Systematic Review and Meta-Analysis

Medicine®

OPEN

Association of *Glutathione S-Transferase M1* null genotype with inflammatory bowel diseases

A systematic review and meta-analysis

Yu-Jie Zhou, MM[a], Bao-Lin Zhao, MM[b], Zheng Qian, MM[a], Yi Xu, MM[a], Ya-Qing Ding, PhD[c,*]

Abstract

Background: Ulcerative colitis (UC) and Crohn disease (CD) are the 2 main types of inflammatory bowel diseases (IBDs). Several studies have been conducted to investigate the association of *Glutathione S-Transferase M1* (*GSTM1*) null genotype with UC and CD, but the results are inconsistent. Here, we performed a meta-analysis to clarify this controversy based on relative large sample size.

Methods: A systematic article searching was conducted in the PubMed, EMBASE, SCOPUS, WOS, ProQuest, Chinese National Knowledge Infrastructure (CNKI), and Chinese Wanfang databases up to August 31, 2019. Meta-analysis results were synthesized by using crude odds ratio (OR) with its 95% confidence interval (CI). Heterogeneity, sensitivity analysis, subgroup analysis, and publication bias were assessed by using STATA 11.0 software.

Results: A total of 15 relevant studies including 4353 IBDs patients (1848 CD cases, 2505 UC cases) and 5413 controls were included in this meta-analysis. Totally, we found a significant association between *GSTM1* null genotype and risk to IBDs in the overall populations (OR = 1.37, 95%CI = 1.13−1.65, *P* = .001). Stratified by ethnicity, we found a significant association between *GSTM1 null* genotype and risk to IBDs in the Asian population (OR = 2.54, 95%CI = 2.15−3.00, *P* = .001), but not in the Caucasian population. Stratified by disease type, we found a significant association between *GSTM1 null* genotype with CD in the Asian population (OR = 2.37, 95%CI = 1.11−5.06, *P* = .026), and with UC in the Asian (OR = 2.48, 95%CI = 1.93−3.20, *P* = .001) population. In addition, funnel plot and Egger linear regression test suggests no publication bias in all genetic models.

Conclusion: *GSTM1 null* genotype is associated with susceptibility to IBD, UC, and CD in the Asian population. Further well-designed studies are still needed to confirm these findings.

Abbreviations: CD = Crohn disease, CI = confidence interval, *GSTM1* = *Glutathione S-Transferase M1*, IBD = inflammatory bowel disease, OR = odds ratio, ROS = reactive oxygen species, UC = ulcerative colitis.

Keywords: Crohn disease, *Glutathione S-Transferase M1*, meta-analysis, polymorphism, ulcerative colitis

1. Introduction

Inflammatory bowel diseases (IBDs) are a group of chronic and nonspecific inflammatory diseases that mainly comprise ulcerative colitis (UC) and Crohn disease (CD). Clinical features in both disorders include diarrhea, abdominal pain, weight loss, and increased risk of developing colorectal cancer.[1] The precise etiology of IBDs is not yet fully understood, but evidence suggested that multiple factors, such as the heredity, environment, infection, and immunity and the interactions among each other, contribute to the development and exacerbation of the diseases.[2] In past years, with the wide application of genome-wide association studies and candidate gene association studies, considerable susceptibility loci for the predisposition of IBDs has been identified in the populations of Northern European origin, such as *NOD2*, *ATG16L1*, and *IRGM*.[3–8] Up to now, more than 30 single-nucleotide polymorphisms are definitively known to be associated with IBDs, although these loci account only for a minority of the genetic variance to IBDs in this population.[9]

Glutathione S-transferases (GSTs) are a family of enzymes that have an essential role within cells, including the conjugation and detoxification of toxic or carcinogenic compounds, such as reactive oxygen species (ROS).[10] Polymorphisms in GSTs can lead to a decreased enzymatic function, and an inadequate detoxification of ROS might modulate the susceptibility for IBD.[11] Biopsies of colonic mucosa of IBD patients showed an increased ROS production compared with healthy controls.[12] A reduced enzymatic function of GSTs and there with impaired scavenging of ROS can contribute to a state of oxidative stress, which can trigger the onset of IBD.[13,14]

Editor: Undurti N. Das.

Ethical approval: This study is a meta-analysis and does not involve patient and animal experiments so the ethical approval is not necessary.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Nantong Hospital of Traditional Chinese Medicine, Nantong, [b] Nanjing Pukou Hospital of Traditional Chinese Medicine, Nanjing, Jiangsu Province, [c] LongHua Hospital Shanghai University of Traditional Chinese Medicine, Shanghai, China.

[*] Correspondence: Ya-Qing Ding, LongHua Hospital Shanghai University of Traditional Chinese Medicine, No. 725, Wanping South Road, Xuhui District, Shanghai 200032, China (e-mail: lhdingyaqing@sina.com).

How to cite this article: Zhou YJ, Zhao BL, Qian Z, Xu Y, Ding YQ. Association of Glutathione S-Transferase M1 null genotype with inflammatory bowel diseases. Medicine 2019;98:44(e17722).

Received: 12 April 2019 / Received in final form: 20 June 2019 / Accepted: 30 September 2019

http://dx.doi.org/10.1097/MD.0000000000017722

Human GSTs can be divided in 4 main classes, GST Alpha (GSTA), GST Mu (Glutathione S-Transferase M1 [GSTM1]), GST Pi (GSTP1), and GST Theta (GSTT1). For GSTM1, 3 alleles have been described of which one, GSTM1*0, is characterized by a gene deletion, leading to a nonfunctional protein. The distributions of GSTM1*0 allele in different populations were fluctuated, with African population being 33% to 48%, Asian population being 33% to 63%, European population being 39% to 62%, and American population being 23% to 62%.[15] In the past decade, an increasing number of studies have been conducted to explore the association between *GSTM1* null genotype and susceptibility to IBDs in different populations.[16–31] However, the role of *GSTM1* null genotype in the progression of UC and CD remain undetermined.

We performed a comprehensive literature search in the above databases. We only find one systematic reviews on the association between *GSTM1* null genotype and IBD.[16] In their meta-analysis, relevant articles for the analyses were retrieved by searching PubMed, EMBASE, and Web of Science on October 13, 2013. They did not conduct subgroup analysis according to ethnicity.

Therefore, in the present study, we conducted an overview of systematic reviews and meta-analyses in a comprehensive manner, including different ethnicities and genotype models, in order to assess the association between *GSTM1* null genotype and the risk of IBD. Cumulative meta-analyses were also performed to investigate the tendency of results in genotype models with possible risk for IBD.

In form of PICOS (participants, interventions, comparisons, outcomes, and study design), the study was described as follows: P: This study focused on participants diagnosed with IBD. I: The associations between *GSTM1* null genotype and IBD susceptibility. C: Unrelated healthy subjects without autoimmune diseases, tumors, and IBD family history. O: The influence of *GSTM1* null genotype on IBD susceptibility will be demonstrated as the pooled effect size (odds ratio [OR] with 95% confidence interval [CI]) of multiple research articles; We will also analyze the effect of moderators and confounders: disease type, ethnicity, genotyping method, and publication year; Cumulative meta-analyses were also performed to investigate the tendency of results in genotype models with possible risk for IBD. S: Case–control studies which have explored the relationship of *GSTM1* null genotype and IBD susceptibility; In addition, to be included, we will accept peer-reviewed papers, published in English and Chinese language, featuring patients of any ethnicity, with no date limits, including published, and unpublished data.

2. Materials and methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analysis. The role of GSTM1 null genotype in the progression of UC and CD remains undetermined. Thus, the aim of this study was to clarify the relationship between GSTM1 null genotype with IBD risk by mean of a systematic review and meta-analysis. The protocol was registered in PROSPERO.

2.1. Identification of eligible studies

A comprehensive literature search in the following databases: PubMed, EMBASE, SCOPUS, WOS, ProQuest, Chinese National Knowledge Infrastructure (CNKI), and Chinese Wanfang, with search time ranged from database inception to August 31, 2019. The search terms and keywords were as follows: "polymorphisms or variants," "Glutathione S-Transferase M1 or GSTM1," and "ulcerative colitis or Crohn's disease or inflammatory bowel disease." We limited our results to studies published in English or Chinese. The detailed search strategies were presented in supplementary Table S1, http://links.lww.com/MD/D313. References from retrieved papers were also examined for additional studies that not included in the above databases. Gray literature were searched according to CADTH Grey Matters Light.

2.2. Inclusion criteria

Studies were included in the meta-analysis if they met the following criteria: study on the genetic relationship of GSTM1 with UC or CD or IBD; case–control study design; genotype distributions were available for both cases and controls to calculate an OR and its 95%CI; diagnosis of IBD was made on clinical, radiological, endoscopic, and histopathologic findings according to Lennard–Jones criteria; and controls were unrelated healthy subjects without autoimmune diseases, tumors, and IBD family history. Exclusion criteria were as follows: abstract, case report, editorial comment, and review; repeated publication; studies with insufficient genotypic data; and studies performed on animal models.

2.3. Quality score assessment

The Newcastle-Ottawa scale was used to evaluate the quality of studies. The scale was constituted of 3 aspects as selection, comparability, and exposure with a maximum score of 9.[31] A total score of $\leq$3, 4–6, $\geq$7 was considered to indicate low, medium, and high-quality studies, respectively. Any disagreements were adjusted by a 3rd reviewer.

2.4. Data extraction

Two investigators independently and carefully extracted available data from each eligible study. The following details were extracted from all eligible studies: the fist author's name; year of study publication; origin of participants; race of included subjects; sample size of cases and controls, and genotype distribution of cases and controls. Discrepancies were resolved by discussion within our research team.

2.5. Statistical analysis

The effect sizes were calculated using ORs and 95%CI to evaluate the association between the GSTM1 null genotype and IBD, UC, and CD risk. Only studies with similar designs were included in the forest plot, as meta-analysis can provide misleading results if different study designs and studies variations across studies are grouped together. For this reason, in order to avoid methodological heterogeneity in meta-analysis, only case–control studies were grouped. Heterogeneity among the eligible studies was analyzed by the chi-square test based on the Q statistic, with significant heterogeneity considered to be present when the P-value $< .10$.[32] Heterogeneity was also quantified by the I^2 test, the values of I^2 in 0% to 25%, 26% to 50%, and 50% to 100% were considered as lower, moderate, and high heterogeneity, respectively. The fixed-effects model on the Mantel–Haenszel method was used to estimate the pooled OR if $I^2 < 50\%$; otherwise, the random-effects model on the DerSimonian–Laird method was used.

We evaluated the potential publication bias by using the Begg funnel plot and the Egger linear regression test,[33,34] which measures funnel plot asymmetry on the natural logarithm scale of the effect size. One-way sensitivity analysis was used to assess which study has a significant impact on the stability of results.

All statistical analyses were performed using STATA version 11.0 software (STATA Corporation, College Station, TX). The *P*-value of 2-sided less than .05 was considered statistically significant.

3. Results

3.1. Characteristics of eligible studies

As Figure 1 shows, the selection process of the studies involved in this meta-analysis was according to PRISMA flow diagram. Firstly, we found 220 potentially relevant papers from databases. A search of the Grey Literature Report and OpenGrey databases revealed there were no unpublished studies (gray literature). Among these, 72 duplicates were removed from retrieval, and another 102 studies were removed due to irrelevant topics, reviews, and not about IBDs or *GSTM1* null genotype. The remaining 46 studies underwent full publication review carefully, 31 studies were excluded due to insufficient data for calculating OR and 95%CI. Finally, thus, there were 15 studies included in this meta-analysis. The IBD patients in all of the included studies were random recruited in hospitals. The basic characteristics of these studies are shown in Table 1.

3.2. GSTM1 null genotype with IBDs

The detailed results of the association between *GSTM1* null genotype and risk of IBDs are shown in Table 2. The heterogeneity analysis of *GSTM1* null genotype showed

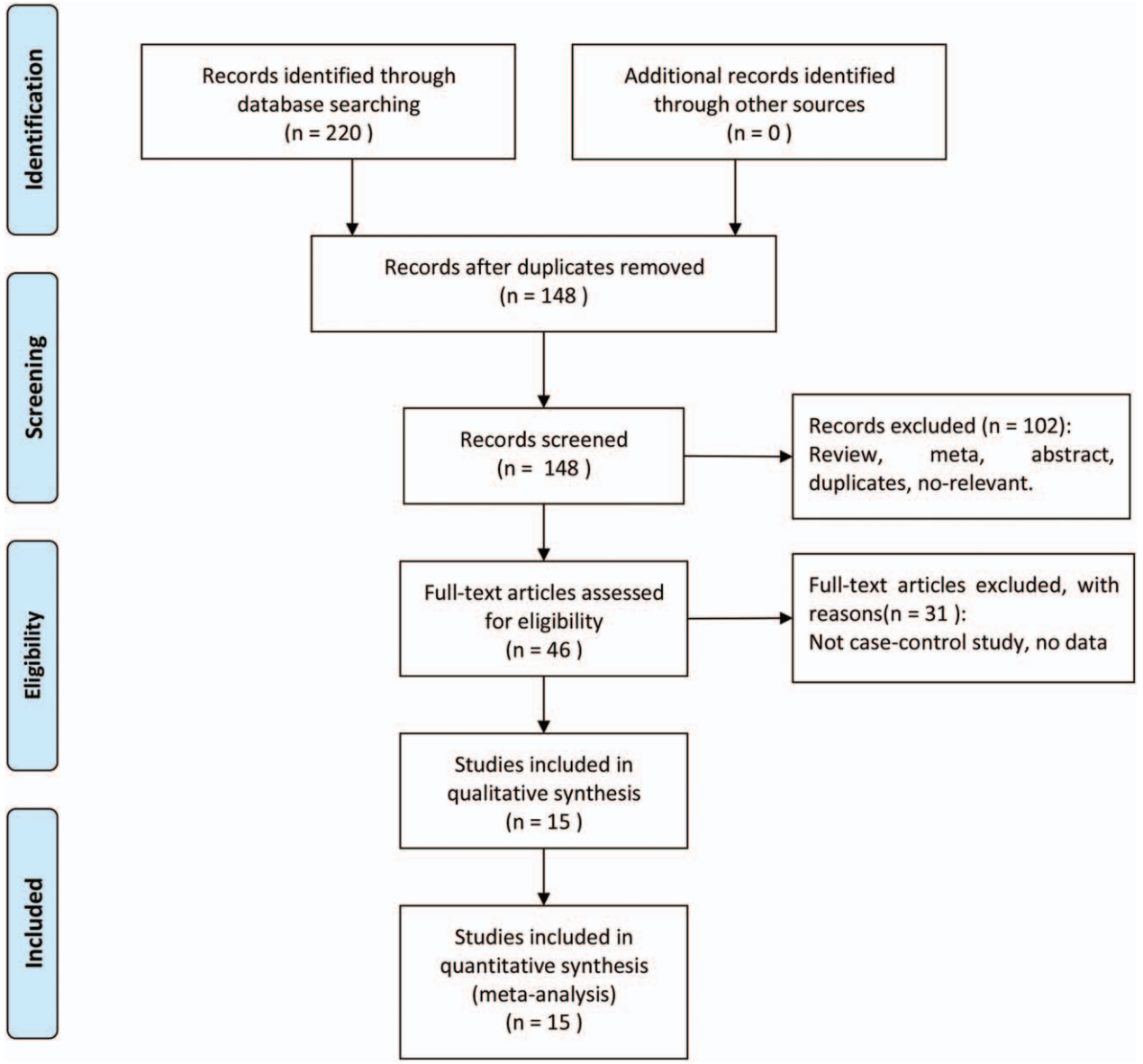

Figure 1. Selection of studies on the association between *GSTM1* null genotype and IBDs. *GSTM1* = *Glutathione S-Transferase M1*, IBD = inflammatory bowel disease.

Table 1

Characteristics of inclusive literature and distribution of GSTM1 genotypes on case and control groups.

Author [ref.]	Year	Country	Ethnicity	NOS scores	Disease	Sample size		Genotype in cases		Genotype in controls	
						Case	Control	(−)	(+)	(−)	(+)
Broekman[16]	2014	Netherlands	Caucasian	7	CD	552	972	289	263	530	442
Broekman[16]	2014	Netherlands	Caucasian	7	UC	233	972	54	179	203	769
Buyukgoze[17]	2013	Turkey	Caucasian	5	UC	161	198	81	80	85	113
de Jong[18]	2003	Netherlands	Caucasian	7	CD	151	149	82	69	74	75
Duncan [19]	1995	England	Caucasian	6	CD	110	373	68	42	203	170
Duncan[19]	1995	England	Caucasian	6	UC	230	373	112	118	203	170
Ernst[20]	2010	Denmark	Caucasian	7	CD	386	791	215	171	417	374
Ernst[20]	2010	Denmark	Caucasian	7	UC	563	791	296	267	417	374
Feng[21]	2016	China	Asian	6	UC	78	78	46	32	31	47
Hertervig[22]	1994	Sweden	Caucasian	5	CD	109	449	65	64	219	230
Hertervig[22]	1994	Sweden	Caucasian	5	UC	179	449	101	78	219	230
Karban[23]	2011	Israel	Caucasian	5	CD	431	369	205	226	205	164
Karban[23]	2011	Israel	Caucasian	5	UC	131	369	65	66	205	164
Mittal[24]	2007	India	Asian	5	CD	20	164	9	11	49	115
Mittal[24]	2007	India	Asian	5	UC	85	164	52	33	49	115
Senhaji[25]	2015	Morocco	African	5	CD	77	100	42	35	51	49
Senhaji[25]	2015	Morocco	African	5	UC	33	100	20	13	51	49
Varzari[26]	2015	Moldova	Caucasian	5	UC	128	136	76	52	75	61
Wu[27]	2010	China	Asian	6	UC	252	628	175	77	318	310
Ye[28]	2011	China	Asian	5	UC	270	623	191	79	260	363
Moini[29]	2017	Iran	Asian	6	CD	12	243	9	3	115	128
Moini[29]	2017	Iran	Asian	6	UC	94	243	56	38	115	128
Xia[30]	2007	China	Asian	6	UC	68	140	43	25	63	77

CD = Crohn disease, GSTM1 = Glutathione S-Transferase M1, NOS = Newcastle-Ottawa scale, UC = ulcerative colitis.

significant heterogeneity in the overall population, but it was resolved by subgroup analysis based on ethnicity. Overall, significant associations between *GSTM1* null genotype and risk for IBDs were found in the overall population (OR = 1.37, 95% CI = 1.13−1.65, $P = .001$). Stratified by ethnicity, we found a significant association between GSTM1 null genotype and risk to IBDs in the Asian population (OR = 2.54, 95%CI = 2.15−3.00, $P = .001$) (Fig. 2A), but not in the Caucasian population (OR = 1.01, 95%CI = 0.93−1.10, $P = .837$). Stratified by publication year, we found a significant association between GSTM1 null genotype and risk to IBDs in the years before (OR = 1.40, 95% CI = 1.10−1.78, $P = .006$) and after 2010 (OR = 1.38, 95%CI = 1.06−1.83, $P = .048$) (Table 2).

3.3. GSTM1 null genotype with CD

The detailed results of the association between GSTM1 null genotype and risk of CD are shown in Table 2. Overall, no significant association was found in the overall population (OR = 1.25, 95%CI = 0.97−1.61, $P = .089$). However, stratification by population, significant associations were found in the Asian population (OR = 2.37, 95%CI = 1.11−5.06, $P = .026$), but not

Table 2

Summary of meta-analysis on GSTM1 null genotype and IBDs susceptibility.

Diseases	Subgroups	No. of studies	Test of association			Model	Test of heterogeneity		Egger test (*P*)
			OR	95% CI	*P*-value		*P*-value	I^2, %	
IBD	All	23	1.37	1.13−1.65	**.001**	R	.001	81.7	.062
	Asian	9	2.54	2.15−3.00	**.001**	F	.183	30.7	.662
	Caucasian	13	1.01	0.93−1.10	.837	F	.102	35.1	.185
	Before 2010 (≤2010)	11	1.40	1.10−1.78	**.006**	R	.001	77.8	.106
	After 2010 (>2010)	12	1.38	1.06−1.83	**.048**	R	.001	85.3	.294
CD	All	9	1.25	0.97−1.61	.089	R	.001	74.3	.093
	Asian	2	2.37	1.11−5.06	**.026**	F	.504	0.0	.265
	Caucasian	6	0.98	0.87−1.11	.787	F	.101	45.8	.325
	Before 2010 (≤2010)	5	1.18	0.99−1.40	.058	F	.770	0.0	.109
	After 2010 (>2010)	4	0.93	0.69−1.26	.636	R	.085	54.7	.269
UC	All	14	1.53	1.16−2.01	**.002**	R	.001	85.0	.339
	Asian	6	2.48	1.93−3.20	**.001**	R	.087	47.9	.595
	Caucasian	7	1.02	0.89−1.17	.743	F	.129	41.5	.649
	Before 2010 (≤2010)	6	1.57	1.03−2.38	.035	R	.001	88.2	.169
	After 2010 (>2010)	8	1.50	1.02−2.20	.039	R	.001	83.2	.602

CD = Crohn disease, CI = confidence interval, F = fixed effects model, GSTM1 = Glutathione S-Transferase M1, IBD = inflammatory bowel disease, OR = odds ratio, R = random-effects model, UC = ulcerative colitis.

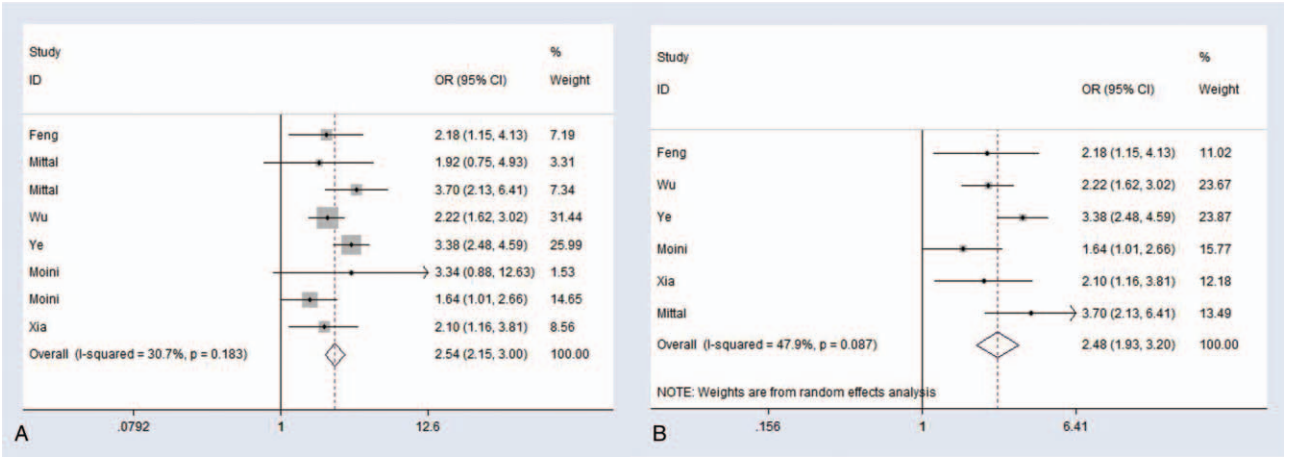

Figure 2. Forest plots for pooled ORs for the associations between *GSTM1* null genotype and IBDs (A) and UC (B) risk in the Asian population. *GSTM1* = *Glutathione S-Transferase M1*, IBD = inflammatory bowel disease, OR = odds ratio, UC = ulcerative colitis.

in the Caucasian population (OR = 0.98, 95%CI = 0.87–1.11, *P* = .787) (Table 2). Stratified by publication year, we found no significant association between GSTM1 null genotype and risk to CD in the years before (OR = 1.18, 95%CI = 0.99–1.40, *P* = .058) and after 2010 (OR = 0.93, 95%CI = 0.69–1.26, *P* = .636) (Table 2).

3.4. GSTM1 null genotype with UC

The detailed results of the association between GSTM1 null genotype and risk of UC are shown in Table 2. A significant association between GSTM1 null genotype and risk of UC was found in the overall population (OR = 1.53, 95%CI = 1.16–2.01, *P* = .002). Subgroup analysis showed that GSTM1 null genotype was associated with UC risk in the Asian population (OR = 2.48, 95%CI = 1.93–3.20, *P* = .001) (Fig. 2B), but not in the Caucasian population (OR = 1.02, 95%CI = 0.89–1.17, *P* = .743) (Table 2). Stratified by publication year, we found a significant association between GSTM1 null genotype and risk to UC in the years before (OR = 1.57, 95% CI = 1.03–2.38, *P* = .035) and after 2010 (OR = 1.50, 95%CI = 1.02–2.20, *P* = .039) (Table 2).

3.5. Sensitive analysis and publication bias

Sensitive analysis was conducted to estimate if our results were substantially affected by the presence of any individual. Our results suggested that the pooled effects were not significantly influenced by the omission of any individual study (Fig. 3A and B). Moreover, the 2 studies were published at 1994 and 1995, which may employ the different examination method different from current clinical practice. We did subgroup analysis by the year of publication. There was a significant associations between GSTM1 null genotype and risk for IBDs in the year after 1995 (OR = 1.441, 95%CI = 1.150–1.805, *P* = .002). The year of publication had no significant influence on the results of meta-analysis. Begg funnel plots were performed in all comparisons showed the shape was symmetrical, and Egger linear regression

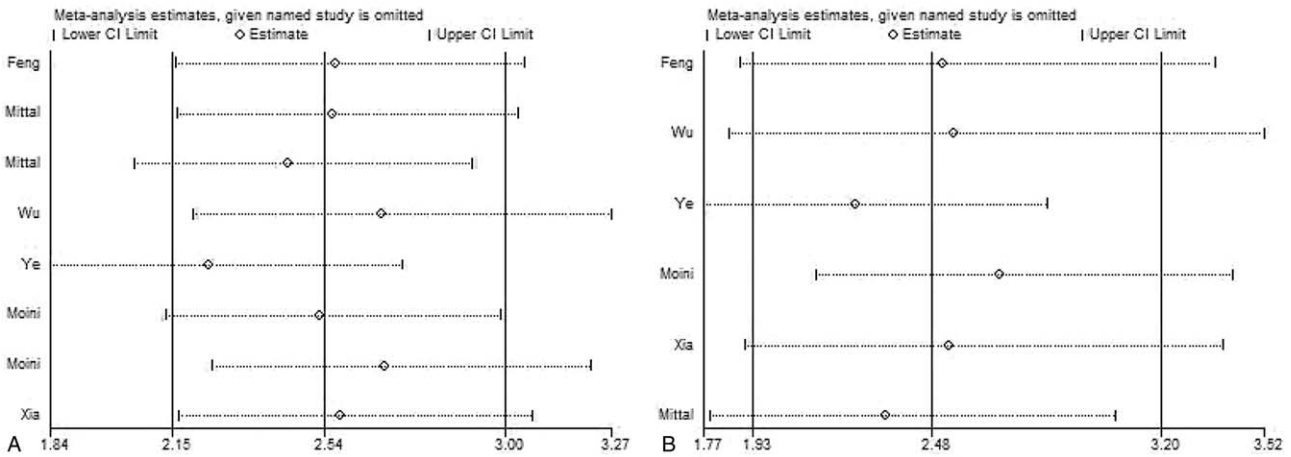

Figure 3. Sensitive analysis for the associations between *GSTM1* null genotype and IBDs (A) and UC (B) risk in the Asian population. *GSTM1* = *Glutathione S-Transferase M1*, IBD = inflammatory bowel disease, UC = ulcerative colitis.

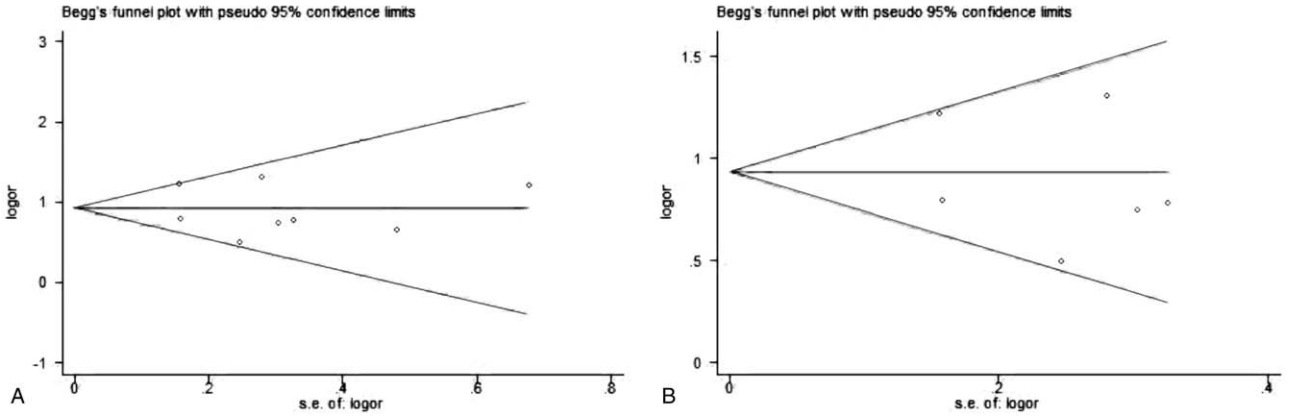

Figure 4. Begg funnel plots for association between *GSTM1* null genotype and IBDs (A) and UC (B) risk in the Asian population. *GSTM1* = *Glutathione S-Transferase M1*, IBD = inflammatory bowel disease, UC = ulcerative colitis.

analysis further indicating that no publication bias existed in this meta-analysis (Table 2 and Fig. 4A and B).

3.6. Cumulative analysis

After cumulative analysis by year sequence, OR and its CI tend to be stable and have a good change trend. The relationship has been stable since 2007 on a given set of threshold (Fig. 5).

4. Discussion

Although unknown etiology and pathology of IBDs, previous study has shown that multiple gene polymorphisms may link to the development of diseases.[35] An increasing number of studies in recent years have studied the association between GSTM1 null genotype and the risk of inflammatory diseases.[36,37] Nevertheless, whether it is associated specifically with the risk of IBDs remains controversial.

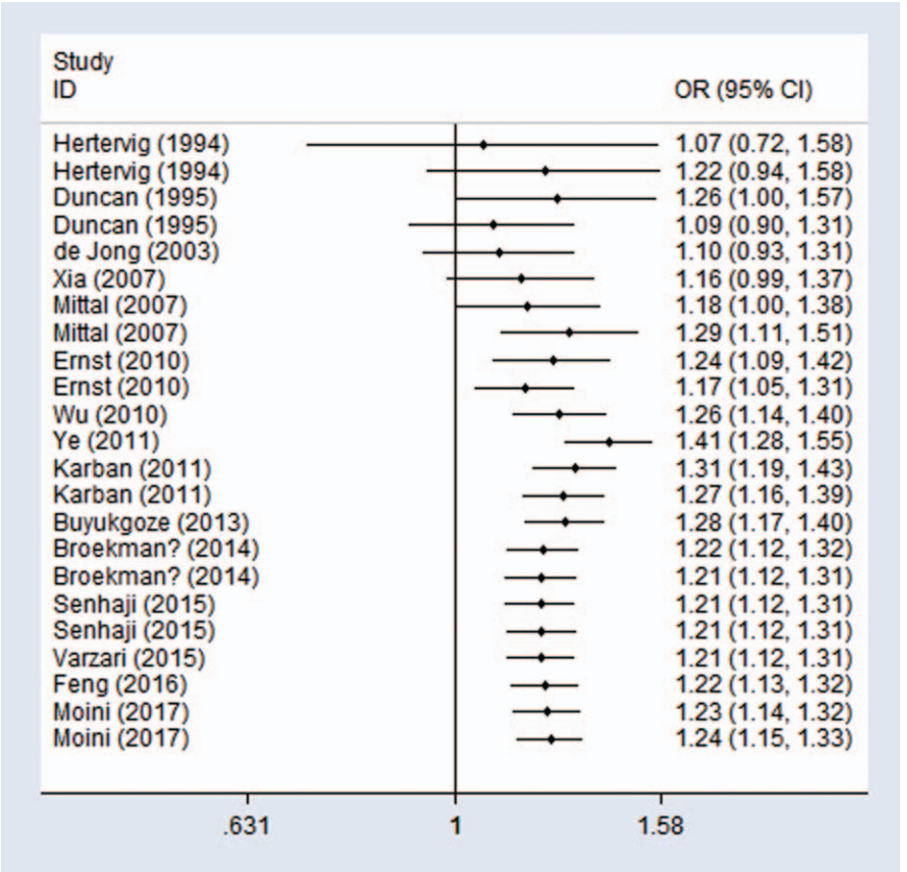

Figure 5. Cumulative analysis of forest plots for pooled ORs for the associations between *GSTM1* null genotype and IBDs risk. *GSTM1* = *Glutathione S-Transferase M1*, IBD = inflammatory bowel disease, OR = odds ratio.

The inconsistency among different studies seems to be mainly owing to the relatively small sample size of most studies and the different populations of researches, there is little statistical power to detect a slight association between *GSTM1* null genotype and susceptibility to IBDs. Another explanation is that diverse study designs and methods, differences in race and geography, and publication bias. Meta-analysis is an effective statistical method that could pool the results of several independent studies together to get comprehensive results.[38] It has been widely utilized in evaluating the relationship between candidate genes and complex diseases with genetic predisposition.[39]

This systematic review and meta-analysis was performed to determine the association between *GSTM1* null genotype and susceptibility to IBDs. The results demonstrated *GSTM1* null genotype was associated with IBDs in the Asian population, but not in the Caucasian population. After stratified by disease type, similar results were also presented in UC and CD. The different results presented in different populations illustrated that *GSTM1 null genotype* with IBDs susceptibility might be determined by ethnicity.

Glutathione is a protective compound in the body capable of removing potential toxins, GST catalyzed glutathione binding to various ROS and biotransformation to maintain the balance of oxidation-antioxidant system.[40] The mechanism that absence of GSTT1 enzyme activity in GSTT1 null individuals contributes to the risk for UC might be explained by the important role of this enzyme in the detoxification of ROS, which may provide a trigger in the etiology of IBD.[40] Also, in other inflammatory-driven diseases, such as asthma or type 2 diabetes mellitus, an increased susceptibility was found with the GSTT1 null genotype.[41,42]

Although advantage of this meta-analysis is that pooling good quality of individual study together with relative lager sample size for a comprehensive result, several limitations should be addressed when interpreting our results. Firstly, we included relevant articles published only in English and Chinese so that potential language bias may exist in this study. Secondly, most of the studies are conducted in Chinese population, the number of studies was small in Caucasians subgroup analyses, which could have led to insufficient statistic power to detect slight relationships. Thirdly, several risk factors such as age, gender, genetic variants, and exposure opportunity to environment factors and their interaction each other have impacts on onset of IBD. However, only gene polymorphisms were considered in this study. The effects of gene−gene and gene−environment interactions on the initiation and development of the disease need to be further studied in the future.

Current meta-analysis provided statistical evidence that the *GSTM1* null genotype is associated with IBD, UC, and CD, especially in the Asian population and these results might not be generalized to other ethnic populations. Further studies with more sample size and including other confounding factors are still needed in the future for a definitive conclusion.

Author contributions

Conceptualization: Yi Xu.
Data curation: Yujie Zhou, Zheng Qian.
Formal analysis: Baolin Zhao, Zheng Qian.
Funding acquisition: Ya-Qing Ding.
Methodology: Yujie Zhou.
Project administration: Zheng Qian, Yi Xu.
Resources: Zheng Qian, Yi Xu.
Software: Yujie Zhou.
Writing – original draft: Yujie Zhou, Ya-Qing Ding.
Writing – review & editing: Yujie Zhou, Ya-Qing Ding.

References

[1] Kulaylat MN, Dayton MT. Ulcerative colitis and cancer. J Surg Oncol 2010;101:706–12.
[2] Monteleone G, Fina D, Caruso R, et al. New mediators of immunity and inflammation in inflammatory bowel disease. Curr Opin Gastroenterol 2006;22:361–4.
[3] Rehman A 1, Sina C, Gavrilova O, et al. Nod2 is essential for temporal development of intestinal microbial communities. Gut 2011;60: 1354–62.
[4] Quince C, Lundin EE, Andreasson AN, et al. The impact of Crohn's disease genes on healthy human gut microbiota: a pilot study. Gut 2013;62:952–4.
[5] Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006;314:1461–3.
[6] Hampe J, Franke A, Rosenstiel P, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. Nat Genet 2007;39:207–11.
[7] Rioux JD, Xavier RJ, Taylor KD, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet 2007;39:596–604.
[8] Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 2001;411:599–603.
[9] Barrett JC, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet 2008;40:955–62.
[10] Hayes JD, Strange RC. Glutathione S-transferase polymorphisms and their biological consequences. Pharmacology 2000;61:154–66.
[11] Conner EM, Brand SJ, Davis JM, et al. Role of reactive metabolites of oxygen and nitrogen in inflammatory bowel disease: toxins, mediators, and modulators of gene expression. Inflamm Bowel Dis 1996;2:133–47.
[12] Simmonds NJ, Allen RE, Stevens TR, et al. Chemiluminescence assay of mucosal reactive oxygen metabolites in inflammatory bowel disease. Gastroenterology 1992;103:186–96.
[13] Pavlick KP, Laroux FS, Fuseler J, et al. Role of reactive metabolites of oxygen and nitrogen in inflammatory bowel disease. Free Radic Biol Med 2002;33:311–22.
[14] Alzoghaibi MA. Concepts of oxidative stress and antioxidant defense in Crohn's disease. World J Gastroenterol 2013;19:6540–7.
[15] Garte S, Gaspari L, Alexandrie AK, et al. Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev 2001;10:1239–48.
[16] Broekman MM, Bos C, Te Morsche RH, et al. GST Theta null genotype is associated with an increased risk for ulcerative colitis: a case-control study and meta-analysis of GST Mu and GST Theta polymorphisms in inflammatory bowel disease. J Hum Genet 2014;59:575–80.
[17] Buyukgoze O, Osmanoglu N, Arslan S, et al. Association of the CYP1A1*2A, GSTT1 null, GSTM1 null, mEPHX*3, and XRCC1-399 genetic polymorphisms with ulcerative colitis. Int J Colorectal Dis 2013;28:593–5.
[18] de Jong DJ, van der Logt EM, van Schaik . Genetic polymorphisms in biotransformation enzymes in Crohn's disease: association with microsomal epoxide hydrolase. Gut 2003;52:547–51.
[19] Duncan H, Swan C, Green J, et al. Susceptibility to ulcerative colitis and Crohn's disease: interactions between glutathione S-transferase GSTM1 and GSTT1 genotypes. Clin Chim Acta 1995;31240:53–61.
[20] Ernst A, Andersen V, Østergaard M, et al. Genetic variants of glutathione S-transferases mu, thetaand pi display no susceptibility to inflammatory bowel disease in the Danish population. Scand J Gastroenterol 2010;45:1068–75.
[21] Feng XJ, Liu WW. The relationship of glutathione S-transferase gene polymorphism and ulcerative colitis. Ningxia Med J 2016;38:988–90.
[22] Hertervig E, Nilsson A, Seidegård J. The expression of glutathione transferase mu in patients with inflammatory bowel disease. Scand J Gastroenterol 1994;29:729–35.
[23] Karban A, Krivoy N, Elkin H. Non-Jewish Israeli IBD patients have significantly higher glutathione S-transferase GSTT1-null frequency. Dig Dis Sci 2011;56:2081–7.

[24] Mittal RD, Manchanda PK, Bid HK, et al. Analysis of polymorphisms of tumor necrosis factor-alpha and polymorphicxenobiotic metabolizing enzymes in inflammatory bowel disease: study from northern India. J Gastroenterol Hepatol 2007;22:920–4.
[25] Senhaji N, Kassogue Y, Fahimi M, et al. Genetic polymorphisms of multidrug resistance gene-1 (MDR1/ABCB1) and glutathione S-Transferase gene and the risk of inflammatory bowel disease among moroccan patients. Mediators Inflamm 2015;248060.
[26] Varzari A, Deyneko IV, Tudor E, et al. Polymorphisms of glutathione S-transferase and methylenetetrahydrofolatereductase genes in Moldavian patients with ulcerative colitis: genotype-phenotype correlation. Meta Gene 2015;10:76–82.
[27] Wu H, Zheng B, Wang JZ, et al. Relationship between genetic polymorphisms of glutathione S-transferase genes and susceptibility to ulcerative colitis in Zhejiang Han population. World Chin J Dig 2010;18:2780–4.
[28] Ye X, Jiang Y, Wang H, et al. Genetic polymorphisms of glutathione S-transferases are associated with ulcerative colitis in central China. Cell Biochem Biophys 2011;60:323–8.
[29] Moini M, Saadat M, Saadat H, et al. Association study of Glutathione S-transferases Gene Polymorphisms (GSTM1 and GSTT1) with ulcerative colitis and Crohn's disease in the south of Iran. Adv Biomed Res 2017;6:67.
[30] Xia XP, Wang WX, Jiang Y, et al. Relationship between gene polymorphism of Glutathione S-transferase M1 and susceptibility to ulcerative colitis. Chin J Gastroenterol 2007;12:295–7.
[31] Li P, Yang XK, Wang X, et al. A meta-analysis of the relationship between MYO9B gene polymorphisms and susceptibility to Crohn's disease and ulcerative colitis. Hum Immunol 2016;77:990–6.
[32] Li P, Tao SS, Zhao MQ, et al. Association study of matrix metalloproteinases gene polymorphisms with susceptibility to rheumatoid arthritis: a meta-analysis. Immunol Invest 2015;44:603–15.
[33] Begg CB, Berlin JA. Publication bias and dissemination of clinical research. J Natl Cancer Inst 1989;81:107–15.
[34] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[35] Ventham NT, Kennedy NA, Nimmo ER, et al. Beyond gene discovery in inflammatory bowel disease: the emerging role of epigenetics. Gastroenterology 2013;145:293–308.
[36] Aliomrani M, Sahraian MA, Shirkhanloo H, et al. Correlation between heavy metal exposure and GSTM1 polymorphism in Iranian multiple sclerosis patients. Neurol Sci 2017;38:1271–8.
[37] İnal EE, Görükmez O, Eroğlu S, et al. Association of GSTM1, GSTT1, GSTP1-ILE105VAL and ACE I/D polymorphisms with ankylosing spondylitis. Rheumatol Int 2016;36:17–23.
[38] Efthimiou O. Practical guide to the meta-analysis of rare events. Evid Based Ment Health 2018;21:72–6.
[39] Bashir Y, Conlon KC. Step by step guide to do a systematic review and meta-analysis for medical professionals. Ir J Med Sci 2018;187:447–52.
[40] Fedets OM. Structure and functions of glutathione transferases. Ukr Biochem J 2014;86:23–32.
[41] Raza S, Abbas S, Ahmad A, et al. Association of Glutathione-S-Transferase (GSTM1 and GSTT1) and FTO gene polymorphisms with type 2 diabetes mellitus cases in northern India. Balkan J Med Genet 2014;17:47–54.
[42] Liang S, Wei X, Gong C, et al. Significant association between asthma risk and the GSTM1 and GSTT1 deletion polymorphisms: an updated meta-analysis of case-control studies. Respirology 2013;18:774–83.