The genetic association between iNOS and eNOS polymorphisms and gastric cancer risk: a meta-analysis

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Objective: There are a number of susceptible factors for an increased risk of gastric cancer. Nitric oxide (NO) is considered to be associated with the development of a range of cancers. In particular, inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS) are known to play a central role in the production of NO. Published studies relating to the association between eNOS rs1799983, rs2070744, and iNOS rs2297518 polymorphisms and the risk of gastric cancer risk are conflicting and inconclusive and require further analysis.

Materials and methods: This study involved a meta-analysis of case–control studies relating to eNOS rs1799983, rs2070744, and iNOS rs2297518 polymorphisms published prior to January 2018. Literature searches were carried out in PubMed, Embase, Web of Science, the Cochrane Library databases, and the Chinese National Knowledge Infrastructure. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strength of association based on genotype data.

Results: A total of 1,356 cases and 1,791 controls were included from nine case–control studies involving eNOS rs1799983 (G894T), rs2070744 (T–786C), and iNOS rs2297518 (C150T) polymorphisms. Data analysis indicated that iNOS rs2297518 was a risk factor for Helicobacter pylorus-positive gastric cancer when compared with H. pylorus-negative gastric cancer (p = 0.003, OR [95% CI] = 2.19 [1.31–3.66]). In addition, the allelic, dominant, and recessive models of eNOS rs2070744 were significantly associated with a risk of gastric cancer (allelic model: p < 0.00001, OR [95% CI] = 0.25 [0.15–0.42]; recessive model: p < 0.00001, OR [95% CI] = 0.16 [0.08–0.30]). No association was identified between eNOS rs1799983 and the risk of gastric cancer (p > 0.05).

Conclusion: iNOS rs2297518 and eNOS rs2070744 polymorphisms may represent susceptible factors for gastric cancer.

Keywords: inducible nitric oxide synthase, iNOS, endothelial nitric oxide synthase, eNOS, gastric cancer, meta-analysis

Introduction

Gastric cancer is one of the leading causes of mortality worldwide. 1,2 Multiple factors contribute to the pathogenesis of gastric cancer including genetic parameters, epigenetic predisposition, and environmental risk factors. 3–5 Previous studies have reported that Helicobacter pylorus is the most common risk factor in the pathology of gastric cancer. 6–7 However, one study showed that while 50% of the study population was infected with H. pylorus, the proportion of patients infected with H. pylorus who went on to develop gastric cancer was <5%. 8 Notably, in South Africa, where the incidence of H. pylorus is known to be higher than other areas of the world, the morbidity of...
gastric cancer was shown to be relatively low. Thus, it is important that we investigate the potential association between genetic predisposition and gastric cancer.

Recent research studies have focused on nitric oxide (NO), a short-lived, small molecule, generated from the physiological transformation of L-arginine to L-citrulline by nitric oxide synthase (NOS). NO plays an important role in vasodilatation, smooth muscle relaxation, immunity, and tumor angiogenesis. Four isoforms of NOS have been identified and described as inducible nitric oxide synthase (iNOS), neuronal nitric oxide synthase (nNOS), endothelial nitric oxide synthase (eNOS), and mitochondrial nitric oxide synthase (mNOS). eNOS is a calcium (Ca²⁺)-dependent enzyme and was first identified in vascular endothelial cells. It has also been shown that eNOS regulates blood pressure, platelet aggregation, leukocyte adherence, and vascular smooth muscle cell mitogenesis and angiogenesis. Furthermore, iNOS is one of the most important enzymes involved in the metabolic pathway of reactive oxygen and nitrogen species in the presence of H. pylorus infection. It is also important to note that iNOS can produce larger amounts of NO than either eNOS or nNOS.

eNOS is encoded by the NOS3 gene, located in 7q35-q36, and encodes a protein of 1,203 amino acids. To date, a number of polymorphisms have been reported for the NOS3 gene, including rs1799983, intron 4a/b, and rs2070744; all these have been investigated for their association with the risk of gastric cancer. Significant associations were detected between eNOS rs2070744 and the risk of gastric cancer in two different populations. However, no genetic association was observed between eNOS rs1799983 and the risk of gastric cancer in Guilan and Chinese populations. In terms of the iNOS gene, the rs2297518 polymorphism in exon 16 results in an amino acid substitute, Ser608Leu, and has been reported to be associated with cigarette- and alcohol-induced gastric cancer in the Chinese population and H. pylorus-related gastric cancer in Iran. However, these results were inconsistent and inconclusive.

Considering the limited number of subjects included in previous studies and the inconsistent results arising from different populations, we performed this meta-analysis in order to combine all pertinent published studies and investigate the precise association between eNOS rs2070744, rs1799983, and iNOS rs2297518 and the pathogenesis of gastric cancer.

Materials and methods

Publication searches and selection criteria

This meta-analysis followed the Cochrane collaboration definition and PRISMA 2009 guidelines for meta-analyses and systematic reviews. Literature searches were carried out in PubMed, Embase, Web of Science, the Cochrane Library databases, and the Chinese National Knowledge Infrastructure. We searched for all relevant publications exploring the relationship between iNOS and eNOS polymorphisms and the risk of gastric cancer (until January 1, 2018). The following were used as search terms: “iNOS” or “Inducible nitric oxide synthase” and “eNOS” or “endothelial nitric oxide synthase” or “NOS3” or “nitric oxide synthase 3” and “polymorphism” or “variation” and “gastric cancer” or “stomach cancer” or “gastric adenocarcinoma.” Our search was not limited by language. In addition, other potentially relevant items of literature were identified by cross-reference within eligible studies.

Inclusion criteria

Studies were included if 1) they had a case–control design; 2) they contained sufficient data to calculate an odds ratio (OR) with a 95% CI; 3) they referred to the association between iNOS and eNOS polymorphisms and the risk of gastric cancer; and 4) the genotypic distributions in control groups were in Hardy–Weinberg equilibrium (HWE).

Exclusion criteria

Studies were excluded if 1) they were duplicated studies, abstracts, letters, reviews, or papers presented in a meeting; 2) if they were unrelated to the genetic association between iNOS and eNOS polymorphisms and gastric cancer; 3) if there was insufficient genotype data; and 4) if the control group was not in HWE.

Data extraction and quality assessment

Two authors (Jiang and Chen) extracted the data independently. Information arising from each individual study were summarized as follows: first author, year of publication, ethnicity, case and control, mean ages, gender (proportion of males), genotyping methods, sample source, HWE for control groups, state of H. pylorus, and the number of patients who smoked or suffered from alcoholism. All included studies were independently evaluated by using the Newcastle–Ottawa Scale by two authors (Lu and Li). Any discrepancies in the assessment were resolved by another author (Peng).

Statistical analysis

The strength of the association between iNOS (rs2297518) and eNOS (rs2070744, rs1799983) polymorphisms and the risk of gastric cancer were evaluated by calculating
pooled ORs and their corresponding 95% CIs by using RevMan 5.1 (Copenhagen, Denmark) and Stata 12.0 (StataCorp LP, College Station, TX, USA). Heterogeneity was tested using χ²-based Q test and I² statistics. When there was no significant heterogeneity across studies (I² <50%), the fixed effects model (Mantel–Haenszel method) was used. Otherwise, the random effects model (the DerSimonian and Laird method) was used. Sensitivity analysis was then performed to assess the stability of the results. Publication bias was detected using Begg’s test and Egger’s test. p<0.05 was considered to be statistically significant.

Results
Study selection and characteristics
As shown in Figure 1, a total of 354 relevant publications were retrieved from the selected databases. After screening the titles, 293 of these publications were excluded because they were not related to the genetic association between iNOS and eNOS polymorphisms and gastric cancer, six were removed due to duplication, 46 were removed because they were reviews, abstracts, letters, or editorials. Finally, nine studies21,24–26,32,33 that met the required criteria were retained for meta-analysis, of which five studies referred to the specific association between iNOS rs2297518 and gastric cancer.21,28,29,32,33 Two studies referred to the specific associations between eNOS rs2070744,24,29,33 rs1799983,25,27 and gastric cancer, respectively. The basic characteristics of the enrolled patients are shown in Table 1. The NOS quality assessment of the studies included in this meta-analysis is included in Tables 1 and S1. Only studies with NOS scores >6 were selected for this meta-analysis.

Results of the meta-analysis
The distributions of iNOS rs2297518 in allelic, dominant, and recessive models in the case group were not significantly different from that in the control group (allelic model: p=0.73, OR [95% CI] =1.09 [0.67–1.75]; dominant model: p=0.87, OR [95% CI] =1.03 [0.72–1.48]; recessive model: p=0.85, OR [95% CI] =1.16 [0.31–4.32]) (Figure 2; Table 2). Subgroup analysis, stratified by tests involving an anti-H. pylorus immunoglobulin G (IgG) antibody showed that the dominant model of iNOS rs2297518 was significantly associated with the risk of gastric cancer in H. pylorus CagA-positive cases (p=0.003, OR [95% CI] =2.19 [1.31–3.66]), but not in gastric cancer patients who were H. pylorus CagA-negative (p=0.82, OR [95% CI] =0.96 [0.65–1.41]) (Table 2).

For eNOS rs2070744, significant associations were detected between the allelic, dominant, and recessive models of eNOS rs2070744 (allelic model: p=0.00001, OR [95% CI] =0.23 [0.16–0.34]; dominant model: p<0.00001, OR [95% CI] =0.25 [0.15–0.42]; recessive model: p=0.00001, OR [95% CI] =0.16 [0.08–0.30]) (Figure 3; Table 2). However, the frequencies of allelic, dominant, and recessive models for eNOS rs1799983 were not significantly different when compared between case and control groups (p>0.05), which showed no significant correlation between eNOS rs1799983 and the risk of gastric cancer (Figure 4; Table 2). Because of a lack of data, it was not possible to perform subgroup analyses based on ethnicity, anti-H. pylorus IgG antibody status, smoking, and alcoholism.

Sources of heterogeneity
Significant heterogeneity was observed for allelic, dominant, and recessive models of iNOS rs2297518 (allelic model: I²(%) =83, dominant: I²(%) =60, and recessive model: I²(%) =76) (Table 2). This level of heterogeneity was contributed predominantly by two studies.28,33 Removal of these two studies from our meta-analysis resulted in 0% (p=0.90) heterogeneity, thus showing that this had the highest effect on association between iNOS rs2297518 and the risk of gastric cancer.

Figure 1 PRISMA flowchart of inclusion and exclusion of studies.
Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the influence of an individual study on the overall OR. Analyses showed that ORs were not significantly altered for iNOS rs2297518, eNOS rs2070744, or rs1799983 (Figure 5). This evidence indicated that the present results were statistically stable and reliable. Funnel plots, Begg's test, and Egger's test were additionally performed to assess publication bias; results revealed that there was no obvious publication bias in our overall analysis for iNOS rs2297518 (\(p_{\text{egger}}=0.564; p_{\text{begg}}=0.327\)) and eNOS rs1799983 (\(p_{\text{egger}}=0.511; p_{\text{begg}}=0.602\)) (Figure 6; Table 3).

Discussion

In the present meta-analysis, we investigated the genetic associations between iNOS rs2297518, eNOS rs2070744, and rs1799983 and the risk of gastric cancer. Our combined results showed that the dominant model of iNOS rs2297518 was significantly associated with \(H.\) pylorus-positive gastric cancer risk. In addition, eNOS rs2070744, but not rs1799983, was identified as susceptible factor for the risk of gastric cancer.

Interestingly, the rs2297518 polymorphism in the iNOS gene has been reported to be associated with an increased risk for genotype gastric cancer in Asian populations,\textsuperscript{31} but not in Iran\textsuperscript{29} or Japanese populations.\textsuperscript{21} Our meta-analysis failed to find any statistically significant relationship between the allelic, dominant, and recessive models of iNOS rs2297518 and the risk of gastric cancer. However, the distribution of the dominant model of iNOS rs2297518 among the \(H.\) pylorus-positive gastric cancer group of patients and the \(H.\) pylorus-negative gastric cancer group of patients was statistically significant, which indicated that \(H.\) pylorus infection might play a key role in the development of gastric cancer. Epidemiological studies have also indicated that \(H.\) pylorus infection is a risk factor for gastric cancer.\textsuperscript{34,35} However, most patients with \(H.\) pylorus infection do not appear to develop gastric cancer. The reasons for this inconsistency remain unclear and cannot be explained by bacterial virulence factors alone.

iNOS is shown to be upregulated in response to \(H.\) pylorus infection and leads to excessive release of NO which would then contribute to the development of gastric atrophy.\textsuperscript{21} An earlier hypothesis suggested that a higher level of iNOS can cause more oxidative DNA damage, thus increasing the risk of cancer development.\textsuperscript{36} A number of reports have addressed the high expression of iNOS in gastric cancer, which is known to increase as the stage of cancer increases and with lymph node metastasis.\textsuperscript{37,38} Previous research has shown that iNOS contributes to \(H.\) pylorus-associated gastric carcinogenesis and that \(H.\) pylorus is associated with
Table 2 The main results of the association between eNOS 894G>T, -786T>C, and iNOS C150T polymorphisms and gastric cancer

<table>
<thead>
<tr>
<th>SNPs</th>
<th>Genetic model</th>
<th>Number of studies</th>
<th>Numbers</th>
<th>Test of association</th>
<th>Model</th>
<th>Test of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Case</td>
<td>Control</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>iNOS C150T</td>
<td>T</td>
<td>5</td>
<td>1,454</td>
<td>2,512</td>
<td>1.09 (0.67–1.75)</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>TT/CT+CC</td>
<td>5</td>
<td>727</td>
<td>1,256</td>
<td>1.16 (0.31–4.32)</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>TT/CC</td>
<td>5</td>
<td>727</td>
<td>1,256</td>
<td>1.03 (0.72–1.48)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>H. pylorus positive</td>
<td>3</td>
<td>126</td>
<td>181</td>
<td>2.19 (1.31–3.66)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>H. pylorus negative</td>
<td>3</td>
<td>226</td>
<td>402</td>
<td>0.96 (0.65–1.41)</td>
<td>0.82</td>
</tr>
<tr>
<td>eNOS G894T</td>
<td>T</td>
<td>3</td>
<td>914</td>
<td>776</td>
<td>0.80 (0.62–1.03)</td>
<td>0.09</td>
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<tr>
<td></td>
<td>TT/GT+GG</td>
<td>3</td>
<td>457</td>
<td>388</td>
<td>0.52 (0.22–1.25)</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>TT/GT/CC</td>
<td>3</td>
<td>457</td>
<td>388</td>
<td>0.79 (0.59–1.07)</td>
<td>0.13</td>
</tr>
<tr>
<td>eNOS C786T</td>
<td>T</td>
<td>2</td>
<td>400</td>
<td>482</td>
<td>0.23 (0.16–0.34)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td>TT/CT+CC</td>
<td>2</td>
<td>200</td>
<td>241</td>
<td>0.16 (0.08–0.30)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td>TT/CT/CC</td>
<td>2</td>
<td>200</td>
<td>241</td>
<td>0.25 (0.15–0.42)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Abbreviations: iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; OR, odds ratio; CI, confidence interval; R, random model; F, fixed model; NA, not available.
Figure 3 Forest plots of odds ratios for the association between eNOS C786T and gastric cancer. (A) Allelic model; (B) dominant model; (C) recessive model.

Abbreviations: eNOS, endothelial nitric oxide synthase; CI, confidence interval.

Figure 4 (Continued)
non-cardiac tumors but not with cardiac tumors. Several studies have also demonstrated a link between iNOS polymorphism and the risk of gastric cancer development. For example, Rafiei et al reported a significant association between a TT+CT genetic model and H. pylorus-positive gastric cancer. However, research conducted by Goto et al and Shen et al could not replicate this result. To our knowledge, the present study is the first to investigate and identify a significant association between iNOS rs2297518 and H. pylorus-positive gastric cancer risk, which implies that the iNOS rs2297518 polymorphism might affect H. pylorus infection and iNOS expression. To confirm this result, it is now necessary to investigate a larger number of subjects in a case–control study.

Both iNOS and eNOS have been reported as an important form of NOS. The eNOS rs2070744 polymorphism was found to significantly reduce the rate of mRNA transcription, thus resulting in reduced levels of NO in the serum and stimulating tumor proliferation, angiogenesis, and metastasis. The eNOS rs2070744 polymorphism has been reported to play

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C  | Study or subgroup | Experimental Events | Total Control Events | Weight (%) | Odds ratio M–H, fixed, 95% CI | Odds ratio M–H, fixed, 95% CI
---|------------------|---------------------|---------------------|------------|-----------------------------|-----------------------------
| Arjmand et al25  | 4                   | 87                  | 6                    | 90         | 38.0                         | 0.67 (0.18–2.48)            |
| Chen et al27     | 2                   | 324                 | 1                    | 200        | 8.3                          | 1.24 (0.11–13.72)           |
| Tecder et al24   | 2                   | 46                  | 13                   | 98         | 53.7                         | 0.30 (0.06–1.38)            |
| Total (95% CI)   | 8                   | 457                 | 20                   | 388        | 100                          | 0.52 (0.22–1.25)            |

Heterogeneity: $x^2=1.16$, df=2 ($p=0.56$); $I^2=0$
Test for overall effect: $Z=1.46$ ($p=0.14$)

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Figure 4 Forest plots of odds ratios for the association between eNOS G894T and gastric cancer. (A) Allelic model; (B) dominant model; (C) recessive model.

Abbreviations: eNOS, endothelial nitric oxide synthase; CI, confidence interval.

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A  | Meta-analysis random effects estimates (exponential form) study omitted
---|--------------------------------------------------
| Goto 2006                                | Arjmand et al25 |
| Rafiei et al29                            | Chen et al27    |
| Shen et al28                              | Tecder et al24  |
| Yu et al25                                |                   |

B  | Meta-analysis fixed effects estimates (exponential form) study omitted
---|--------------------------------------------------
| Goto 2006                                | Arjmand et al25 |
| Rafiei et al29                            | Chen et al27    |
| Shen et al28                              | Tecder et al24  |
| Yu et al25                                |                   |

C  | Meta-analysis fixed effects estimates (exponential form) study omitted
---|--------------------------------------------------
| Krishnani et al23                         | Tecder et al24  |

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Figure 5 Sensitivity analyses between eNOS C786T, G894T, and iNOS C150T and gastric cancer. (A) iNOS C150T; (B) eNOS C786T; (C) eNOS G894T.

Abbreviations: eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase.
a critical role in cardiovascular disease, breast cancer, colorectal cancer, and diabetic neuropathy. Two previous meta-analyses have investigated the statistical genetic associations between eNOS rs2070744 and the risk of cancer; however, results differed between these two studies. This inconsistency may have arisen due to the different number of studies included in two data sets. Two studies included in the present analysis identified a significant association between the rs2070744 polymorphism and gastric cancer, and our combined results were the same as those of the individual studies, which might indicate a potential role for this variant in the risk of gastric cancer. Notably, the results of the present meta-analysis relating to the correlation between the rs2070744 polymorphism and gastric cancer should be interpreted carefully because the number of studies included was relatively small.

The eNOS rs1799983 polymorphism is located in exon 7 of the NOS3 gene and leads to the amino acid substitution, Glu298Asp, which alters susceptibility to cleavage, while also reducing enzyme activity and basal NO production. Several previous meta-analyses have investigated the association between the eNOS rs1799983 polymorphism and the risk of cancer, although most studies observed negative results. However, no meta-analysis has been conducted on the potential association between the eNOS rs1799983 polymorphism and gastric cancer. We included only two studies and found no statistical association of eNOS rs1799983 and the risk of gastric cancer, which indicates that the eNOS rs1799983 polymorphism might not be a risk factor for gastric cancer. Although significant associations were detected between iNOS rs2297518, eNOS rs2070744, and the risk of gastric cancer, several limitations should be taken into account.

### Table 3

<table>
<thead>
<tr>
<th>Models of test</th>
<th>Polymorphisms</th>
<th>iNOS C150T</th>
<th>eNOS C786T</th>
<th>eNOS G894T</th>
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</thead>
<tbody>
<tr>
<td>P-value</td>
<td>0.564</td>
<td>0.511</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-33.78177</td>
<td>-41.67948</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to 22.38564</td>
<td>to 35.79079</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric oxide synthase; OR, odds ratio; CI, confidence interval; NA, not available.
First, the number of studies and subjects included was relatively small. In particular, the association between eNOS rs2070744, rs1799983, and gastric cancer was investigated by only two studies enrolled by the present study; this might affect the reliability of our results. Thus, a larger number of studies, with more subjects, are now necessary to confirm our results. Second, the subjects in the present study were mostly of Asian origin. The prevalence of gastric cancer in Europeans and Latin Americans cannot be ignored. However, due to the lack of genetic association studies in Europeans and Latin Americans, we were not able to carry out subgroup analysis stratified by ethnicity. Third, apart from H. pylorus infection, smoking, diet, and alcohol abuse were also considered to be risk factors for gastric cancer, although we could not analyze the influence of these factors in regard to the risk of gastric cancer because of insufficient data.

**Conclusion**

Our meta-analysis showed that the dominant model of iNOS rs2297518 may represent a risk factor for H. pylorus-positive gastric cancer, while eNOS rs2070744, but not rs1799983, represents a protective factor for the risk of gastric cancer. To confirm these results, a larger number of cohorts should be investigated, using a case–control design.

**Acknowledgment**

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**Disclosure**

The authors report no conflicts of interest in this work.

**References**


Supplementary material

Table S1 Newcastle–Ottawa scale for quality assessment of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen et al²</td>
<td>2004</td>
<td>****</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Goto et al²</td>
<td>2006</td>
<td>***</td>
<td>**</td>
<td>#</td>
</tr>
<tr>
<td>Rafiei et al³</td>
<td>2012</td>
<td>***</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>Shen et al⁴</td>
<td>2002</td>
<td>***</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Yu et al⁴</td>
<td>2017</td>
<td>*</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Arjmand et al⁵</td>
<td>2014</td>
<td>***</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Chen et al⁶</td>
<td>2010</td>
<td>***</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Tecder et al⁷</td>
<td>2010</td>
<td>***</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Krishnaveni et al⁸</td>
<td>2015</td>
<td>***</td>
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</tbody>
</table>

Note: The number of “*” means the consistency of each study according to the Newcastle-Ottawa Scale.

References