Association between MTHFR genetic polymorphism and Parkinson’s disease susceptibility: a meta-analysis

Abstract: Folate metabolism plays quite a critical role in Parkinson’s disease (PD). Previous published research works have studied the link existing between the folate metabolism genetic polymorphisms and PD susceptibility; nevertheless, the results continue having controversies and inconclusiveness. Accordingly, we carried out the present meta-analysis for the assessment of the potential link between the folate metabolism genetic polymorphisms and the susceptibility to PD. In addition we carried out a literature search in the PubMed, EMBASE, Cochrane Library, and WanFang databases till November 10, 2018. The odds ratios (ORs) with corresponding 95% credible interval (95%CI) were put to use for evaluating the strength of the association of three folate metabolism genetic polymorphism (C677T, A1298C, and A2756G) with the susceptibility to PD. Each statistical analysis was carried out with the use of STATA 15.0. An aggregate of twenty-one case-control investigations were retrieved, which involved 3,944 PD patients and 4,412 controls. We discovered the existence of no substantial link between the C677T and A1298C polymorphism and PD risk in any genetic framework comparisons. With regard to A2756G polymorphism, we discovered that there was an association between the A2756G genetic polymorphism and an augmented threat of PD in the co-dominant genetic model (GG vs. AA: OR=1.86, 95%CI=1.02-3.37, P=0.042) and the recessive genetic model (GG vs. GA+AA: OR=1.90, 95%CI=1.06-3.41, P=0.031). To summarize, our research work indicates that the A2756G polymorphism of the folate metabolism gene had an association with an augmented threat of PD. Also, A1298C polymorphisms is unlikely to significantly contribute towards the susceptibility to PD. Further large-scale case-control studies are still required.

Keywords: Parkinson’s disease; MTHFR; MTR; Polymorphism; Meta-analysis

1 Introduction

Parkinson’s disease (PD) is termed as the second most frequently prevalent neurodegenerative disorder following the Alzheimer’s disease, which impacts approximately 1% of the individuals aged more than 60 across the globe and 4-5% of people aged more than 85 years [1, 2]. Clinically, PD is manifested by the classical motor symptoms, which include not only the tremor, but also the rigidity, bradykinesia, and postural instability, significantly impacting the patients’ quality of life [2, 3]. These medicinal presentations constitute the results of dopaminergic neuron loss in the substantia nigra, leading the lowered degrees of dopamine in the striatum and disrupted motor control. Despite the fact that the reason leading to the neuronal loss is not clear, more and more evidence has suggested that mitochondrial impairment, endothelial damage, inflammatory process, and oxidative stress are considered as playing key roles when it comes to the selective dopaminergic cell death in the brain of those patients, who have PD [4, 5].

Homocysteine (Hcy) has been observed as enhancing mitochondrial dysfunction, apoptosis, and oxidative stress, together with being a contributing determinant in the pathophysiological process to a number of neurodegenerative diseases that include PD [6, 7]. Hcy is a sulfur-containing amino acid, which is derived from the demethylation of methionine by means of the methionine cycle and the folate cycle [8]. Methyleneheterofolate reductase (MTHFR) is a folate-reliant enzyme that cata-
lyzes 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. The output is termed as the dominant form of circulating folate, besides providing a methyl group for the re-methylation of Hcy back to methionine [8]. Three common variants (C677T, A1298C, and A2756G) in the MTHFR gene, which lower the function of MTHFR, in addition to further resulting into the metabolic disruption of Hcy, have been indicated as having association with the risk of patients with PD [8, 9].

A number of case-control investigations have explored the potential link that exists between the MTHFR genetic polymorphisms and susceptibility to PD, but the findings are still inconclusive [9-12]. Hence, we carried out the present meta-analysis in order to clarify the link existing between the MTHFR polymorphisms and susceptibility to PD with the use of qualified data attained from the published case-control research works.

2 Materials and methods

The current meta-analysis was carried out in accordance with the consensus statement of the Meta-analysis of Observational Studies in Epidemiology recommendations [13]. All the analysis was carried out on the basis of previously published works; in this manner, ethical approval and patient consent were not required.

2.1 Identification of eligible studies

A literature search in the PubMed, as well as in the EMBASE, Cochrane Library, and WanFang databases was carried out to figure out the eligible studies, and the latest search was updated in November 2018. The terms presented as follows, together with their combinations,

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**Figure 1:** Flow diagram of included and excluded studies.
were searched: ‘methyleneetetrahydrofolate reductase’ OR ‘MTHFR’ AND ‘Parkinson’s disease’ OR ‘PD’ AND ‘polymorphism*’ OR ‘variant*’. Each of the search was constrained to English or Chinese language papers.

2.2 Inclusion and exclusion

The qualified research works mandatorily require meeting the inclusion criteria as hereunder: (1) evaluate the link existing between the MTHFR polymorphisms and susceptibility to PD; (2) case-control research design; (3) enough amount of data for the calculation of the odds ratios (ORs), coupled with 95 percent confidence interval (95%CI). The research works were not counted on for any of the following reasons: (1) inadequate amount of information for extracting the data; (2) only case study; (3) case reports, reviews, letters; (4) studies carried out in non-humans, and duplicated publication. For the research works having copied data, the biggest or the latest publication was chosen.

2.3 Data extraction

All data were independently extracted by two investigators in accordance with the above-mentioned inclusion criteria. Moreover, the following information was extracted from all of the research works included: the first author, in addition to the year of publication, country, ethnicity, genotype distributions in cases as well as controls, besides the detection methodology of genotypes. The disagreement existing between scholars were removed through the consultation with a 3rd scholar.
2.4 Statistical analysis

The Hardy-Weinberg equilibrium (HWE) was calculated by the Chi-squared test in control groups in all of the research works; the P-value more than 0.001 demonstrated that the population was in genetic equilibrium. Besides that, the odds ratios (ORs) that had 95 percent confidence interval (CI) were adopted for the purpose of calculating the strength of the link between PD susceptibility and the MTHFR polymorphisms. The importance associated with the accumulated OR was investigated in accordance with the Z-test; in addition, \( P < 0.05 \) was regarded as having statistical significance. The evaluation of the between-study heterogeneity was carried out with the help of the Q-test as well as \( I^2 \) statistics [14]. Moreover, the application of the fixed-effects framework was made at \( P_h > 0.1 \) or \( I^2 < 50\% \) [15]; or else, the random-effects framework was followed [16]. The sensitivity analysis was carried out through the omission of the single research work always for the evaluation of the robustness of the findings. Also, the underlying publication partiality was assessed with the help of the Begg’s funnel plots and Egger’s test [17, 18]. All of the statistical analysis was carried out with the use of the STATA version 15.0 software (Stata Corporation, College Station, TX, USA). A \( P \)-value below 0.05 was regarded as having statistical significance.

3 Results

3.1 Study characteristics

The flow chart presented in Figure 1 shed light on the research selection mechanism. An aggregate of 256 papers were figured out by means of the preliminary search of databases. In accordance with the inclusion and exclusion criteria presented earlier, an aggregate of 21 case-control research works, which involved 3,944 PD patients and 4,412 controls, were included [10-12, 19-36]. Among the selected studies, 20 studies involving 3,712 PD patients and 4,167 controls were carried out for the purpose of evaluating MTHFR C677T polymorphism [10-12, 19-35]; 10 studies were carried out for the assessment of MTHFR

### Table 1: Main characteristics of included studies in this meta-analysis.

| Author          | Year | Country | Ethnicity | Control Source | Sample Size | Genotyping Methods | HWE in controls |
|-----------------|------|---------|-----------|----------------|-------------|--------------------|-----------------|
| Dorszewska      | 2007 | Poland  | Caucasian | PB            | 98          | PCR-RFLP           | 0.495           |
| Lin             | 2007 | China   | Asian     | PB            | 94          | PCR-RFLP           | 0.410           |
| Yasui           | 2000 | Japan   | Asian     | PB            | 90          | PCR               | 0.194           |
| Harmon          | 1997 | Ireland | Caucasian | PB            | 188         | PCR               | 0.132           |
| Bialecka        | 2012 | Poland  | Caucasian | HB            | 320         | PCR-RFLP           | 0.855           |
| Caccamo         | 2007 | Italy   | Caucasian | PB            | 49          | PCR               | 0.376           |
| Camiciolli      | 2009 | Canada  | Caucasian | HB            | 51          | PCR               | 0.804           |
| Fong            | 2011 | China   | Asian     | HB            | 211         | PCR               | 0.494           |
| Wullner          | 2005 | Germany | Caucasian | NA           | 342         | PCR               | 0.021           |
| Garcia          | 2015 | Mexico  | Caucasian | PB            | 140         | TaqMan            | 0.118           |
| Gorgone         | 2012 | Italy   | Caucasian | PB            | 60          | PCR               | 0.430           |
| Kumuduni        | 2014 | India   | Asian     | PB            | 151         | PCR-RFLP           | 0.352           |
| Liao            | 2014 | China   | Asian     | PB            | 765         | PCR               | 0.013           |
| Religa          | 2006 | Poland  | Caucasian | HB            | 114         | PCR               | 0.901           |
| Rodriguez-Oroz  | 2009 | Spain   | Caucasian | PB            | 77          | PCR-RFLP           | 0.748           |
| Todorovic       | 2006 | Serbia  | Caucasian | PB            | 113         | PCR               | 0.583           |
| Yuan            | 2016 | China   | Asian     | PB            | 512         | PCR               | 0.347           |
| Yuan            | 2009 | China   | Asian     | HB            | 76          | PCR-RFLP           | 0.652           |
| Zahra           | 2016 | Malta   | Caucasian | PB            | 100         | PCR               | 0.382           |
| Chao            | 2014 | China   | Asian     | HB            | 161         | PCR               | 0.198           |
| Momose          | 2002 | Japan   | Asian     | PB            | 232         | PCR               | 0.849           |

**Abbreviations:** HWE, Hardy-Weinberg equilibrium; PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; PB, Population-based; HB, Hospital-based.
MTHFR polymorphism and Parkinson’s disease susceptibility

A1298C polymorphism with an aggregate of 1,861 PD patients, together with 1,987 controls [12, 19, 23-25, 27, 31, 33, 34, 36]; 4 research works that contained 541 PD patients as well as 709 controls, were performed for the purpose of evaluating MTHFR A2756G polymorphism [19, 26, 29, 31]. Moreover, the key attributes of all of the investigations and HWE examination results were presented in Table 1. The allocations of the MTHFR genetic mutation in controls were observed as showing consistency with HWE in all studies (P>0.001).

3.2 MTHFR C677T and PD Susceptibility

With regard to the MTHFR C677T polymorphism, as revealed by the meta-analysis, there was no statistically significant association in any of the genetic frameworks in the population, in general (Figure 2A). For the stratification in accordance with ethnicity, no substantial link in any of the genetic frameworks in Caucasians or Asians (Figure 2B) was observed. In the meantime, we conducted the stratified analysis in accordance with the source of controls, substantially augmenting the risk of PD discovered in the allelic genetic framework (T vs. C: OR=1.18, 95%CI=1.01-1.39, P=0.043), co-dominant genetic framework (TC vs. CC: OR=1.24, 95%CI=1.02-1.51, P=0.034), and dominant genetic framework (TT+TC vs. CC: OR=1.27, 95%CI=1.03-1.55, P=0.023) in the hospital-based study (Figure 2C and 2D). Table 2 summarizes the meta-analysis findings between MTHFR C677T polymorphism and PD susceptibility.

| Genetic models | Study subjects | No. of studies | OR (95%CI) | p-meta | Test of heterogeneity | Test of Egger’s |
|----------------|----------------|----------------|------------|--------|----------------------|----------------|
|                |                |                |            |        |                       |                |
| T vs. C        |                |                |            |        |                       |                |
| Overall        | 20             | 1.07(0.94-1.22)| 0.297      | 66.5   | <0.001               | R              | 0.206 |
| Asian          | 8              | 1.08(0.89-1.32)| 0.429      | 71.8   | 0.001                | R              |
| Caucasian      | 12             | 1.06(0.89-1.27)| 0.497      | 61.0   | 0.003                | R              |
| PB             | 13             | 1.03(0.86-1.22)| 0.781      | 69.6   | <0.001               | R              |
| HB             | 6              | 1.18(1.01-1.39)| 0.043      | 22.5   | 0.265                | R              |
| TC vs. CC      |                |                |            |        |                       |                |
| Overall        | 20             | 1.06(0.90-1.25)| 0.494      | 56.3   | 0.001                | R              | 0.581 |
| Asian          | 8              | 1.06(0.81-1.40)| 0.676      | 70.9   | 0.001                | R              |
| Caucasian      | 12             | 1.09(0.90-1.30)| 0.377      | 23.4   | 0.213                | R              |
| PB             | 13             | 0.93(0.76-1.16)| 0.491      | 48.6   | 0.025                | F              |
| HB             | 6              | 1.24(1.02-1.51)| 0.034      | 0      | 0.426                | F              |
| TT vs. CC      |                |                |            |        |                       |                |
| Overall        | 20             | 1.08(0.83-1.42)| 0.567      | 58.6   | 0.001                | R              | 0.064 |
| Asian          | 8              | 1.07(0.74-1.54)| 0.719      | 53.9   | 0.034                | R              |
| Caucasian      | 12             | 1.05(0.70-1.57)| 0.812      | 62.3   | 0.002                | R              |
| PB             | 13             | 1.03(0.70-1.52)| 0.878      | 66.3   | <0.001               | R              |
| HB             | 6              | 1.30(0.96-1.77)| 0.094      | 0      | 0.469                | R              |
| TT+TC vs. CC   |                |                |            |        |                       |                |
| Overall        | 20             | 1.08(0.91-1.29)| 0.386      | 64.6   | <0.001               | R              | 0.075 |
| Asian          | 8              | 1.09(0.82-1.45)| 0.547      | 75.3   | <0.001               | R              |
| Caucasian      | 12             | 1.09(0.88-1.34)| 0.442      | 45.0   | 0.045                | R              |
| PB             | 13             | 0.98(0.78-1.22)| 0.842      | 63.5   | 0.001                | R              |
| HB             | 6              | 1.27(1.03-1.55)| 0.023      | 11.5   | 0.342                | R              |
| TT vs. CC+CT   |                |                |            |        |                       |                |
| Overall        | 20             | 1.06(0.86-1.30)| 0.942      | 43.3   | 0.021                | F              | 0.186 |
| Asian          | 8              | 0.99(0.79-1.24)| 0.926      | 15.5   | 0.308                | R              |
| Caucasian      | 12             | 1.04(0.74-1.47)| 0.814      | 55.9   | 0.009                | R              |
| PB             | 13             | 1.07(0.78-1.45)| 0.690      | 56.6   | 0.006                | R              |
| HB             | 6              | 1.17(0.88-1.54)| 0.283      | 0      | 0.557                | R              |

**Abbreviations:** Bold values indicate statistically significant results; OR, Odds ratio; CI, Confidence interval; p-meta, p-value of pooled effect; R, Random-effect model; F, Fixed-effect model;

A1298C polymorphism with an aggregate of 1,861 PD patients, together with 1,987 controls [12, 19, 23-25, 27, 31, 33, 34, 36]; 4 research works that contained 541 PD patients as well as 709 controls, were performed for the purpose of evaluating MTHFR A2756G polymorphism [19, 26, 29, 31]. Moreover, the key attributes of all of the investigations and HWE examination results were presented in Table 1. The allocations of the MTHFR genetic mutation in controls were observed as showing consistency with HWE in all studies (P>0.001).
3.3 MTHFR A1298C and PD Susceptibility

With regard to MTHFR A1298C polymorphism, the findings, on the basis of all of the involved research works, did not provide any proof of a link between MTHFR A1298C polymorphism and PD risk in any of the genetic framework in the population, in general (Figure 3A). For the stratified analysis in accordance with ethnicity, no substantial link in any genetic models in Caucasians or Asians (Figure 3B) was discovered. In the subgroup analysis in accordance with the source of controls, the significantly augmented susceptibility of PD was discovered in the allelic genetic framework (C vs. A: OR=1.17, 95%CI=1.02-1.35, P=0.029), co-dominant genetic model (CA vs. AA: OR=1.25, 95%CI=1.04-1.51, P=0.016), and dominant genetic model (TT+TC vs. CC: OR=1.25, 95%CI=1.05-1.49, P=0.014) in the population-based study (Figure 3C and 3D). Table 3 provides the summary of the findings of comparisons.

3.4 MTHFR A2756G and PD Susceptibility

In terms of MTHFR A2756G polymorphism, there was statistically significant association discovered in the co-dominant genetic model (GG vs. AA: OR=1.86, 95%CI=1.02-3.37, P=0.042) and recessive genetic model (GG vs. AA+AG: OR=1.90, 95%CI=1.06-3.41, P=0.031) in the overall population (Figure 4A and 4B). With regard to the subgroup analysis in accordance with ethnicity, we found no substantial link in any genetic models in Caucasians or Asians. Additionally, in the subgroup analysis in accordance with the source of controls, MTHFR A2756G polymorphism was found to be linked to the increased susceptibility of PD
Table 3: Summary ORs and 95%CI of the association between A1298C polymorphism and Parkinson disease susceptibility.

| Genetic models          | Study subjects | No. of studies | OR (95%CI)                  | p-meta | Test of heterogeneity | Test of Egger's |
|-------------------------|----------------|----------------|----------------------------|--------|------------------------|-----------------|
|                         |                |                |                            |        | F                      | Model           |
|                         |                |                |                            |        | 0.275                  |                 |
| C vs. A                 | Overall        | 10             | 1.02 (0.92-1.14)           | 0.652  | 26.4                   | 0.201           | F               |
|                         | Asian          | 3              | 1.15 (0.97-1.36)           | 0.115  | 0                      | 0.631           | F               |
|                         | Caucasian      | 7              | 0.96 (0.84-1.09)           | 0.503  | 29.7                   | 0.201           | F               |
|                         | PB             | 6              | 1.17 (1.02-1.35)           | 0.029  | 0                      | 0.869           | F               |
|                         | HB             | 3              | 0.93 (0.75-1.15)           | 0.515  | 10.3                   | 0.328           | F               |
| CA vs. AA               | Overall        | 10             | 1.11 (0.97-1.28)           | 0.144  | 0                      | 0.608           | F               |
|                         | Asian          | 3              | 1.17 (0.95-1.45)           | 0.131  | 0                      | 0.638           | F               |
|                         | Caucasian      | 7              | 1.06 (0.88-1.28)           | 0.542  | 0                      | 0.439           | F               |
|                         | PB             | 6              | 1.25 (1.04-1.51)           | 0.016  | 0                      | 0.738           | F               |
|                         | HB             | 3              | 0.95 (0.71-1.26)           | 0.703  | 0                      | 0.734           | F               |
| CC vs. AA               | Overall        | 10             | 0.93 (0.72-1.19)           | 0.557  | 0                      | 0.491           | F               |
|                         | Asian          | 3              | 1.21 (0.75-1.94)           | 0.437  | 0                      | 0.830           | F               |
|                         | Caucasian      | 7              | 0.83 (0.62-1.13)           | 0.237  | 5.4                    | 0.386           | F               |
|                         | PB             | 6              | 1.24 (0.86-1.79)           | 0.251  | 0                      | 0.975           | F               |
|                         | HB             | 3              | 0.85 (0.52-1.40)           | 0.527  | 6.1                    | 0.345           | F               |
| CC+CA vs. AA            | Overall        | 10             | 1.08 (0.95-1.23)           | 0.261  | 11.5                   | 0.337           | F               |
|                         | Asian          | 3              | 1.18 (0.97-1.44)           | 0.107  | 0                      | 0.611           | F               |
|                         | Caucasian      | 7              | 1.01 (0.84-1.20)           | 0.942  | 23.4                   | 0.250           | F               |
|                         | PB             | 6              | 1.25 (1.05-1.49)           | 0.014  | 0                      | 0.757           | F               |
|                         | HB             | 3              | 0.93 (0.71-1.22)           | 0.603  | 0                      | 0.505           | F               |
| CC vs. AA+AC            | Overall        | 10             | 0.88 (0.69-1.12)           | 0.310  | 0                      | 0.726           | F               |
|                         | Asian          | 3              | 1.15 (0.72-1.84)           | 0.561  | 0                      | 0.873           | F               |
|                         | Caucasian      | 7              | 0.80 (0.60-1.06)           | 0.124  | 0                      | 0.656           | F               |
|                         | PB             | 6              | 1.09 (0.76-1.54)           | 0.642  | 0                      | 0.973           | F               |
|                         | HB             | 3              | 0.87 (0.54-1.41)           | 0.574  | 0                      | 0.427           | F               |

Abbreviations: Bold values indicate statistically significant results; OR, Odds ratio; CI, Confidence interval; p-meta, p-value of pooled effect; R, Random-effect model; F, Fixed-effect model; NA, Not available.

in the co-dominant genetic model (GG vs. AA: OR=2.22, 95%CI=1.10-4.49, P=0.027) and recessive genetic model (GG vs. AA+AG: OR=2.29, 95%CI=1.15-4.56, P=0.018) in the population-based study (Figure 4C and 4D). Table 4 presents the summary findings of comparisons.

3.5 Sensitivity analysis

For the purpose of assessing the stability of the findings of the meta-analysis, we carried out a sensitivity analysis with the help of the sequentially excluded separate research works. The results, having statistical similarity, were attained subsequent to the sequential exclusion of all studies (Figure 5).

3.6 Publication bias

The evaluation of the publication bias was carried out in accordance with the Begg’s funnel plots and Egger’s test. None of the shapes of the funnel plots indicated any proof of significant asymmetry (Figure 6). Nevertheless, the Egger’s test yielded no proof suggesting publication bias. Moreover, the key results as presented in Table 2-4.

4 Discussion

Parkinson’s disease (PD) is termed as a frequently found neurodegenerative illness that symptoms worsened gradually, ultimately impacting the quality of life of patients. As fully acknowledged, PD is termed as a multifactorial illness, which is a result of intricate gene-gene and
gene-environment contacts [37]. Even though the therapy steps have advanced continuously for controlling symptoms, so far no methodology exists for the prevention of the incidence of PD. The latest observations have shed light on the involving homocysteine (Hcy) in the pathogenesis of PD [6, 8, 38]. There are some research works that have discovered an augmented incidence of the illness in those subjects, who carry the MTHFR genotype and identified a major role for Hcy in the promotion of the susceptibility and growth of PD; on the other hand, other research works reached the contrary conclusion [11, 12, 24, 26, 34].

The MTHFR gene is located on chromosome 1p36.3 spanning more than 20 kb and containing a noncoding exon as well as 11 coding exons [39]. In addition, the encoded enzyme catalyzes the conversion of 5,10-methylenetetrahydrofolate, a carbon donor in nucleotide biosynthesis, to 5-methyltetrahydrofolate, the key form of circulatory folate, together with providing a methyl group for the re-methylation of Hcy back to methionine [8]. Genetic mutations in the MTHFR gene have the potential to causing the autosomal recessive homocystinuria because of the MTHFR shortage. In addition, gene variants have been extensively studied in lots of illness, which also include PD.

Even though the augmented number of case-control research works studied the link between MTHFR genetic polymorphism and PD risk; however, the findings remain controversial. In the year 2014, a large case-control study by Liao was conducted for the purpose of investigating the function of the MTHFR genetic polymorphism in PD susceptibility and the results demonstrated that the MTHFR C677T genetic polymorphism had an association with the decreased PD susceptibility [26]. Fong et al. carried out study for the discovery of the link of MTHFR genetic polymorphism with PD susceptibility; the results shed light on

| Genetic models | Study subjects | No. of studies | OR (95%CI) | p-meta | Test of heterogeneity | Test of Egger's |
|----------------|----------------|----------------|-----------|---------|-----------------------|----------------|
| G vs. A        | Overall        | 4              | 1.09(0.90-1.33) | 0.373   | 0         | 0.699 | F | 0.748 |
|                | Asian          | 2              | 1.09(0.88-1.35) | 0.428   | 0         | 0.687 | F |
|                | Caucasian      | 2              | 1.11(0.68-1.79) | 0.683   | 21.0      | 0.260 | F |
|                | PB             | 3              | 1.13(0.88-1.44) | 0.343   | 0         | 0.527 | F |
|                | HB             | 1              | 1.04(0.75-1.44) | 0.818   | NA        | NA   | F |
| GA vs. AA      | Overall        | 4              | 0.96(0.75-1.23) | 0.742   | 0         | 0.943 | F | 0.406 |
|                | Asian          | 2              | 0.97(0.74-1.28) | 0.852   | 0         | 0.747 | F |
|                | Caucasian      | 2              | 0.90(0.51-1.59) | 0.711   | 0         | 0.642 | F |
|                | PB             | 3              | 0.92(0.67-1.27) | 0.614   | 0         | 0.892 | F |
|                | HB             | 1              | 1.02(0.69-1.51) | 0.921   | NA        | NA   | F |
| GG vs. AA      | Overall        | 4              | **1.86(1.02-3.37)** | **0.042** | 0        | 0.525 | F | 0.943 |
|                | Asian          | 2              | 1.76(0.93-3.32) | 0.084   | 0         | 0.408 | F |
|                | Caucasian      | 2              | 2.53(0.45-14.21) | 0.292   | 40.3      | 0.195 | F |
|                | PB             | 3              | **2.22(1.10-4.49)** | **0.027** | 0        | 0.450 | F |
|                | HB             | 1              | 1.20(0.39-3.69) | 0.744   | NA        | NA   | F |
| GG+GA vs. AA   | Overall        | 4              | 1.02(0.80-1.30) | 0.856   | 11.5      | 0.887 | F | 0.582 |
|                | Asian          | 2              | 1.03(0.79-1.35) | 0.827   | 0         | 0.987 | F |
|                | Caucasian      | 2              | 0.99(0.57-1.73) | 0.972   | 23.4      | 0.430 | F |
|                | PB             | 3              | 1.02(0.75-1.38) | 0.919   | 0         | 0.727 | F |
|                | HB             | 1              | 1.03(0.70-1.52) | 0.870   | NA        | NA   | F |
| GG vs. AA+AG   | Overall        | 4              | **1.90(1.06-3.41)** | **0.031** | 0        | 0.518 | F | 0.933 |
|                | Asian          | 2              | 1.79(0.96-3.35) | 0.066   | 0         | 0.366 | F |
|                | Caucasian      | 2              | 2.62(0.47-14.66) | 0.274   | 36.7      | 0.209 | F |
|                | PB             | 3              | **2.29(1.15-4.56)** | **0.018** | 0        | 0.472 | F |
|                | HB             | 1              | 1.20(0.39-3.62) | 0.752   | NA        | NA   | F |

**Abbreviations:** Bold values indicate statistically significant results; OR, Odds ratio; CI, Confidence interval; p-meta, p-value of pooled effect; R, Random-effect model; F, Fixed-effect model; NA, Not available.
The fact that the augmented PD susceptibility is expected to have more significance in the carriers that have the polymorphisms of MTHFR gene [26].

The present meta-analysis is carried out on the basis of the systematic review, which follows the PRISMA guidelines. The robustness of a systematic review involves including the papers that are not based on the selection of authors but the number of papers retrieved from electronic databases. That is why it depends not only on the quality but also the specimen size of investigations involved in the systematic review. Furthermore, a meta-analysis is termed as a methodology pooling the effect sizes of the current scientific literature. A meta-analysis can be carried out on two or more papers. Therefore, it is of great significance to perform a meta-analysis of all of the qualified research works for the clarification of the impacts of the MTHFR genetic polymorphism with PD susceptibility.

As illustrated by the current meta-analysis, the A2756G polymorphism in MTHFR gene had an association with an increased risk of PD. However, the C677T and A1298C polymorphisms are not likely to perform a significant function in the risk to PD. Moreover, the meta-analysis carried out by Liu et al. in the year 2018 demonstrated that MTHFR (C677T and A1298C) polymorphism is likely to have an association with the augmented PD susceptibility, which was different from our result [40].

The possible constraints of the meta-analysis require consideration. At first, the specimen in this meta-analysis was small in size, which was likely to give rise to the partiality of the findings in the course of the evaluation of the link between MTHFR genetic polymorphisms and risk to PD. Second, the genuine data in some of the research works was deficient that was likely to constrain enough statistical power for the evaluation of the underlying impacts of

Figure 4: Forest plot of the association between MTHFR A2756G polymorphism and PD susceptibility: (A) co-dominant and (B) recessive genetic model in the overall populations; (C) co-dominant and (D) recessive genetic model, stratified by source of control.

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gene-gene and gene-environment contacts on the growth of PD. Third, the meta-analysis just counts on the research works that were published in English or Chinese that are likely to give rise to the selection partiality in the accumulated findings. Fourthly, a substantial difference exists in numbers between PD cases and controls that is likely to exert an influence on the dependability of our findings. Based on the above reasons, the pooled estimates of our meta-analysis require careful interpretation.

To conclude, the current meta-analysis illustrated the fact that the MTHFR A2756G genetic polymorphism confers susceptibility to PD, but no link was observed to exist between the C677T and A1298C polymorphisms and PD susceptibility. More efficiently formulated investigations, which have larger specimens, are required for the purpose of clarifying the link of the MTHFR genetic polymorphism with PD risk.
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Figure 6: Begg's funnel plots of publication bias for the association between MTHFR genetic polymorphism and PD: (A) allelic and (B) co-dominant genetic model for C677T polymorphism; (C) allelic and (D) co-dominant genetic model for A1298C polymorphism.
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