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Vitamin D status in patients with systemic lupus erythematosus (SLE): A systematic review and meta-analysis

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease where chronic inflammation and tissue or organ damage is observed. Due to various suspected causes, inadequate levels of vitamin D (a steroid hormone with immunomodulatory effects) has been reported in patients with SLE, however, contradictory.

Aims: The aim of this systematic review and meta-analysis was to evaluate the serum levels of vitamin D in patients with SLE in compared to healthy controls.

Methods: PubMed, SCOPUS, ScienceDirect and Google Scholar electronic databases were searched systematically without restricting the languages and year (up to March 2, 2019) and studies were selected based on the inclusion criteria. Mean difference (MD) along with 95% confidence intervals (CI) were used and the analyses were carried out by using a random-effects model. Different subgroup and sensitivity analyses were conducted. Study quality was assessed by the modified Newcastle-Ottawa Scale (NOS) and publication bias was evaluated by a contour-enhanced funnel plot, Begg's and Egger's tests.

Results: We included 34 case-control studies (2265 SLE patients and 1846 healthy controls) based on the inclusion criteria. Serum levels of vitamin D was detected significantly lower in the SLE patients than that in the healthy controls (MD: −10.44, 95% CI: −13.85 to −7.03; $p < .00001$). SLE patients from Asia (MD: −13.75, 95% CI: −21.45 to −6.05; $p = .0005$), South America (MD: -3.16, 95% CI: −4.62 to −1.70; $p < .0001$) and Africa (MD: −16.15, 95% CI: −23.73 to −8.56; $p < .0001$); patients residing below 37° latitude (MD: −11.75, 95% CI: −15.79 to −7.70; $p < .00001$); serum vitamin D during summer season (MD: -7.89, 95% CI: −11.70 to −4.09; $p < .0001$), patients without vitamin D supplementation (MD: -15.57, 95% CI: −19.99 to −11.14; $p < .00001$) or on medications like hydroxychloroquine, corticosteroids or immunosuppressants without vitamin D supplementation (MD: -16.46, 95% CI: −23.86 to −9.05; $p < .0001$) are in higher risk in presenting inadequate serum levels of vitamin D. The results remained statistically significant from different sensitivity analyses which represented the robustness of this meta-analysis. According to the NOS, 91.2% of the studies were considered as of high methodological quality (low risk of bias). No significant publication bias was detected from contour-enhanced and trim and fill funnel plots or Begg's test.

Conclusion: Inadequate levels of serum vitamin D is significantly high in patients with SLE compared to healthy subjects, therefore, vitamin D supplementation with regular monitoring should be considered as part of their health management plans.

Abbreviations: 25(OH)2D, 1 25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ACR, American college of rheumatology; BMI, body mass index; CI, confidence interval; ECLAM, European consensus lupus activity measurement; ELISA, enzyme-linked immunosorbent assay; MD, mean difference; MOOSE, meta-analysis of observational studies in epidemiology; NOS, Newcastle-Ottawa scale; PRISMA, preferred reporting items for systematic review and meta-analysis; SELENA, safety of estrogens in lupus national assessment; SLAM, systemic lupus activity measure; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, systemic lupus international collaborating clinics

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1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease which can cause chronic inflammation and damage in several tissues and organs including the brain, joints, blood vessels, kidneys and the skin [1]. The diagnosis of SLE is based on a set of clinical manifestations and positive serological tests. Classification as having SLE by the Systemic Lupus International Collaborating Clinics (SLICC) criteria requires either that a patient satisfy at least four of 17 criteria, including at least one of the 11 clinical criteria and one of the six immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANA) or anti-double-stranded DNA (dsDNA) antibodies [2,3]. SLE majorly affects women of childbearing age (15–44 years), where, female to male ratio could be up to 13:1 [4]. The clinical onset and progression of SLE manifestations and of have been linked to a combination of genetic, environmental and hormonal factors [4]. In SLE, the autoimmune process is developed via the upregulation of innate and adaptive immune system, impaired apoptotic clearance, inflammation and complement activation [5,6], although the complete diseases pathogenesis of SLE is still far away to be fully understood. In line with this, the treatment of SLE has not been changed during last fifty years and still include antimalarials, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants [7]. Therefore, there is still a need to seek for potentially reversible risk factors including chemical compounds, microbiome status and nutrients, that may modulate the course of the disease.

Vitamin D is one of such environmental factors which is a vital steroid hormone having a well-established effect on skeletal health, cardiovascular system and mineral metabolism. Over the past two decades, it has increasingly been recognized to exert some non-classical actions including immunomodulatory effects [8,9]. Vitamin D production is stimulated by the sunlight exposure (wavelengths of 280 to 315 nm) in the epidermal layer of the skin (epidermis) [10]. In addition, < 10% of the vitamin D can be obtained through some foods and supplements [i.e., eggs, liver, fatty fishes (i.e., salmon, eel, mackerel, trout, sturgeon, swordfish and sardine), fish oil, cod liver and mushrooms] [11]. Vitamin D becomes biologically active after a gradual process of hydroxylation in the liver converting first into 25-hydroxyvitamin D [25(OH)D] and then in the kidneys where ultimately 1, 25-dihydroxyvitamin D [1, 25(OH)2D] is synthesized [10,12,13]. Excess 25(OH)D is degraded under the influence of sunlight, so that even intense exposure to sunlight does not lead to vitamin D intoxication [14]. Vitamin D status is determined by measuring the serum levels of 25(OH)D as this is the major circulating form of vitamin D (half-life approximately 3-weeks). There is no consensus to the optimal 25(OH)D, insufficiency or deficiency levels; however, majority of researchers have considered a serum level of > 30 ng/mL as sufficient. There are several methods for measuring serum 25(OH)D level, such as, enzyme-linked immunosorbent assay (ELISA), chemiluminescent immunoassay, radio immunoassay, immunoradiometric assay and competitive protein binding assay [9,13,15].

High prevalence of low serum levels of vitamin D has been observed worldwide involving both healthy and diseased subjects including patients with rheumatic diseases [16]. Vitamin D insufficiency and/or deficiency have been observed in many autoimmune diseases like rheumatoid arthritis [17], Sjögren syndrome [18], antiphospholipid syndrome [19], Behçet's disease [20], multiple sclerosis [21] and systemic sclerosis [22]. Interestingly, vitamin D deficiency has been observed to be associated with SLE disease expression, relapses and pathogenesis [23,24].

There is a growing body of evidences indicating the tendency of manifesting low serum levels of vitamin D in patients with SLE when compared to healthy controls [25–27], however, there are some contradictory findings [28–30]. Therefore, the aim of this systematic review and meta-analysis was to evaluate the serum levels of vitamin D in patients with SLE in compared to healthy controls.

2. Methods

2.1. Eligibility criteria

The systemic review and meta-analysis was developed in accordance with the guidelines and recommendations of *Meta-analysis of Observational Studies in Epidemiology* (MOOSE) [31] and *Preferred Reporting Items for Systematic Review and Meta-Analysis* (PRISMA) Statements [32] (Appendix A). A predefined protocol was registered with PROSPERO (an international database of prospectively registered systematic reviews), University of York, York, UK (Registration No. CRD42019127582). Case-control studies assessing the serum levels of vitamin D in patients with SLE of adult age (≥18 years), of any sex or race were considered eligible patients. Healthy subjects without the history of any autoimmune disorders including SLE of adult age (≥18 years), any sex or race were considered eligible control participants.

2.2. Literature search

Search strategies for different databases were developed and comprehensive searches combining the appropriate keywords with Boolean logical operators ('AND' & 'OR') using 'Advanced' and 'Expert' search options were conducted (Appendix B). Electronic databases including PubMed, SCOPUS, ScienceDirect and Google Scholar were searched and screened independently by three authors (MAI, SSK and SSA). The final systematic search was conducted on March 2, 2019. There were no year and language restrictions. Non-human subjects, review articles, case reports, editorials, letters, comments and duplicate articles among different databases were excluded. Duplicate studies which resulted from different electronic databases were removed and managed by EndNote software (version X8). In addition, references in the primary selected studies were also examined to identify any other possible relevant studies.

2.3. Data extraction

The studies were selected based on the inclusion criteria and selection methodology as illustrated in Fig. 1. The types of data extracted from the selected studies are as follows: country, location and latitude of origin of the participants, number of study population (both SLE and control), age of the participants, body mass index (BMI), SLE diagnostic criteria, SLE duration, disease activity measurement scales, disease activity scores, serum vitamin D measurement methods, cut-off for vitamin D insufficiency and deficiency levels (ng/mL), current medication and vitamin D supplementation status of the patients. Three authors (MAI, SSK and SSA) took part in the discussion to resolve any discrepancies, unclear or missing data presentation. If unresolved, either the corresponding or the first author of the respective study was contacted for further clarifications.

2.4. Data analyses

Mean difference (MD) along with 95% confidence intervals (CI) were used to evaluate the serum levels of vitamin D in SLE patients compared to healthy controls, where, $p < .05$ was considered as statistically significant. Serum vitamin D level measurement unit was followed as ng/mL. If in a study, serum vitamin D levels were presented in nmol/L, it was converted into ng/mL (1 nmol/L = 0.4 ng/mL). Random-effects model was used for the analyses. Predefined subgroup analyses including vitamin D levels in different continents, latitudes, seasons, BMI and vitamin D supplementation, medications with or without medications were planned to conduct on SLE patients. To assess the heterogeneity (I^2) of the included studies, Tau-squared test was used

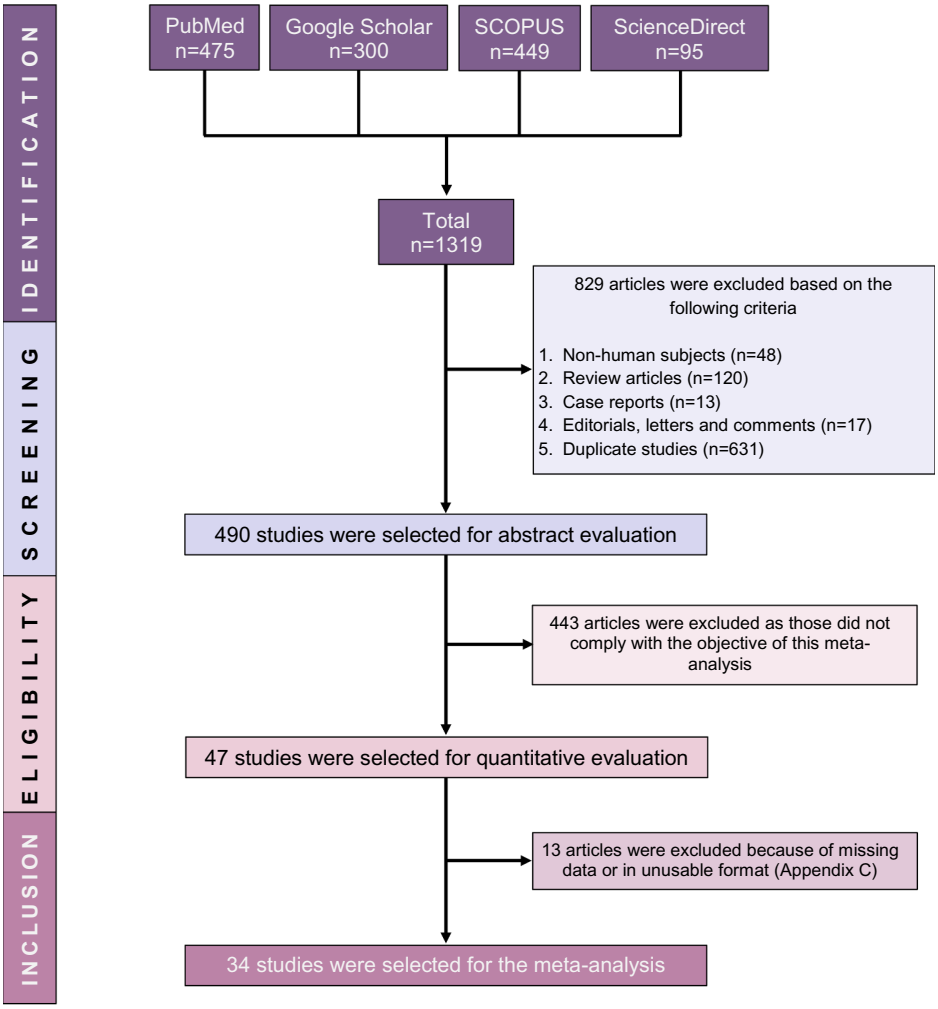

Fig. 1. PRISMA flow diagram of study selection.

where I^2 assessed the quantity of inconsistency across the studies ($p < .10$ was considered as significant). A value of I^2 close to zero indicates homogeneity, whereas, the following ranges of I^2 were used to interpret heterogeneity: low heterogeneity if $I^2 = 25–50\%$, moderate heterogeneity if $I^2 = 51–75\%$ and substantial heterogeneity if $I^2 > 75\%$ [33].

Quality assessment of each of the included studies was evaluated by three authors (MAI, SSK and SSA) based on a modified version (nine-star scoring system) of the Newcastle-Ottawa Scale (NOS) for case-control studies [34]. Studies with NOS scores of above or equal to the median were considered as high-quality (low risk of bias) [33,34]. To visually inspect asymmetry due to publication bias, a contour-enhanced funnel plot was constructed. Additionally, Begg's and Egger's tests were performed for the quantitative analysis of publication bias, where, $p < .05$ was considered as statistically significant. Results of publication bias were further validated by constructing trim and fill funnel plot.

To identify the source of heterogeneity and to check the robustness of the results, sensitivity analyses were performed. Firstly, it was performed by the leave-one-out method (removing one study each time and repeating the analysis). This analysis allowed us to determine the impact of each study on the overall effect size. Secondly, by following the exclusion of studies with NOS score less than the median (poor-quality studies). Thirdly, by changing the analysis method from random-effects model to fixed-effects model [35]. Fourthly, by only considering the studies where the study sample size is ≥100. Fifthly, by considering the studies conducted on only female subjects. Additionally, to identify possible sources of heterogeneity, a Galbraith plot was generated.

RevMan (version 5.3.5) [36] was used to generate the forest plots. Begg's and Egger's tests, contour-enhanced funnel, trim and fill funnel and Galbraith plots were constructed by using metafor package (version 2.0–0) of R (version 3.5.1) in RStudio (version 1.1.463) software [37].

3. Results

3.1. Selection and inclusion of studies

Based on the database search, a total of 1319 articles were retrieved, from which 47 met the inclusion criteria. Thirteen studies were excluded as required data for meta-analysis were missing and couldn't be retrieved (Appendix C). The remaining 34 studies comprising 4111 participants (2265 SLE patients and 1846 healthy controls) published between 1999 and 2018 were included in the meta-analysis. The PRISMA flow diagram of study selection process is illustrated in Fig. 1.

3.2. Study characteristics

Table 1 summarizes the major characteristics of the included studies. All of the included studies were journal articles [25–30,38–64] except for one meeting abstract [65]. Among the included studies, 13 were on Asian population (China [42,49,64,65], Indonesia [51–54], Korea [56,58], Iran

Table 1
Major characteristics of the included studies.

Study ID	Country, location (latitude)	Study population	Age of the participants (mean ± SD) (years)	Body mass index (mean ± SD)	SLE diagnostic criteria	SLE duration [mean ± SD /median (range)] (years)	Disease activity measurement scale	Disease activity score (mean ± SD)	Vitamin D measurement method	Cut-off for vitamin D insufficiency & deficiency (ng/mL)	Current medication status of SLE	SLE patients received vitamin D supplement?	References
Yao 2018	China, Beijing (39.90° N)	SLE: 80 Control: 80	SLE: 32.8 ± 12.4 Control: 30.2 ± 4.5	SLE: 22.1 ± 2.9 Control: 21.3 ± 3.0	ACR 1997	0.6 (0.2–1.9)	SLEDAI	16.0 ± 8.0	ELISA	NR	None	No	[64]
Elsaid 2018	Egypt, Mansoura (31.04° N)	SLE: 60 Control: 30	SLE: 39.0 ± 9.0 Control: 41.3 ± 7.5	NR	ACR 1997	8.4 ± 4.0	SLEDAI-2 K	NR	ELISA	16–29 & < 15	Hydroxychloroquine (n = 60) & Corticosteroids (*n* = 60)	No	[25]
Abdel Galil 2018	Egypt, Zagazig (30.57° N)	SLE: 123 Control: 100	SLE: 38.3 ± 9.3 Control: 36.2 ± 7.5	NR	ACR 1997	7.3 ± 4.0	SLEDAI-2 K	6.5 ± 3.8	ELISA	21–29 & ≤20	NR	No	[26]
Farid 2017	Bahrain, Manama (26.22° N)	SLE: 58 Control: 58	SLE: 39.8 ± 13.0 Control: 44.8 ± 5.4	NR	ACR 1997	NR	NP	NR	Chemiluminescent immunoassay	12–20 & < 12	NR	NR	[47]
Eloi 2017	Brazil, São Paulo (23.55° S)	SLE: 199 Control: 150	SLE: 37.2 ± 11.1 Control: 36.5 ± 10.9	SLE: 27.7 ± 6.0 Control: 27.4 ± 5.5	ACR 1997	9.7 ± 7.2	SLEDAI	NR	ELISA	20–29 & < 20	Hydroxychloroquine (*n* = 152); Corticosteroids (*n* = 76) & Immunosuppressants (*n* = 126)	Yes (*n* = 74)	[44]
Abaza 2016	Egypt, Cairo (30.04° N)	SLE: 60 Control: 30	SLE: 29.6 ± 10.0 Control: 31.0 ± 9.1	NR	ACR 1997	4.4 ± 0.6	SLEDAI-2 K	13.9 ± 1.8	Chemiluminescent immunoassay	10–30 & < 10	Hydroxychloroquine (n = 60); Corticosteroids (n = 60) & Immunosuppressants (n = 60)	No	[38]
Gao 2016	China, Zhengzhou (34.74° N)	SLE: 121 Control: 150	SLE: 32.6 ± 11.7 Control: Matched	SLE: 22.2 ± 2.5 Control: 22.2 ± 1.8	ACR 1997	2.1 (0.3–5.3)	SLEDAI-2 K	NR	Chemiluminescent immunoassay	10–30 & < 10	Corticosteroids (*n* = 96); Hydroxychloroquine (*n* = 91) & Immunosuppressants (*n* = 22)	No	[49]
Tayel 2016	Egypt, Alexandria (31.20° N)	SLE: 60 Control: 20	SLE: 28.7 ± 6.6 Control: 27.3 ± 5.1	NR	SLICC 2012	3.0 ± 3.8	SLEDAI	6.6 ± 5.7	NR	10–30 & < 10	NR	Yes (n = 15)	[62]
Buleu 2015	Romania, Timisoara (45.74° N)	SLE: 20 Control: 12	SLE: 44.1 ± 11.6 Control: 42.2 ± 12.7	NR	ACR 1997	2.7 ± 1.6	SLEDAI	9.5 ± 7.3	NR	15–29 & < 15	Corticosteroids (*n* = 13); Chloroquine (*n* = 14) & Immunosuppressants (*n* = 11)	No	[41]

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Table 1 (*continued*)

Study ID	Country, location (latitude)	Study population	Age of the participants (mean ± SD) (years)	Body mass index (mean ± SD)	SLE diagnostic criteria	SLE duration [mean ± SD /median (range)] (years)	Disease activity measurement scale	Disease activity score (mean ± SD)	Vitamin D measurement method	Cut-off for vitamin D insufficiency & deficiency (ng/mL)	Current medication status of SLE	SLE patients received vitamin D supplement?	References
Handono 2014	Indonesia, Malang (7.96° S)	SLE: 15 Control: 5	SLE: 30.0 ± 8.9 Control: 33.0 ± 3.7	SLE: 22.8 ± 5.1 Control: 19.1 ± 0.9	ACR 1997	NR (0.1–4.5)	SLEDAI	10.8 ± 5.3	ELISA	15–30 & < 15	NR	No	[54]
Squance 2014	Australia, New South Wales (31.25° S)	SLE: 80 Control: 41	SLE: 47.7 ± 13.5 Control: 49.8 ± 12.4	SLE: 27.4 ± 5.6 Control: 25.9 ± 4.8	ACR 1997	7.7 ± 6.2	NP	NR	Radio immunoassay	21–29 & ≤20	Corticosteroids (n = 34) & Immunosuppressants (n = 67)	Yes (n = 29)	[27]
Habeeb 2014	Egypt, Cairo (30.04° N)	SLE: 40 Control: 40	NR	NR	ACR 1997	7.0 ± 3.0	SLEDAI-2 K	NR	Enzyme immunoassay	NR	NR	NR	[50]
Sahebari 2014	Iran, Mashhad (36.26° N)	SLE: 82 Control: 49	SLE: 29.6 ± 11.6 Control: 29.2 ± 10.5	NR	ACR 1982	3.0 ± 2.5	SLEDAI-2 K	10.9 ± 9.1	NR	12–20 & < 12	Hydroxychloroquine (n = 82)	Yes (n = 82)	[61]
Jung 2014	Korea, Suwon (37.26° N)	SLE: 102 Control: 52	SLE: 38.8 ± 7.0 Control: 38.1 ± 8.7	SLE: 21.1 ± 2.8 Control: 21.8 ± 2.5	ACR 1997	6.5 ± 4.4	SLEDAI	4.4 ± 3.0	Immunoradiometric assay	10–29 & < 10	Corticosteroids (n = 75); Hydroxychloroquine (n = 97) & Immunosuppressants (n = 24)	NR	[56]
Emam 2014	Egypt, Cairo (30.04° N)	SLE: 40 Control: 20	SLE: 29.7 ± 6.9 Control: Matched	NR	ACR 1982	5.2 ± 4.2	SLEDAI	9.8 ± 4.7	Enzyme immunoassay	12–30 & < 12	NR	NR	[45]
Handono 2013a	Indonesia, Malang (7.96° S)	SLE: 63 Control: 20	SLE: 31.2 ± 11.2 Control: 34.6 ± 4.7	SLE: 20.9 ± 3.7 Control: 22.3 ± 2.6	ACR 1997	2.1 ± 2.1	SLEDAI	14.4 + 7.9	ELISA	20–30 & < 20	Corticosteroids (n = 63) & Immunosuppressants (n = 33)	No	[53]
Korah 2013	Egypt, Menoufia (30.59° N)	SLE: 60 Control: 20	SLE: 36.0 ± 8.8 Control: 34.3 ± 7.1	SLE: 27.1 ± 5.8 Control: 25.1 ± 3.1	ACR 1997	5.1 ± 4.1	SLEDAI	13.7 + 6.9	Competitive protein binding assay	10–30 & < 10	Corticosteroids (n = 48)	Yes (n = 9)	[59]
Hoffecke 2013	USA, Charleston (32.77° N)	SLE: 59 Control: 59	SLE: 39.8 ± 11.6 Control: 39.8 ± 11.5	NR	ACR 1997	7.4 ± 6.7	SLEDAI	NR	Radio immunoassay	10–30 & < 10	NR	NR	[55]
Handon 2013b	Indonesia, Malang (7.96° S)	SLE: 28 Control: 15	SLE: 31.3 ± 11.4 Control: 33.0 ± 11.7	SLE: 20.9 + 3.7 Control: 22.3 ± 2.5	SLICC 2012	2.0 ± 0.7	SLEDAI	12.4 ± 4.4	ELISA	21–29 & ≤20	NR	NR	[51]
Handon 2013c	Indonesia, Malang (7.96° S)	SLE: 41 Control: 20	NR	NR	ACR 1997	NR (0.1–4.5)	SLEDAI	NR	ELISA	< 30	NR	No	[52]
Bogaczewic 2012	Poland, Lodz (51.75° N)	SLE: 49 Control: 49	SLE: 43.7 ± 11.5 Control: Matched	NR	ACR 1997	6.9 ± 7.2	SLAM	10.5 ± 5.9	ELISA	21–29 & ≤20	NR	No	[39]
Stockton 2012	Australia, Melbourne (20.91° S)	SLE: 24 Control: 21	SLE: 39.6 ± 11.4 Control: 40.9 ± 13.3	SLE: 27.2 ± 6.2 Control: 24.2 ± 3.8	ACR 1982 & ACR 1997	11.0 ± 10.4	SLEDAI-2 K	4.3 ± 4.3	Chemiluminescent immunoassay	NR	Corticosteroids (n = 19); Hydroxychloroquine (n = 16);	Yes (n = 13)	[28]

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Table 1 (*continued*)

Study ID	Country, location (latitude)	Study population	Age of the participants (mean ± SD) (years)	Body mass index (mean ± SD)	SLE diagnostic criteria	SLE duration [mean ± SD /median (range)] (years)	Disease activity measurement scale	Disease activity score (mean ± SD)	Vitamin D measurement method	Cut-off for vitamin D insufficiency & deficiency (ng/mL)	Current medication status of SLE	SLE patients received vitamin D supplement?	References
Fragoso 2012	Brazil, Recife (8.05° S)	SLE: 78 Control: 64	SLE: 36.9 ± 10.6 Control: 38.1 ± 9.7	NR	ACR 1982	NR	SLEDAI	NR	Chemiluminescent immunoassay	< 30	Immunosuppressants (n = 15); Statin (n = 4) & Antidepressant (*n* = 4) Corticosteroids (*n* = 61) & Chloroquine (*n* = 32)	NR	[48]
Kim 2011	Korea, Suwon (37.26° N)	SLE: 104 Control: 49	SLE: 36.2 ± 10.2 Control: 35.3 ± 6.1	SLE: 21.5 ± 3.0 Control: 22.2 ± 3.1	ACR 1982	NR	SLEDAI	2.82 ± 2.82	Radio immunoassay	10–30 & < 10	Corticosteroids (n = NR) & Hydroxychloroquine (n = NR)	No	[58]
Ezzat 2011	Egypt, Cairo (30.04° N)	SLE: 50 Control: 22	SLE: 29.3 ± 9.2 Control: 30.4 ± 7.1	SLE: 25.8 ± 6.4 Control: NR	ACR 1982	5.4 ± 4.5	SLEDAI	17.5 ± 8.3	Radio immunoassay	10–30 & < 10	Corticosteroids (*n* = 50); Hydroxychloroquine (*n* = 45) & Immunosuppressants (*n* = 40)	NR	[46]
Ritterhouse 2011	USA, Oklahoma (35.00° N)	SLE: 32 Control: 32	NR	NR	ACR 1982 & ACR 1997	NR	SELENA-SLEDAI	NR	Enzyme immunoassay	21–29 & ≤20	Corticosteroids (n = NR); Hydroxychloroquine (n = NR) & Immunosuppressants (n = NR)	NR	[60]
Mok 2010	China, Hong Kong (22.28° N)	SLE: 52 Control: 52	NR	NR	NR	15.5 ± 8.6	SLEDAI	NR	Radio immunoassay	< 30	NR	NR	[65]
Breslin 2009	Ireland, Belfast (54.76° N)	SLE: 19 Control: 19	NR	NR	NR	NR	SLAM-R	9.1 ± 3.8	Enzyme immunoassay	NR	Corticosteroids (*n* = 19)	Yes (n = 19)	[29]
Damanhouri 2009	Saudi Arabia, Jeddah (21.48° N)	SLE: 165 Control: 214	SLE: 27.8 ± 8.8 Control: 27.9 ± 5.1	NR	ACR 1997	NR	NP	NR	Competitive protein binding assay	21–29 & ≤20	Corticosteroids (n = NR); Hydroxychloroquine (n = NR) & Immunosuppressants (n = NR)	NR	[43]
Borba 2009	Brazil, Curitiba (25.48° S)	SLE: 36 Control: 26	SLE: 29.8 ± 7.9 Control: 32.8 ± 6.3	SLE: 23.8 ± 4.8 Control: 23.3 ± 4.5	ACR 1982	4.9 (0.2–15.0)	SLEDAI	11.8 ± NR	Radio immunoassay	21–29 & ≤20	Hydroxychloroquine (*n* = 16) & Immunosuppressants (n = 4)	No	[40]
Chen 2007	China, Shanghai (31.23° N)	SLE: 57 Control: 28	SLE: 33.8 ± 1.5 Control: NR	NR	ACR 1997	4.5 ± 0.5	SLEDAI	6.5 ± 0.9	ELISA & Radio immunoassay	NR	Corticosteroids (n = NR)	NR	[42]
Kamen 2006	USA, Charleston (32.77° N)	SLE: 123 Control: 240	NR	NR	ACR 1982 & ACR 1997	NR	NP	NR	NR	10–29 & < 10	NR	NR	[57]
Redlich 2000	Austria, Vienna (48.20° N)	SLE: 30 Control: 39	SLE: 33.0 ± 1.5 Control: 32 ± 0.1	NR	ACR 1982	6.5 ± 1.0	ECLAM	NR	Radio immunoassay	NR	Corticosteroids (n = 24)	Yes (NR)	[30]
					ACR 1982	NR	NP	NR	Radio immunoassay	NR		NR	[63]

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Table 1 (*continued*)

Study ID	Country, location (latitude)	Study population	Age of the participants (mean ± SD) (years)	Body mass index (mean ± SD)	SLE diagnostic criteria	SLE duration [mean ± SD /median (range)] (years)	Disease activity measurement scale	Disease activity score (mean ± SD)	Vitamin D measurement method	Cut-off for vitamin D insufficiency & deficiency (ng/mL)	Current medication status of SLE	SLE patients received vitamin D supplement?	References
Teichmann 1999	Germany, Giessen (50.58° N)	SLE: 55 Control: 20	SLE: 49.2 ± 5.5 Control: 33.2 ± 2.7	SLE: 26.1 ± 3.4 Control: 26.2 ± 2.2							Corticosteroids (n = 35)		

ACR: American college of rheumatology; SLICC: Systemic lupus international collaborating clinics; SLEDAI: Systemic lupus erythematosus disease activity index; NP: Not performed; NR: Not reported; SLAM: Systemic lupus activity measure; SELENA: Safety of estrogens in lupus national assessment; SLAM-R: Revised systemic lupus activity measure; SD: Standard deviation; ECLAM: European consensus lupus activity measurement; ELISA: Enzyme-linked immunosorbent assay.

[61], Bahrain [47] and Saudi Arabia [43]), five were on European (Ireland [29], Poland [39], Romania [41], Austria [30] and Germany [63]), three with North American (USA [55,57,60]), three on South American (Brazil [40,44,48]), eight with African (Egypt [25,26,38,45,46,50,59,62]) and two studies on Australian participants (Australia [27,28]). Mean age of the SLE and controls subjects ranged from 27.8 ± 8.8 to 49.2 ± 5.5 years and from 27.3 ± 5.1 to 49.8 ± 12.4 years, respectively. BMI ranges were normal (18.5–24.9) in eight studies [40,49,51,53,54,56,58,64], whereas, overweight BMI ranges (25–29.9) were detected among six study participants [27,28,44,46,59,63]. Most of the SLE subjects were diagnosed based on the American college of rheumatology (ACR) [25–28,30,38–50,52–61,63,64] or SLICC criteria [51,62]. Mean SLE duration ranged from 2.0 ± 0.7 to 15.5 ± 8.6 years. SLE disease activity was measured by SLE disease activity index (SLEDAI) [40–42,44–46,48,51–56,58,59,62,64,65], SLEDAI-2 K [25,26,28,38,49,50,61], safety of estrogens in lupus national assessment (SELENA)-SLEDAI [60], systemic lupus activity measure (SLAM) [39], revised SLAM [29] or European consensus lupus activity measurement (ECLAM) scales [30]. Serum vitamin D was measured using different methods including ELISA [25,26,39,44,51–54,64], chemiluminescent immunoassay [28,38,47–49], radio immunoassay [27,30,40,42,46,48,55,58,63,65], enzyme immunoassay [29,45,50,60], immunoradiometric assay [56] and competitive protein binding assay [43,59]. Different cut-off values (ng/mL) were used to define sufficient, insufficient and deficient levels of serum vitamin D. Among the included studies, SLE participants of 21 studies [25,27–30,38,40–44,46,48,49,53,56,58–61,63] were on corticosteroids and/or hydroxychloroquine and/or different immunosuppressants and none in one study [64]; while, 12 studies [26,39,45,47,50–52,54,55,57,62,65] did not report any medication status of SLE patients. SLE patients of the eight included studies [27–30,44,59,61,62] were on vitamin D supplementation while 12 studies [25,26,38–41,49,52–54,58,64] were not and the status was not reported in 14 studies [42,43,45–48,50,51,55–57,60,63,65].

3.3. Main results: vitamin D levels in SLE

Serum levels of vitamin D was significantly lower in the SLE patients than that in the healthy control subjects (MD: -10.44, 95% CI: −13.85 to −7.03; p < .00001; serum levels of vitamin D in SLE vs healthy controls: 20.7 ± 8.4 ng/mL vs 31.4 ± 9.5 ng/mL) (Fig. 2).

3.4. Subgroup analyses

Based on the subgroup analyses on participants from different continents, significantly lower levels of vitamin D was observed in SLE patients of Asia (MD: -13.75, 95% CI: −21.45 to −6.05; p = .0005; 18.7 ± 8.0 ng/mL vs 32.5 ± 8.9 ng/mL), South America (MD: -3.16, 95% CI: −4.62 to −1.70; p < .0001; 28.8 ± 10.6 ng/mL vs 33.2 ± 10.6 ng/mL) and Africa (MD: -16.15, 95% CI: −23.73 to −8.56; p < .0001; 17.9 ± 7.9 ng/mL vs 35.0 ± 11.0 ng/mL) (Fig. 3). Vitamin D levels were however not significantly low in SLE patients of Europe (MD: −3.96, 95% CI: −13.29 to 5.38; p = .41; 24.0 ± 9.0 ng/mL vs 28.2 ± 8.8 ng/mL), North America (MD: -4.06, 95% CI: −9.38 to 1.27; p = .14; 19.1 ± 7.4 ng/mL vs 23.5 ± 9.5 ng/mL) and Australia (MD: -1.15, 95% CI: −11.83 to 9.52; p = .83; 26.4 ± 8.8 ng/mL vs 27.3 ± 6.7 ng/mL) compared to the healthy controls (Fig. 3).

Studies conducted on participants residing equal or above the latitude of 37° (both from North and South of the equator) demonstrated that vitamin D levels were not significantly different between SLE patients and healthy controls (MD: -6.20, 95% CI: −12.97 to 0.57; p = .07; 25.0 ± 9.8 ng/mL vs 31.3 ± 9.3 ng/mL). However, latitude below 37° (both from North and South of the equator) exhibited significant difference between SLE and healthy controls (MD: -11.75, 95% CI: −15.79 to −7.70; p < .00001; 19.3 ± 7.9 ng/mL vs

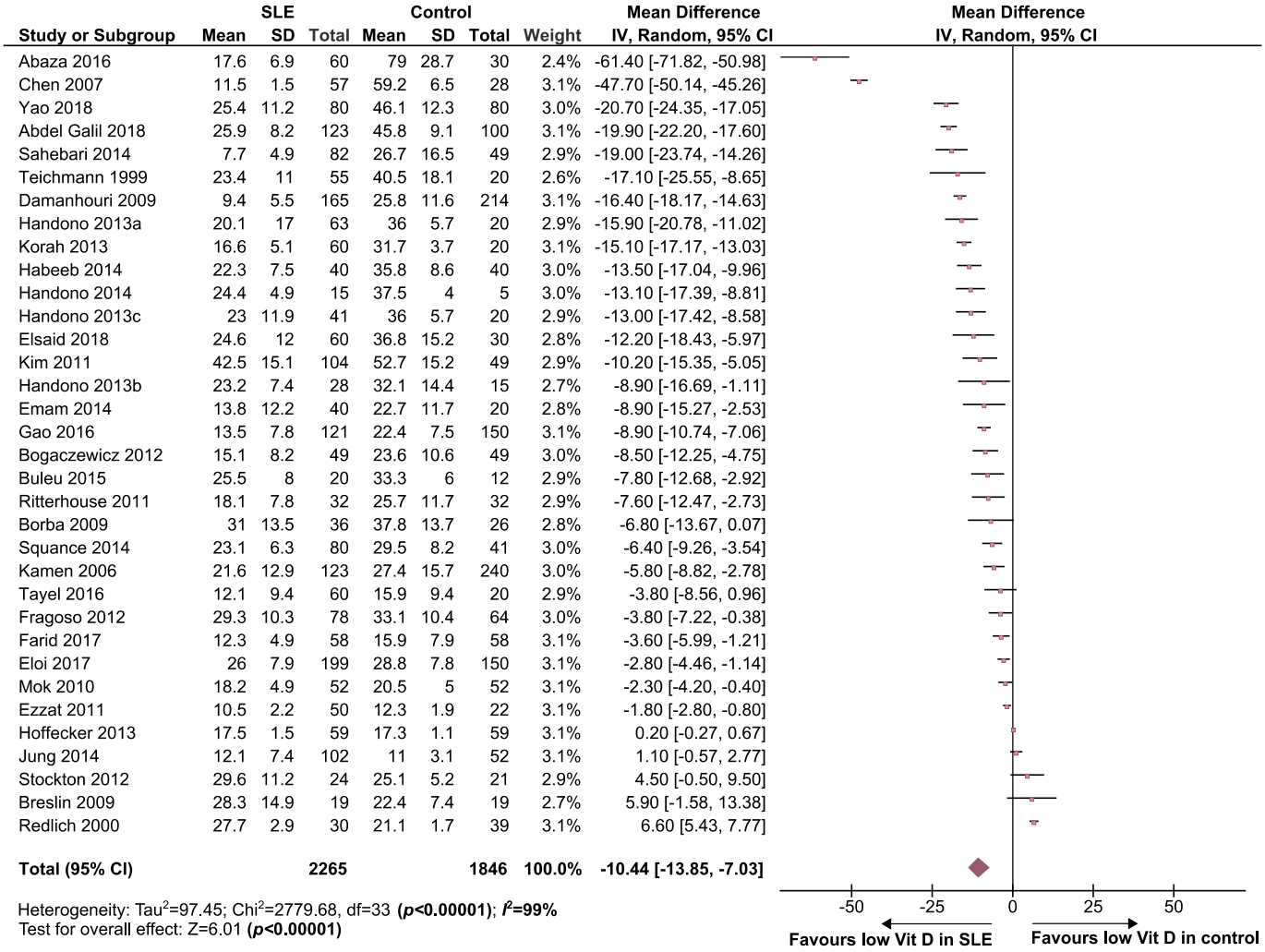


Fig. 2. Forest plot showing mean difference of vitamin D levels in patients with SLE in compared to healthy controls.

31.4 ± 9.5 ng/mL). Nevertheless, MD between these two groups (latitude ≥37° vs latitude < 37°) were not statistically significant ($p = .17$) (Fig. 4).

SLE patients with both normal weight (BMI between 18.5 and 24.9) (24.0 ± 10.5 ng/mL vs 34.5 ± 9.5 ng/mL) and overweight (BMI between 25 and 29.9) (21.5 ± 7.3 ng/mL vs 28.0 ± 7.5 ng/mL) showed significantly lower vitamin D levels when compared with healthy controls (MD: -10.41, 95% CI: −16.27 to −4.54; $p < .00001$ vs MD: -6.06, 95% CI: −11.09 to −1.03; $p = .02$) while the MD between these two groups were not statistically significant ($p = .27$) (Fig. 5).

During the summer season, MD of serum vitamin D levels was significantly different between SLE patients and healthy controls (MD: −7.89, 95% CI: −11.70 to −4.09; $p < .0001$; 21.4 ± 9.3 ng/mL vs 29.5 ± 12.1 ng/mL), while in winter, the MD was not significantly different (MD: −1.72, 95% CI: −5.12 to 1.69; $p = .32$; 20.1 ± 10.0 ng/mL vs 21.1 ± 8.5 ng/mL). Interestingly, MDs of vitamin D levels between SLE subjects and healthy controls in summer and winter seasons were significantly different ($p = .02$) (Fig. 6).

SLE patients on vitamin D supplementation exhibited insignificant MD of vitamin D compared to healthy controls (MD: -3.86, 95% CI: −10.80 to 3.07; $p = .27$; 21.4 ± 7.8 ng/mL vs 25.2 ± 7.5 ng/mL), although SLE subjects without vitamin D supplementation presented with significant MD of vitamin D levels between SLE patients and healthy controls (MD: -15.57, 95% CI: −19.99 to −11.14; $p < .00001$; 24.1 ± 10.4 ng/mL vs 40.6 ± 11.1 ng/mL) (Fig. 7). Interestingly, there was a significant difference between these two groups ($p = .005$).

Another subgroup analysis revealed that the MD was significant when SLE patients were on medications (i.e., hydroxychloroquine, corticosteroids or immunosuppressants) without vitamin D supplementation (MD: -16.46, 95% CI: −23.86 to −9.05; $p < .0001$; 25.0 ± 11.5 ng/mL vs 42.6 ± 13.1 ng/mL), however, the MD was not significant when medications (i.e., hydroxychloroquine, corticosteroids or immunosuppressants) were prescribed in combination with vitamin D supplement (MD: -3.87, 95% CI: −11.46 to 3.72; $p = .32$; 22.7 ± 7.6 ng/mL vs 26.5 ± 7.2 ng/mL) (Fig. 8). Interestingly, there was a significant difference between these two groups ($p = .02$).

3.5. Quality assessment

Quality assessment of the included studies by using NOS for case-control studies is shown in Table 2. The median score of NOS was 8. Therefore, among the 34 studies, 91.2% of the studies were considered as of high methodological quality (low risk of bias) which scored ≥8 [25–30,38–40,43–64]. Three studies [41,42,65] which scored lower than 8, were therefore considered as of low methodological quality studies (high risk of bias).

3.6. Publication bias assessment

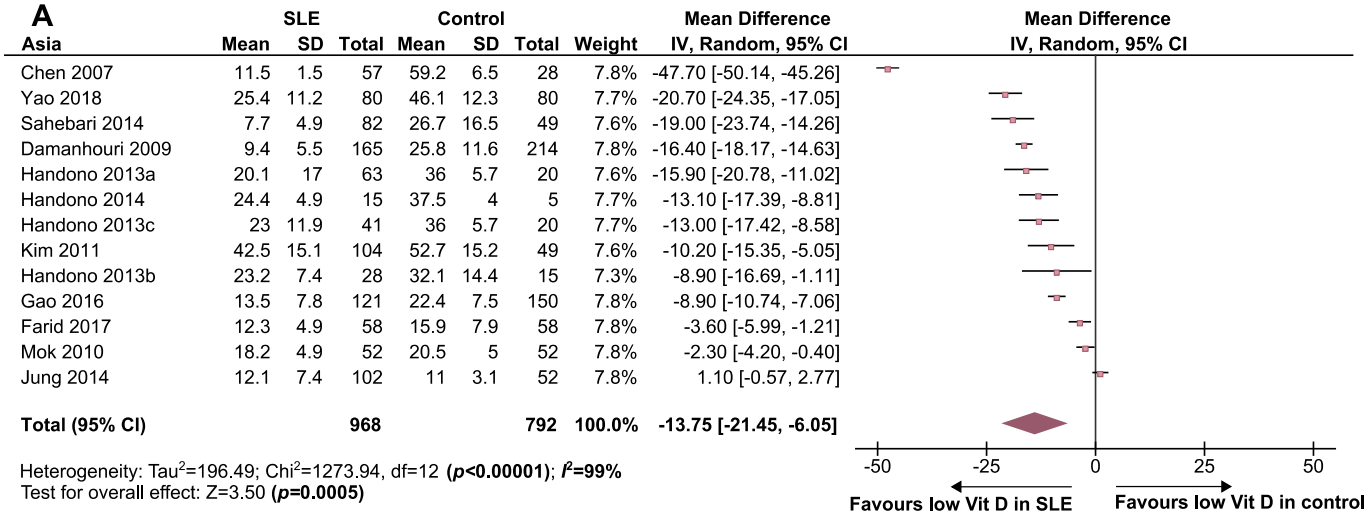
Contour-enhanced funnel plot representing MD of serum levels of vitamin D in SLE compared to healthy was used to evaluate publication bias in this meta-analysis. Though based on visual inspection of the

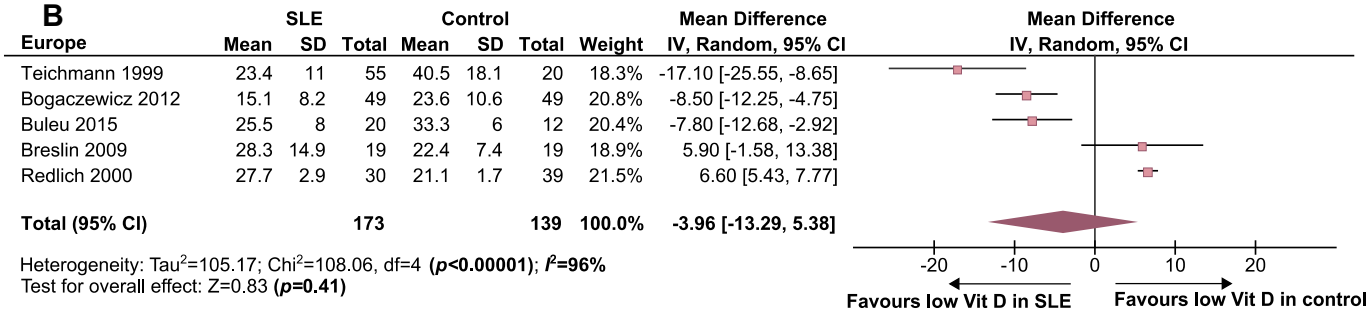
contour-enhanced funnel plots, it seems that there is no obvious asymmetry representing a possibility of publication bias which is further supported by the Begg's test ($p = .51$), however, statistically significant in Egger's test ($p = .05$) (Fig. 9). Further verification by trim and fill funnel plot showed no evidence of missing studies, thereby confirming the absence of publication bias (Appendix D).

3.7. Heterogeneity and sensitivity analysis

Main result assessing vitamin D levels in SLE patients showed significant level of substantial heterogeneity ($I^2 = 99\%$, $p < .0001$). Subgroup analyses on Asia, Europe, North America, Africa and Australia showed significantly high substantial heterogeneity ($I^2 = 92\%$–99%) whereas, subgroup analysis on SLE patients from South America exhibited no significant heterogeneity ($I^2 = 0\%$, $p = .50$).

Sensitivity analyses revealed that firstly, by excluding individual studies the results were not modified when compared to the main results. Secondly, after excluding the poor-quality studies [41,42,65], the results remained statistically significant (MD: -9.37, 95% CI: −12.12 to −6.61; $p < .00001$) (Fig. 10A). A third sensitivity analysis with fixed-effects model demonstrated that the results were still statistically significant (MD: -3.28, 95% CI: −3.60 to −2.96; $p < .00001$) (Fig. 10B). Fourthly, while only larger sample size (≥100) studies were considered, the results were persistently significant (MD: -8.35, 95% CI: −12.23 to −4.47; $p < .0001$) likewise the main findings (Fig. 10C). Fifthly, when we considered studies conducted on only female subjects, the results continued to be significant (MD: -6.76, 95% CI: −10.03 to −3.48; $p < .0001$) (Fig. 10D). Therefore, overall, sensitivity analyses revealed that the results produced in this meta-analysis were robust. Galbraith plot identified two potential included studies [38,42] as possible major contributors of heterogeneity (Fig. 11).





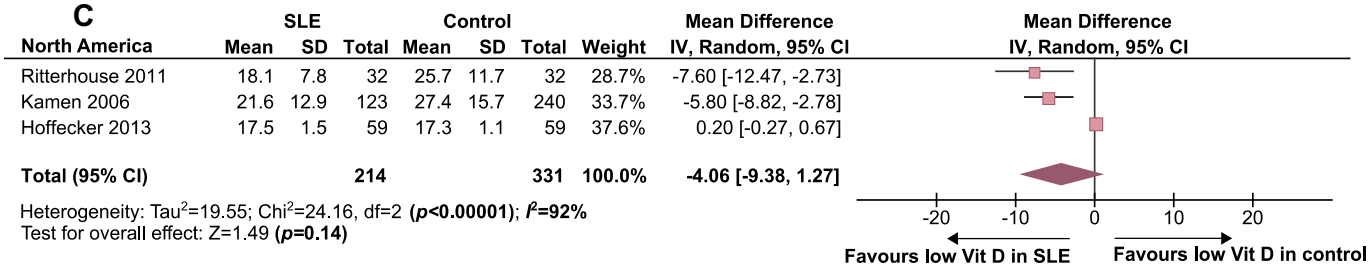


Fig. 3. Subgroup analysis showing mean difference of vitamin D levels in patients with SLE in compared to healthy controls from A) Asia, B) Europe, C) North America, D) South America, E) Africa and F) Australia.

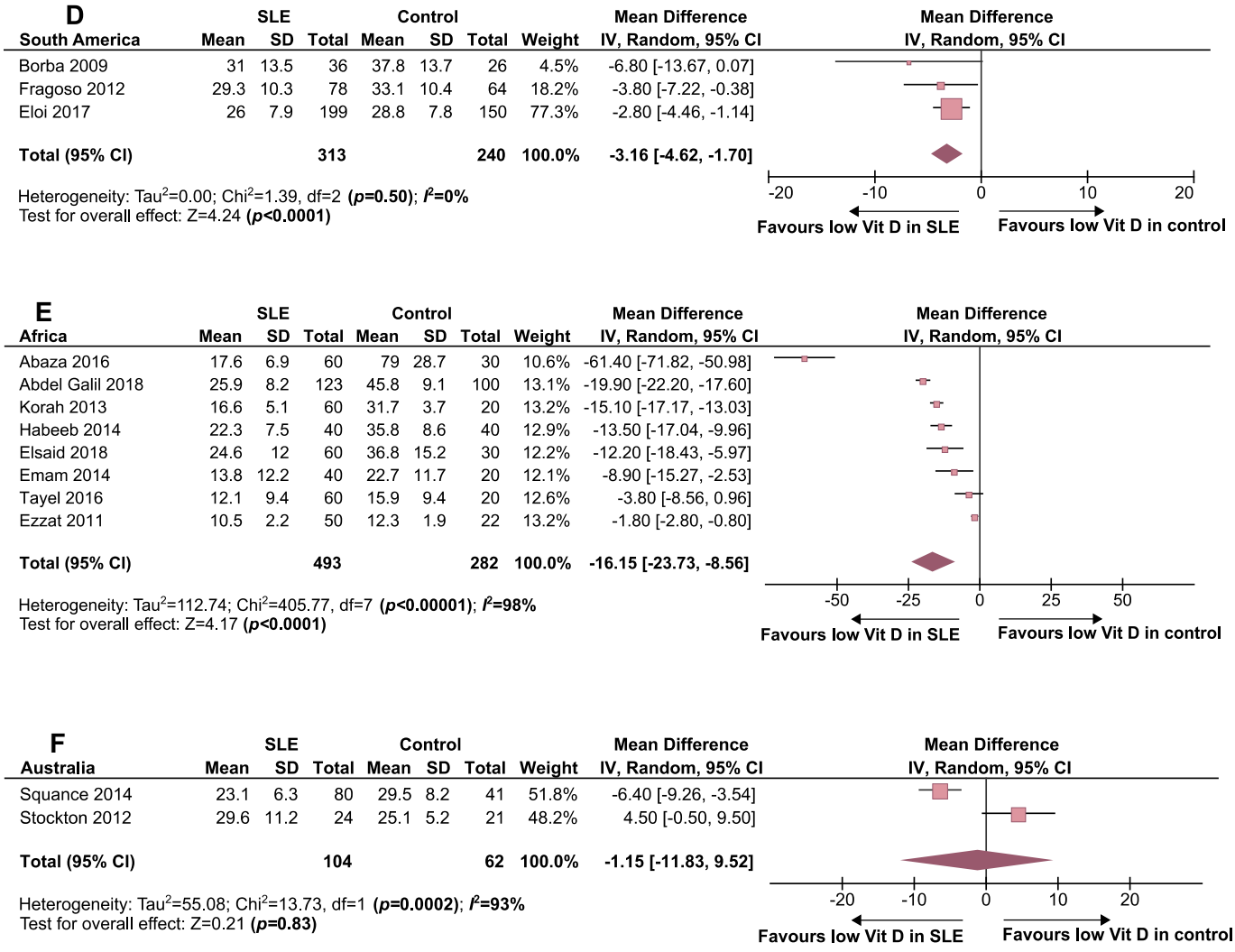


Fig. 3. (*continued*)

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis that demonstrates a significantly lower serum levels of vitamin D in patients with SLE when compared to healthy controls. Vitamin D is synthesized in the skin in presence of sunlight. Particularly, this photosynthesis is dependent upon certain intensities of ultraviolet radiation. However, as photosensitivity is a key feature of SLE, in which, exposure to sunlight can be a common trigger of SLE flares, therefore, SLE patients are advised to avoid sunlight exposure or are advised to use sunscreens with minimum sun protection factor (SPF) of 50 (which blocks UVB radiation) or other sun protective measures [66]. As a consequence, SLE patients are prone to develop vitamin D deficiency [39,57]. In a cross-sectional study on Spanish SLE patients [67], vitamin D insufficiency (75%) and deficiency (15%) were observed, whereas Spain is usually exposed to plenty of sunny days. Based on the results of our meta-analysis, eight studies on Egyptian SLE patients [25,26,38,45,46,50,59,62] exhibited significantly lower levels of serum vitamin D (MD: -16.15, 95% CI: −23.73 to −8.56; $p < .0001$), although sunshine duration is high all over Egypt with mean monthly sunshine between 3300 and 4000 h [68]. Similarly, three of our included studies from Brazil [40,44,48] exhibited significantly lower levels of serum vitamin D (MD: -3.16, 95% CI: −4.62 to −1.70; $p < .0001$) in SLE patients, whereas, Brazil gets mean monthly sunshine of approximately 2000 to 2800 h [69]. From the included Chinese and Indonesian SLE population-based studies in this meta-analysis, serum vitamin D level was significantly low (China: $p = .05$; Indonesia: $p < .00001$), although the mean monthly sunshine in China and Indonesia can be up to 3000 h [70,71]. In contrast, though in USA and Australia, the mean monthly sunshine is high (up to 4000 and 3200 h, respectively) [72,73], included studies of our meta-analysis conducted in USA and Australia didn't show significant difference of vitamin D between SLE and healthy controls (MD: -1.22, 95% CI: −6.00 to 3.57; $p = .62$ and MD: -1.15, 95% CI: −11.83 to 9.52; $p = .83$, respectively). Therefore, sun avoidance, use of sunscreens, taking sun protective measures or even foundation makeup might be some of the causes of low serum vitamin D in SLE as our included studies acknowledged the limitations to collect these data from the patients [48,53,58,59]. Use of traditional or Islamic veils may be another reason of less exposure to sunlight. Among our included studies, people of 15 studies (i.e., Egypt, Saudi Arabia, Bahrain, Iran and Indonesia) use traditional body-covering dresses or Islamic veils, which was possibly the reason of high MD of vitamin D levels (MD: −14.43, 95% CI: −19.08 to −9.79; $p < 00001$) in this population. Another possible explanation may be the modern way of life regardless of tradition and geographic location. In the modern world, people usually spent more time inside buildings and commute to work by using their own or public transportations, so even in sunny countries, sun exposure to these population may be substantially reduced. Insufficient sunlight exposure is, however, unlikely to completely explain all of the observed insufficiency/deficiency in SLE.

In our meta-analysis, it was observed that there was no significant

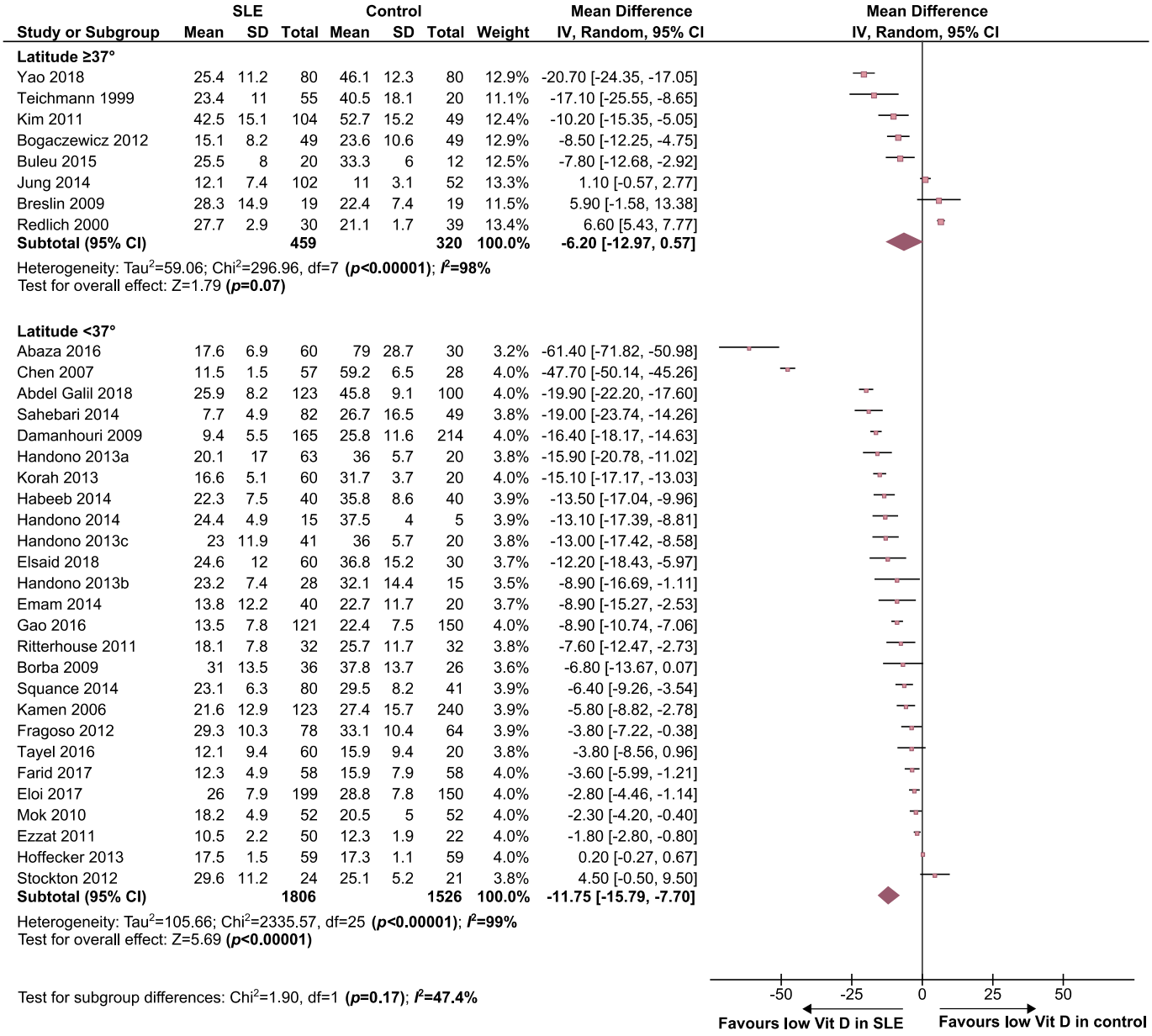


Fig. 4. Subgroup analysis showing mean difference of vitamin D levels in patients with SLE in high (≥37°) or low latitudes (< 37°) in compared to healthy controls.

MD between SLE and healthy control's vitamin D levels (−11.75) when the participants were residents of latitude above 37° ($p = .07$), however, significant MD (−6.20) in case of latitude below 37° ($p < 00001$). This is possibly as increasing latitude has been observed to be associated with higher prevalence of vitamin D insufficiency/deficiency, mainly due to limited UVB radiation (necessary to stimulate vitamin D synthesis) in higher latitude in general population including SLE patients [74,75], in particular above 37° [76].

Studies have shown that higher BMI is negatively correlated with the levels of 25(OH)D and 1, 25 (OH)2D in both general population [77–79] and SLE patients [80–82]. Our meta-analysis results demonstrated that both overweight (BMI: 25–29.9) and normal weight (BMI: 18.5–24.9) SLE subjects had significantly lower vitamin D levels (MD: −6.06, $p < .02$ and MD: −10.41, $p = .0005$, respectively), the difference of these two groups was not statistically significant ($p = .27$).

Serum levels of vitamin D can fluctuate in different seasons due to the differences in sunlight exposure and UVB radiation (i.e., summer and winter). Our subgroup analysis confirmed that during the summer season, levels of vitamin D becomes significantly lower ($p < .0001$) in SLE compared to healthy population (MD: −7.89). This incident is possibly due to the tendency of avoiding sun during the summer season [83–85]. Therefore, summer season could be a risk factor for vitamin D insufficiency/deficiency in SLE subjects.

From one of our subgroup analyses, we observed that SLE patients who were on medications (i.e., hydroxychloroquine, corticosteroids or immunosuppressants) without vitamin D supplementation exhibited significantly low levels of serum vitamin D (MD: −16.46, $p < .0001$). It has been claimed that low serum vitamin D levels are possibly the consequences of the treatment for the disease. Glucocorticoids reduce intestinal absorption of calcium and accelerate the catabolism of 25(OH)D and 1,25(OH)2D [86] with low levels of vitamin D [87]. Among the included studies in this meta-analysis, some studies found SLE patients on glucocorticoids had significantly lower levels of vitamin D compared to patients without corticosteroids [63] or healthy controls [63]. However, low serum levels of vitamin D is found irrespective of steroid use [42,48,58,88,89], therefore, steroids use cannot fully explain vitamin D deficiency in SLE patients. In 2001, an early study [90] reported that low levels of 1,25(OH)2D is the consequence of the use of

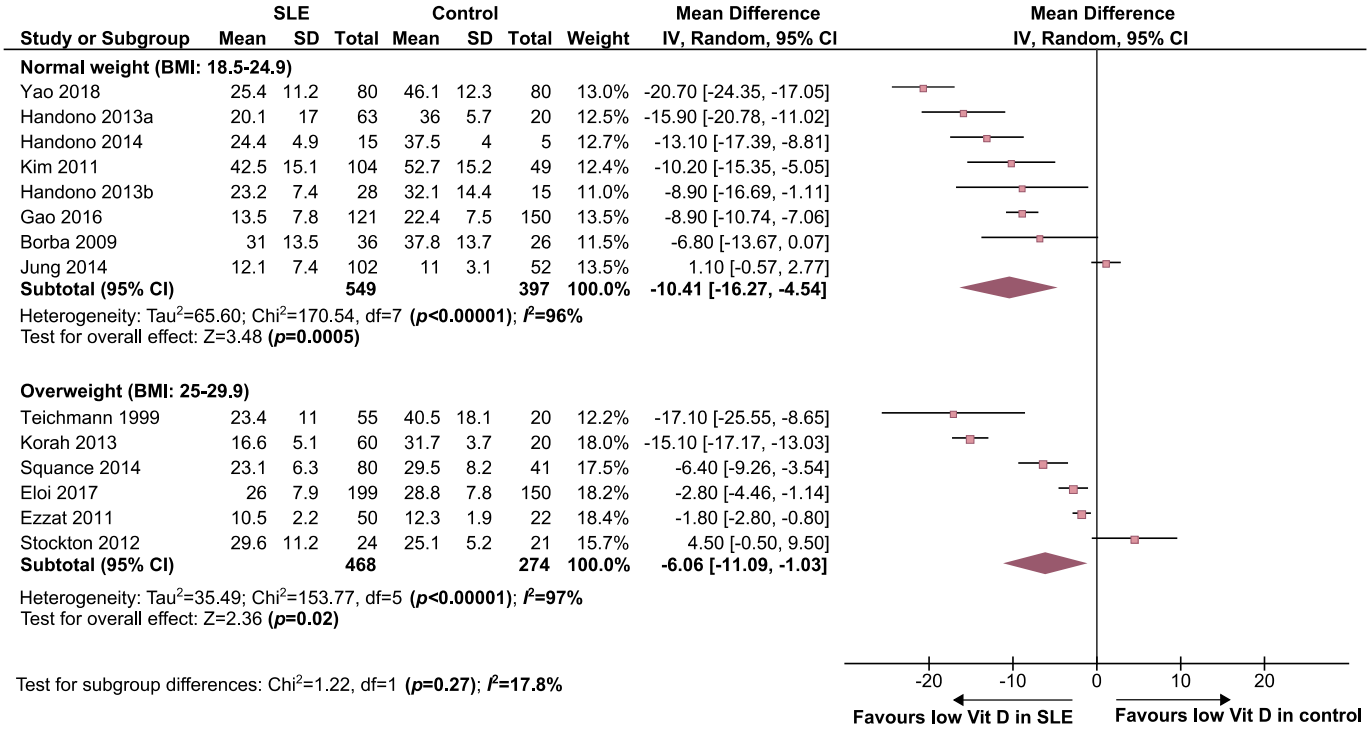


Fig. 5. Subgroup analysis showing mean difference of vitamin D levels in patients with SLE in compared to healthy controls with normal weight (BMI: 18.5–24.9) and overweight (BMI: 25-29.9).

hydroxychloroquine (HCQ), however, later in 2008, protective effects on adequate serum vitamin D [25(OH)D] was detected in SLE patients [67]. HCQ possibly inhibited the conversion of 25(OH)D to metabolically active form of vitamin D (1, 25(OH)2D) [91].

According to our meta-analysis findings, vitamin D supplementation significantly improved the serum 25(OH)D status in SLE patients as the MD between the groups (patients with vitamin D supplementation vs without vitamin D supplementation) was statistically significant (MD: −3.86 vs −15.57; $p = .005$). This indicates that vitamin D supplementation improves the serum status of 25(OH)D in SLE. Generally, in SLE patients, vitamin D supplementation was found to increase serum 25(OH)D levels and reduce inflammation and disease activity in SLE patients [44,92,93]; therefore, vitamin D supplementation with regular monitoring should be considered in SLE patients with vitamin D insufficiency/deficiency to achieve adequate levels of 25(OH)D [4].

According to our meta-analysis, when different medications (i.e.,

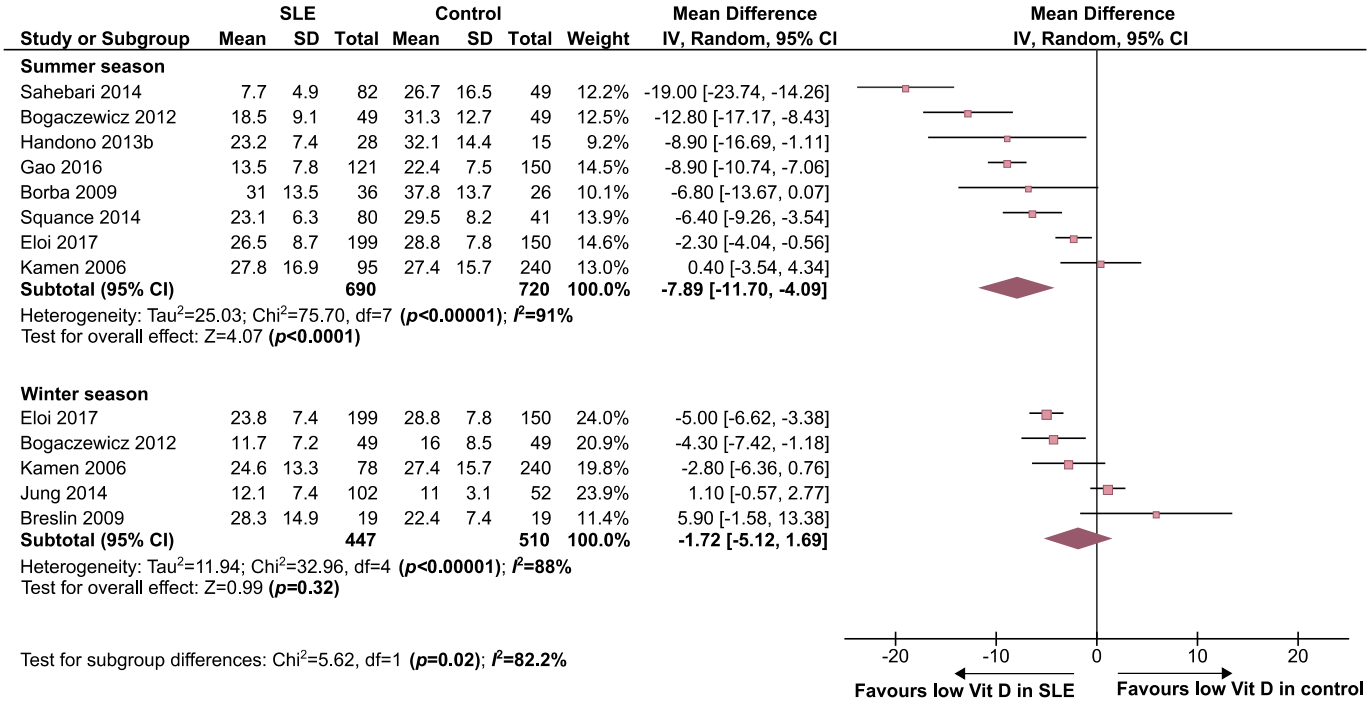


Fig. 6. Subgroup analysis showing mean difference of vitamin D levels in patients with SLE in compared to healthy controls in summer and winter seasons.

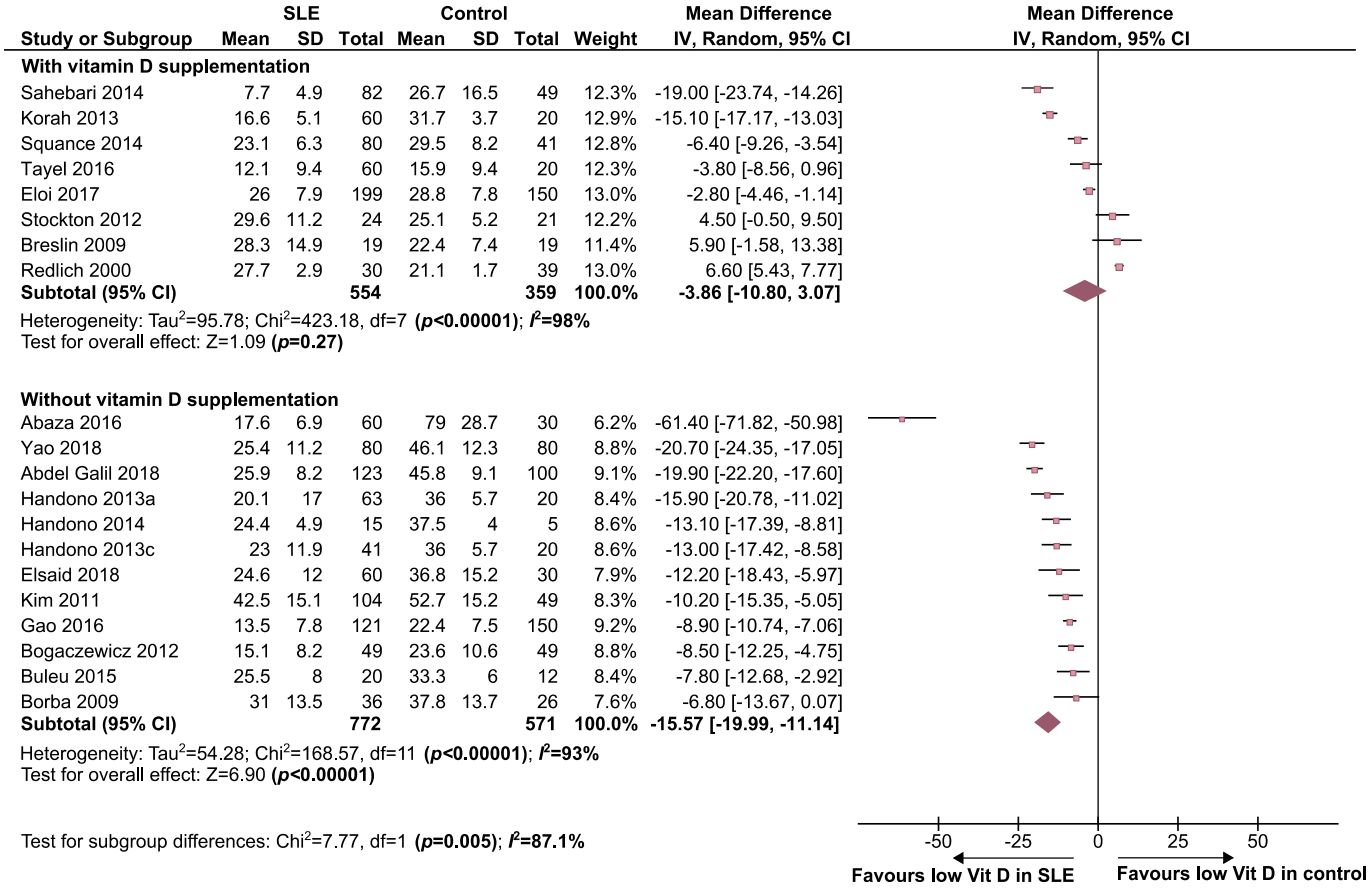


Fig. 7. Subgroup analysis showing mean difference of vitamin D levels in patients with SLE with or without vitamin D supplementation in compared to healthy controls.

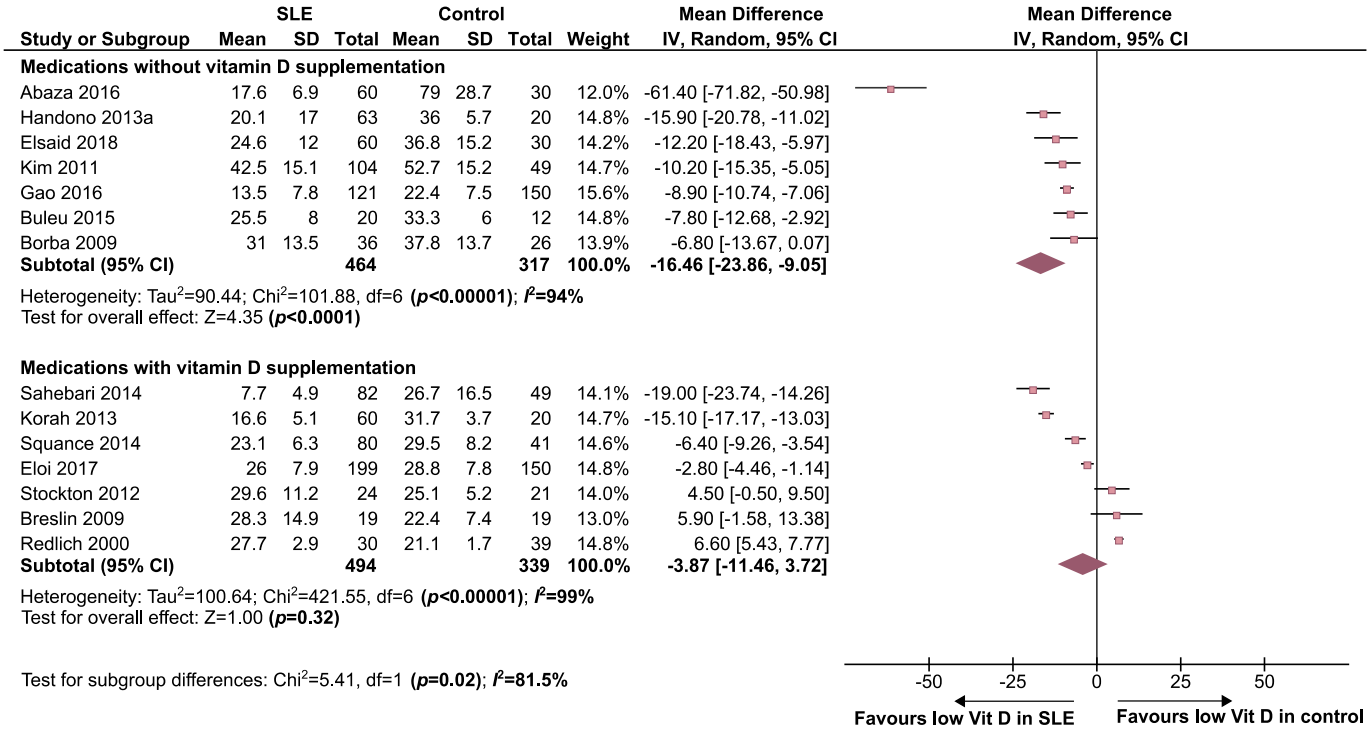


Fig. 8. Subgroup analysis showing mean difference of vitamin D levels while medications were given alone (i.e., hydroxychloroquine, corticosteroids or immunosuppressants) or in combination with vitamin D supplementation in SLE patients when compared to healthy controls.

Table 2
Risk of bias assessment of the included studies.

No.	Study ID	Newcastle-Ottawa quality assessment scale for case-control studies									
		Selection				Comparability		Exposure			Total score
		1	2	3	4	5	6	7	8	9	
1	Yao 2018	★	★	★	★	★	★	★	★	★	9
2	Elsaid 2018	★	★	★	★	★	★	★	★	★	9
3	Abdel Galil 2018	★	★	★	★	★	★	★	★	★	9
4	Farid 2017	★	★	★	★	★	●	★	★	★	8
5	Eloi 2017	★	★	★	★	★	★	★	★	★	9
6	Abaza 2016	★	★	★	★	★	★	★	★	★	9
7	Gao 2016	★	★	★	★	★	★	★	★	★	9
8	Tayel 2016	★	★	★	★	★	★	●	★	★	8
9	Buleu 2015	★	★	★	★	★	★	●	●	★	7
10	Handono 2014	★	★	★	★	★	★	★	★	★	9
11	Squance 2014	★	★	★	★	★	★	★	★	★	9
12	Habeeb 2014	★	★	★	★	★	★	★	★	★	9
13	Sahebari 2014	★	★	★	★	★	★	●	★	★	8
14	Jung 2014	★	★	★	★	★	★	★	★	★	9
15	Emam 2014	★	★	★	★	★	★	★	★	★	9
16	Handono 2013a	★	★	★	★	★	★	★	★	★	9
17	Korah 2013	★	★	★	★	★	★	★	★	★	9
18	Hoffecker 2013	★	★	★	★	★	★	★	★	★	9
19	Handono 2013b	★	★	★	★	★	★	★	★	★	9
20	Handono 2013c	★	★	★	★	★	★	★	★	★	9
21	Bogaczewicz 2012	★	★	★	★	★	★	★	★	★	9
22	Stockton 2012	★	★	★	★	★	★	★	★	★	9
23	Fragoso 2012	★	★	★	★	★	★	★	★	★	9
24	Kim 2011	★	★	★	★	★	★	★	★	★	9
25	Ezzat 2011	★	★	★	★	★	★	★	★	●	8
26	Ritterhouse 2011	★	★	★	★	★	★	★	★	★	9
27	Mok 2010	●	●	★	★	★	★	★	★	★	7
28	Breslin 2009	●	★	★	★	★	★	★	★	★	8
29	Damanhouri 2009	★	★	★	★	★	●	★	★	★	8
30	Borba 2009	★	★	★	★	★	★	★	★	★	9
31	Chen 2007	★	★	★	★	●	●	★	★	★	7
32	Kamen 2006	★	★	★	★	★	★	●	★	★	8
33	Redlich 2000	★	●	★	★	★	★	★	★	★	8
34	Teichmann 1999	★	●	★	★	★	★	★	★	★	8

1: Is the case definition adequate? 2: Representativeness of the cases. 3: Selection of controls. 4: Definition of controls. 5: Study controls for the most important factor. 6: Study controls for the second important factor. 7: Was the measurement method of vitamin D described? 8: Were the methods of measurements similar for cases and controls (e.g., ELISA)? 9: Non-response rate.
★ was awarded when the respective information was available.
● was awarded if the respective information was unavailable.

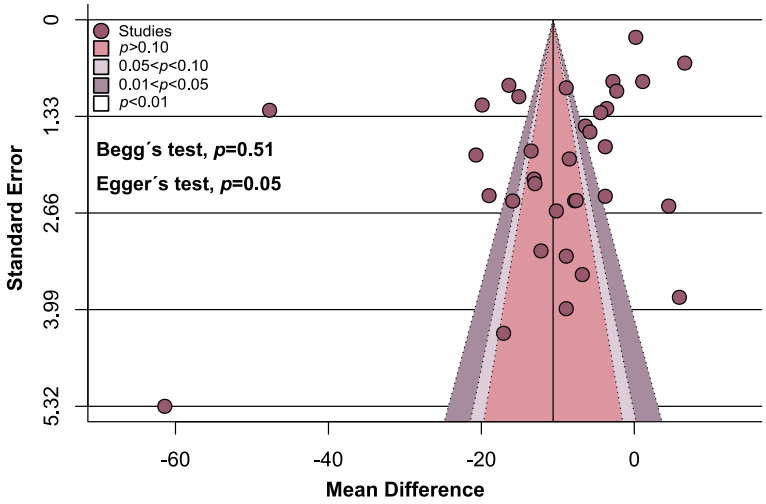


Fig. 9. Contour-enhanced funnel plot assessing publication bias reporting vitamin D levels in patients with SLE in compared to healthy controls.

hydroxychloroquine, corticosteroids or immunosuppressants) were incorporated with vitamin D, the vitamin D status improved, and the MD became narrower (−3.87). Whereas, medications without vitamin D supplementation made the MD significantly wider (−16.46, $p < .0001$). Different medications tend to reduce the levels of serum vitamin D which indicates towards the suggestion of adding vitamin D

supplementation while SLE patients are on medications, in particular -hydroxychloroquine, corticosteroids or immunosuppressants.

Many studies have indicated the link between vitamin D insufficiency/deficiency and involvement of chronic kidney diseases in both healthy population [94,95] and SLE [26,92,96,97], where, renal involvements can disrupt the conversion to make active form of VD [98]. Active lupus nephritis can be the initial presentation in ~30% of the patients with SLE [99] and up to 30% of SLE patients may develop end-stage renal disease 10 years after the first onset of lupus nephritis [100]. Among the included studies of our meta-analysis, some of the study participants were reported renal-associated manifestations [25,26,30,38,46,50–52,56,59] which may be one of the factors responsible for low levels of serum vitamin D in SLE patients.

Based on the results of two recent meta-analyses [101,102], some of the vitamin D receptor gene polymorphisms (i.e., *FokI*, *BsmI*, *TaqI* and *ApaI*) have identified to be significantly involved in patients with SLE and thus vitamin D receptor genotypes may provide a link between low serum 25(OH)D levels in SLE. Though, there are no any genotypic information of the included studies in our meta-analysis, however, the reason of low vitamin D in SLE patients could be explained due to possible vitamin D receptor gene polymorphisms in the participants.

In the recent years, probably due to changes in lifestyle, healthy subjects seem to have low levels of vitamin D. Among the included studies of our meta-analysis, serum vitamin D levels in healthy controls were detected lesser than that of SLE patients in five studies [28–30,55,56]. The reasons were possibly as 1) control subjects being African-American and Korean, among whom, the prevalence of vitamin D insufficiency/deficiency is higher in general population [55,103–106]; 2) studies on Irish [29] and Austrian population [30] gets very low mean monthly sunshine of only approximately 1350 [107] and 1900 h [108], respectively; 3) due to vitamin D supplementation in SLE patients which reduced the MD of serum vitamin compared to healthy controls [28].

Complications associated with joint pain are frequently manifested in SLE patients which could be the cause of low levels (insufficiency/deficiency) of vitamin D [109–111]. Fatigue, sleep disorders, cognitive function and cardiovascular diseases have also been frequently reported to be associated with inadequate serum levels of vitamin D in SLE [9,15,24,112].

Substantial levels of heterogeneity were observed in almost all the analyses of our systematic review and meta-analysis. Though the source of heterogeneity was unidentifiable despite attempting different sensitivity analyses and analysing different subgroups, Galbraith plot identified two studies as potential sources of heterogeneity. In addition, overall, the contributors of heterogeneity were possibly variations in the ethnicity, age, sex, different latitudes the participants were residing, diverse seasons when the level of serum vitamin D was measured, different BMIs, vitamin D level influencing medications, vitamin D supplementations, vitamin D measurement methods and cut-off values.

This systematic review and meta-analysis has several notable strengths. First, to the best of our knowledge, this is the first systematic review and meta-analysis assessing the serum levels of vitamin D in patients with SLE in compared to healthy controls. Second, a comprehensive and robust literature search without year and language

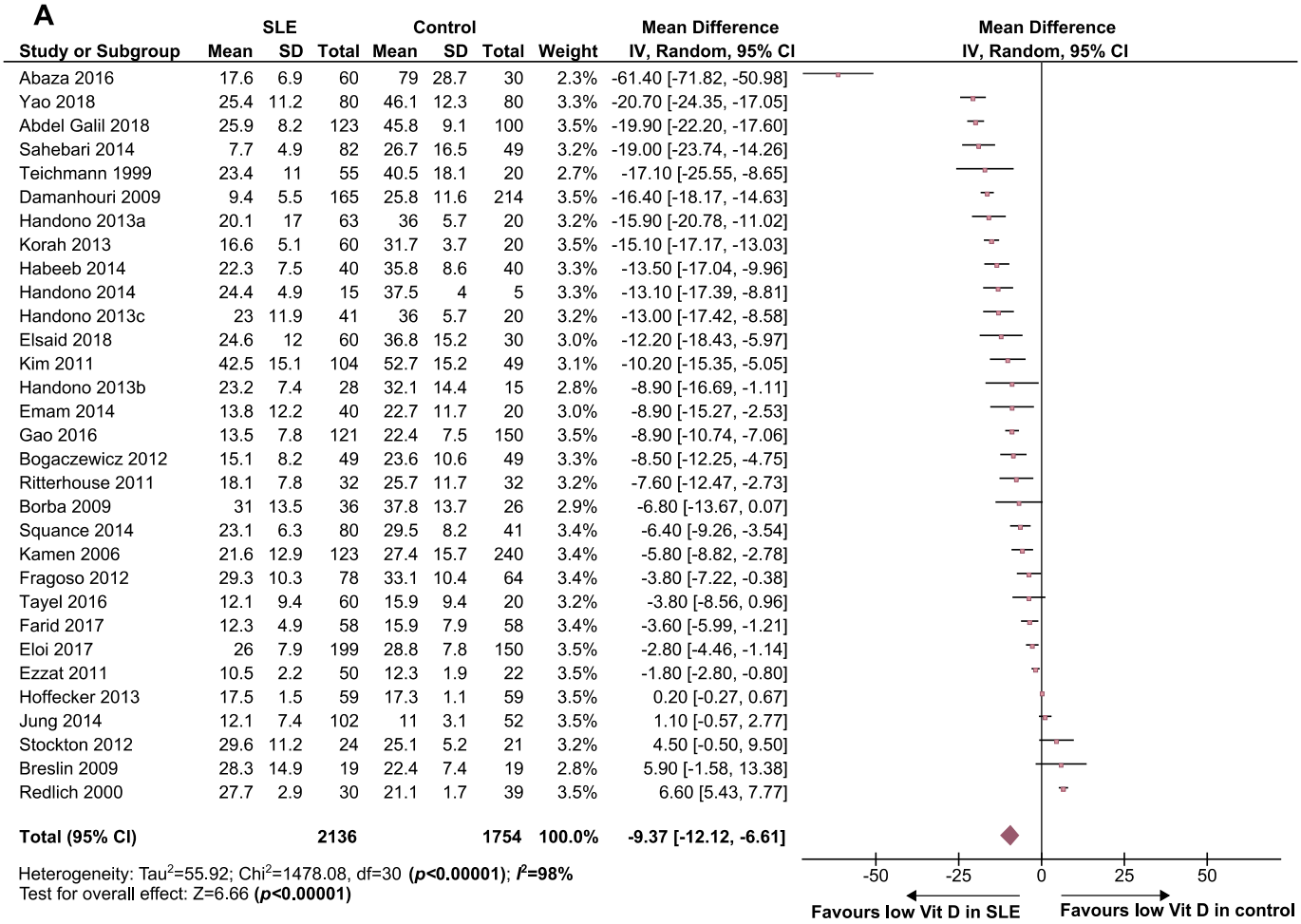
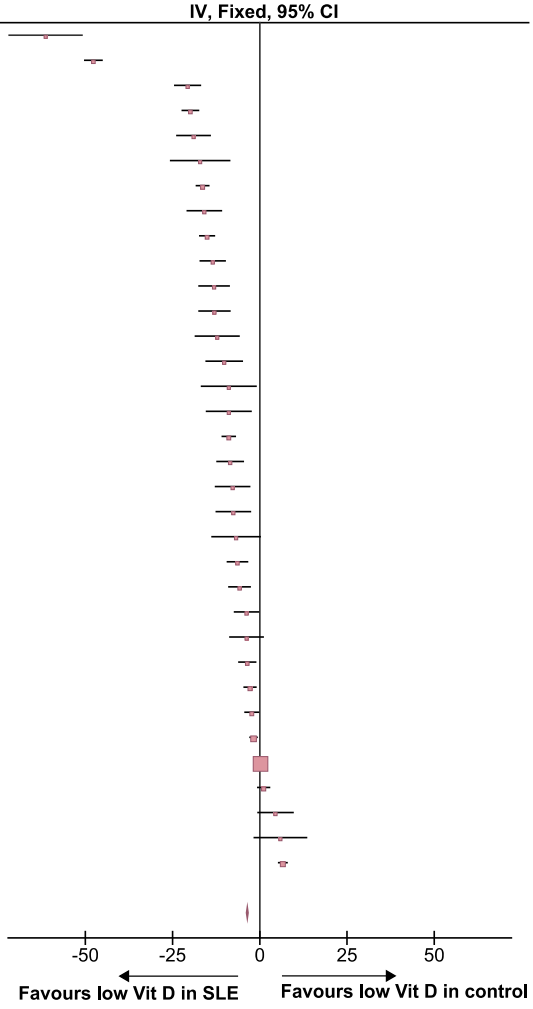


Fig. 10. Sensitivity analyses considering A) high-quality studies, B) fixed-effects model, C) studies with larger sample size (≥100) D) studies with only female subjects demonstrated that results remained statistically significant.

B

Study or Subgroup	SLE Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Abaza 2016	17.6	6.9	60	79	28.7	30	0.1%	-61.40 [-71.82, -50.98]
Chen 2007	11.5	1.5	57	59.2	6.5	28	1.7%	-47.70 [-50.14, -45.26]
Yao 2018	25.4	11.2	80	46.1	12.3	80	0.8%	-20.70 [-24.35, -17.05]
Abdel Galil 2018	25.9	8.2	123	45.8	9.1	100	2.0%	-19.90 [-22.20, -17.60]
Sahebari 2014	7.7	4.9	82	26.7	16.5	49	0.5%	-19.00 [-23.74, -14.26]
Teichmann 1999	23.4	11	55	40.5	18.1	20	0.1%	-17.10 [-25.55, -8.65]
Damanhouri 2009	9.4	5.5	165	25.8	11.6	214	3.3%	-16.40 [-18.17, -14.63]
Handono 2013a	20.1	17	63	36	5.7	20	0.4%	-15.90 [-20.78, -11.02]
Korah 2013	16.6	5.1	60	31.7	3.7	20	2.4%	-15.10 [-17.17, -13.03]
Habeeb 2014	22.3	7.5	40	35.8	8.6	40	0.8%	-13.50 [-17.04, -9.96]
Handono 2014	24.4	4.9	15	37.5	4	5	0.6%	-13.10 [-17.39, -8.81]
Handono 2013c	23	11.9	41	36	5.7	20	0.5%	-13.00 [-17.42, -8.58]
Elsaid 2018	24.6	12	60	36.8	15.2	30	0.3%	-12.20 [-18.43, -5.97]
Kim 2011	42.5	15.1	104	52.7	15.2	49	0.4%	-10.20 [-15.35, -5.05]
Handono 2013b	23.2	7.4	28	32.1	14.4	15	0.2%	-8.90 [-16.69, -1.11]
Emam 2014	13.8	12.2	40	22.7	11.7	20	0.3%	-8.90 [-15.27, -2.53]
Gao 2016	13.5	7.8	121	22.4	7.5	150	3.1%	-8.90 [-10.74, -7.06]
Bogaczewicz 2012	15.1	8.2	49	23.6	10.6	49	0.7%	-8.50 [-12.25, -4.75]
Buleu 2015	25.5	8	20	33.3	6	12	0.4%	-7.80 [-12.68, -2.92]
Ritterhouse 2011	18.1	7.8	32	25.7	11.7	32	0.4%	-7.60 [-12.47, -2.73]
Borba 2009	31	13.5	36	37.8	13.7	26	0.2%	-6.80 [-13.67, 0.07]
Squance 2014	23.1	6.3	80	29.5	8.2	41	1.3%	-6.40 [-9.26, -3.54]
Kamen 2006	21.6	12.9	123	27.4	15.7	240	1.1%	-5.80 [-8.82, -2.78]
Fragoso 2012	29.3	10.3	78	33.1	10.4	64	0.9%	-3.80 [-7.22, -0.38]
Tayel 2016	12.1	9.4	60	15.9	9.4	20	0.5%	-3.80 [-8.56, 0.96]
Farid 2017	12.3	4.9	58	15.9	7.9	58	1.8%	-3.60 [-5.99, -1.21]
Eloi 2017	26	7.9	199	28.8	7.8	150	3.8%	-2.80 [-4.46, -1.14]
Mok 2010	18.2	4.9	52	20.5	5	52	2.9%	-2.30 [-4.20, -0.40]
Ezzat 2011	10.5	2.2	50	12.3	1.9	22	10.4%	-1.80 [-2.80, -0.80]
Hoffecker 2013	17.5	1.5	59	17.3	1.1	59	46.1%	0.20 [-0.27, 0.67]
Jung 2014	12.1	7.4	102	11	3.1	52	3.7%	1.10 [-0.57, 2.77]
Stockton 2012	29.6	11.2	24	25.1	5.2	21	0.4%	4.50 [-0.50, 9.50]
Breslin 2009	28.3	14.9	19	22.4	7.4	19	0.2%	5.90 [-1.58, 13.38]
Redlich 2000	27.7	2.9	30	21.1	1.7	39	7.6%	6.60 [5.43, 7.77]
Total (95% CI)			**2265**			**1846**	**100.0%**	**-3.28 [-3.60, -2.96]**

Heterogeneity: Chi^2=2779.68; df=33 **(p<0.00001)**; **I^2=99%**
Test for overall effect: Z=19.94 **(p<0.00001)**



C

Study or Subgroup	SLE Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Yao 2018	25.4	11.2	80	46.1	12.3	80	7.0%	-20.70 [-24.35, -17.05]
Abdel Galil 2018	25.9	8.2	123	45.8	9.1	100	7.2%	-19.90 [-22.20, -17.60]
Sahebari 2014	7.7	4.9	82	26.7	16.5	49	6.7%	-19.00 [-23.74, -14.26]
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Squance 2014	23.1	6.3	80	29.5	8.2	41	7.1%	-6.40 [-9.26, -3.54]
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Fragoso 2012	29.3	10.3	78	33.1	10.4	64	7.0%	-3.80 [-7.22, -0.38]
Farid 2017	12.3	4.9	58	15.9	7.9	58	7.2%	-3.60 [-5.99, -1.21]
Eloi 2017	26	7.9	199	28.8	7.8	150	7.3%	-2.80 [-4.46, -1.14]
Mok 2010	18.2	4.9	52	20.5	5	52	7.3%	-2.30 [-4.20, -0.40]
Hoffecker 2013	17.5	1.5	59	17.3	1.1	59	7.4%	0.20 [-0.27, 0.67]
Jung 2014	12.1	7.4	102	11	3.1	52	7.3%	1.10 [-0.57, 2.77]
Total (95% CI)			**1426**			**1358**	**100.0%**	**-8.35 [-12.23, -4.47]**

Heterogeneity: Tau^2=52.71; Chi^2=811.18, df=13 **(p<0.00001)**; **I^2=98%**
Test for overall effect: Z=4.22 **(p<0.0001)**

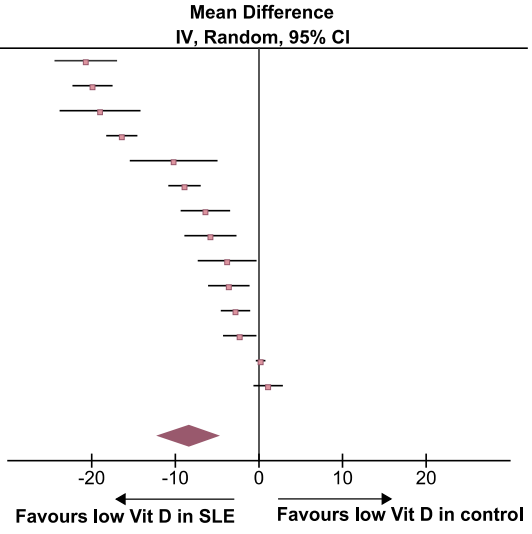

Fig. 10. (*continued*)

restriction were conducted across four electronic databases following a standard methodology. Third, the result of this meta-analysis is represented by apparently a large sample size (n = 4111) from 34 case-control studies. Third, the included 34 studies were conducted in 14 countries across the six continents (i.e., Asia, Europe, North America, South America, Africa and Australia), therefore, the result is represented at a global scale. Fourth, no publication bias was observed from both visual (contour-enhanced funnel plot) and quantitative analysis (Begg's test). Additionally, the absence of missing studies from the trim and fill funnel plot analysis further confirms that we were

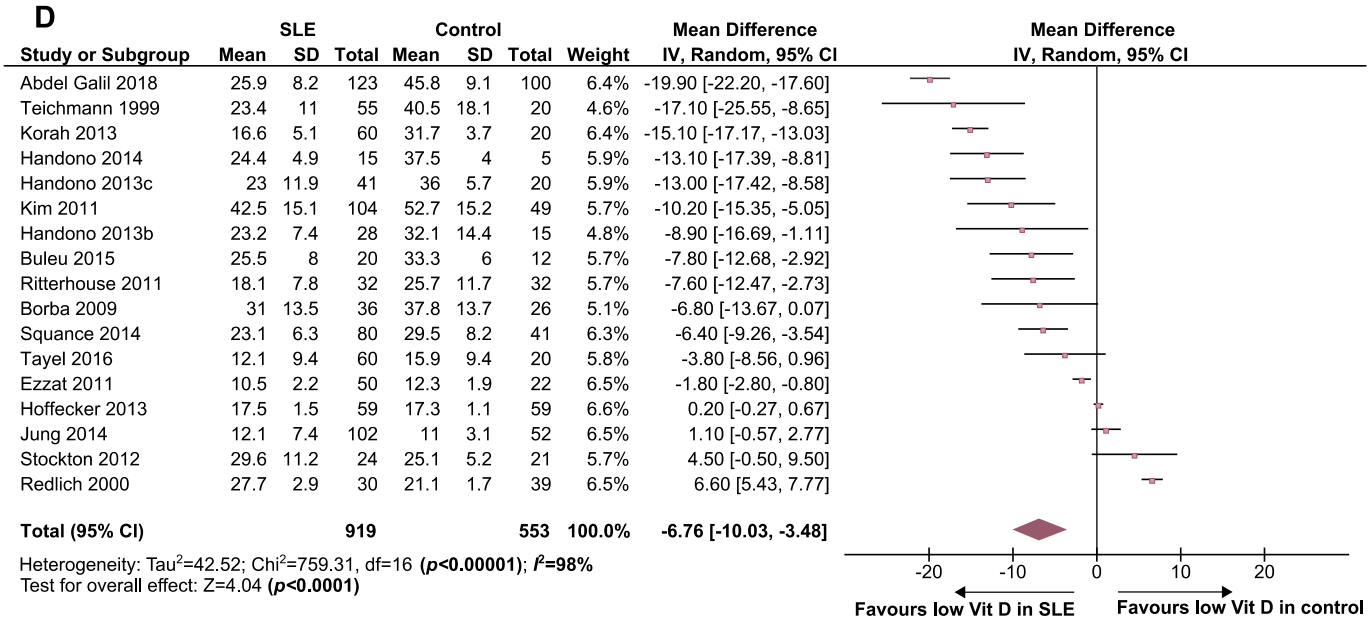

Fig. 10. (*continued*)

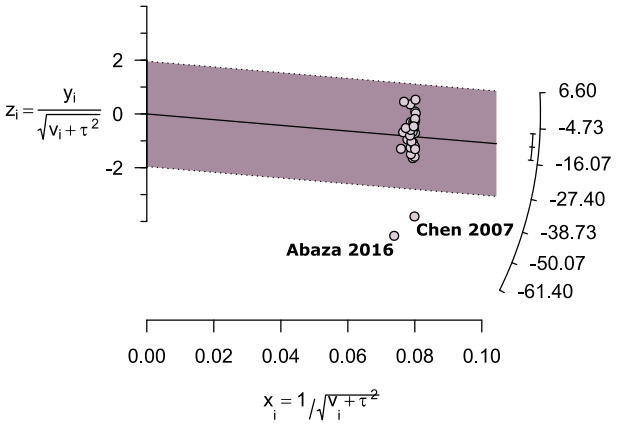

Fig. 11. Galbraith plot representing the possible sources of heterogeneity. Studies within the limits are interpreted as homogeneous. Studies outside the limits may be outliers.

unlikely to have missed studies that could have altered the meta-analysis findings. Fifth, despite of performing four different sensitivity analyses, the statistical results remained identical which represented the robustness of the findings of this meta-analysis. Sixth, 91.2% of the studies were considered as of high methodological quality (low risk of bias) which represented the credibility of the results of this meta-analysis.

Despite these strengths, we do acknowledge certain limitations. First, among the included studies, there were variations in the SLE diagnostic criteria, disease complications (i.e., presence of lupus nephritis), assay techniques and measurement methods. Second, due to lack of data for meta-analysis or data in unusable format, thirteen of the eligible studies were excluded. We couldn't retrieve the required information even after requesting the corresponding and first authors of those studies. Third, a substantial level of heterogeneity was noted in the main and subgroup analyses. Although the source of heterogeneity couldn't be identified after conducting different sensitivity analyses, however, Galbraith plot detected two studies as possible major contributors of heterogeneity.

5. Conclusions

In conclusion, our meta-analysis demonstrated that SLE patients overall exhibited significantly low serum levels of vitamin D compared to healthy controls. SLE patients from Asia, South America and Africa; patients residing below 37° latitude; serum vitamin D during winter season, patients without supplementation or on medication like hydroxychloroquine, corticosteroids or immunosuppressants without vitamin D supplementation are in higher risk of presenting inadequate serum levels of vitamin D. Although the fact of vitamin D insufficiency/deficiency in SLE is a cause or consequence, or both is still a matter of debate, however, to maintain adequate serum levels, vitamin D supplementation with regular monitoring should be considered as part of SLE health management plans.

Declaration of Competing Interest

The authors declare that they do not have any conflict of interests.

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Author contributions

MAI conceived and designed the study. MAI designed the study protocol and developed the search strategies. MAI, SSK and SSA searched the databases and participated in the study selection process and data extraction. MAI analysed and interpreted the data. MAI drafted the manuscript. PK and RH contributed to the intellectual content, critically edited and reviewed the manuscript. All authors approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2019.102392.

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