Association of *NQO1* and *TNF* polymorphisms with Parkinson's disease: A meta-analysis of 15 genetic association studies

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Abstract. Parkinson's disease (PD) is a neurodegenerative movement d'isorder that affects ~2% of the population aged ≥65 years. NAD(P)H-quinone oxidoreductase 1 (NQO1) and tumor necrosis factor-α (TNF-α) are two important factors in the generation of oxidative stress in PD. The aim of the present study was to assess the association of *NQO1* and tumor necrosis factor (*TNF*) polymorphisms with PD. A meta-analysis was performed that included data from 15 studies comprising 2,858 patients and 2,907 healthy controls. The results showed that *TNF*-1031 (rs1799964) was significantly associated with PD in the recessive [P=0.0005; odds ratio (OR), 3.19; 95% confidence interval (CI), 1.66-6.13] and additive models (P=0.0006; OR, 3.15; 95% CI, 1.63-3.51). However, there was no significant association in *NQO1* C609T (rs1800566) and *TNF*-308 (rs1800629) with PD. To the best of our knowledge, the present study is the first meta-analysis of *NQO1* and *TNF* polymorphisms with PD demonstrating that *TNF*-1031 polymorphism may be a risk factor for PD under either the recessive or additive models. However, the meta-analyses did not support the involvement of *NQO1* C609T and *TNF*-308 in the risk of PD.

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Introduction

Parkinson's disease (PD; OMIM: #168600), which is attributed to the death of nigrostriatal dopaminergic neurons, is a neurodegenerative movement disorder that affects ~2% of the population aged ≥65 years. The clinical features of PD, including tremor, rigidity and bradykinesia (1) and other severe complications (2), leading to considerable damage to human body.

PD is a complex disease affected by genetic and environmental factors. Environmental factors comprise of oxidative stress (3), smoking (4) and environmental toxins (5). These environmental risk factors have been found to play an important role in the progression of PD. In addition, genetic predisposition plays a clear role in this complex disease. Previous genetic studies have identified numerous genetic markers of PD (6-8).

Oxidative stress caused by the accumulation of oxidative species is closely associated with PD (9). The quinone intermediates that are derived from dopamine metabolism are pivotal to the generation of oxidative stress. *NQO1*, which is located on chromosome 16q22.1, encodes NAD(P)H-quinone oxidoreductase 1 (NQO1), which is a detoxification enzyme involved in dopamine metabolism. *NQO1* has been found to be expressed in astroglial and endothelial cells in substantia nigra pars compacta (10). Tumor necrosis factor (*TNF*) is located in the human leukocyte antigen class III region on chromosome 6p21.3 (11). *TNF* encodes TNF-α, which is one of the principal cytokines involved in promoting inflammation and oxidative stress (12).

A number of case-control studies have been carried out previously to identify the association between PD and the *NQO1* and *TNF* polymorphisms (13-29). There were four positive and four negative studies for the association of the *NQO1* C609T polymorphism and PD. There was one positive and six negative studies for the association between the *TNF*-308 polymorphism and PD, and there were two positive and one negative study between TNF-1031 polymorphism and PD. The inconsistent conclusions may be due to the limited power of each study and difference in ethnicity in these genetic loci.

Table I. Characteristics of the case-control studies in the present meta-analyses.

Genetic locus	Authors	Year	Country	Ethnicity	Cases/ controls	Control source	HWE	Result	Power	(Refs.)
NQO1 C609T	Harada *et al*	2001	Japan	Asians	111/100	Hospital	Yes	NS	0.152	(13)
	Shao *et al*	2001	China	Asians	126/136	Hospital	Yes	S	0.179	(14)
	Jiang *et al*	2004	China	Asians	274/161	Hospital	No	S	0.195	(15)
	Okada *et al*	2005	USA	Europeans	163/269	Hospital	Yes	NS	0.188	(16)
	Shao *et al*	2005	China	Asians	140/144	Population	Yes	S	0.117	(17)
	Xu *et al*	2007	China	Asians	52/133	Population	Yes	NS	0.184	(18)
	Fong *et al*	2007	China	Asians	149/153	Hospital	No	NS	0.199	(20)
	Punia *et al*	2011	Indian	Asians	339/344	Population	Yes	S	0.373	(19)
TNF-308	Kruger *et al*	2000	Germany	Europeans	237/177	Population	Yes	S	0.133	(21)
	Ross *et al*	2004	UK	Europeans	90/93	Hospital	Yes	NS	0.102	(22)
	Wahner *et al*	2007	USA	Europeans	289/269	Population	Yes	NS	0.281	(23)
	Wu *et al*	2007	China	Asians	369/326	Hospital	Yes	NS	0.199	(24)
	Bialecka *et al*	2008	Poland	Europeans	316/300	Population	Yes	NS	0.106	(25)
	Du *et al*	2009	China	Asians	114/133	Population	Yes	NS	0.081	(26)
	Pascale *et al*	2010	Italy	Europeans	146/156	Hospital	Yes	NS	0.184	(27)
TNF-1031	Nishimura *et al*	2001	Japan	Asians	172/157	Hospital	Yes	S	0.126	(28)
	Wu *et al*	2007	China	Asians	369/326	Hospital	Yes	S	0.180	(24)
	Infante *et al*	2008	Spain	Europeans	194/170	Population	Yes	NS	0.096	(29)

HWE, Hardy-Weinberg equilibrium; NQO1, NAD(P)H-quinone oxidoreductase 1; NS, not significant; S, significant; TNF, tumor necrosis factor.

Meta-analyses are able to enhance the credibility of association studies by combining data from different studies and drawing a more comprehensive conclusion (30). In the present study, a comprehensive meta-analysis was conducted to establish the role of these loci in the risk of PD.

Materials and methods

Data collection. A systematic literature search was performed using online databases [PubMed, WanFang, WeiPu and China National Knowledge Infrastructure (CNKI)], without time and language restriction, and by searching the following keywords: 'Parkinson *NQO1* association or Parkinson *NQO1* polymorphism' and 'Parkinson *TNF* association or Parkinson *TNF* polymorphism' to collect available studies. The studies were involved when they met the following criteria: i) The study was an original case-control study with assessment of the association between PD and polymorphisms of *NQO1* and *TNF* in humans; ii) it contained sufficient information to infer the odd ratios (ORs) and 95% confidence intervals (CIs); and iii) the genotype distribution of each polymorphism in the controls met the Hardy-Weinberg equilibrium (HWE). All the studies included in the meta-analyses were carefully considered and selected in January 2014. As shown in previous studies (31-34), the following information was precisely extracted or calculated from each study: Genetic locus, first author's name, year of publication, country, ethnicity, the numbers of cases and controls, control source, HWE for controls, the power of individuals and whether the study had significant association with PD and the power of individuals (Table I).

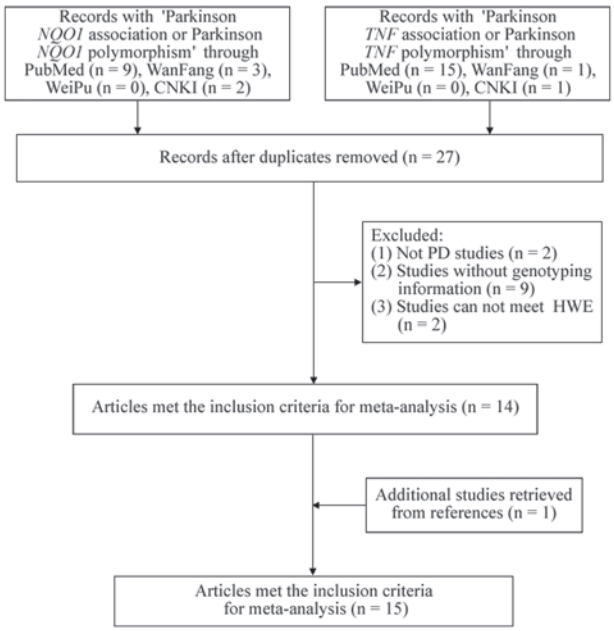

Figure 1. Flowchart of selection process in the meta-analyses.

Statistical analysis. The Arlequin program was used to test HWE (35). The power of each study was calculated by the Power and Sample Size Calculation program (36). The statistical heterogeneity across the studies included in the meta-analysis was assessed by Cochran's Q statistic and I^2 tests (37) to determine the type of analysis. In the meta-analysis, the fixed-effects model was used for the

Table II. Meta-analyses of the association between *NQO1* C609T, *TNF*-308 and *TNF*-1031 and Parkinson's disease.

Genetic model	Cases/ Controls	Ethnicity	No. of studies	OR (95% CI)	P-value	I^2 (%)	Power
NQO1 C609T							
Overall (T vs. C)	931/1126	Overall	6	1.07 (0.76-1.50)	0.69	83	0.791
	768/852	Asians	5	1.15 (0.78-1.70)	0.48	85	0.715
	163/269	Europeans	1	0.76 (0.52-1.09)	0.14	NA	0.188
Dominant (TT/TC vs. CC)	805/990	Overall	5	1.24 (0.67-2.31)	0.49	88	0.771
	642/721	Asians	4	1.43 (0.63-3.27)	0.39	90	0.641
	163/269	Europeans	1	0.76 (0.50-1.16)	0.20	NA	0.245
Recessive (TT vs. TC/CC)	805/990	Overall	5	0.77 (0.44-1.34)	0.36	51	0.402
	642/721	Asians	4	0.83 (0.47-1.47)	0.53	57	0.381
	163/269	Europeans	1	0.23 (0.03-1.90)	0.17	NA	0.077
Additive (TT vs. CC)	429/574	Overall	5	0.92 (0.32-2.61)	0.87	83	0.356
	314/395	Asians	4	1.13 (0.36-3.53)	0.83	87	0.320
	115/179	Europeans	1	0.22 (0.03-1.78)	0.15	NA	0.077
TNF-308							
Overall (A vs. G)	1561/1454	Overall	7	1.08 (0.93-1.24)	0.31	28	0.719
	1078/995	Europeans	5	1.08 (0.92-1.27)	0.35	5	0.609
	483/459	Asians	2	0.79 (0.29-2.18)	0.65	76	0.216
Dominant (AA/AG vs. GG)	1245/1154	Overall	6	0.96 (0.69-1.31)	0.78	60	0.793
	842/752	Europeans	4	0.98 (0.66-1.44)	0.90	64	0.638
	403/402	Asians	2	0.77 (0.27-2.22)	0.63	76	0.332
Recessive (AA vs. AG/GG)	1254/1154	Overall	6	1.34 (0.80-2.23)	0.26	15	0.163
	762/695	Europeans	4	1.40 (0.82-2.41)	0.22	32	0.149
	483/459	Asians	2	0.88 (0.18-4.40)	0.88	NA	0.062
Additive (AA vs. GG)	960/896	Overall	6	1.31 (0.78-2.20)	0.31	0	0.163
	567/514	Europeans	4	1.36 (0.79-2.35)	0.27	18	0.148
	393/382	Asians	2	0.93 (0.19-4.64)	0.93	NA	0.062
TNF-1031							
Overall (C vs. T)	735/653	Overall	3	1.24 (0.85-1.79)	0.26	58	0.383
Dominant (CC/CT vs. TT)	735/653	Overall	3	1.12 (0.70-1.78)	0.64	62	0.495
Recessive (CC vs. CT/TT)	735/653	Overall	3	3.19 (1.66-6.13)	0.0005[a]	0	0.101
Additive (CC vs. TT)	587/507	Overall	3	3.15 (1.63-1.07)	0.0006[a]	0	0.101

[a]P≤0.05. NQO1, NAD(P)H-quinone oxidoreductase 1; TNF, tumor necrosis factor; OR, odds ratio; CI, confidence interval; NA, not applicable.

studies with minimal to moderate heterogeneity (I^2<50%) and the random-effects model was used for the studies with significant heterogeneity (I^2≥50%). In addition to the allelic analysis model, the meta-analyses were performed under the dominant, recessive and additive models. Funnel plots were also drawn to observe the potential publication bias. The statistical analyses of the meta-analyses were carried out in Review Manager 5 (The Cochrane Collection, Copenhagen, Denmark) (38).

Results

Data selection. As shown in Fig. 1, nine relevant *NQO1* studies and 16 *TNF* studies were selected from PubMed. In addition, three *NQO1* studies and one *TNF* study from the WanFang literature database, and two *NQO1* studies and one *TNF* study from CNKI were included. Following the removal of the duplicates, two studies with no PD association, nine without genotyping information and two with significant deviation from HWE (P<0.05) in the controls were excluded (Table I). A study was also found from the references in the retrieved literature. Finally, 15 eligible studies (16 stages) (13,14,16-19,21-29) were included in the meta-analyses (Table I).

Meta-analyses of NQO1 and TNF polymorphisms with PD. As shown in Table II, the meta-analysis of the *NQO1* C609T polymorphism included 931 PD patients and 1,126 healthy controls among six studies. The statistical heterogeneity was observed in the meta-analyses of *NQO1* C609T (allelic, I^2=83%; dominant, I^2=88%; recessive, I^2=51%; and additive models, I^2=83%). The frequency of the *NQO1* C609T-C allele in Europeans was 0.788 (HapMap-CEU), which was much higher than that of the Asian population (HapMap-CHB=0.478;

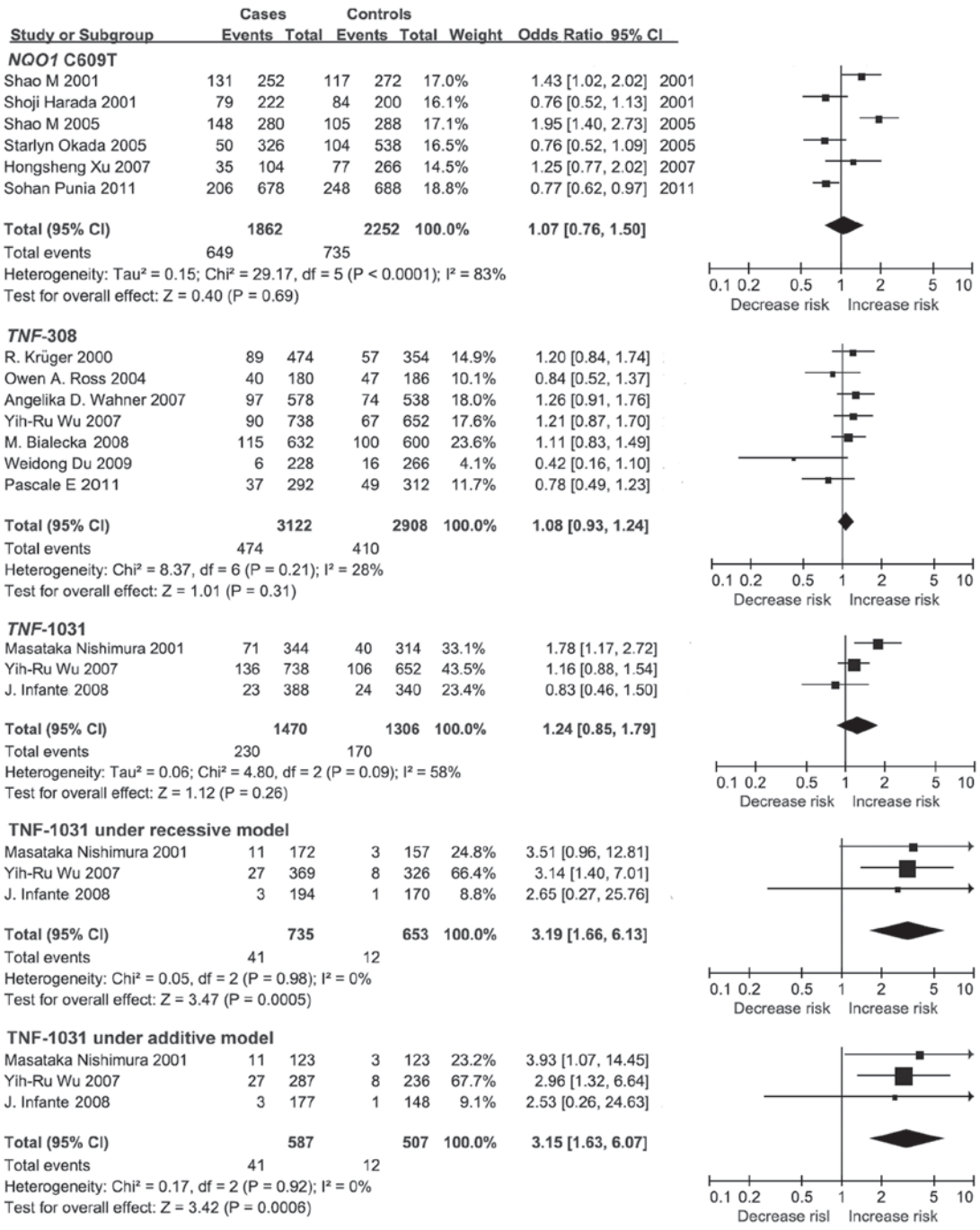

Figure 2. Forest plots of NAD(P)H-quinone oxidoreductase 1 (NQO1) and tumor necrosis factor (TNF) polymorphisms with Parkinson's disease. CI, confidence interval.

HapMap-JPT=0.611). A further analysis showed a difference in ethnicity of the *NQO1* C609T polymorphism between Europeans and Asians (Fst=0.103). As a different genotypic distribution existed in the *NQO1* C609T polymorphism between Europeans and Asians, further subgroup meta-analyses were performed by ethnicity. There was no significant association observed in *NQO1* C609T (P=0.69; OR, 1.07; 95% CI, 0.76-1.50; Table II; Fig. 2), and no significant association was found in other subgroup meta-analyses by genotype and ethnicity (Table II).

Meta-analysis of the *TNF*-308 polymorphism was involved with 3,122 PD patients and 2,908 healthy controls among seven studies (Table II). No significant heterogeneity was found in the meta-analysis under the allelic model (I^2=28%), and no significant association of *TNF*-308 with PD was observed (P=0.31; OR, 1.08; 95% CI, 0.93-1.24; Table II; Fig. 2). Analysis of the association between *TNF*-308 with PD in ethnicity and genetic models was performed, but no positive result was found (Table II).

The meta-analysis of the *TNF*-1031 polymorphism was conducted with 735 PD patients and 653 healthy controls among three studies (Table II). The *TNF*-1031 polymorphism was shown to be a risk factor of PD in the meta-analyses under the recessive (P=0.0005; OR, 3.19; 95% CI, 1.66-6.13) and additive models (P=0.0006, OR, 3.15; 95% CI, 1.63-6.07), however, there was no significant association in the meta-analysis under

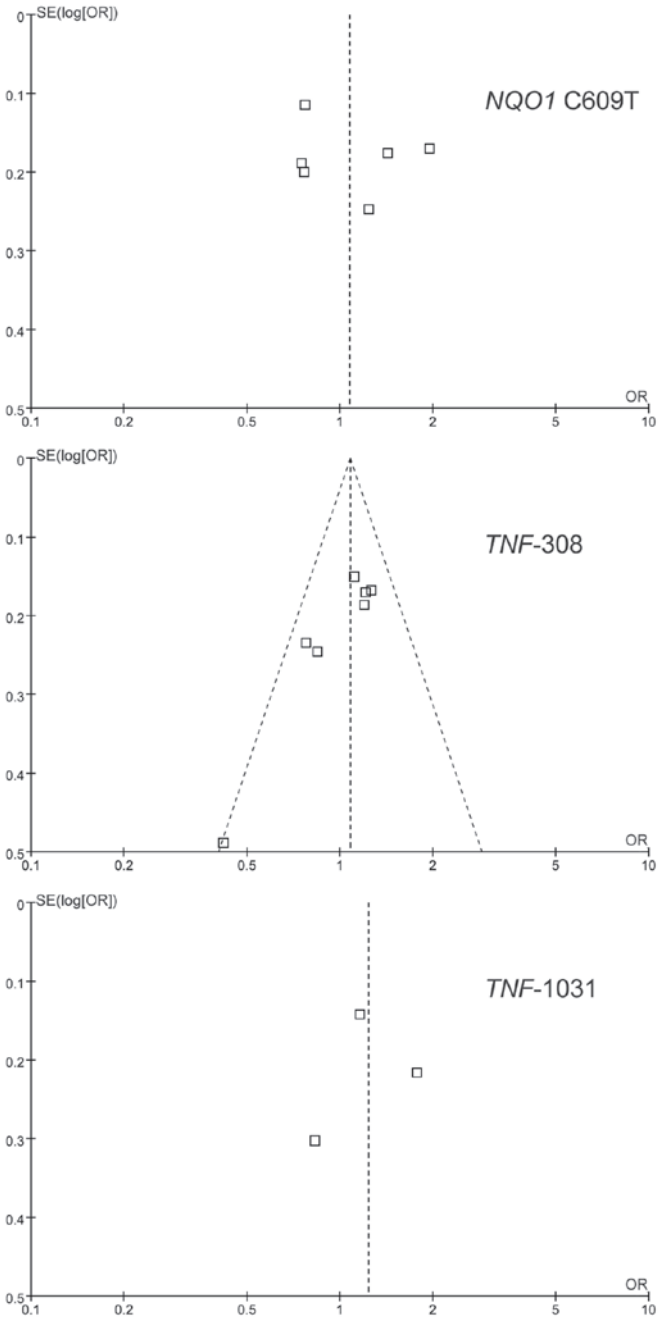

Figure 3. Funnel plots of NAD(P)H-quinone oxidoreductase 1 (NQO1) C609T, tumor necrosis factor (TNF)-308 and TNF-1031. SE, standard error; OR, odds ratio.

the allelic model (P=0.26, OR, 1.24; 95% CI, 0.85-1.79; Table II; Fig. 2). As there were only three studies in the meta-analysis of the *TNF*-1031 polymorphism, the result of this strong association requires interpreting with caution (Table II). No publication bias was found for all the meta-analyses (Fig. 3).

Discussion

To the best of our knowledge, the present study is the first meta-analysis on *NQO1* and *TNF*. The meta-analysis involved 15 studies with 2,858 patients and 2,907 healthy controls. Allelic analysis and genetic models were performed for the meta-analyses and subgroup analyses were also conducted by ethnicity in *NQO1* C609T and *TNF*-308. The power of the study was 0.791 in *NQO1* C609T and 0.719 in *TNF*-308, which were much stronger than each of the original case-control studies (power≤0.373).

There was no significant association observed between *NQO1* C609T and PD. The same conclusion was drawn when a further subgroup study by ethnicity was conducted. The result of *NQO1* C609T was consistent with three involved studies (13,16,18), whereas it was inconsistent with another three involved studies (14,17,19) that had a stronger power. The present meta-analysis draws a more reliable conclusion than the previous studies. Notably, as there were five Asian studies and only one European study (Table I), the conclusion may have shown a deviation to the Asian population, and the lower power of the European data suggested that larger case-control studies are required.

The meta-analysis also suggested that *TNF*-308 had no association for PD. This result is consistent with the majority of previous studies (22-27), and only one study presented an opposing conclusion (21). In comparison to the former studies, the meta-analysis showed a stronger power and involved subgroup analyses by genetic models and ethnicity, which allowed for a more stable and comprehensive conclusion.

TNF-1031 was observed to significantly increase the risk of PD in the recessive and additive models (P=0.0005 and P=0.0006, respectively). *TNF*-1031 is a key polymorphism located in the promoter of *TNF* that influences the transcriptional regulation of TNF production (39). Among the three studies included in the meta-analysis of *TNF*-1031, two studies showed that *TNF*-1031 was associated with an increased risk of PD (24,28). The present meta-analysis may provide novel information for the association between *TNF*-1031 and PD. However, due to the small power of *TNF*-1031, the positive result of *TNF*-1031 should be interpreted with caution.

Certain limitations of the meta-analysis should be considered. Firstly, PD is a complicated disorder influenced by numerous factors, including gender and age differences. The aforementioned information was not provided in the original case-control studies. Thus, a subgroup meta-analysis cannot be performed by gender or age to establish a more credible result. Secondly, there were a number of populations involved in the meta-analyses of *NQO1* C609T (Chinese, Japanese, Indian and American populations), *TNF*-308 (German, Italian, United Kingdom, American, Polish and Chinese populations) and *TNF*-1031 (Chinese, Japanese and Spanish populations). Future studies in other ethnic populations are required to completely assess the contribution of these polymorphisms to PD. Thirdly, the clinical diagnostic accuracy of PD is only 70% (40). Different diagnostic criteria among the various case-control studies may have an impact on the results of the meta-analyses. Fourthly, there are 1,574 polymorphisms on the *NQO1* and *TNF* loci, respectively. The present meta-analyses only focused on specific polymorphisms, *NQO1* (*NQO1* C609T) and *TNF* (*TNF*-308 and *TNF*-1031). These findings may not completely represent the overall contribution of *NQO1* and *TNF* to PD.

In conclusion, the results of the present study indicated that *TNF*-1031 polymorphism may be a risk factor for PD under either the recessive or additive models. However, the meta-analyses did not support the involvement of *NQO1* C609T and *TNF*-308 in the risk of PD.

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