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REVIEW ARTICLE

Association Between Null Genotypes of Glutathione S-Transferase M1 and T1 and Susceptibility to Systemic Lupus Erythematosus: A Meta-Analysis

Mostafa Saadat[1]

Abstract

Oxidative stress is involved in the development of systemic lupus erythematosus (SLE). It is well known that activity of the glutathione S-transferase superfamily has a protective effect against oxidative stress. Several studies have investigated the association between the *GSTT1/GSTM1* polymorphisms and the risk of SLE with inconsistent results. The present meta-analysis was performed to investigate the association between susceptibility to SLE and the null genotypes of *GSTT1* and *GSTM1*. Eligible publications were identified by searching several databases, 18 case-control studies with 2483 cases and 3643 controls met the inclusion criteria. The raw data of three reports have internal inconsistencies, therefore these studies were excluded from the final analysis. The results showed that the *GSTM1* null genotype significantly increased the risk of SLE (OR = 1.17, 95 % CI: 1.03-1.32, p = 0.012) with no evidence of significant heterogeneity (Q = 14.53, df = 14, p = 0.411; I^2 = 3.4 %). The *GSTT1* null genotype was not associated with the risk of SLE (OR = 0.94, 95 % CI: 0.80-1.10, p = 0.447). There was no evidence of heterogeneity between studies. The present study showed that the null genotype of *GSTM1* was weakly associated with the risk of SLE.

Key words: Glutathione S-transferases; *GSTT1*; *GSTM1*; Meta-analysis; SLE.

1. Department of Biology, School of Science, Shiraz University, Iran.

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Corresponding author:
MOSTAFA SAADAT
T: +98-71-36137432
E: saadat@shirazu.ac.ir

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Introduction

Systemic lupus erythematosus (SLE) is one of the best studied autoimmune diseases. Although the aetiology of SLE is not fully understood, oxidative stress (an imbalance between free radical production and cellular antioxidant capacity) has been implicated in its pathogenesis. Oxidative stress has been positively correlated with the risk of SLE.[1, 2] The enzyme activity of some antioxidant enzymes, such as the activity of paraoxonase 1 (PON1)[3] and catalase (CAT),[4] is decreased in SLE patients compared to controls. Familial aggregation and twin studies have shown a high degree of heritability.[5-7]

Glutathione S-transferases (GSTs, EC 2.5.1.18) are a superfamily of detoxification enzymes that catalyse the conjugation of numerous xenobiotics with glutathione. GSTs are classified into several classes, including alpha, mu, theta, etc. The mu and theta classes have 5 and 2

members, respectively. *GSTM1* (MIM: 138350) and *GSTT1* (MIM: 600436) genes belong to the mu and theta classes, respectively. Deletion of the entire *GSTT1* and *GSTM1* genes is a rare genetic variation that produces *GSTT1* and *GSTM1* null alleles, respectively. Homozygous individuals for each null allele are referred to as null genotypes. The *GSTT1* (and *GSTM1*) null genotype results in the absence of the gene, protein and enzyme activity.[8, 9] The *GSTT1* and *GSTM1* null genotypes are important genetic markers for studying the role of these genes. There are many association studies investigating the relationship between these genetic variations and susceptibility to many multifactorial diseases.[10-19]

It is well known that GST enzyme activity has protective effect against oxidative stress.[8, 9] Alteration of GST enzyme activity due to the above-mentioned gene deletion, reduces cellular detoxification capacity. Considering that oxidative stress has been associated with SLE, it is reasonable to assume that the null genotypes of *GSTT1* and *GSTM1* may have a significant contribution to the pathological process and risk of SLE.

From 1999 to date, many studies have investigated the association between the *GSTT1/GSTM1* polymorphisms and the risk of SLE, with inconsistent results.[20-32] Because many association studies are conducted with limited numbers of participants (patients and controls), they usually fail to detect weak associations. Meta-analysis of published data can increase the sample size and statistical power to overcome the weakness of small studies and provide more precise estimates of the association between a given polymorphism and susceptibility to a multifactorial disease. Two meta-analyses have investigated the association between *GSTT1/GSTM1* polymorphisms and susceptibility to SLE. The first meta-analysis, published in 2015, was based on 9 original articles,[33] and surprisingly, the second, published in 2016, was based on 4 original articles.[34] Unfortunately, both meta-analyses suffer from the authors' inaccuracy in finding relevant articles and the authors did not include some of the studies published at the time. Therefore, their results are not reliable and a new meta-analysis is needed.

The present meta-analysis was performed to investigate the association between susceptibility to SLE and the null genotypes of *GSTT1* and *GSTM1*.

Methods

The current meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. Eligible publications were identified by searching multiple databases, including PubMed, Europe PMC, Web of Science, Scopus, Directory open access journals (DOAJ), ProQuest, African journals online (AJOL) and Islamic science citation (ISC). Last search updated on 15 July 2023. The following keywords were used to search the literature search: (*GSTT1* OR *GSTM1*) AND ("systemic lupus erythematosus" OR SLE). The search was not limited by language. References of eligible studies were also reviewed to identify additional relevant studies.

Inclusion and exclusion criteria

Inclusion criteria were as follows: studies comparing SLE patients and healthy controls; articles with sufficient genotype data to calculate odds ratios (ORs) and corresponding 95 % confidence intervals (CIs); studies written in English. Exclusion criteria were as follows: case studies, meta-analyses, reviews, letters to the editor, poster presentations, overlapping data, studies of family members based on linkage analysis, articles that did not report raw data, duplicate studies and articles written in languages other than English.

Data extraction

A customised and standardised form was used for data extraction. The researcher extracted the required information twice with an interval of 2 weeks. There was no discrepancy between two extractions. For each study, the following information was extracted: first author's surname, year of publication, country in which the study was conducted, number of cases and controls, ethnicity, genotyping method, source of controls, mean age of participants (in cases and controls), percentage of female participants (in cases and controls) and number of cases and controls with respect to the *GSTT1/GSTM1* genotypes. Ethnicity was categorised as African, Asian, Caucasian and mixed. Source of controls was categorised as population-based and hospital-based studies. For studies investigating on more than one ethnic group, data were extracted separately as independent studies.

Statistical analysis

Associations were expressed as OR with 95 % CIs. Heterogeneity between studies was measured using Cochran's Q statistic and inconsistency was quantified using I^2 statistic. The Q statistic was considered statistically significant if the p-value was less than 0.10 ($p < 0.10$). I^2 values of 0-25 %, 26-50 %, 51-75 % and > 0.75 % represent no, low, moderate and high heterogeneity, respectively. If heterogeneity was present, a random-effects model was used according to the DerSimonian and Laird method,[35] otherwise, a fixed-effects model was used for comparisons according to the Mantel-Haenszel method.[36]

Subgroup meta-analyses were performed according to ethnicity, source of control and sample size. Sensitivity analyses were performed to assess the robustness and stability of the results. To perform sensitivity analyses, a single study was serially removed from the studies included in the analysis and the effect of removal on the level of heterogeneity and the strength of the association was measured. The potential publication bias of the eligible studies was assessed using the Begg[37] and Egger[38] regression tests. Statistical analysis and generation of plots were performed using the "Comparative Meta-Analysis" software (version 2.2.064, USA).

In addition, to assess whether statistically significant associations detected in this meta-analysis were "noteworthy", the false positive report probability (FPRP) value was calculated with a prior probability level (π) of 0.001 for significant associations. A FPRP cut-off value of 0.20 was used, as previously suggested.[39] Therefore, associations with the FPRP values less than 0.20 were considered as "noteworthy" associations.

Results

A flowchart of the study selection process is shown in Figure 1. At the end of the search process, a total of 121 original articles were reviewed. Duplicate articles (n = 65) between databases were excluded. Further screening resulted in the exclusion of 43 articles due to study design, article type (review, abstract, meta-analysis, etc) and not related to the *GSTT1/GSTM1* polymorphisms or research topic. Finally, 13 articles were selected for analysis.

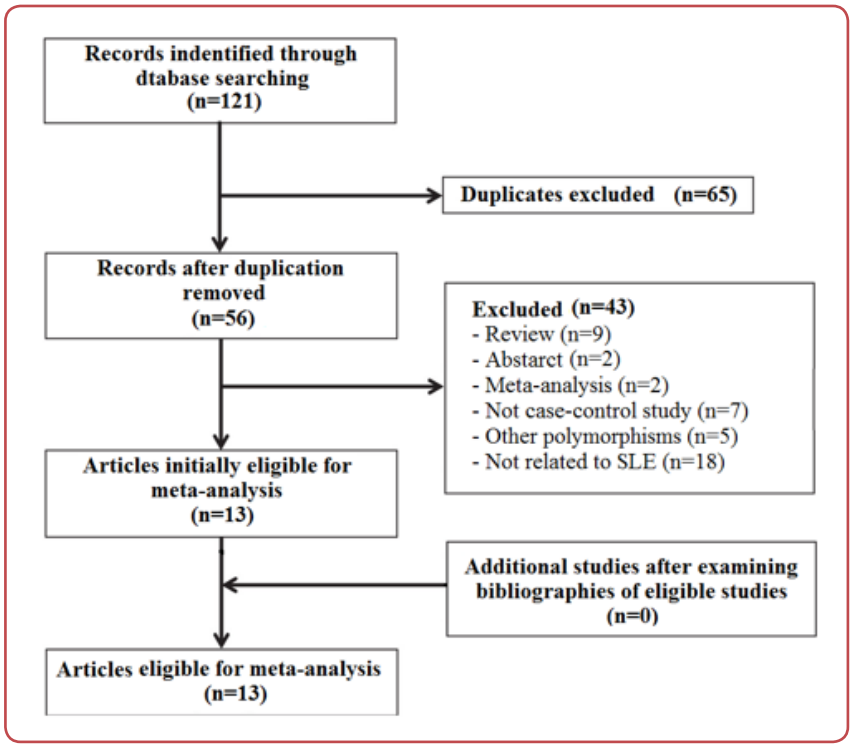

Figure 1: Flow diagram for identifying and including studies in the current meta-analysis

Table 1: Characteristics of included studies in this meta-analysis

Authors	Year	Country	Ethnicity	Source of controls	Cases			Controls		
					n*	Age	Female proportion (%)	n	Age	Female proportion (%)
Ollier et al[28]	1996	UK	Caucasian	NA	90	-	90.0	569	-	90.0
Tew et al (1)[31]	2001	USA	African	NA	105	-	-	56	-	-
Tew et al (2)[31]	2001	USA	Caucasian	NA	76	-	-	78	-	-
Tew et al (3)[31]	2001	USA	Hispanic	NA	71	-	-	42	-	-
Fraser et al (1)[27]	2003	USA	Caucasian	PB	85	-	-	202	-	-
Fraser et al (2)[27]	2003	USA	African	PB	144	-	-	72	-	-
Fraser et al (3)[27]	2003	USA	Mixed	PB	14	-	-	44	-	-
Kang et al[26]	2005	Korea	Asian	NA	330	33.3 (11.8)	96.6	270	34.9 (9.9)	94.5
Horiuchi et al[32]	2009	Japan	Asian	PB	152	-	100.0	427	-	100.0
Zhang et al[25]	2010	China	Asian	NA	298	-	-	284	-	-
Kiyohara et al[29]	2012	Japan	Asian	PB	151	41.2 (13.0)	100.0	421	31.7 (14.1)	100.0
Rupasaree et al[24]	2013	India	Caucasoid	HB	194	28.4 (9.8)	98.0	445	29.9 (9.9)	98.0
Glesse et al (1)[23]	2014	Brazil	Caucasian	PB	282	49.3 (15.0)	91.5	241	-	-
Glesse et al (2)[23]	2014	Brazil	African	PB	87	48.0 (13.6)	93.2	88	-	-
Salimi et al[22]	2015	Iran	Caucasian	PB	163	32.6 (8.6)	93.0	179	32.1 (11.7)	93.0
Nasr et al[30]	2017	Egypt	African	PB	40	28.1 (4.5)	100.0	40	27.3	100.0
Jevtovic-Stoimenov et al[21]	2017	Serbia	Caucasian	PB	88	52.0 median	-	88	-	-
de Oliveora et al[20]	2021	Brazil	Mixed	HB	144	33.7 (9.8)	100.0	145	32.7 (6.8)	100.0

n: number of participants; NA: data not available; PB: population based controls; HB: hospital based controls; age values are presented as mean (standard deviation);

Reports by Tew,[31] Fraser[27] and Glesse[23] that included participants from different ethnic groups were considered as three, three and two studies, respectively. The application of these criteria resulted in 18 case-control studies eligible for meta-analysis.

Table 1 shows the characteristics of the 18 eligible studies included in the meta-analysis. Of these 7, 4 and 4 studies were conducted in Caucasians, Asians, and Africans, respectively. Controls were population-based (PB) and hospital-based (HB) in 10 and 2 studies, respectively. Some studies (n = 6) did not report the source of controls. In all studies, the polymorphism was determined by PCR assays. The sample size ranged from 38 to 659 participants (patients and controls).

Table 2: Associations between GSTM1 null genotype and systemic lupus erythematosus risk

Authors	Year	Ethnicity	Cases		Controls		OR	95 % CI	P-value
			Present	Null	Present	Null			
Ollier et al[28]	1996	Caucasian	35	55	253	316	1.25	0.79-1.98	0.322
Tew et al (1)[31]	2001	African	84	21	43	13	0.82	0.37-1.81	0.634
Tew et al (2)[31]	2001	Caucasian	37	39	47	31	1.59	0.84-3.02	0.150
Tew et al (3)[31]	2001	Hispanic	40	31	25	17	1.14	0.52-2.47	0.741
Fraser et al (1)[27]	2003	Caucasian	48	37	110	92	0.92	0.55-1.53	0.754
Fraser et al (2)[27]	2003	African	111	33	54	18	0.89	0.46-1.72	0.734
Fraser et al (3)[27]	2003	Mixed	9	5	15	9	0.92	0.23-3.64	0.912
Kang et al[26]	2005	Asian	144	186	129	141	1.18	0.85-1.63	0.311
Horiuchi et al[32]	2009	Asian	75	77	231	196	1.21	0.83-1.75	0.313
Zhang et al[25]	2010	Asian	108	190	138	146	1.66	1.19-2.31	0.003
Kiyohara et al[29]	2012	Asian	75	76	227	194	1.18	0.81-1.72	0.370
Rupasaree et al[24]	2013	Caucasoid	143	51	289	154	0.66	0.46-0.97	0.036
Glesse et al (1)[23]	2014	Caucasian	149	133	112	129	0.77	0.54-1.09	0.147
Glesse et al (2)[23]	2014	African	54	33	63	25	1.54	0.81-2.90	0.182
Salimi et al[22]	2015	Caucasian	76	87	100	79	1.44	0.94-2.21	0.088
Nasr et al[30]	2017	African	18	22	23	17	1.65	0.68-4.00	0.265
Jevtovic-Stoimenov et al[21]	2017	Caucasian	34	54	37	51	1.15	0.63-2.10	0.645
de Oliveora et al[20]	2021	Mixed	98	15	101	18	0.85	0.41-1.79	0.687

OR: odds ratio; CI: confidence interval;

For the *GSTM1* polymorphism, a total of 13 articles (including 18 case-control studies) with 2483 cases and 3643 controls met the inclusion criteria (Table 2). The results showed that the *GSTM1* null genotype significantly increased the risk of SLE (OR = 1.12, 95 % CI: 1.004-1.25, p = 0.042) with no evidence of significant heterogeneity (Q = 24.19, df = 17, p = 0.114; I^2 = 29.7 %).

The raw data presented in three reports by Ollier,[32] Rupasree[24] and Salimi[22] have internal inconsistencies. Therefore, these studies were excluded from the meta-analysis. Further analysis showed that the level of heterogeneity decreased and there was no evidence of heterogeneity between studies (Q = 14.53, df = 14, p = 0.411; I^2 = 3.4 %). The association between the null genotype of *GSTM1* and the risk of SLE increased

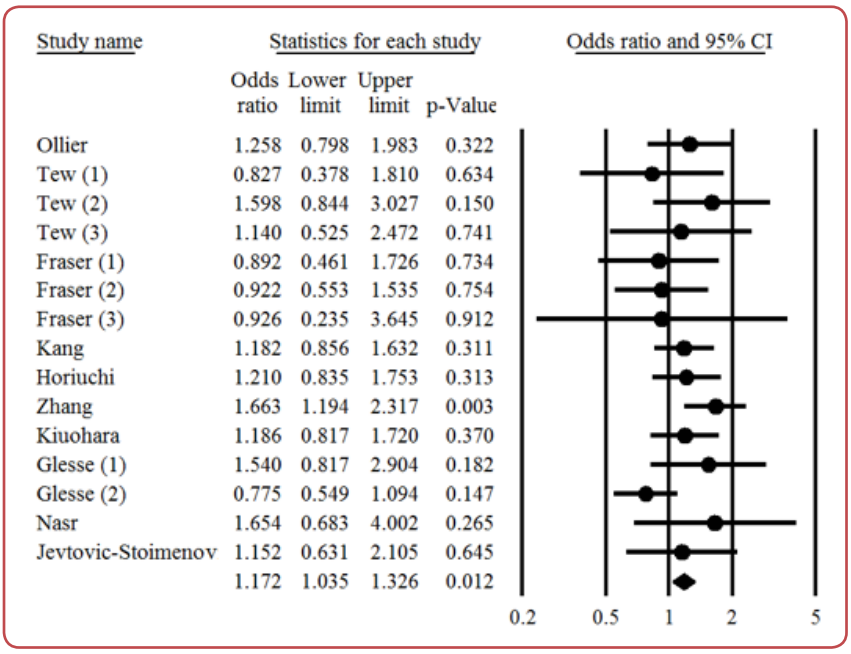

Figure 2: Forest plot of the association between GSTM1 null genotype and systemic lupus erythematosus risk

Table 3: Associations between GSTT1 null genotype and systemic lupus erythematosus risk

Authors	Year	Ethnicity	Cases		Controls		OR	95 % CI	P-value
			Present	Null	Present	Null			
Ollier et al[28]	1996	Caucasian	71	18	368	86	1.08	0.61-1.91	0.779
Tew et al (1)[31]	2001	African	78	27	38	18	0.73	0.35-1.48	0.387
Tew et al (2)[31]	2001	Caucasian	62	14	61	17	0.81	0.36-1.78	0.602
Tew et al (3)[31]	2001	Hispanic	61	10	35	7	0.82	0.28-2.34	0.711
Fraser et al (1)[27]	2003	Caucasian	73	12	181	21	1.41	0.66-3.02	0.369
Fraser et al (2)[27]	2003	African	114	30	59	13	1.17	0.57-2.42	0.669
Fraser et al (3)[27]	2003	Mixed	12	2	22	1	3.83	0.31-46.6	0.292
Kang et al[26]	2005	Asian	160	170	121	149	0.86	0.62-1.19	0.370
Horiuchi et al[32]	2009	Asian	-	-	-	-	-	-	-
Zhang et al[25]	2010	Asian	163	135	137	147	0.77	0.55-1.06	0.119
Kiyohara et al[29]	2012	Asian	-	-	-	-	-	-	-
Rupasaree et al[24]	2013	Caucasoid	131	63	360	85	2.03	1.39-2.98	< 0.001
Glesse et al (1)[23]	2014	Caucasian	226	56	197	44	1.10	0.71-1.72	0.643
Glesse et al (2)[23]	2014	African	73	14	69	18	0.73	0.34-1.59	0.435
Salimi et al[22]	2015	Caucasian	122	41	152	27	1.89	1.10-3.25	0.021
Nasr et al[30]	2017	African	30	10	35	5	2.33	0.71-7.58	0.159
Jevtovic-Stoimenov et al[21]	2017	Caucasian	71	17	75	13	1.46	0.66-3.20	0.342
de Oliveora et al[20]	2021	Mixed	98	46	101	44	1.07	0.65-1.77	0.769

OR: odds ratio; CI: confidence interval;

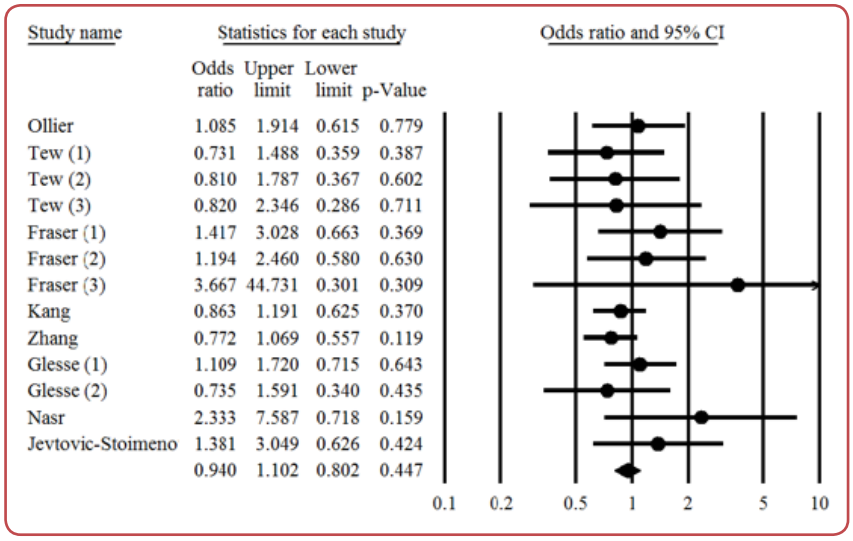

Figure 3: Forest plot of the association between GSTT1 null genotype and systemic lupus erythematosus risk

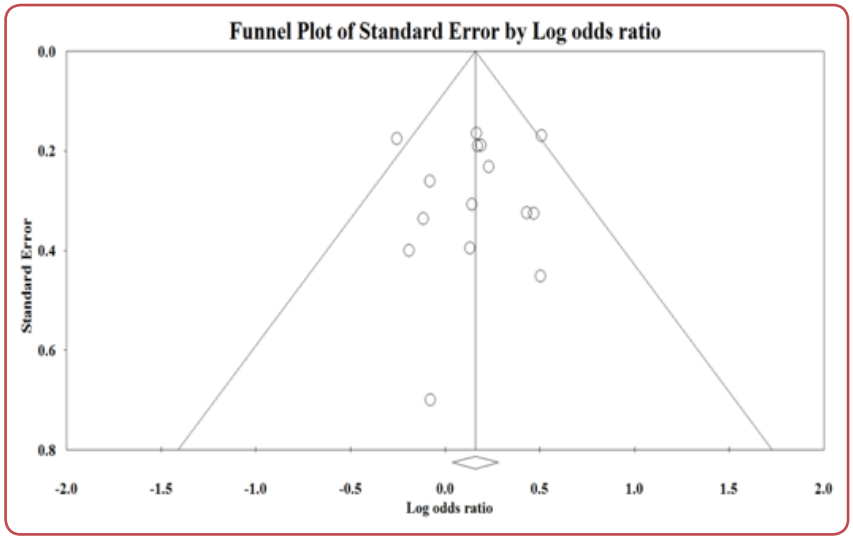

Figure 4: Funnel plot of the GSTM1 null genotype and systemic lupus erythematosus risk

slightly (OR = 1.17, 95 % CI: 1.03-1.32, p = 0.012). The forest plot for the association between the *GSTM1* null genotype and the risk of SLE is shown in Figure 2.

For the *GSTT1* polymorphism, a total of 16 case-control studies with 2211 SLE patients and 2706 controls were selected for the present analysis (Table 3). There was moderate heterogeneity among the studies (Q = 26.99, df = 15, p = 0.029; I^2 = 44.4 %). The *GSTT1* null genotype was not associated with the risk of SLE (OR = 1.12, 95 % CI: 0.92-1.37, p = 0.250).

After excluding studies due to internal inconsistency, the heterogeneity decreased remarkably (Q = 9.41, df = 12, p = 0.667; I^2 = 0.0 %), but the association was still not significant (OR = 0.94, 95 % CI: 0.80-1.10, p = 0.447). The forest plot for the association between the *GSTT1* null genotype and the risk of SLE is shown in Figure 3.

Some investigators[23, 25, 27] reported the combination genotypes in cases and controls. These reports were used to investigate the risk of SLE based on the combination of *GSTM1* and *GSTT1* genotypes. There was no association between the genotype combination and the risk of SLE (data not shown).

In meta-analyses with high heterogeneity between studies, researchers should identify the source(s) of heterogeneity. In such cases, studies are usually stratified based on some aspect (such as ethnicity, source of controls, etc) to reduce heterogeneity. In the present study, where there was no heterogeneity between studies, further analysis did not seem necessary.

Sensitivity analysis was performed to assess the influence of each study and showed that almost none of the studies significantly the results, indicating that the present findings are robust.

Finally, it should be noted that there was no evidence of publication bias for the studies used in *GSTM1* and risk of SLE (Figure 4; p-values for Begg and Egger tests were 0.656 and 0.896, respectively).

As shown in Figure 2, there was a weak association between the null genotype of *GSTM1* and the risk of SLE (OR = 1.17, 95 % CI: 1.03-1.32, p = 0.012). With a statistical power of 0.998, the FPRP value was estimated under two prior probability assumptions. With prior probabilities of 0.001 and 0.010, the FPRP value was estimated to be 0.923 and 0.545, respectively.

Discussion

There are several original articles reporting the association between *GSTT1/GSTM1* polymorphism and susceptibility to SLE, with inconsistent results.[20-32] As mentioned in the Introduction section, although there are two other meta-analyses investigating the relationship between *GSTT1/GSTM1* polymorphisms and the risk of SLE[32, 33] unfortunately, the authors of the meta-analyses did not include some of the studies published at that time, so both analyses suffer from the authors' inaccuracy in finding relevant articles. Therefore, the present study was performed. This is the first meta-analysis to comprehensively investigate the association between null genotypes of *GSTT1/GSTM1* and SLE. A weak association (OR = 1.17) was found between the *GSTM1* null genotype and susceptibility to SLE.

It is well known that SLE is a clinically heterogeneous disease and this may reflect heterogeneity in its genetic component. Therefore, the present finding of no evidence of heterogeneity between studies is unexpected. Most likely, the low strength of the association is a reason for the observed homogeneity between studies.

Some limitations of the present meta-analysis should be acknowledged. First, the uneven geographical distribution of the original articles used in the study is a very important limitation. There was only one report from Eastern Europe and one report from Northern Europe, but no report from Western and Southern Europe and Australia. Second, a high proportion of the studies used in the meta-analysis did not report the source of the control groups.[25, 26, 28, 31] Third, the false positive report probability (FPRP) value of the association between the null genotype of the *GSTM1* and the risk of SLE under two assumptions for prior probabilities of 0.001 and 0.010 was 0.923 and 0.545, respectively. These values are much higher than the FPRP cut-off value of 0.20,[39] indicating that the association was not noteworthy (true positive). Further well-designed large studies are needed to investigate the relationship between gene polymorphisms and risk of SLE.

Conclusion

In conclusion the current meta-analysis suggests that the null genotype of the *GSTM1* (but not *GSTT1*) polymorphism is associated with increased susceptibility to SLE. It should be noted that the FPRP value for this association is much higher than the previously proposed FPRP cut-off value of 0.2. Further case-control studies with larger sample sizes are needed to confirm the present findings.

Ethics

This study was a secondary analysis based on the currently existing multiple databases, including PubMed, Europe PMC, Web of Science, Scopus, Directory open access journals (DOAJ), ProQuest, African journals online (AJOL) and Islamic science citation (ISC) and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The author declares that there is no conflict of interest.

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Data access

All data were recorded in Tables 1 and 2.

Author ORCID numbers

Mostafa Saadat (MS):
0000-0002-0021-4055

Author contributions

Contributed to the conceptualisation, methodology, validation, formal analysis, data curation, writing - original draft, writing - review and editing: MS

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