (P = 0.0003) 1.1.2 Discoid Rash Brazi2013 0 72 46 816 2.0% 1.52 (D 63, 3.69) Lina2014 0 2 23 92 72 216 3.2% 2.34 (1.70, 3.20) Lina2014 0 2 23 92 72 216 3.2% 2.34 (1.70, 3.20) Lina2014 0 2 23 92 72 217 32% 2.34 (1.70, 3.20) Lina2014 0 2 23 92 72 73 6% 1.54 (D 21, 4.44) Spanz000 7 4 43 67 327 7 42 % 1.54 (D 21, 4.44) Spanz000 7 4 43 67 327 7 42 % 1.54 (D 21, 4.44) Spanz000 7 7 43 7 32 74 2.1% 1.54 (D 21, 4.44) Turkey013 4 29 69 399 1.7% 0.77 (D 26, 2.27) Lina2017 17 55 6769 2.2.7% 1.17 (D 78, 4.00) Lina2017 17 55 6769 2.2.7% 1.17 (D 78, 4.00) Lina1 America 1996 30 107 56 1200 $Q = 2.9\%$ 0.46 (D 30, 0.7) Heterogenety: Tat" = 0.25, CDF = 3.137, df = 10 (P = 0.0004); P = 69% Test for overall effect Z = 0.79 (P = 0.43) 1.1.7 Raymaud Phanomenon China2017 1 6 72 80 816 2.0% 0.34 (D 30, 0.7) Heterogenety: Tat" = 0.25, CDF = 3.137, df = 10 (P = 0.0004); P = 69% Test for overall effect Z = 0.79 (P = 0.43) 1.1.7 Raymaud Phanomenon China2017 1 6 72 80 816 2.0% 0.34 (D 35, 1.99) Calial events 98 1136 Heterogenety: Tat" = 0.25, CDF = 2.25, df = 9 (P = 0.0008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.2008); P = 60% Test for overall effect Z = 1.09 (P = 0.27) 1.1.13 Neurological Brazi2013 6 72 20 8 816 20% 0.24 (D 35, 1.99) Candid 983 9 50 19 95 1.9% 0.56 (D 44, 0.09) Candid 983 9 50 19 95 0.19% 0.56 (D 44, 0.09) Candid 983 9 50 19 95 0.19% 0.58 (D 44, 1.20) Data events 98 1136 Heterogenety: Tat" = 0.25, CDF = 2.07 P = 0.0009; P = 6.07% Turkey013 8 23 107 2.8 3 162 (P = 0.0009; P = 72% Test for overall effect Z = 1.0								
Heterogeneity: $Tat^2 = 0.12$; $Ch^2 = 34.98$, $d = 1.3 (P = 0.0009)$; $P = 63\%$ Test for overall effect: $Z = 2.94$ ($P = 0.003$) 1.1.2 Discuid Rash Brazil2013 6 7 72 46 816 2.0% 1.52 (0.63, 3.69) (Increated America2007 20 63 99 555 2.6% 2.44 (1.21, 3.80) Iran2014 6 22 2.39 2.76 2.116 3.2% 2.34 (1.70, 3.20) Malaysia.2011 1 21 77 122 0.7% 0.56 [0.07, 6.8] South Koran2014 9 53 57 120 2.2% 0.33 (0.15, 0.73) Spann2036 9 46 56 3.77 2.2% 1.13 [0.52, 2.43] Spann2037 1 22 55 71 72 1.9% 0.54 [0.21, 4.6] Spann2037 1 22 55 71 22 1.9% 0.54 [0.21, 4.6] Spann2030 1 7 23 55 71 72 1.9% 0.54 [0.21, 4.6] Spann2030 1 7 23 55 71 72 1.9% 0.54 [0.21, 4.6] Subtal ($g S\%$ CI) 755 6769 2.2.7% 1.17 [0.78, 4.0] Characterize 175 1006 Heterogeneity: $Tat^2 = 0.25$; $Ch^2 = 31.97$, $d = 10$ ($P = 0.0004$; $P = 69\%$ Test for overall effect: $Z = 0.70$ ($P = 0.43$) 1.17 Raymaud Phenomenon China2012 8 55 83 458 2.1% 1.77 [0.78, 4.0] Latin America1996 30 107 566 129 2.9% 0.46 [0.30, 0.71] Malaysia2001 2 12 17 17 122 10% 1.24 [0.25, 6.13] Spann2030 22 4 45 105 317 2.5% 1.155 (0.48, 2.57] Spann2030 22 4 45 105 317 2.5% 1.55 (0.48, 2.56] Spann2030 22 4 45 105 317 2.5% 1.55 (0.48, 0.57] Spann2030 22 4 45 105 317 2.5% 1.55 (0.48, 0.57] Spann2030 2 2 4 45 105 2.17 1.2% 0.268 (0.41, 0.20] Spann2030 2 4 45 105 2.17 1.12 (0.48, 2.57] Spann2030 2 2 4 45 105 317 2.5% 1.55 (0.48, 0.48] Spann2030 2 6 2 4 45 105 317 2.5% 1.55 (0.48, 0.48] Spann2030 2 6 2 4 45 105 317 0.5% (0.48 (0.40, 0.57] Tutika2002 6 7 4 61 2.71 1.9% 0.36 (0.14, 0.20] China2012 1 1 2 28 55 438 1.7% 0.88 (0.49, 1.55] China2012 1 1 2 28 55 438 1.7% 0.88 (0.49, 1.55] China2012 1 1 2 28 5 107 2.6% 1.28 (0.78, 0.73) (0.5, 1.0.6] China2012 1 2 1 28 5 113 6.44 2.7% 0.88 (0.49, 1.55] China2010 1 1 1 24 1 12 2.07% 0.52 (0.14, 0.20] China2012 1 1 2 28 5 127 1.9% 0.32 (0.14, 0.20] China2012 1 1 12 24 12 (2.7% 0.28 (0.49, 1.55] China2012 1 1 12 24 12 (2.7% 0.28 (0.49, 1.55] China2012 1 12 28 5, 0.48 2.4% 1.14 (0.48, 0.197) China2012 1 12 28 5, 0.48 2.4% 1.14								
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$ \begin{array}{c} 1.12 \ \text{Discoid Rash} \\ \hline \text{Brazilo13} & 6 & 72 & 68 \ \text{Bi} 6 & 2.0\% & 1.52 \ [0.53, 3.69] \\ \hline \text{Certral America2007} & 20 & 63 \ \text{P9} & 552 \ 2.6\% & 2.14 \ [1.21, 3.80] \\ \hline \text{Malaysia201} & 11 \ 12 \ 17 & 122 \ 0.7\% & 0.56 \ [0.07, 15, 0.73] \\ \hline \text{South Kora2014} & 9 & 53 \ 57 \ 150 \ 2.2\% & 0.33 \ [0.15, 0.73] \\ \hline \text{South Kora2013} & 7 \ 2.3 \ 57 \ 127 \ 1.9\% & 0.54 \ [0.21, 1.40] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 57 \ 127 \ 1.9\% & 0.54 \ [0.21, 1.40] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 57 \ 126 \ 2.2\% & 1.30 \ [0.28, 0.0] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 57 \ 126 \ 2.2\% & 1.30 \ [0.28, 1.00] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 57 \ 165 \ 1209 \ 2.7\% & 1.70 \ [0.26, 0.23] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 57 \ 165 \ 1209 \ 2.2\% & 1.30 \ [0.28, 1.00] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 67 \ 126 \ 2.2\% & 1.30 \ [0.28, 1.00] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 67 \ 126 \ 2.2\% & 1.17 \ [0.78, 4.00] \\ \hline \text{Tunialao2007} & 17 \ 37 \ 2.3 \ 67 \ 126 \ 2.2\% & 1.17 \ [0.78, 4.00] \\ \hline \text{Tunialoc2007} & 17 \ 37 \ 67 \ 679 \ 2.2\% & 1.70 \ [0.78, 4.00] \\ \hline \text{Tunialoc2007} & 17 \ 37 \ 67 \ 679 \ 2.2\% & 1.77 \ [0.78, 4.00] \\ \hline \text{Tunialoc2007} & 17 \ 37 \ 67 \ 100 \ 107 \ 56 \ 1209 \ 2.9\% & 0.46 \ [0.30, 0.71] \\ \hline \text{Tunialoc201} & 8 \ 52 \ 127 \ 1.4\% & 0.51 \ 0.49 \ 0.51 \ 0$	Heterogeneity: Tau ² = 0).12; Chi² =	= 34.98	3, df = 13	(P = 0.0	009); l ² =	63%	
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$eq:rest for overall effect: Z = 0.79 (P = 0.47, df = 10 (P = 0.0004); l^2 = 69% Test for overall effect: Z = 0.79 (P = 0.43) \\ \hline 1.17 Raynaud Phenomenon China2012 & 8 58 38 458 2.1% 1.77 [0.76, 4.00] Latin America1996 30 107 556 1209 2.9% 0.46 [0.30, 0.71] Analysia2001 2 12 17 122 1.0% 1.24 (0.25, 6.13] South Korea2014 11 53 42 150 2.3% 0.67 [0.32, 1.43] Spain1992 9 30 64 231 2.1% 1.12 (0.49, 2.57) Spain2006 22 46 105 317 2.5% 1.65 [0.99, 3.46] Spain2006 22 46 1105 317 2.5% 1.65 [0.90, 3.46] Turkley2013 3 2 23 52 127 1.4% 0.02 [0.06, 0.77] Turkland2007 0 37 9 74 0.4% 0.09 [0.01, 1.62] Turkley2013 7 29 192 399 2.0% 0.34 [0.14, 0.82] Subtotal (95% CI) 4119 3388 18.7% 0.76 [0.46, 1.24] Turkley2013 7 29 192 399 2.0% 0.34 [0.14, 0.82] Subtotal (95% CI) 4119 3388 18.7% 0.76 [0.46, 1.24] Turkley2013 7 29 19 50 1.9% 0.36 [0.14, 0.90] Canadaf1983 9 50 19 50 1.9% 0.36 [0.14, 0.90] Canadaf1983 9 50 19 50 1.9% 0.36 [0.14, 0.90] Canadaf1983 9 50 19 50 1.9% 0.36 [0.14, 0.95] Canadaf1983 9 50 19 50 1.9% 0.36 [0.14, 0.95] China2009 14 176 145 1614 2.7% 0.88 [0.48, 1.55] China2012 12 26 55 458 2.4% 151 [0.95, 3.83] Latin America1996 28 107 266 1209 2.9% 1.26 [0.80, 1.97] Analysia2001 1 12 24 122 0.7% 0.37 [0.05, 3.02] South Korea2014 7 53 9 150 1.7% 2.38 [0.84, 6.76] Spain2006 7 46 17 317 1.3% 3.17 [1.24, 8.12] Spain2013 2 23 5 127 0.9% 2.32 [0.42, 127] Turkley2013 8 29 47 339 2.50% 1.46 [0.80, 1.69] Turkley2013 8 29 47 339 2.50% 1.46 [0.80, 1.69] Turkley2013 8 29 47 339 2.50% 1.46 [0.80, 1.69] Turkley2013 8 29 47 339 2.50% 1.46 [0.80, 1.69] Turkley2013 8 29 47 339 2.50% 1.26 [0.80, 1.69] Turkley2013 8 2.9 47 339 2.50% 1.26 [0.80, 1.69] Turkley2013 8 2.9 47 339 2.50% 1.26 [0.80, 1.69] Turkley2013 8 2.9 47 339 2.50% 1.16 [0.80, 1.69] Turkley2013 8 2.9 47 339 2.50% 1.65 [1.20, 6.81] Turkley2013 8 2.9 47 339 2.50% 1.66 [1.20, 6.81] Turkley2013 8 2.9 47 339 2.50% 1.66 [1.20, 6.81] Turkley2013 8 2.9 47 339 2.50\% 1.16 [0.80, 1.69] Turkley2013 8 2.9 47 339 2.50\% 1.16 [0.80, 1.69] Turkley2013 8 2.9 47 339 2.50\% 1.16 [0.80, 1.6$			/ 55		6769	22.1%	1.17 [0.79, 1.73]	
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$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1.1.13 Neurological							
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Brazil2013	6	72	80	816	2.0%	0.84 [0.35, 1.99]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Canada1983	9	50	19	50	1.9%		
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Latin America 1996 28 107 266 1209 2.9% 1.26 [0.80, 1.97] Malaysia 2001 1 12 24 122 0.7% 0.37 [0.05, 3.02] South Korea 2014 7 53 9 150 1.7% 2.38 [0.84, 6.76] Spain 1992 0 30 27 231 0.4% 0.12 [0.01, 2.05] Spain 2006 7 46 17 317 1.9% 3.17 [1.24, 8.12] Spain 2013 2 23 5 127 0.9% 2.32 [0.42, 12.77] Thailand 2007 5 37 22 74 1.7% 0.37 [0.13, 1.07] Tunisia 2002 3 24 38 271 1.4% 0.88 [0.25, 3.08] Turkey 2013 8 29 47 399 2.0% 2.85 [1.20, 6.81] Subtotal (95% CI) 780 6393 25.2% 1.16 [0.80, 1.69] Total events 115 835 Heterogeneity: Tau ² = 0.25; Chi ² = 30.17, df = 13 (P = 0.004); l ² = 57% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneity: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% Test for overall effect: Z = 1.12 (P = 0.26) Test for overall effect: Z = 1.12 (P = 0.26) Test for overall effect: Z = 1.12 (P = 0.04), l ² = 64.1%	China2009	14	176	145	1614	2.7%	0.88 [0.49, 1.55]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	China2012	12	58	55	458	2.4%	1.91 [0.95, 3.83]	
South Korea2014 7 53 9 150 1.7% 2.38 [0.84, 6.76] Spain1992 0 30 27 231 0.4% 0.12 [0.01, 2.05] Spain2006 7 46 17 317 1.9% 3.17 [1.24, 8.12] Spain2013 2 23 5 127 0.9% 2.32 [0.42, 12.77] Thailand2007 5 37 22 74 1.7% 0.37 [0.13, 1.07] Turksy2013 8 29 47 399 2.0% 2.85 [1.20, 6.81] Subtotal (95% CI) 780 6393 25.2% 1.16 [0.80, 1.69] Total events 115 835 Heterogeneity: Tau² = 0.25; Chi² = 30.17, df = 13 (P = 0.004); l² = 57% Test for overall effect: Z = 0.80 (P = 0.42) 25243 100.0% 0.89 [0.74, 1.09] Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 865 8146 <th< td=""><td>Latin America1996</td><td>28</td><td>107</td><td>266</td><td>1209</td><td>2.9%</td><td>1.26 [0.80, 1.97]</td><td>+</td></th<>	Latin America1996	28	107	266	1209	2.9%	1.26 [0.80, 1.97]	+
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Malaysia2001	1	12	24	122	0.7%	0.37 [0.05, 3.02]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	South Korea2014	7	53	9	150	1.7%	2.38 [0.84, 6.76]	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Spain1992	0	30	27	231	0.4%	0.12 [0.01, 2.05]	· · · · · · · · · · · · · · · · · · ·
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Spain2006	7	46	17	317	1.9%	3.17 [1.24, 8.12]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Spain2013	2	23	5	127	0.9%	2.32 [0.42, 12.77]	
Turkey2013 8 29 47 399 2.0% 2.85 $1.20, 6.81$ Subtotal (95% CI) 780 6393 25.2% 1.16 $0.80, 1.69$ Total events 115 835 Heterogeneity: Tau ² = 0.25; Chi ² = 30.17, df = 13 (P = 0.004); l ² = 57% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneity: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% 0.01 0.1 10 100 Test for overall effect: Z = 1.12 (P = 0.26) Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]	Thailand2007	5	37	22	74	1.7%	0.37 [0.13, 1.07]	
Subtotal (95% CI) 780 6393 25.2% 1.16 [0.80, 1.69] Total events 115 835 Heterogeneity: Tau² = 0.25; Chi² = 30.17, df = 13 (P = 0.004); l² = 57% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneity: Tau² = 0.28; Chi² = 170.96, df = 48 (P < 0.00001); l² = 72%	Tunisia2002	3	24	38	271	1.4%		
Total events 115 835 Heterogeneity: Tau ² = 0.25; Chi ² = 30.17, df = 13 (P = 0.004); l ² = 57% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% Cl) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneity: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% 0.01 0.1 1 100 100 Test for overall effect: Z = 1.12 (P = 0.26) Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]		8		47				
Heterogeneity: Tau ² = 0.25; Chi ² = 30.17, df = 13 (P = 0.004); l ² = 57% Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneity: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% 0.01 0.1 10 Test for overall effect: Z = 1.12 (P = 0.26) Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]			780		6393	25.2%	1.16 [0.80, 1.69]	₹
Test for overall effect: Z = 0.80 (P = 0.42) Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneitly: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% 0.01 0.1 10 Test for overall effect: Z = 1.12 (P = 0.26)								
Total (95% CI) 2994 25243 100.0% 0.89 [0.74, 1.09] Total events 885 8146 Heterogeneity: Tau² = 0.28; Chi² = 170.96, df = 48 (P < 0.00001); l² = 72%					(P = 0.0	04); l² = 5	7%	
Total events 885 8146 Heterogeneity: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% 10.01 0.1 100 Test for overall effect: Z = 1.12 (P = 0.26) Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]	Test for overall effect: Z	z = 0.80 (P	= 0.42	2)				
Total events 885 8146 Heterogeneity: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% 0.01 0.1 1 100 Test for overall effect: Z = 1.12 (P = 0.26) Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]	T. (050.55	400.000	0.00.00.00.00.00.00.00	
Heterogeneitly: Tau ² = 0.28; Chi ² = 170.96, df = 48 (P < 0.00001); l ² = 72% Image: transmission of the system of the s			2994		25243	100.0%	0.89 [0.74, 1.09]	•
Test for overall effect: Z = 1.12 (P = 0.26) 0.01 1 10 100 Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]								
Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), l ² = 64.1% Favours [males] Favours [females]					8 (P < 0.	00001); l ²	= /2%	0.01 0.1 1 10 100
Test for subgroup differences: Chi ² = 8.35, df = 3 (P = 0.04), I^2 = 64.1%						A) 10	10/	
Figure 6. Malar rash, discoid rash, Raynaud phenomenon, neurological.	lest for subgroup differ	ences: Ch	r= 8.3	s5, df = 3	(P = 0.0	4), I ² = 64	.1%	
		Figure	6. N	lalar ras	sh, dis	coid ras	sh, Raynaud phene	omenon, neurological.

Figure 6. Malar rash, discoid rash, Raynaud phenomenon, neurological.

This has been attributed to genetic predisposition or the decreasing response of an aging immune system.^[40] Little research exists pertaining to the incidence or prevalence of SLE in many populations or their comprising ethnic groups. In the USA, the average incidence of SLE has been estimated to

range between 1.8 and 7.6 cases per 100,000 person-years,^[41] and in Europe, the incidence rates range from 3.3 to 4.8 per 100,000 person-years.^[42] A study in Brazil detected an annual incidence of 8.4 per 100,000 habitants.^[43] The incidence of SLE is reported to be greater in Afro-Americans, Afro-Caribbeans,

	males	s	femal	es		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 Leukopenia							
Brazil2013	13	72	151	816	4.5%	0.97 [0.52, 1.81]	
Central America2007	24	63	222	555	5.0%	0.92 [0.54, 1.58]	-
Iran2014	68	239	758	2116	6.0%	0.71 [0.53, 0.96]	
Latin America1996	40	107	471	1209	5.5%	0.94 [0.62, 1.41]	-
South Korea2014	13	53	80	150	4.2%	0.28 [0.14, 0.57]	
Spain2006	16	46	164	317	4.4%	0.50 [0.26, 0.95]	
Spain2000	8	23	59	127	3.3%	0.61 [0.24, 1.55]	
Thailand2007	30	37	55	74	3.1%	1.48 [0.56, 3.92]	
Tunisia2002	11	24	121	271	3.6%	1.05 [0.45, 2.42]	
USA2012	74						
Subtotal (95% CI)	74	157 821	785	1822 7457	5.9% 45.6%	1.18 [0.85, 1.63] 0.80 [0.62, 1.04]	▲ ⁻
. ,	007	021	0000	1401	40.070	0.00 [0.02, 1.04]	
Total events	297	40.50	2866		. 12 - 5 401		
Heterogeneity: Tau ² = (· = 0.02); I [∠] = 54%		
Test for overall effect: 2	∠ = 1.68 (F	' = 0.09)				
1.1.2 Anti-Sm							
Brazil2013	21	72	173	816	5.0%	1.53 [0.90, 2.61]	+
China2012	10	58	40	458	4.0%	2.18 [1.02, 4.63]	
Latin America1996	20	37	47	314	4.1%	6.68 [3.26, 13.69]	
Malaysia2001	2	12	19	122	1.6%	1.08 [0.22, 5.34]	
Spain1992	6	30	34	231	3.1%	1.45 [0.55, 3.81]	
Spain2006	3	46	25	317	2.3%	0.81 [0.24, 2.81]	
Tunisia2002	10	24	160	271	3.6%	0.50 [0.21, 1.16]	<u> </u>
USA2012	36	157	308	1822	5.6%	1.46 [0.99, 2.16]	
Subtotal (95% CI)	50	436	000	4351	29.3%	1.56 [0.94, 2.59]	•
Total events	108		806				-
Heterogeneity: Tau ² = (= 24 96		P = 0 00	$(12) \cdot 1^2 = 72$	2%	
Test for overall effect: 2				- 0.00	00), 1 - 72	- /0	
	(0.00	/				
1.1.3 Anticardiolipin		=0		450			
China2012	15	58	52	458	4.4%	2.72 [1.42, 5.24]	
				a			
Spain1992	11	30	39	231	3.7%	2.85 [1.26, 6.46]	
Spain1992 Spain2006	11 12	30 46	39 90	317	4.2%	0.89 [0.44, 1.80]	
Spain1992 Spain2006 Spain2013	11 12 8	30 46 23	39 90 58	317 127	4.2% 3.3%		
Spain1992 Spain2006 Spain2013 Tunisia2002	11 12 8 12	30 46 23 24	39 90 58 153	317 127 271	4.2% 3.3% 3.6%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012	11 12 8	30 46 23 24 157	39 90 58	317 127 271 1822	4.2% 3.3% 3.6% 5.9%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012	11 12 8 12	30 46 23 24	39 90 58 153	317 127 271	4.2% 3.3% 3.6%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78]	
Spain1992 Spain2006 Spain2013	11 12 8 12	30 46 23 24 157	39 90 58 153	317 127 271 1822	4.2% 3.3% 3.6% 5.9%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012 Subtotal (95% CI)	11 12 8 12 76 134	30 46 23 24 157 338	39 90 58 153 849 1241	317 127 271 1822 3226	4.2% 3.3% 3.6% 5.9% 25.1%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (11 12 8 12 76 134 0.20; Chi ²	30 46 23 24 157 338 = 14.40	39 90 58 153 849 1241 , df = 5 (F	317 127 271 1822 3226	4.2% 3.3% 3.6% 5.9% 25.1%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	11 12 8 12 76 134 0.20; Chi ²	30 46 23 24 157 338 = 14.40 2 = 0.33	39 90 58 153 849 1241 , df = 5 (F	317 127 271 1822 3226 P = 0.01	4.2% 3.3% 3.6% 5.9% 25.1%); ² = 65%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total (95% CI)	11 12 8 12 76 134 0.20; Chi ² Z = 0.98 (F	30 46 23 24 157 338 = 14.40	39 90 58 153 849 1241 , df = 5 (F)	317 127 271 1822 3226 P = 0.01	4.2% 3.3% 3.6% 5.9% 25.1%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total (95% CI) Total events	11 12 8 12 76 134 0.20; Chi ² Z = 0.98 (P 539	30 46 23 24 157 338 = 14.40 2 = 0.33 1595	39 90 58 153 849 1241 , df = 5 (F) 4913	317 127 271 1822 3226 2 = 0.01	4.2% 3.3% 3.6% 5.9% 25.1%); I ² = 65% 100.0%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00]	
Spain1992 Spain2006 Spain2013 Tunisia2002 USA2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Total (95% CI) Total events Heterogeneity: Tau ² = (11 12 8 12 76 134 0.20; Chi ² Z = 0.98 (F 539 0.22; Chi ²	30 46 23 24 157 338 = 14.40 2 = 0.33 1595 = 81.32	39 90 58 153 849 1241 , df = 5 (F) 4913 , df = 23 (317 127 271 1822 3226 2 = 0.01	4.2% 3.3% 3.6% 5.9% 25.1%); I ² = 65% 100.0%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00]	
Spain1992 Spain2006 Spain2013 Tunisia2002 JSA2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Fest for overall effect: 2 Total (95% CI) Total events	11 12 8 12 76 134 0.20; Chi ² Z = 0.98 (F 539 0.22; Chi ² Z = 0.72 (F	30 46 23 24 157 338 = 14.40 2 = 0.33 1595 = 81.32 2 = 0.47	39 90 58 153 849 1241 , df = 5 (F) 4913 , df = 23 (317 127 271 1822 3226 P = 0.01 15034 (P < 0.0)	4.2% 3.3% 3.6% 5.9% 25.1%); l ² = 65% 100.0%	0.89 [0.44, 1.80] 0.63 [0.25, 1.60] 0.77 [0.33, 1.78] 1.08 [0.78, 1.49] 1.26 [0.79, 2.00] 1.09 [0.86, 1.38]	0.01 0.1 1 10 100 Favours [males] Favours [females]

Native Americans, and Asians compared with Caucasians.^[44–46] In Taiwan, the incidence was reported to be 8.1per 100,000 persons in 2007.^[47] Geographic and environmental factors play an important role in the prevalence and general manifestations of SLE. Vilar and Sato^[43] described a high prevalence of cutaneous manifestations leading to a high incidence of the disease in Brazil due to the great amount of sunlight exposure. Genetic susceptibility interacts with lifestyle and environmental factors, which include socioeconomic status, infectious agents (triggering or protective agents), and environmental hazards in determining the risk of developing autoimmunity.

Although the included studies were from countries of different geographical locations with distinct environmental, sociocultural, economic and behavioral backgrounds, and unalike accessibility to health service facilities, they showed some similar outcomes when clinical features of males and females were compared. Serositis, pleurisies, and renal involvement were noted to be significantly higher in male lupus patients, whereas in female patients, arthritis and cutaneous manifestations such as malar rash, oral ulcers, alopecia, and photosensitivity were predominant in almost all of them. This is reflected in several other previous studies. Impaired renal function,^[48] renal failure,^[49,50] renal transplantation,^[51] chronic renal insufficiency,^[50] and renal end-stage disease^[52] were found to be more frequent in men than in women with SLE. Some series with biopsy results have shown a higher incidence of proliferative nephritis in males.^[53,54] Renal involvement in men is indicator of poor prognosis. It has been suggested that the main female hormone, 17 β estradiol, is capable of inhibiting inflammatory and proapoptotic processes, and protecting the renal tissue, as opposed to the male hormones, testosterone and dehydroepiandrosterone.^[55] With respect to hematological and autoantibody

			6			Odda Datia	Odda Datia
Study or Subgroup	males		femal Events		Weight	Odds Ratio M-H, Fixed, 95% C	Odds Ratio M-H, Fixed, 95% Cl
1.1.1 ANA	Lvents	Total	Lvents	TOLAT	weight	M-H, FIXeu, 5576 C	
China2012	55	58	449	458	0.9%	0.37 [0.10, 1.40]	
Iran2014	180	239	1672	2116	14.1%	0.81 [0.59, 1.11]	
Latin America1996	37	37	311	314	0.1%	0.84 [0.04, 16.63]	
Malaysia2001	12	12	115	122	0.1%	1.62 [0.09, 30.15]	
South Korea2014	50	53	149	150	0.7%	0.11 [0.01, 1.10]	
Tunisia2002	24	24	248	271	0.1%	4.63 [0.27, 78.66]	
Subtotal (95% CI)		423		3431	16.1%	0.79 [0.59, 1.06]	•
Total events	358		2944				
Heterogeneity: Chi ² = 5. Test for overall effect: Z				14%			
1.1.2 Anti-ds DNA							
Brazil2013	33	72	279	816	4.1%	1.63 [1.00, 2.65]	
China2012	15	58	77	458	2.2%	1.73 [0.91, 3.26]	
Iran2014	162	239	1509	2116	16.6%	0.85 [0.64, 1.13]	
Latin America1996	20	37	116	314	1.9%	2.01 [1.01, 3.99]	
Malaysia2001	7	12	82	122	1.0%	0.68 [0.20, 2.29]	
Spain2006	41	46	262	317	1.2%	1.72 [0.65, 4.55]	
Tunisia2002	20	24	198	271	0.9%	1.84 [0.61, 5.57]	
USA2012 Subtotal (05% CI)	107	157 645	1120	1822 6236	9.5% 37.4%	1.34 [0.95, 1.90]	
Subtotal (95% CI)	105	045	0040	0230	37.470	1.22 [1.02, 1.45]	
Total events	405	7 (D	3643	400/			
Heterogeneity: Chi ² = 12 Test for overall effect: Z				46%			
1.1.3 Lupus anticoagu	lant						
Brazil2013	4	72	45	816	1.2%	1.01 [0.35, 2.89]	
Central America2007	13	63	43 50	555	1.2 %	2.63 [1.34, 5.16]	
Spain1992	13	30	39	231	1.4%	2.85 [1.26, 6.46]	
Spain2006	6	46	33	317	1.2%	1.29 [0.51, 3.27]	
USA2012	62	157	446	1822	7.2%	2.01 [1.44, 2.82]	
Subtotal (95% CI)	02	368	-+0	3741	11.9%	1.98 [1.53, 2.57]	•
Total events	96		613				•
Heterogeneity: Chi ² = 3.		(P = 0))%			
Test for overall effect: Z							
			,				
1.1.4 Low Complemen	t levels C	3 and/	or C4				
Spain2013	19	23	107	127	1.0%	0.89 [0.27, 2.89]	
Tunisia2002	20	24	203	271	0.9%	1.67 [0.55, 5.07]	
Subtotal (95% CI)		47		398	1.9%	1.27 [0.57, 2.84]	-
Total events	39		310				
Heterogeneity: Chi ² = 0.	.59, df = 1	(P = 0	.44); ² = ()%			
Test for overall effect: Z	= 0.59 (P	= 0.55)				
4451 001 1							
1.1.5 Low C3 levels							
China2012	39	58	268	458	3.3%	1.46 [0.82, 2.60]	
Malaysia2001	1	12	13	122	0.4%	0.76 [0.09, 6.39]	
Spain2013	14	23	69	127	1.4%	1.31 [0.53, 3.24]	
Turkey2013	11	29	107	399	1.5%	1.67 [0.76, 3.65]	
USA2012	94	157	967	1822	10.3%	1.32 [0.95, 1.84]	
Subtotal (95% CI)		279	4	2928	16.9%	1.36 [1.06, 1.76]	
Total events	159	-	1424				
Heterogeneity: Chi ² = 0.)%			
Test for overall effect: Z	2.37 (P	= 0.02	.)				
1.1.6 Low C4 level							
	0	10	10	100	0 50/	1 16 [0 22 5 74]	
Malaysia2001	2	12	18	122	0.5%	1.16 [0.23, 5.71]	
Spain2013 Turkey2013	16 9	23 29	102 117	127 399	1.6%	0.56 [0.21, 1.51]	
USA2012			117 851		1.8% 12.0%	1.08 [0.48, 2.45]	<u> </u>
Subtotal (95% CI)	74	157 221	851	1822 2470	12.0% 15.9%	1.02 [0.73, 1.41] 0.98 [0.74, 1.31]	↓
	101		1088	2-41 U	10.070	0.00 [0.74, 1.01]	T
Total events Heterogeneity: Chi ² = 1.		(D - 0		10/			
Test for overall effect: Z			,	0/0			
Total (95% CI)		1022		10204	100.0%	1 23 [1 40 4 27]	A
Total (95% CI)	4450	1983	10000	19204	100.0%	1.23 [1.10, 1.37]	▼
Total events	1158	00 /5	10022	2 _ 4001			
Heterogeneity: Chi ² = 5				- = 43%			0.01 0.1 1 10 100
Test for overall effect: Z					00001 12	- 70 50/	Favours [males] Favours [females]
Test for subgroup different	ences: Ch	r ⁻ = 24.	42, df = 5	(P = 0.)	∪∪∪∠), I [∠] =	- 19.5%	
F	igure 8	. ANA	, anti-de	sDNA,	lupus a	nticoagulant, low l	evel of C3, low C4 level.

profiles, the incidence of leukopenia, presence of lupus anticoagulant, low levels of C3, and positive titers of ANA were higher in females, whereas in males, thrombocytopenia and positive titers of anti-dsDNA were more prevalent. Scofiel et al suggested that men are more likely to have thrombocytopenia, which is associated with serositis, neuropsychiatric disease, renal disease, and positive dsDNA titer, and which is an indicator of a more severe disease in SLE. Thrombocytopenia has been linked to genetic predisposition.^[56] Some of the antibodies have been associated with specific manifestations of the disease; for

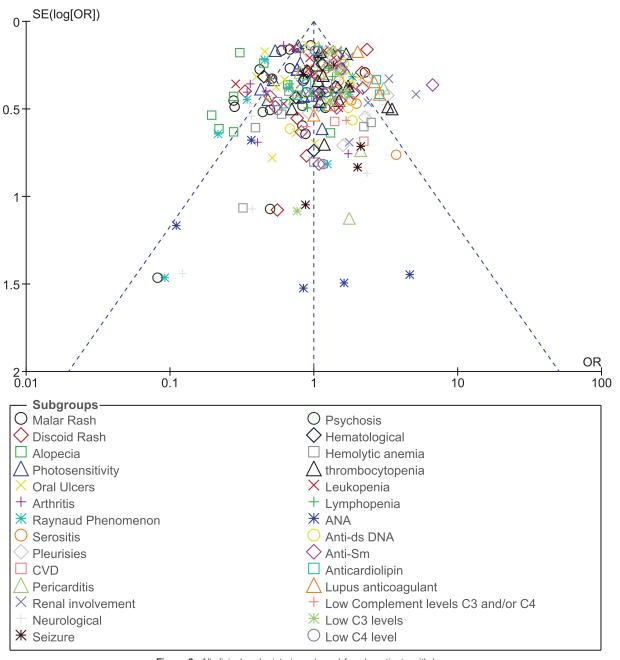


Figure 9. All clinical endpoints in male and female patients with lupus.

example, anti-dsDNA and anti-Sm antibodies are associated with nephritis. $^{\left[57\right] }$

4.1. Limitations

Several limitations are present in this current study. Firstly, variability in cohort sizes and lengths of follow-up may not bring uniformity among the included studies. Secondly, we have not elaborated on the sex-specific differences in each ethnic group of each study due to lack of data. Moreover, the specific differences in pathogenesis and target organ damage amongst sexes, which have only been explained partly though genetic, hormonal, and immune responses, have been analyzed.

5. Conclusions

This is a quantitative analysis of multiple studies comparing various clinical manifestations, autoantibodies, and laboratory results of male and female lupus patients. The results of this metaanalysis suggest that alopecia, photosensitivity, oral ulcers, arthritis, malar rash, lupus anticoagulant level, and low level of C3 were significantly higher in female lupus patients, whereas renal involvement, serositis and pleurisies, thrombocytopenia and antidsDNA level were predominant in male patients. However, more clinical and population-based research is warranted to further elucidate these differences and permit the development of optimal sex-tailored treatment and better outcomes for patients.

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