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# Meta-analysis of *FOXP3* gene rs3761548 and rs2232365 polymorphism and multiple sclerosis susceptibility

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**Abstract**

**Background:** Multiple sclerosis (MS) is a common autoimmune disease of the central nervous system (CNS), and is associated with genetic factors. *FOXP3* gene polymorphism has been reported as the risk factor for MS, however, previous studies have showed conflicting results. The purpose of this study is to investigate the association between *FOXP3* gene polymorphism and the susceptibility to MS.

**Methods:** Pubmed, Embase, library of Cochrane, and Web of Science were used to search the eligible articles from January 1980 up to October 2018. The odds ratio (ORs) and its 95% confidence intervals (CI) were used to evaluate the strength of association. Allele model, homozygote model, heterozygote model, dominant model, and recessive model were used to evaluate the association between *FOXP3* gene polymorphism and MS.

**Results:** A total of 5 studies contained 1276 MS patients and 1447 controls (for rs3761548) and 600 MS patients and 640 controls (for rs2232365) were enrolled in this meta-analysis. The association showed significant differences in allele and dominant model for rs3761548 polymorphism. In addition, a clear tendency to significance was detected in homozygote and recessive model for rs3761548 ($P = .052$). Subgroup analysis indicated a significant risk of MS in all genotype models but heterozygotes in Asians.

**Conclusion:** *FOXP3* gene polymorphism rs3761548 was associated with a higher MS risk, especially in Asians. This conclusion needs to be validated in more large samples and multiracial studies.

**Level of evidence:** Level III diagnostic study.

**Abbreviations:** CI = confidence intervals, FOXP3 = transcription factor forkhead box P3, MS = multiple sclerosis, OR = odd ratio.

**Keywords:** *FOXP3* gene, meta-analysis, multiple sclerosis, single nucleotide polymorphism

## 1. Introduction

Multiple sclerosis (MS) is an immune-related central nervous disease, which manifests as variable symptoms including optic neuritis, fatigue, spasticity, neuro-urological dysfunction, paresthesia and hypesthesia, and headache.[1] In pathophysiology, this disease was characterized by inflammation, demyelination, proliferation of astrocytes, and varying degrees of axonal degeneration.[2] Meanwhile, variant cells and their markers such as T cells, clonal expansion of B cells, and their antibody products were found in MS patients, indicating the involvement of abnormalities of T-cells especially CD4 and CD8 T cells and B-cells response.[3,4] It was considered that the occurrence and progression of MS may attribute to the virus infection, vitamin deficiency, mitochondrial dysfunction, and oxidative stress.[5] However, up to now, the exact reason for MS has not been determined.

Recently, more and more studies focus on the effect of single nuclei polymorphisms (SNPs) on some autoimmune disease including MS.[6] Previous literatures have reported several genetic variants (IL-6, HLA-DRB1, and STAT4) were correlated with development of MS.[2,7,8] The transcription factor forkhead box P3 (FOXP3) which belongs to the fork-winged helix family and encoded by the *FOXP3* gene was regarded as an important molecular marker that regulate T-reg cell development and function.[9] The prior study demonstrated that $CD4^+CD25^+Foxp3^+$ T-regs played a crucial role in preventing autoimmunity and

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undesirable T cell responses.[10] Moreover, mutation of the *FOXP3* gene has been shown to be a risk in unexplained recurrent spontaneous abortions, Grave's disease, and allergic rhinitis.[11–13] Currently, some studies reported two key SNPs (rs3761548 and rs2232365) on *FOXP3* gene may be involved in the development of MS.[14,15] However, recent studies still obtained conflicting results that may lead to inconsistent outcomes.

In this meta-analysis, we collected data from several databases and combined them for analyzing to investigate the overall influence of *FOXP3* gene polymorphism on the risk of MS.

## 2. Methods

The authors performed the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Meanwhile, since the present study is based on data from published studies, the informed consent of the patients and the ethical approval were not required.

### 2.1. Study strategy

Pubmed, Embase, Cochrane library, and Web of Science were used for the potential studies searching. (Polymorphism OR "single-nucleotide polymorphism" OR "SNP" OR "mutant" OR "mutation" OR "variant" OR "variation") AND ("FOXP3" OR "transcription factor forkhead box P3" OR "rs3761548" OR "rs2232365") AND ("multiple sclerosis" OR "multiple sclerosis") were used as the key words or Mesh terms for searching. The final search was conducted up to October 1, 2018 and the language of searched literatures was not restricted.

### 2.2. Inclusion and exclusion criteria

The included studies met the following criteria:

1. case-control;
2. the study evaluated the association between *FOXP3* gene polymorphism and MS;
3. the study contained sufficient data of genotype frequency.

The exclusion criteria were as follows:

1. studies without controls groups;
2. studies with only abstracts and reviews;
3. studies without specific distribution of genotype;
4. studies reported animal models.

The 9-point Newcastle-Ottawa Scale (NOS) was used for quality assessment of the included studies.

### 2.3. Data extraction

Two independent reviewers (YJ Z and B P) assessed and reviewed all identified studies in terms of inclusion and exclusion criteria. Conflicts were reached to agreement via the discussion with the third authors (HL Y). Authors, date of publication, race, sample size, genotype and allele distribution of cases and controls were all extracted and recorded from the enrolled studies.

### 2.4. Statistical analysis

This meta-analysis preformed the data analyzing by using Stata version 11.0 (Stata Corp, College Station, TX, USA). The odds ratio (OR) and 95% confidence interval (CI) were used to assess the relationship between rs3761548 and rs2232356 polymorphism and the risk of MS. The allelic contrast, dominant, recessive, and homozygotes models were all conducted in this study. The evaluation of heterogeneity of studies was using the $Q$ test and was quantified using $I^2$. The fixed-effects model was used when $I^2 < 50\%$. In contrast, the random-effects model was applied when $I^2 > 50\%$. The subgroup analysis was performed stratified by ethnicity. The Begg and Egger's test were used for the assessment of publication bias and the sensitivity analysis was conducted by assessing the change of combined ORs values after elimination of each individual study. A $P$ value equal to or $<.05$ was considered the threshold for statistical significance.

## 3. Results

### 3.1. Literatures search

Based on the database of Pubmed, Embase, Cochrane library, Web of Science, and other resources, a total of 95 articles were relevant to the search terms. After elimination of duplicated studies and exclusion of improper studies via titles and abstracts, 18 articles remained for full text reviewing. Then, 13 articles were excluded for following reasons (lack of sufficient data of distribution of genotype, animal models, and comment/editorial articles). Ultimately, 5 articles were eligible in quantitative synthesis (current meta-analysis). The specific flow chart was shown in Figure 1.

### 3.2. Characteristic of eligible studies

For the 5 included studies,[16–20] 4 studies reported the comparison of rs3761548 polymorphism, and 3 studies stated comparison of rs2232365 polymorphism between MS and controls. The analysis of rs3761548 polymorphism contained 1276 MS patients and 1447 controls. The scores of NOS scale of all included studies were larger than 6 points, indicating a good quality (Table 1). There was a significant difference in the sex of patients and controls (OR: 0.76, 95% CI: 0.65–0.90, $P=.001$), and no significant difference in age (OR: 0.06, 95% CI: −0.01–0.14, $P=.088$) (Table 2). The analysis of re2232365 polymorphism contained 600 MS patients and 640 controls. Here, there was no significant difference in both sex (OR: 0.77, 95% CI: 0.48–1.25, $P=.295$) and age between patients and controls (OR: 0.08, 95% CI: −0.03 to 0.19, $P=.156$) (Table 3).

### 3.3. Quantitative synthesis

For rs3761548 polymorphism, there was a significantly decreased risk of MS under allele model (OR: 0.76, 0.58–1.00, $P=.049$) and dominant model (OR: 0.77, 0.64–0.94, $P=.008$) (Table 4). No significant association was detected between rs37651548 and MS under the homozygote model (OR: 0.63, 0.40–1.00, $P=.052$), heterozygote model (OR: 0.89, 0.72–1.10, $P=.276$), and the recessive model (OR: 0.67, 0.45–1.01, $P=.056$) (Figs. 2 and 3). Further, subgroup analysis was performed by ethnicity. There were significant differences in all genetic models but heterozygote model in Asians (Table 5). In contrast, no significant difference was detected in European population under any genetic model (Figs. 4 and 5).

For rs2232365 polymorphism, we did not find a significant difference in the distribution of genotypes between MS

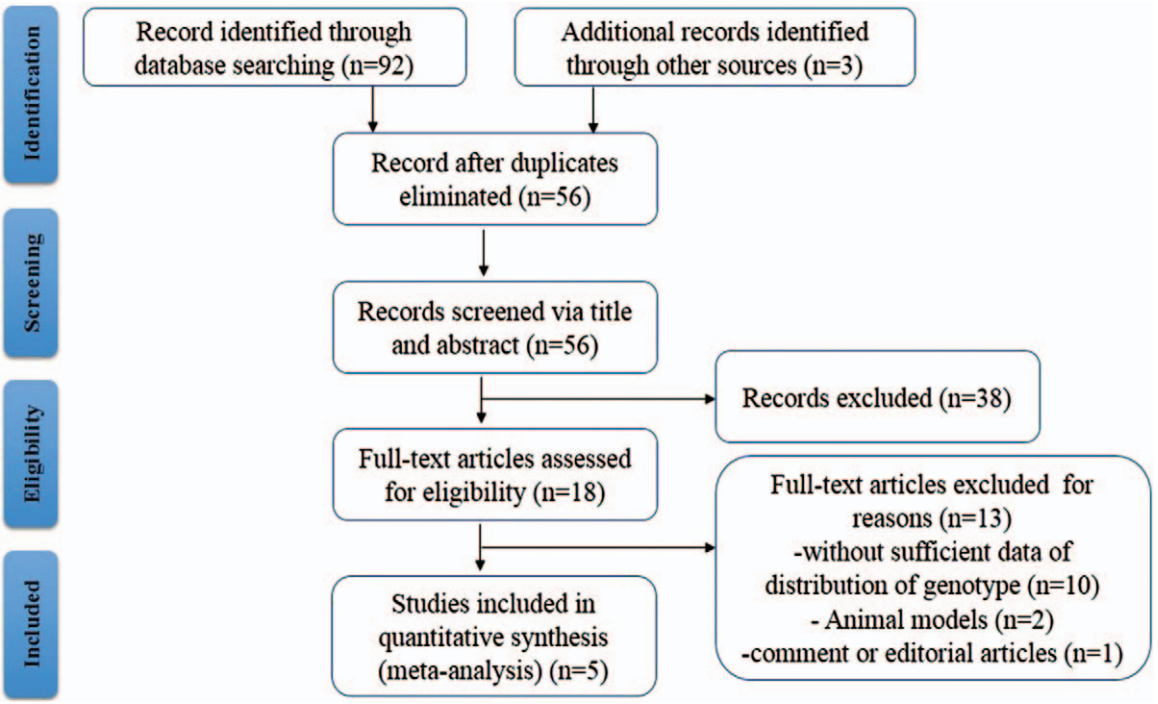


**Figure 1.** Flow diagram of the selection of literature.

**Table 1**

**The scores of each study based on Newcastle-Ottawa scale.**

| Author | Year | Selection | Comparability | Exposure |
|---|---|---|---|---|
| Jafarzadeh | 2014 | ★★★ | ★★ | ★★★ |
| Eftekharian | 2016 | ★★ | ★★ | ★★★ |
| Gholami | 2016 | ★★★ | ★★ | ★★★ |
| Gajdošechová | 2017 | ★★★ | ★★ | ★★★ |
| Mahdavi | 2016 | ★★ | ★★ | ★★★ |

and controls under allele model (OR: 1.22, 0.68–2.18, $P=.503$), homozygote model (OR: 1.40, 0.52–3.77, $P=.507$), heterozygote model (OR: 1.37, 0.67–2.79, $P=.383$), dominant model (OR: 1.40, 0.63–3.09, $P=.411$), and recessive model (OR: 1.15, 0.61–2.16, $P=.663$) (Figs. 6 and 7).

### 3.4. Publication bias

We performed the Begg funnel plot and Egger's test to assess the potential publication bias in the identified studies. The results showed no evidence of publication bias in this meta-analysis (Egger test: $P=.733$ under allele model for rs3761548, $P=.925$ under dominant model for rs3761548) (Fig. 8).

**Table 2**

**Characteristics of eligible studies for SNPs of rs3761548.**

| | | | | | Case | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Year | Ethnicity | Case | Control | AA | AC | CC | AA | AC | CC |
| Jafarzadeh | 2014 | Asian | 140 | 140 | 34 | 50 | 56 | 21 | 34 | 85 |
| Eftekharian | 2016 | Asian | 410 | 446 | 131 | 205 | 74 | 105 | 204 | 137 |
| Gholami | 2016 | Asian | 189 | 192 | 49 | 85 | 55 | 48 | 87 | 57 |
| Gajdošechová | 2017 | European | 375 | 426 | 75 | 179 | 121 | 82 | 201 | 143 |

**Table 3**

**Characteristics of eligible studies for SNPs of rs2232365.**

| | | | | | Case | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Study | Year | Ethnicity | Case | Control | AA | AC | CC | AA | AC | CC |
| Eftekharian | 2016 | Asian | 410 | 446 | 126 | 191 | 93 | 97 | 211 | 138 |
| Gholami | 2016 | Asian | 190 | 194 | 24 | 71 | 95 | 39 | 80 | 75 |
| Mahdavi | 2016 | Asian | 90 | 90 | 45 | 30 | 15 | 35 | 20 | 35 |

**Table 4**

**Meta-analysis of the association between FOXP3 polymorphism and multiple sclerosis.**

| | | Allelic model | | | Homozygote model | | | Heterozygote model | | | Dominant model | | | Recessive model | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SNPs | N | OR (95%CI) | *P* | $I^2$ | OR (95% CI) | *P* | $I^2$ (%) | OR (95% CI) | *P* | $I^2$ (%) | OR (95% CI) | *P* | $I^2$ (%) | OR (95% CI) | *P* | $I^2$ (%) |
| rs2232365 | 2 | 1.22 (0.68–2.18) | .503 | 91.5% | 1.40 (0.52–3.77) | .507 | 89.5 | 1.37 (0.67–2.79) | .383 | 84.1 | 1.40 (0.63~3.09) | .411 | 89.7 | 1.15 (0.61~2.16) | .663 | 80.9 |
| rs3761548 | 2 | 0.76 (0.58–1.00) | **.049** | 80.2% | 0.63 (0.40–1.00) | .052 | 73.3 | 0.89 (0.72–1.10) | .276 | 0 | 0.77 (0.64~0.94) | **.008** | 33.8 | 0.67 (0.45~1.01) | .056 | 79.0 |

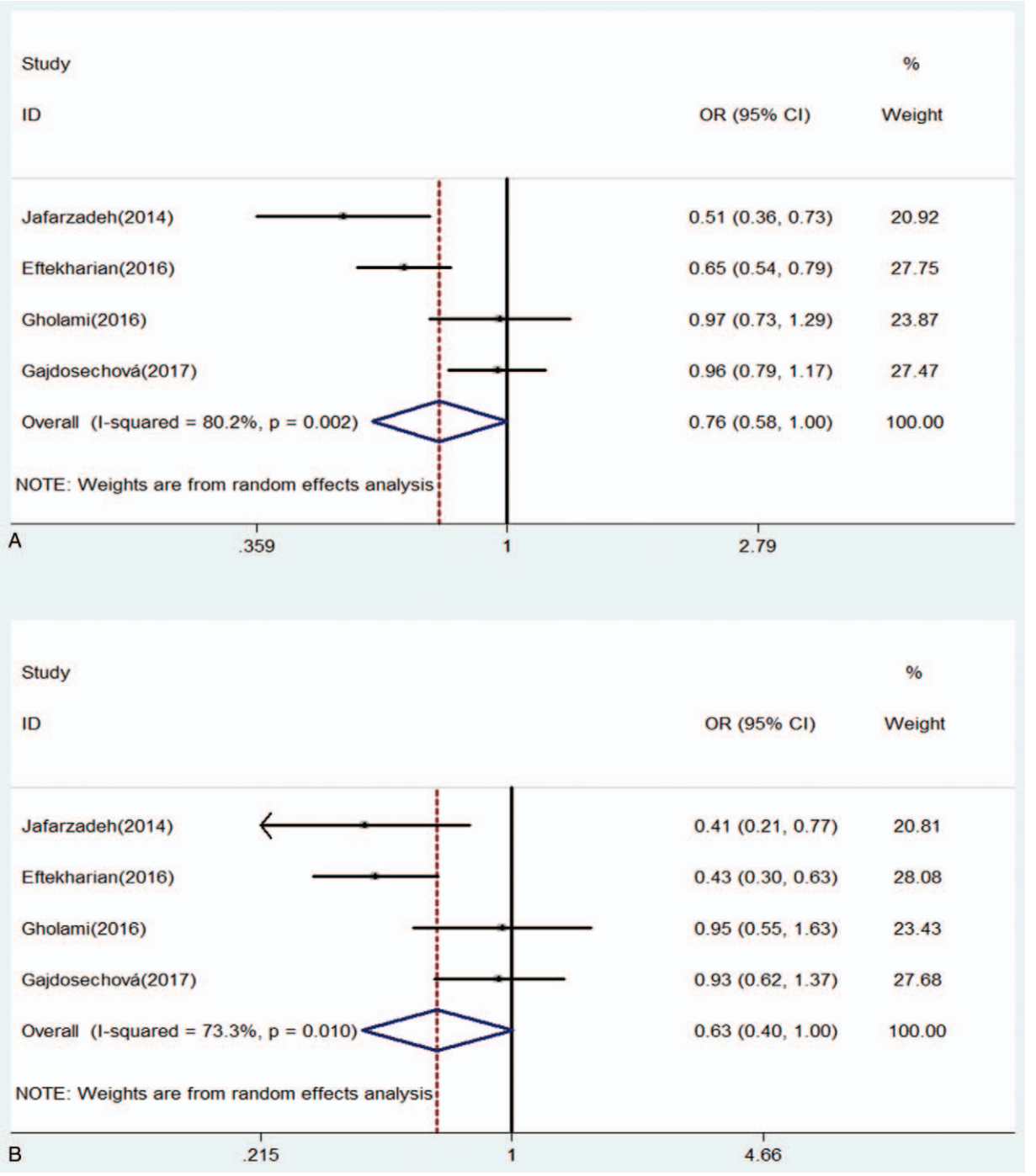


**Figure 2.** Forest of association between rs3761548 polymorphism of *FOXP3* gene and risk of MS under (A) allele model (C/A); (B) homozygote model (CC/AA). CI = confidence interval, OR = odd ratio.

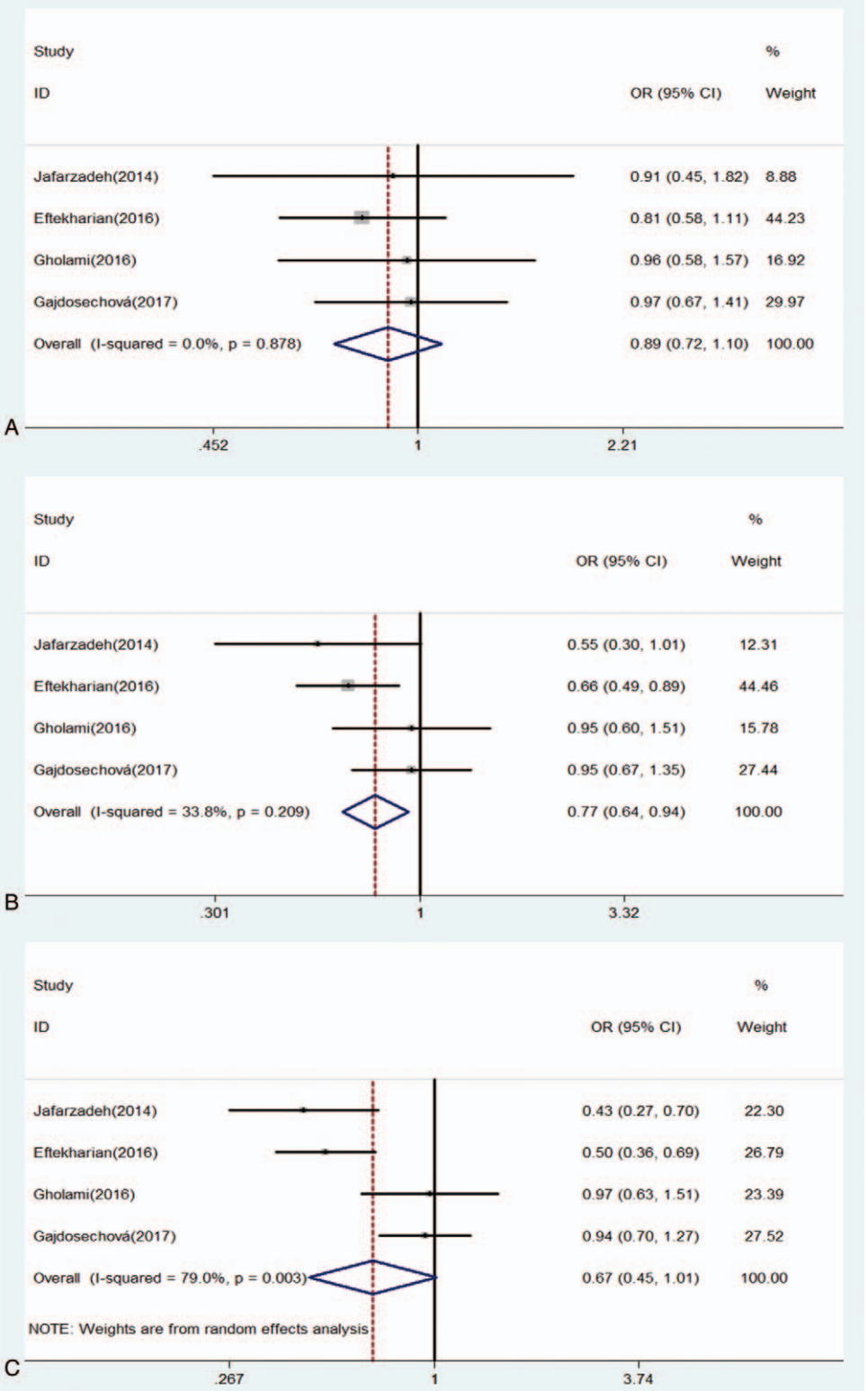


**Figure 3.** Forest of association between rs3761548 polymorphism of *FOXP3* gene and risk of MS under (A) heterozygote model (CA/AA); (B) dominant model (CC + CA/AA); (C) recessive model (CC/CA + AA).

### *3.5. Sensitive analysis*

Sensitive analysis was conducted to assess the influence of one study on the pooled ORs value (allele model and dominant model for rs3761548), and whether the results can be reverted by eliminating the individual study. The result did not alter after deleting each study, indicating the stability of the results of this meta-analysis (Fig. 9).

**Table 5**

**Subgroup-analysis of the association between rs3761548 polymorphism and multiple sclerosis.**

| | | Allelic model | | | Homozygote model | | | Heterozygote model | | | Dominant model | | | Recessive model | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs3761548 | N | OR (95%CI) | *P* | $I^2$ | OR (95% CI) | *P* | $I^2$ | OR (95% CI) | *P* | $I^2$ | OR (95% CI) | *P* | $I^2$ | OR (95% CI) | *P* | $I^2$ |
| Asian | 3 | 0.69 (0.50–0.96) | **.027** | 76.6% | 0.55 (0.33–0.92) | **.023** | 67.1% | 0.86 (0.66–1.10) | .223 | 0% | 0.70 (0.56∼0.89) | **.003** | 20.1% | 0.59 (0.37∼0.94) | **.026** | 73.8% |
| European | 1 | 0.96 (0.79–1.17) | .679 | NA | 0.93 (0.62–1.37) | .700 | NA | 0.97 (0.72–1.10) | .888 | NA | 0.95 (0.67∼1.35) | .789 | NA | 0.94 (0.70∼1.27) | .696 | NA |

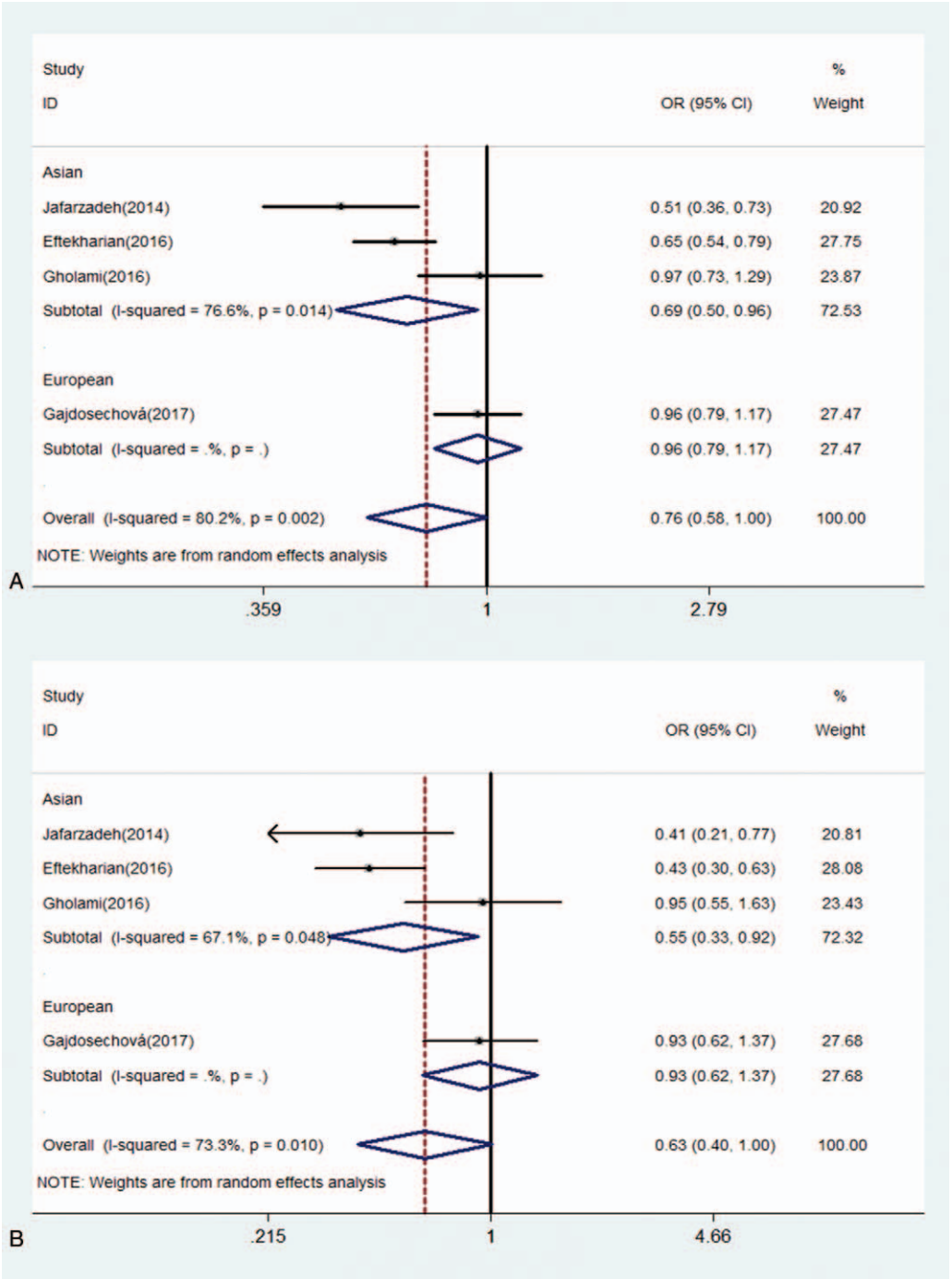


**Figure 4.** Forest of association between rs3761548 polymorphism of *FOXP3* gene and risk of MS for subgroup analysis by ethnicity under (A) allele model (C/A); (B) homozygote model (CC/AA).

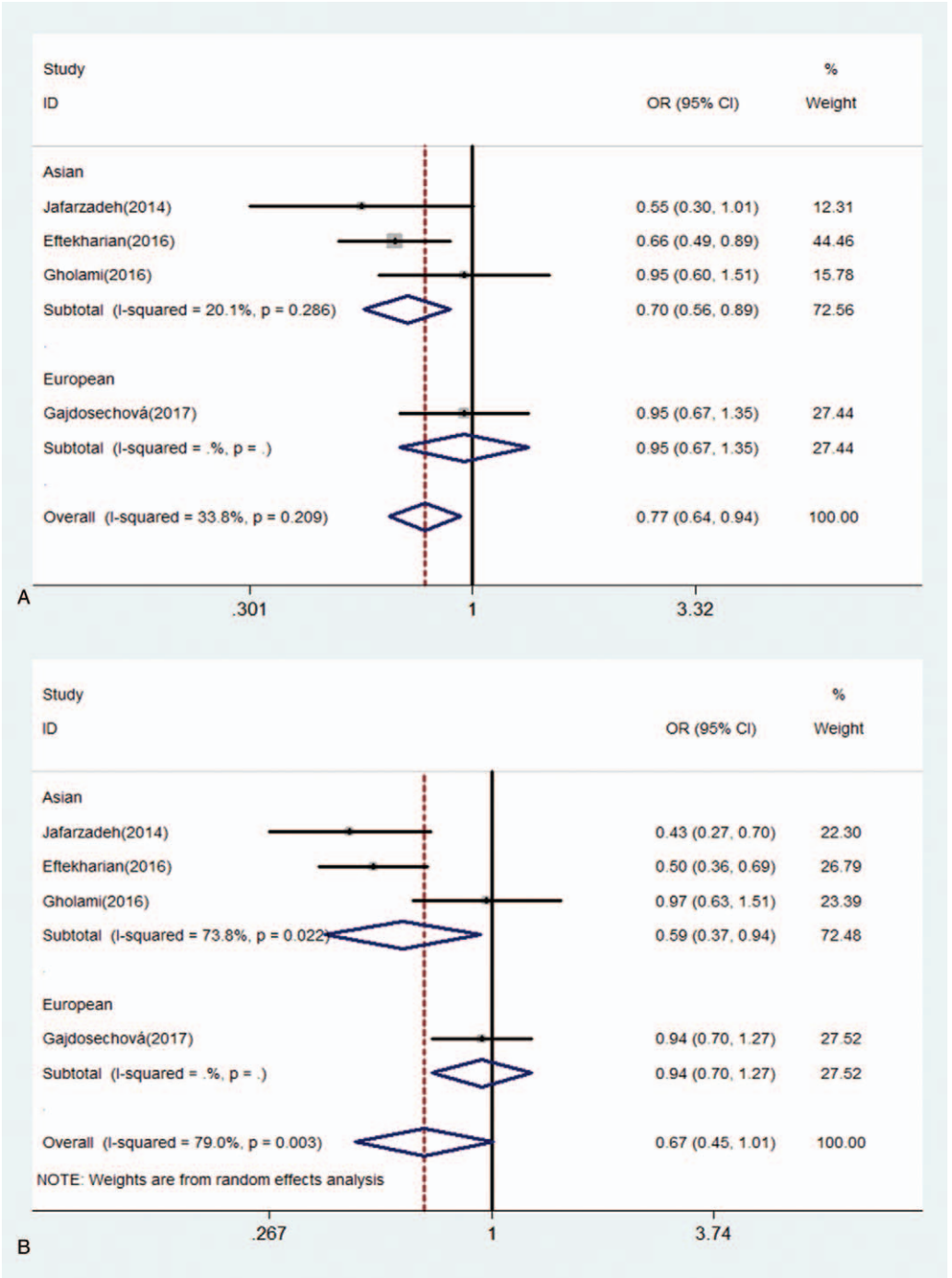


**Figure 5.** Forest of association between rs3761548 polymorphism of *FOXP3* gene and risk of MS for subgroup analysis by ethnicity under (A) dominant model (CC + CA/AA); (B) recessive model (CC/CA + AA).

## 4. Discussion

As a kind of chronic inflammatory demyelinating disorder of the central nervous system, MS usually occurs in young adults and causes torturous symptoms and complications.[21] Unfortunately, until now, no exact etiology of this disease was found. It was widely believed that MS may be the result of the interaction between genetic and environmental factors together.[22] Lots of potential genetic polymorphisms have also been identified and proved to be associated with the development of MS. A prior case-control study investigated the distribution of the Vitamin D receptor (VDR) gene in MS and revealed five VDR genetic polymorphisms as the risk factors for MS susceptibility.[23] Similar results were also reported between HLA alleles variant and MS.[24]

*FOXP3* gene was located on the *p* arm of the X chromosome and contained 11 coding exons and 3 non-coding exons in the 5' upstream region in humans.[25] Meanwhile, this gene was mainly expressed in $CD4^+$ $CD25^+$ thymocytes and $CD4^+$ $CD25^+$ peripheral T cells, which play a crucial role in

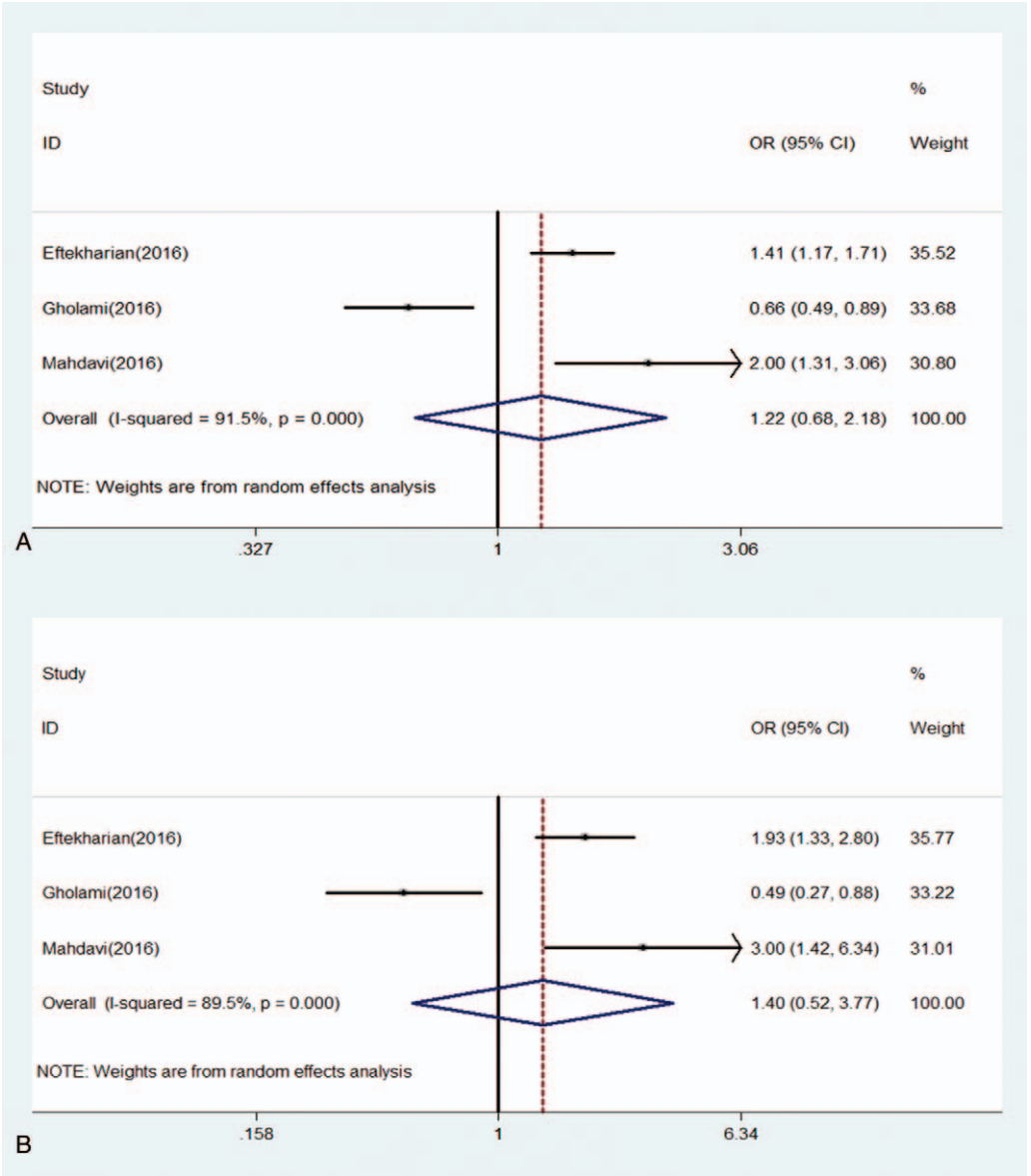


**Figure 6.** Forest of association between rs2232365 polymorphism of *FOXP3* gene and risk of MS under (A) allele model (A/C); (B) homozygote model (AA/CC).

immune regulation.[26] Several studies had reported that FOXP3 acted as a key target in the generation and maturation of T-reg cells, indicating the mutation of this gene may cause the dysfunction of T-reg cells even reversed the process of naïve T cells transfer to T-reg cells.[27] Further, recessive X-linked mutations of *FOXP3* gene have been identified as a potential reason for immune-dysregulation, which means that even mild alterations of FOXP3 expression may result in common autoimmune diseases.[28] Due to its X-linked characteristic, the genetic polymorphism of FOXP3 has been regarded as a marked risk factor in breast cancer among different ethnic populations (Chinese, Israeli, and Indians).[29] Similarly, the balance between Th1 and Th2 cells in the maternal uterus may be broken because of mutation of *FOXP3* gene, which can harm the fetus during pregnancy and subsequently result in a re-iterant abortion.[30] Additionally, such disturbance of immune system function and aberrant immune response can affect other organs in body and cause several immune-related disorders including autism, Wilms' tumor, thyroid cancer, recurrent infertility and so on.[31–34] In recent studies, *FOXP3* gene polymorphism was correlated with MS. However, these studies were small sample sizes and had low statistical power which may lead to contradictory results. Hence, we performed this meta-analysis by combining the independent studies and estimating the overall effect to overcome the individual limitation and to draw more convinced conclusions.

In present meta-analysis, after searching and reviewing 95 potential articles, we finally consolidated a total of 5 eligible studies to seek the variant polymorphism of two representative genes (rs3761548 and rs2232365) in MS susceptibility. To our limited knowledge, this study is the first meta-analysis that investigated the correlation between FOXP3 polymorphism and MS. Our results revealed that the variant allele and dominant model for rs3761548 can significantly decrease the risk of MS compared with the wild genotype. Meanwhile, under homozygote and recessive model, the difference between MS

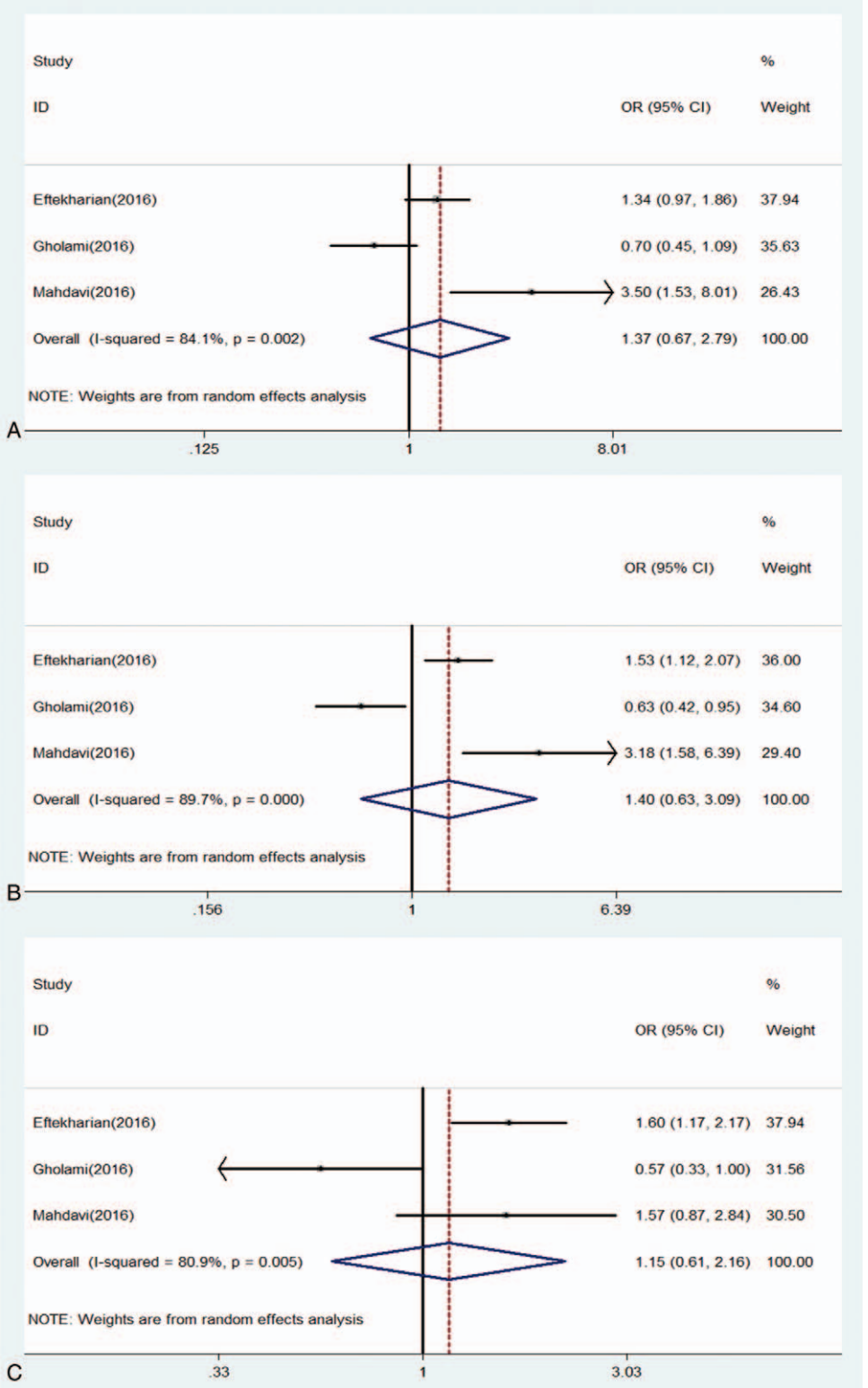


**Figure 7.** Forest of association between rs2232365 polymorphism of *FOXP3* gene and risk of MS under (A) heterozygote model (AC/CC); (B) dominant model (AA + AC/CC); (C) recessive model (AA/AC + CC).

patients and controls also showed a marginal trend toward significance ($P = .052$ and $P = .056$). Considering the discrepancy of ethnicity between articles, we also performed stratified analysis categorized by race (3 studies from Asia and 1 study from Europe). The outcomes of subgroup analysis showed a significant association between *rs3761548* gene polymorphism and MS under all genetic models except for heterozygotes in Asians. Above data supported the hypothesis that *FOXP3* gene polymorphism (rs3761548) was associated with MS. On the other hand, no significant trend was identified for the

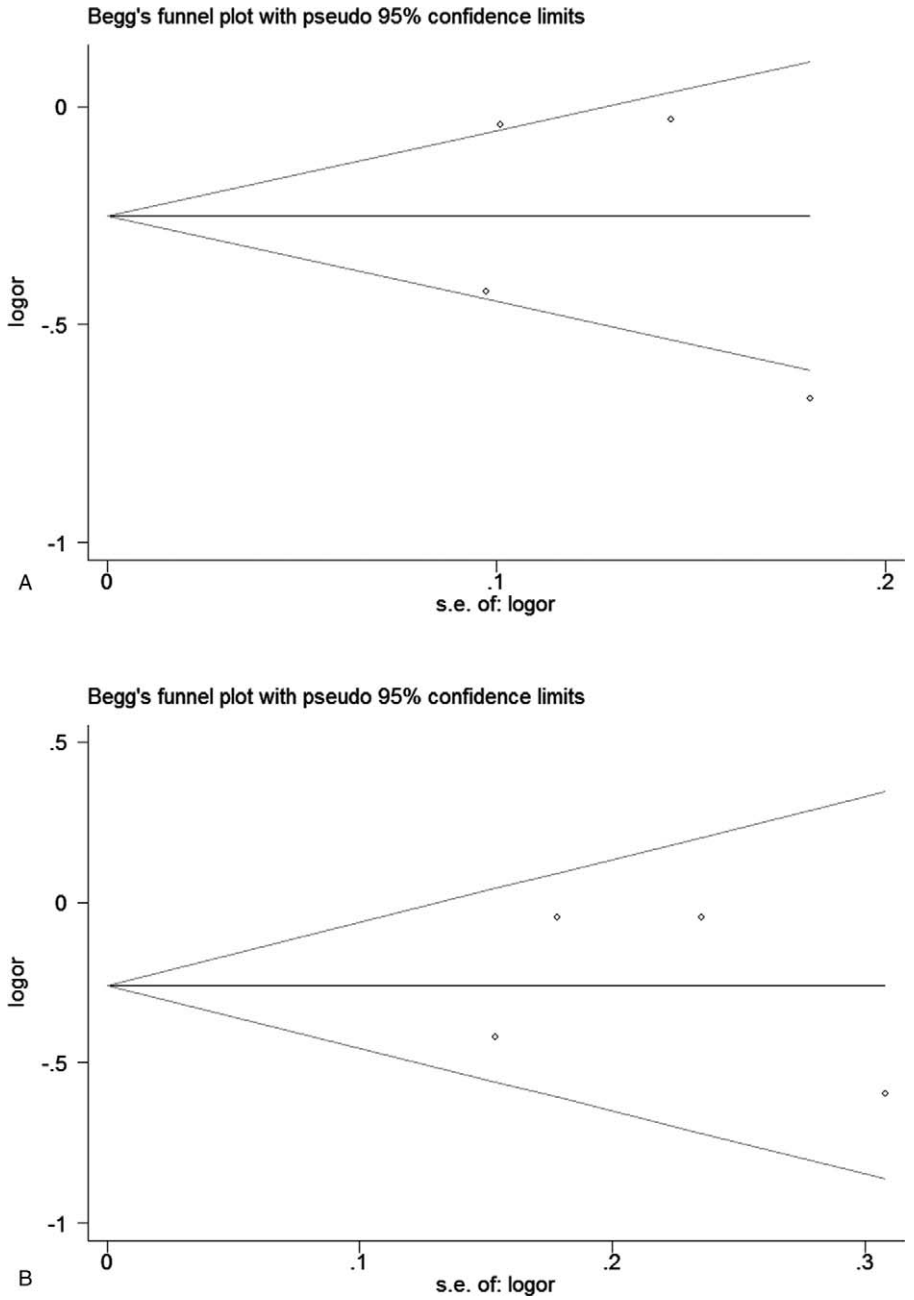


**Figure 8.** Sensitive analysis of association between rs3761548 polymorphism of *FOXP3* gene and risk of MS under (A) allele model (C/A); (B) homozygote model (CC/AA).

occurrence of MS in each genetic model of *rs2232365* gene. Moreover, either the sensitive analysis or the publication bias analysis showed no statistical significance in both the allele and dominant model for rs3761548. Hence, we speculated that rs3761538 polymorphism in *FOXP3* gene may have an association with the susceptibility to MS, especially for Asians.

Although the genetic polymorphism in the promoter region of *FOXP3* gene including rs3761548 has been studied for several years, the specific impacts of these SNPs were still unclear. It was widely considered that T-regs acted as an important component in immune system and inflammatory response, which implied that defective T-regs could lead to various autoimmune diseases.[10] At the same time, previous studies found that FOXP3 was an indispensable molecular in the development and function of T-reg cells.[35] Therefore, some opinions hypothesized that the mutation of FOXP3 can affect T-reg function and thereby lead to immune-related diseases. With modifying the transcription and altering the binding specificity of transcription factors, rs3761548 polymorphism was able to affect the expression of *FOXP3* genes.[25] In addition, the allelic alteration of rs3761548C > A can disturb the binding of E47 and c-Myb on the FOXP3 promoter site, resulting in the defective transcription of FOXP3.[36] Furthermore, another study suggested that rs3761548 polymorphism was located in the core sequence of the putative binding site for transcription factor, specificity protein 1 (Sp1), indicating the mutation of C to A may obstruct the interaction between Sp1 and FOXP3 promoter

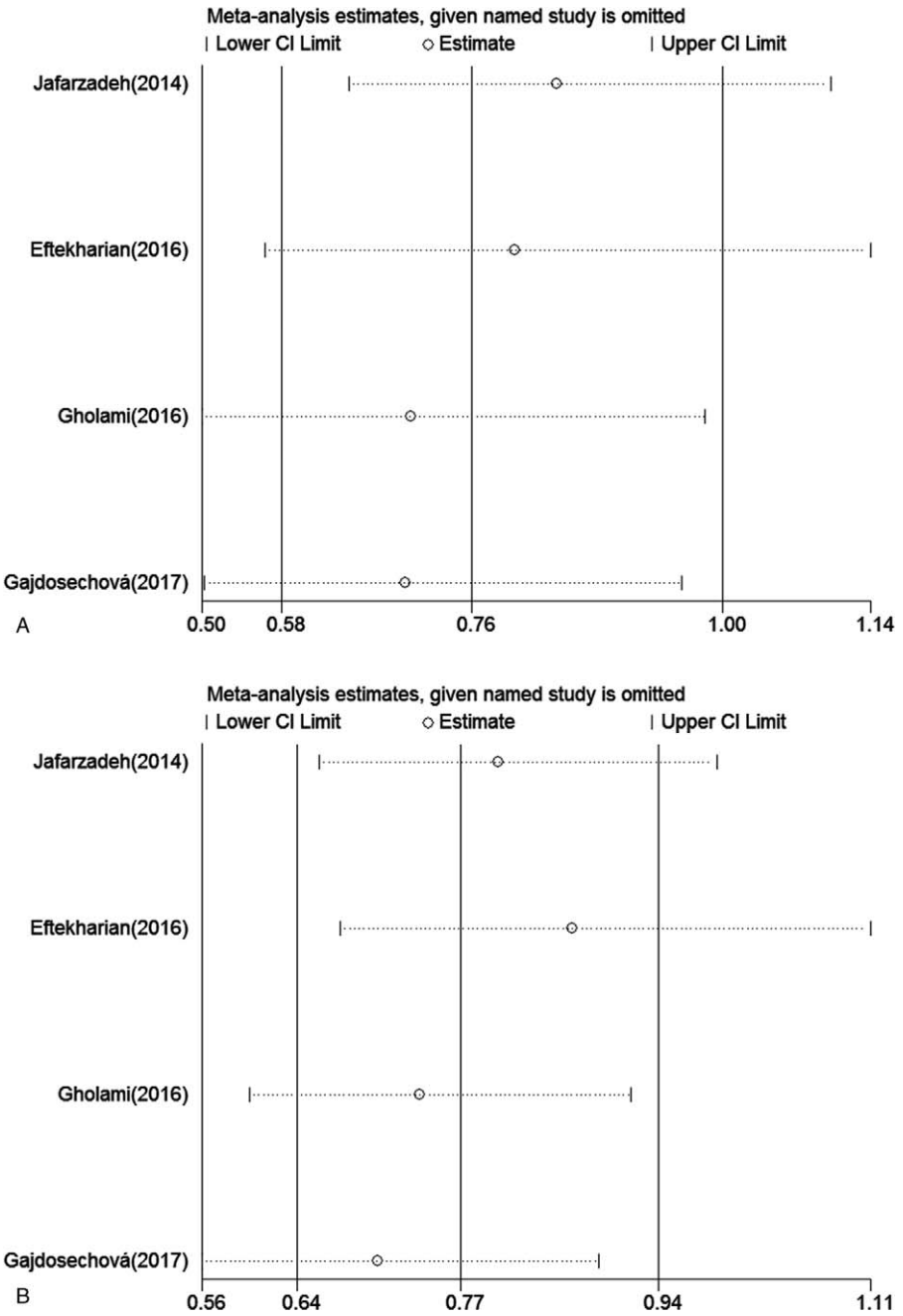


**Figure 9.** Begg funnel plot for the potential missing studies under (A) dominant model (CC + CA/AA); (B) recessive model (CC/CA + AA).

subsequent disturb the expression of *FOXP3* gene.[37] Our preliminary findings revealed that rs3761538 polymorphism in FOXP3 may be a vital factors in development of MS, which provide a new insight to understanding the genetic factors of MS susceptibility. Moreover, with the development of gene therapy, modification of rs3761538 polymorphism may be regarded as a potential therapeutic target in future.

### *4.1. Limitations and future directions*

Considering several limitations of this meta-analysis, the results should be interpreted carefully. First, due to the insufficient data, this study did not investigate the influence of the other three SNPs of FOXP3 (rs3761547, rs3761549, and rs2280883) on MS susceptibility. Second, we could not perform the subgroup analysis by gender and stages of MS due to the limited data of included studies. Third, the number of the enrolled studies in this meta-analysis was small due to the limited number of reports about the *FOXP3* gene on MS, which may introduce some bias. Fourth, the heterogeneity of rs2232365 was at a high level because of only three identified studies. Last, four of the five eligible studies were from Asians, which may limit our conclusion. For future studies, more attention should be paid to several research directions:

1. more SNPs polymorphism of FOXP3 should be analyzed and summarized;

2. gender, age, and other parameters can be considered as subgroup variables for data processing;
3. other ethnic populations including European and American subjects, should be performed to confirm the effect of *FOXP3* gene polymorphism on MS risk.

## 5. Conclusion

Based on the limited data, our meta-analysis preliminary indicated that rs3761548 polymorphism was associated with the elevated susceptibility of MS especially among Asian populations. However, more well-designed studies with large sample sizes and multiple ethnicities studies are needed to corroborate our conclusions.

## Acknowledgments

We thank all the participants for their contribution to this work.

## Author contributions

YJ Z and JX Z contributed equally to this work. YJ Z and B P designed the study. JX Z and H L did the literature search, study quality assessment and data extraction. YJ Z and JX Z performed the statistical analysis and drafted the tables and figures. YJ Z wrote the first draft of this analysis, and HL Y helped to finish the final version. All authors approved the conclusions of our study.
**Data curation:** Junxin Zhang, Hao Liu.
**Methodology:** Fan He.
**Writing – original draft:** Yijian Zhang.
**Writing – review & editing:** Angela Chen, Huilin Yang, Bin Pi.

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