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*Original Article*

# Catechol-O-methyl transferase SNP rs4680 influence risk of mood disorder: a meta-analysis

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**Abstract:** Background: The association between Val158Met (rs4680) polymorphism in the catechol-O-methyl transferase (COMT) gene and mood disorder (MD) risk remains controversial and inconclusive. Therefore, a meta-analysis involving latest relevant studies was performed to assess the quality reevaluation of their association. Methods: Six major public databases (Medline, Embase, Cochrane Library, China National Knowledge Infrastructure, Wangfang and CBM) were searched for eligible studies. Pooled odds ratios (OR) with 95% confidence intervals were calculated to estimate the association between COMT Val158Met mutation and mood disorder risk. Results: Our meta-analysis results indicate that the COMT rs4680 Met carrier was associated with increased risks of bipolar disorder (BPD) and major depressive disorder (MDD). Similarly, a subgroup analysis based on ethnicity suggests that COMT rs4680 polymorphism only influenced BPD risk in the Asian subgroup, and increased MDD risk in both the Asian and Caucasian subgroups. However, the influence of COMT rs4680 gene polymorphism on BPD and MDD risks varied in other subgroups. Limitations: Our results should be treated with caution due to the lack of data to perform gene-gene and gene-environment interactions. In addition, some subgroups lack a more in-depth meta-analysis. Conclusions: This meta-analysis study indicates that COMT rs4680 polymorphism may play a role in BPD and MDD development.

**Keywords:** Catechol-O-methyl transferase, meta-analysis, mood disorder, SNP

## Introduction

Mood disorders (MDs) include all types of depressions and bipolar disorders (BPDs). As described in the classification system of the Diagnostic and Statistical Manual of Mental Disorders, MD affects thoughts, emotions and behavior; which appears to be the most prominent causes of disability and disease burden [1, 2]. According to the World Health Organization, unipolar disorder accounts for the loss of 65.5 million disability-adjusted life years (DALYs) and ranks third among the leading causes of global disease burden. More specifically, major depressive disorder (MDD) has been believed to be one of the major factors that contributes to DALYs [3-5]. A number of studies have revealed that MD is a multifactorial disease, and that genetic factors play an important role in its pathogenesis. The heritability of bipolar disorder is estimated at 90%, while unipolar disorder is approximately 40% [6, 7].

Molecular genetic studies have identified a number of gene variants that appeared to affect mood disorders [8]. In particular, genes involved in dopaminergic pathways have received broad attention. Among them, the catechol-O-methyl-transferase (COMT) gene has been extensively investigated. The COMT gene inactivates dopamine and norepinephrine by catalyzing the transfer of a methyl group from S-adenosyl-methionine. It is located in human chromosome 22 and mapped at the 22q11.1-q11.2 position [9, 10]. The size of this gene is approximately 27 kb, and approximately 345 different polymorphisms have been identified in this gene. In recent years, a particular polymorphism (rs4680) within this gene has been

**Table 1.** Methodological quality of included studies according to the newcastle-ottawa scale

| Studies | Adequacy of case definition | Representativeness of the case | Selection of controls | Definition of controls | Comparability | Ascertainment of exposure | Same method of ascertainment |
|---|---|---|---|---|---|---|---|
| BPD | | | | | | | |
| BIOMED [38] | * | NG | * | | * | * | * |
| Lachman et al. [11] | * | NG | NG | * | NG | * | * |
| Gutierrez et al. [39] | * | NG | NG | * | * | * | * |
| Kunugi et al. [40] | * | NG | NG | * | * | * | * |
| Li et al. [41] | * | NG | NG | * | * | * | * |
| Ohara et al. [42] | * | NG | * | * | NG | * | * |
| Kirov et al. [43] | * | NG | NG | NG | * | * | * |
| Mynett-Johnson et al. [34] | * | NG | * | NG | * | * | * |
| Rotondo et al. [44] | * | NG | * | NG | * | * | * |
| Dickerson et al. [45] | * | NG | NG | NG | * | * | * |
| Prata et al. [46] | * | NG | NG | NG | * | * | * |
| Van Den Bogaert et al. [47] | * | NG | | | * | * | * |
| Burdick et al. [48] | * | NG | NG | * | NG | * | * |
| Zhang et al. [16] | * | NG | NG | * | * | * | * |
| Benedetti et al. [18] | * | NG | * | NG | * | * | * |
| Lee et al. [17] | * | NG | * | * | * | * | * |
| Virit et al. [49] | * | NG | NG | * | * | * | * |
| MDD | | | | | | | |
| Kunugi et al. [40] | * | NG | NG | * | * | * | * |
| Ohara et al. [42] | * | NG | * | * | NG | * | * |
| Frisch et al. [50] | * | NG | NG | | * | * | * |
| Potter et al. [51] | * | NG | * | * | NG | * | * |
| Illi et al. [21] | * | NG | * | NG | * | * | * |
| Kocabas et al. [52] | * | NG | * | NG | * | * | * |
| Åberg et al. [19] | * | * | * | * | * | * | * |
| Qin et al. [53] | * | * | NG | * | * | * | * |
| Wang et al. [20] | * | NG | * | * | NG | * | * |
| Shen et al. [15] | * | * | * | * | NG | * | * |

*: Given; NG: Not given.

widely studied. This polymorphism is due to the mutation of nucleotide G to A at codon 158 of this gene, which results in the substitution of amino acid valine to methionine [11]. This mutation impairs the functional ability of the enzyme to catabolize dopamine [12]. To date, rs4680 has been the most extensively studied variant within this gene. Nevertheless, some studies have also highlighted the role of other variants within the COMT gene in modulating the functional ability of this enzyme or its expression in the brain [13, 14].

In the past few years, a number of studies have investigated the association of COMT polymorphisms with depression and BPD [15, 16]. A meta-analysis study carried out by Zhang and his colleagues revealed a significant association between rs4680 and BPD [16]. However, they only included studies up to 2008 and did not consider relevant articles published in Chinese databases. Since 2008, some new studies that evaluated the association of COMT rs4680 polymorphism with BPD have been published; and these studies analyzed an additional 1,301 subjects (773 cases and 528 controls) [17, 18]. Surprisingly, some of these studies did not show a positive association between COMT rs4680 polymorphism and BPD [17]. Thus, these conflicting reports and lack of additional meta-analysis studies led us to investi-

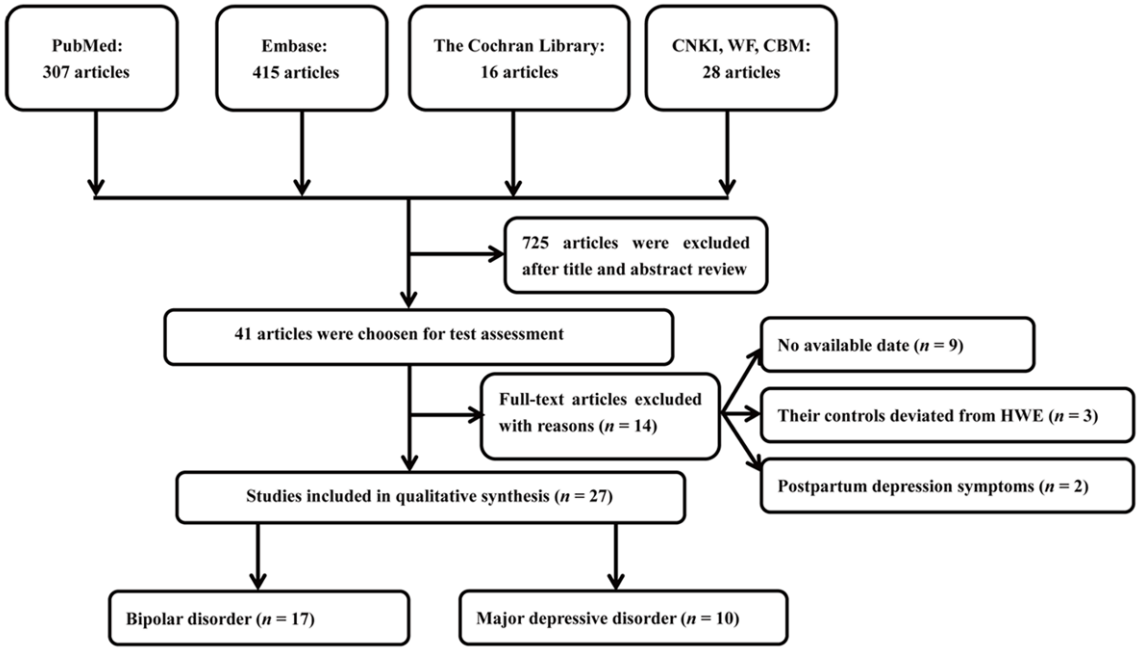


**Figure 1.** Flowchart depicting the detailed screening process for identifying studies.

gate whether the association between COMT rs4680 polymorphism and BPD remains significant. In the present study, we performed a meta-analysis of all studies published from 1997 to November 2014 to validate the association between COMT rs4680 polymorphism and BPD. These data were further analyzed on the basis of ethnicity, gender, BPD type and first episode of BPD.

Similarly, COMT rs4680 polymorphism has also been linked as a predisposing factor for MDD. However, results were again conflicting and inconclusive. Some studies reported a significant association between COMT rs4680 polymorphism and MDD risk [15, 19], while other studies did not find any significant difference in allele or genotype frequency for COMT rs4680 polymorphism [20, 21]. The inconsistency in these published findings could be due to different factors such as: (a) different ethnicities of the studied populations, or (b) quality and statistical power of these primary studies. Since there has been neither a systematic review nor meta-analysis on the association between COMT rs4680 polymorphism and MDD, we performed a systematic review and a meta-analysis of all available studies that suggested an association between COMT rs4680 gene polymorphism and MDD.

## Materials and methods

### *Search strategy*

Articles regarding the association between COMT rs4680 polymorphism and MD risk were searched up to November 8, 2014 in the following databases: Medline by PubMed, Embase by Ovid, The Cochrane Library, China National Knowledge Infrastructure (CNKI), Wangfang and CBM. The following keywords were used for the search: *MD or depression or mood disorder or affective disorder or depressive disorder or bipolar disorder or unipolar disorder or manic or major depressive disorders or major depression* and *COMT or catechol-O-methyl transferase or rs4680 or Val158Met* and *polymorphism or polymorphisms or SNP or variation*. In order to identify relevant publications, cross-references of the searched articles were also screened.

### *Inclusion and exclusion criteria*

The abstracts of all relevant citations and retrieved studies were reviewed. A study was included in the meta-analysis when it contains the following information: (a) case-controls for evaluating COMT rs4680 polymorphism and MD risk; (b) useful genotype frequency; (c) commonly acceptable diagnosis criteria; and (d)

**Table 2.** Study characteristics included in meta-analysis

| Reference | Year | Ethnicity | MD types | Genotype-case (patient) | | | Genotype-case (control) | | | HWE |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Val/Val | Val/Met | MET/Met | Val/Val | Val/Met | MET/Met | |
| BIOMED | 1997 | Caucasians | BPD | 97 | 215 | 100 | 105 | 172 | 91 | Yes |
| Lachman et al. | 1997 | Caucasians | BPD | 20 | 35 | 8 | 30 | 44 | 13 | Yes |
| Gutierrez et al. | 1997 | Caucasians | BPD | 31 | 38 | 19 | 35 | 57 | 21 | Yes |
| Kunugi et al. | 1997 | Caucasians | BPD | 24 | 53 | 30 | 29 | 62 | 30 | Yes |
| Li et al. | 1997 | Caucasians | BPD | 44 | 41 | 8 | 66 | 29 | 3 | Yes |
| Ohara et al. | 1998 | Asian | BPD | 15 | 22 | 3 | 58 | 59 | 18 | Yes |
| Kirov et al. | 1998 | Caucasians | BPD | 49 | 78 | 38 | 41 | 81 | 37 | Yes |
| Mynett-Johnson et al. | 1988 | Caucasians | BPD | 28 | 73 | 46 | 46 | 65 | 36 | Yes |
| Rotondo et al. | 2002 | Caucasians | BPD | 30 | 45 | 36 | 47 | 61 | 19 | Yes |
| Dickerson et al. | 2006 | Caucasians | BPD | 41 | 39 | 27 | 33 | 40 | 22 | Yes |
| Prata et al. | 2006 | Caucasians | BPD | 54 | 110 | 45 | 45 | 97 | 51 | Yes |
| Bogaert et al. | 2006 | Caucasians | BPD | 32 | 96 | 54 | 81 | 172 | 111 | Yes |
| Burdick et al. | 2007 | Caucasians | BPD | 14 | 29 | 9 | 29 | 47 | 26 | Yes |
| Zhang et al. | 2009 | Asian | BPD | 230 | 196 | 52 | 267 | 176 | 26 | Yes |
| Benedetti et al. | 2011 | Asian | BPD | 45 | 87 | 31 | 29 | 62 | 30 | Yes |
| Lee et al. | 2011 | Asian | BPD | 232 | 194 | 49 | 139 | 80 | 17 | Yes |
| Virit et al. | 2011 | Caucasians | BPD | 39 | 72 | 24 | 54 | 80 | 37 | Yes |
| Kunugi et al. | 1997 | Caucasians | MDD | 19 | 31 | 12 | 29 | 62 | 30 | Yes |
| Ohara et al. | 1998 | Asian | MDD | 18 | 40 | 8 | 58 | 59 | 18 | Yes |
| Frisch et al. | 1999 | Caucasians | MDD | 27 | 61 | 14 | 48 | 89 | 35 | Yes |
| Potter et al. | 2009 | Caucasians | MDD | 29 | 67 | 30 | 24 | 50 | 31 | Yes |
| Illi et al. | 2010 | Caucasians | MDD | 14 | 54 | 31 | 84 | 205 | 106 | Yes |
| Kocabas et al. | 2010 | Caucasians | MDD | 89 | 223 | 82 | 68 | 140 | 83 | Yes |
| Aberg et al. | 2011 | Caucasians | MDD | 60 | 225 | 120 | 442 | 1054 | 655 | Yes |
| Qin et al. | 2013 | Asian | MDD | 139 | 103 | 8 | 219 | 70 | 11 | Yes |
| Wang et al. | 2014 | Asian | MDD | 21 | 61 | 15 | 35 | 53 | 15 | Yes |
| Shen et al. | 2014 | Asian | MDD | 19 | 61 | 10 | 30 | 42 | 8 | Yes |

control subjects satisfy the Hardy-Weinberg equilibrium (HWE). Moreover, all relevant studies published in English or Chinese languages were included. Studies were excluded based on the following: (a) studies that were only abstracts, comments, reviews, or an editorial article; (b) studies that have no sufficient data; and (c) MD patients in the study have both alcohol-dependent and post-traumatic stress disorders.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (**Table 1**) for case-control studies [22]. The quality of non-randomized studies was assessed based on three broad categories: (1) patient selection, (2) comparability of study groups, and (3) assessment of outcome.

Data were analyzed using STATA software version 12.0 (Stata Corp, College Station, TX, USA). Results of the meta-analysis are expressed as odds ratios (ORs) with 95% confidence interval (CI). Begg's funnel plot, Egger's test and sensitivity analysis were calculated to assess for publication bias and the stability of this meta-analysis study.

## Results

### *Study characteristics*

A total of 766 studies were initially identified based on the search criteria. Among these studies, 41 studies were selected for more detailed evaluation after screening the abstracts. Full-text review led to the exclusion of 14 studies due to the following reasons: nine studies lack the required data based on inclusion criteria [23-30]; three studies had their controls deviated from HWE ($P<0.05$) [31]; and two studies were related to postpartum depres-

sion symptom susceptibility [32, 33]. The complete screening process is shown in **Figure 1**. Finally, 27 case-control studies were selected for further analysis (BPD, *n*=17; and MDD, *n*=10). All included patients and healthy controls were either Caucasians or Asians (**Table 2**).

*Quantitative data synthesis*

Meta-analysis results of the association between COMT Val158Met polymorphism and MD are presented in **Tables 3** and **4**. A random-effects model was applied for analysis when heterogeneity between different studies was significant (*P*-value of Q-test for heterogeneity, $P \leq 0.1$); otherwise, a fixed-effects model was used [32, 33].

*Analysis of the association of COMT polymorphism with bipolar disorder*

Seventeen independent studies with 3,027 BPD patients and 3,108 healthy controls were included in this meta-analysis. The following genotypes of the COMT Val158Met gene revealed an overall significant ($P<0.05$) association with BPD: (a) Val/Val + Met/Met genotype *vs.* Val/Met genotype, OR=0.87, 95% CI (0.79, 0.97) $P=0.009$, $P\#=0.509$, **Table 3**; (b) MET allele carriers *vs.* Val/Val genotype, OR=1.25, 95% CI (1.12, 1.40) $P<0.001$, $P\#=0.139$, **Table 3**; (c) Val/Val genotype *vs.* Val/Met genotype, OR=0.81, 95% CI (0.72, 0.91) $P=0.001$, $P\#=0.415$, **Figure 2A** and **Table 3**. Similarly, stratified analysis based on ethnicity (**Table 3**) also revealed that the same genotypes of the COMT Val158Met gene were significantly associated with BPD risk in the Asian population (Val/Val + Met/Met genotype *vs.* Val/Met genotype, OR=0.79, 95% CI [0.66, 0.94] $P=0.006$, $P\#=0.555$; MET allele carriers *vs.* Val/Val genotype, OR=1.42, 95% CI [1.19, 1.68] $P<0.001$, $P\#=0.155$; Val/Val genotype *vs.* Val/Met genotype, OR=0.74, 95% CI [0.61, 0.88], $P=0.001$, $P\#=0.364$). However, the trend in the association of COMT Val158-Met polymorphism with BPD was not consistent in the Caucasian population. Moreover, some stratified analyses of other subgroups have also revealed significant associations. For example, female patients usually have a higher proportion of association with Val/Met genotype *vs.* Met/Met genotype (OR=2.34, 95% CI [1.07, 5.09] $P=0.032$, $P\#=0.647$), while patients with type 2 BPD have a higher proportion of the Val/Met genotype compared with the Val/Val genotype (OR=0.64, 95% CI [0.45, 0.91] $P=0.013$, $P\#=0.346$), as shown in **Table 3**. The following genotypes of the COMT Val158Met gene revealed a significantly high heterogeneity in the overall analysis: Val allele carrier *vs.* Met/Met genotype and Val/Val genotype *vs.* Met/Met genotype.

*Analysis of the association of COMT polymorphism with major depressive disorder*

Ten independent studies representing 1,692 MDD patients and 3,853 healthy controls were part of this meta-analysis. MDD revealed a significant ($P<0.05$) association (**Table 4**) with the following genotypes of the COMT Val158Met gene: (a) Val/Val + Met/Met genotype *vs.* Val/Met genotype, OR=0.70, 95% CI (0.61, 0.79) $P<0.001$, $P\#=0.185$; (b) Met allele carrier *vs.* Val/Val genotype, OR=1.44, 95% CI (1.15, 1.80) $P=0.002$, $P\#=0.034$; (c) Val/Met genotype *vs.* Met/Met genotype, OR=1.28, 95% CI (1.09, 1.50) $P=0.003$, $P\#=0.759$; (d) Val/Val genotype *vs.* Val/Met genotype, OR=0.63, 95% CI (0.54, 0.74) $P<0.001$, $P\#=0.119$ (**Figure 2B**). Similarly, stratified analysis based on ethnicity also revealed a significant association between COMT Val158Met polymorphism and MDD risk in both Asian (Val/Val + Met/Met genotype *vs.* Val/Met genotype, OR=0.49, 95% CI (0.38, 0.64) $P<0.001$, $P\#=0.757$; MET allele carrier *vs.* Val/Val genotype, OR=2.09, 95% CI (1.62, 2.71) $P<0.001$, $P\#=0.975$; Val/Val genotype *vs.* Val/Met genotype, OR=0.45, 95% CI (0.34, 0.59) $P<0.001$, $P\#=0.968$) and Caucasian (Val/Val + Met/Met genotype *vs.* Val/Met genotype, OR=0.78, 95% CI (0.68, 0.90) $P=0.001$, $P\#=0.877$; MET allele carrier *vs.* Val/Val genotype, OR=1.22, 95% CI (1.02, 1.46) $P=0.028$, $P\#=0.272$; Val/Met genotype *vs.* Met/Met genotype, OR=1.26, 95% CI (1.06, 1.49) $P=0.008$, $P\#=0.459$; Val/Val genotype *vs.* Val/Met genotype, OR=0.75, 95% CI (0.62, 0.91) $P=0.003$, $P\#=0.506$) populations. In addition, the stratified analysis of other subgroups also revealed a significant association between COMT Val158Met polymorphism and MDD risk. For example, a male population was associated with the following genotypes: Val/Val genotype *vs.* Met/Met genotype, OR=0.45, 95% CI (0.23, 0.86) $P=0.016$; MET allele carrier *vs.* Val/Val genotype, OR=2.26, 95% CI (1.24, 4.10) $P=0.007$; Val/Val genotype *vs.* Val/Met geno-

**Table 3.** Meta-analysis results of different Val158Met genotypes and BPD

| | N | Val/* *vs.* Met/Met | | Val/Val + Met/Met *vs.* Val/Met | | Val/Val *vs.* Met/Met | | MET/* *vs.* Val/Val | | Val/Met *vs.* Met/Met | | Val/Val vs. Val/Met | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *OR (95% CI) P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) |
| Total | 17 | *0.87 (0.70, 1.09) 0.224* | 36.30 (0.003) | **0.87 (0.79, 0.97) 0.009** | 15.22 (0.509) | 0.82 (0.65, 1.02) 0.080 | 30.00 (0.018) | **1.25 (1.12, 1.40) 0.000** | 22.13 (0.139) | 0.98 (0.85, 1.13) 0.752 | 22.53 (0.127) | **0.81 (0.72, 0.91) 0.001** | **16.55 (0.415)** |
| Ethnicity | | | | | | | | | | | | | |
| Caucasian | 12 | *0.91 (0.72, 1.15) 0.443* | -0.017 | 0.92 (0.81, 1.05) 0.228 | -0.523 | 0.87 (0.72, 1.04) 0.130 | -0.17 | 1.14 (0.98, 1.32) 0.083 | -0.374 | 1.02 (0.87, 1.19) 0.847 | -0.231 | 0.87 (0.75, 1.02) 0.088 | -0.508 |
| Asian | 5 | *0.78 (0.45, 1.35) 0.367* | -0.023 | **0.79 (0.66, 0.94) 0.006** | -0.555 | 0.68 (0.37, 1.25) 0.214 | -0.018 | **1.42 (1.19, 1.68) 0.000** | -0.155 | 0.85 (0.63, 1.15) 0.300 | -0.113 | **0.74 (0.61, 0.88) 0.001** | **-0.364** |
| Sex | | | | | | | | | | | | | |
| Male | 2 | *0.71 (0.40, 1.27) 0.100* | -0.856 | 0.83 (0.51, 1.37) 0.472 | -0.395 | 0.53 (0.26, 1.07) 0.074 | -0.882 | 1.75 (0.99, 3.10) 0.055 | -0.623 | 0.85 (0.46, 1.57) 0.607 | -0.64 | 0.60 (0.33, 1.10) 0.100 | -0.523 |
| Female | 2 | *1.91 (0.93, 3.94) 0.215* | -0.174 | 0.59 (0.35, 1.00) 0.049 | -0.083 | 1.44 (0.65, 3.18) 0.369 | -0.014 | 1.64 (0.26, 10.29) 0.598 | -0.004 | **2.34 (1.07, 5.09) 0.032** | -0.647 | 0.51 (0.08, 3.05) 0.457 | -0.008 |
| BPD style | | | | | | | | | | | | | |
| 1 style | 6 | *1.10 (0.85, 1.42) 0.477* | -0.058 | 0.84 (0.69, 1.02) 0.085 | -0.975 | 0.95 (0.55, 1.65) 0.859 | -0.012 | 1.18 (0.95, 1.47) 0.129 | -0.072 | 1.12 (0.86, 1.46) 0.406 | -0.296 | 0.83 (0.66, 1.03) 0.096 | -0.404 |
| 2 style | 2 | *0.91 (0.50, 1.67) 0.769* | -0.748 | **0.66 (0.47, 0.93) 0.019** | -0.373 | 0.73 (0.39, 1.37) 0.328 | -0.851 | **1.53 (1.09, 2.14) 0.014** | -0.404 | 1.19 (0.63, 2.23) 0.595 | -0.635 | **0.64 (0.45, 0.91) 0.013** | **-0.346** |
| Non-rapid cyclers | 1 | *1.26 (0.69, 2.31) 0.444* | | 1.23 (0.76, 2.00) 0.402 | | 1.63 (0.82, 3.27) 0.166 | | 0.65 (0.38, 1.10) 0.107 | | 1.08 (0.57, 2.05) 0.808 | | 1.51 (0.86, 2.65) 0.152 | |
| Rapid cyclers | 1 | *0.67 (0.34, 1.32) 0.243* | | 1.10 (0.60, 2.04) 0.753 | | 0.58 (0.24, 1.41) 0.230 | | 1.37 (0.65, 2.89) 0.414 | | 0.71 (0.34, 1.45) 0.347 | | 0.82 (0.37, 1.83) 0.635 | |
| First episode | | | | | | | | | | | | | |
| ≥28 | 2 | *1.10 (0.76, 1.60) 0.601* | -0.337 | 0.77 (0.56, 1.05) 0.100 | -0.564 | 0.89 (0.55, 1.44) 0.635 | -0.38 | 1.32 (0.90, 1.94) 0.161 | -0.879 | 1.23 (0.83, 1.81) 0.299 | -0.342 | 0.70 (0.47, 1.05) 0.088 | -0.964 |
| ≤22 | 3 | *0.82 (0.34, 2.03) 0.675* | -0.007 | 1.12 (0.80, 1.55) 0.507 | -0.239 | 0.70 (0.45, 1.09) 0.111 | -0.089 | 1.16 (0.82, 1.64) 0.411 | -0.311 | 0.98 (0.57, 1.69) 0.574 | -0.027 | 0.97 (0.66, 1.42) 0.879 | -0.568 |

N: number of articles; OR: odds ratio; CI: confidence interval; P: *P*-value for OR; Q: Q value; P#: *P* value of Q-test for heterogeneity; Bold type: OR with statistical significance.

**Table 4.** Meta-analysis results for different genotypes of Val158Met and MDD

| | N | Val/* *vs.* Met/Met | | Val/Val + Met/Met *vs.* Val/Met | | Val/Val *vs.* Met/Met | | MET/* *vs.* Val/Val | | Val/Met *vs.* Met/Met | | Val/Val *vs.* Val/Met | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) | OR (95% CI) *P* | Q (P#) |
| Total | 10 | 1.14 (0.98, 1.33) 0.088 | 7.20 (0.616) | **0.70 (0.61, 0.79) 0.000** | 12.53 (0.185) | 0.90 (0.74, 1.10) 0.305 | 11.84 (0.222) | **1.44 (1.15, 1.80) 0.002** | 18.08 (0.034) | **1.28 (1.09, 1.50) 0.003** | 5.81 (0.759) | **0.63 (0.54, 0.74) 0.000** | **14.10 (0.119)** |
| Ethnicity | | | | | | | | | | | | | |
| Asian | 4 | 1.01 (0.65, 1.57) 0.955 | -0.972 | **0.49 (0.38, 0.64) 0.000** | -0.757 | 0.67 (0.41, 1.08) 0.098 | -0.891 | **2.09 (1.62, 2.71) 0.000** | -0.975 | 1.41 (0.89, 2.22) 0.142 | -0.812 | **0.45 (0.34, 0.59) 0.000** | **-0.968** |
| Caucasian | 6 | 1.16 (0.99, 1.37) 0.072 | -0.248 | **0.78 (0.68, 0.90) 0.001** | -0.877 | 0.96 (0.77, 1.19) 0.689 | -0.095 | **1.22 (1.02, 1.46) 0.028** | -0.272 | 1.26 (1.06, 1.49) 0.008 | -0.459 | **0.75 (0.62, 0.91) 0.003** | **-0.506** |
| Sex | | | | | | | | | | | | | |
| Male | 1 | 0.84 (0.56, 1.26) 0.398 | | 0.75 (0.51, 1.11) 0.147 | | **0.45 (0.23, 0.86) 0.016** | | **2.26 (1.24, 4.10) 0.007** | | 1.02 (0.67, 1.56) 0.933 | | **0.44 (0.24, 0.82) 0.009** | |
| Female | 1 | 1.15 (0.87, 1.53) 0.331 | | 0.79 (0.61, 1.02) 0.069 | | 0.93 (0.63, 1.38) 0.722 | | 1.23 (0.87, 1.74) 0.236 | | 1.24 (0.92, 1.66) 0.160 | | 0.75 (0.53, 1.08) 0.120 | |
| First episode | | | | | | | | | | | | | |
| >44 | 3 | 0.98 (0.59, 1.61) 0.922 | -0.935 | **0.55 (0.39, 0.78) 0.001** | -0.861 | 0.60 (0.34, 1.06) 0.079 | -0.913 | **2.02 (1.39, 2.94) 0.000** | -0.926 | 1.14 (0.68, 1.91) 0.614 | -0.998 | 0.47 (0.32, 0.70) 0.000 | -0.929 |
| <25 | 1 | 2.52 (0.87, 7.31) 0.090 | | 0.77 (0.36, 1.65) 0.500 | | 0.96 (0.89, 9.90) 0.078 | | 0.61 (0.27, 1.41) 0.251 | | 2.33 (0.77, 7.05) 0.134 | | 1.27 (0.54, 3.02) 0.586 | |

N: number of articles; OR: odds ratio; CI: confidence interval; P: *P*-value for OR; Q: Q value; P#: *P* value of Q-test for heterogeneity; Bold type: OR with statistical significance.

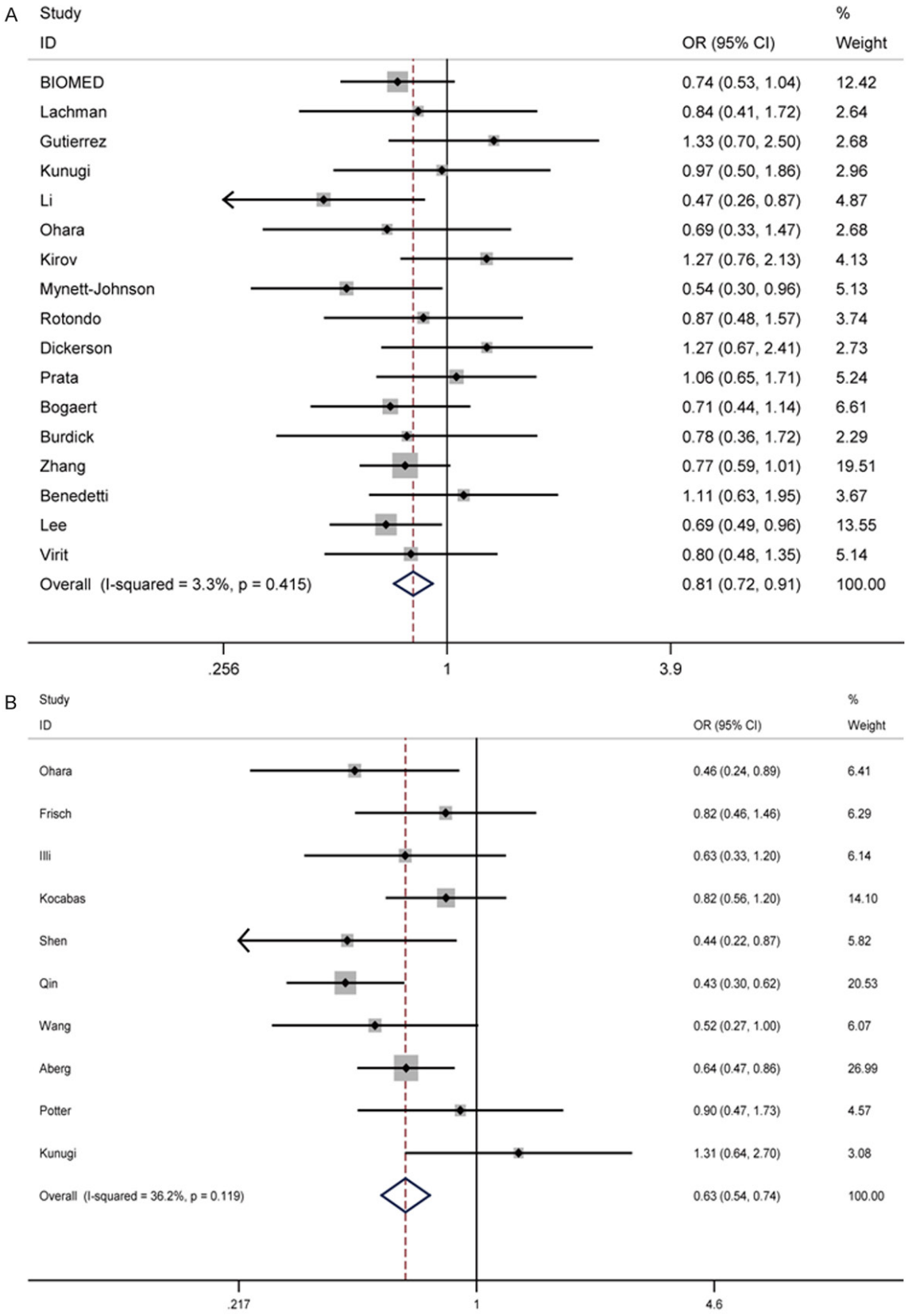


**Figure 2.** Forest plot of the association of BPD (panel A) and MDD (panel B) risks with the COMT rs4680 genotype (Val/Val *vs.* Val/Met) by dominant model comparison.

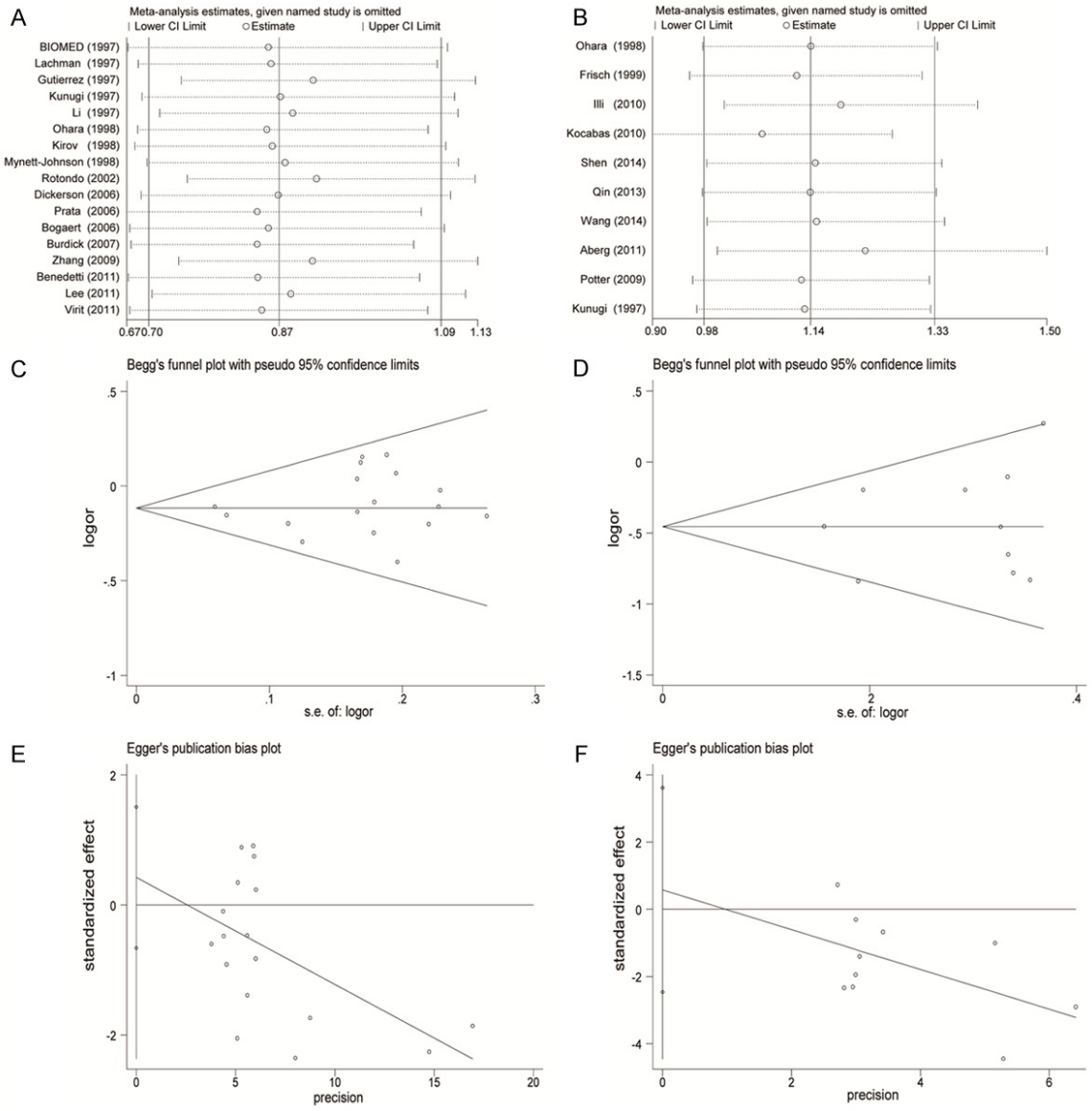


**Figure 3.** Sensitivity analysis of BPD and MDD risks with COMT rs4680 polymorphism are shown in (A) and (B). Begg's funnel plot and Egger's plot for the overall publication bias of BPD risk and COMT rs4680 polymorphism are shown in (C) and (E), while MDD risk and COMT rs4680 polymorphism are shown in (D) and (F).

type, OR=0.44, 95% CI (0.24 0.82) *P*=0.009. Similarly, the first episode subgroup was associated with both the ">44" age group (Val/Val genotype + Met/Met genotype *vs.* Val/Met genotype, OR=0.55, 95% CI [0.39, 0.78] *P*=0.001, *P#*=0.861; MET allele carrier *vs.* Val/Val genotype, OR=2.02, 95% CI [1.39, 2.94] *P*<0.001, *P#*=0.926; Val/Val genotype *vs.* Val/Met genotype, OR=0.47, 95% CI [0.32, 0.70], *P#*=0.929) and "<25" age group (Val/Val genotype *vs.* Met/Met genotype, OR=0.96, 95% CI [0.89, 9.90] *P*<0.001, *P#*=0.929). The overall analysis revealed high heterogeneity in the Val/Val genotype *vs.* Met/Met genotype (*P*-value of Q-test for heterogeneity: *P#*<0.1). All data presented above are shown in **Table 4**.

*Heterogeneity analysis*

Significant heterogeneity was observed in the overall pooled analysis; whereas, the degree of heterogeneity in the stratified analysis was less as shown in **Tables 3** and **4**.

*Sensitivity analysis and publication bias*

In order to assess the stability of this meta-analysis study, a sensitivity analysis was performed by deleting one study at a time and

recalculating the ORs and 95% CIs. Overall, pooled estimates were minimally altered each time a single study was removed, as shown in **Figure 3A** and **3B**; suggesting the stability of the results in both the BPD and MDD groups. In order to assess publication bias in this analysis, Begg's funnel plot and Egger's test were performed. No evidence of publication bias was observed, as shown in **Figure 3C-F**. The values of each test were as follows: (1) BPD: Begg's test $P$=0.650, Egger's test $P$=0.323; (2) MDD: Begg's test $P$=0.858, Egger's test $P$=0.673.

## Discussion

COMT rs4680 polymorphism is due to the mutation of amino acid valine to methionine at codon 158 of the COMT gene, which causes a difference in the functional ability of this enzyme to catabolize dopamine. Some studies have shown that Met allele carriers increase the risk of MD [11]. In contrast, few studies did not show a positive association between COMT rs4680 polymorphism and MD.

Therefore, based on these case-control studies, we made an effort to identify whether an association between the COMT gene and MD exists. This study was conducted with a rationale that the presence of a single Met allele in the COMT Val158Met gene could elevate the risk of MD. These analyzed studies represented high heterogeneity, which could be attributed to study design, location, quality and psychiatric diagnostic criteria. Data were analyzed by random effects model due to high heterogeneity in some genotypes among the included studies.

The meta-analysis results of BPD cases involving 3,027 BPD patients and 3,108 healthy controls revealed that the proportion of rs4680 Met allele carriers are higher in BPD patients compared to healthy individuals. Furthermore, the Val/Met genotype had a more statistically significant association with BPD in the total population. These observations were consistent with the findings of Zhang *et al.*, [16], Lee *et al.*, [17] and Mynett-Johnson *et al.*, [34]; in which, they all reported that Val158Met polymorphism of the COMT gene influences its susceptibility to BPD. However, it is worth mentioning that different subgroups have shown different levels of association. In Caucasians, no significant association was found between BPD and Val158Met polymorphism of the COMT gene ($P$>0.05). However, Met allele carriers do appear to be closely associated with BPD in the Asian group; which means that a high proportion of these Asian patients are Met allele carriers. Since this association is statistically significant in the overall population ($P$<0.05), this indicates that these overall results were mainly derived from the Asian population. The difference of association based on ethnicity could be attributed to the following reasons: (1) diverse genetic composition between ethnic populations; (2) different environmental factors and lifestyle backgrounds; and (3) although there was no evidence of publication bias in this study, we could not ignore the fact that studies with negative results are harder to be published. Furthermore, the assessment of the association of rs4680 with BPD in stratified subgroups involving gender and BPD revealed that female patients had a higher proportion of the Val/Met genotype compared to the Met/Met genotype; and patients with type 2 BPD had a higher proportion of the Val/Met genotype compared with the Val/Val genotype. These results illustrate that the Val/Met genotype is closely correlated with BPD in certain subgroups. However, this subgroup analysis has some limitations: (a) the number of articles in this study was not large enough, which may lead to unstable results; and (b) the different subgroups could not be further classified based on their ethnicity.

Interestingly, this is the first meta-analysis study that assessed the association of COMT Val158Met polymorphism with MDD. This analysis included 10 independent samples with 1,692 MDD patients, and we observed a significant association between MDD and the Val158Met COMT gene with several different genotypes. Overall results suggest that Met allele carriers such as "MET/* *vs.* Val/Val", "Val/Val *vs.* Val/Met" and "Val/Met *vs.* Met/Met" increased the risk of MDD; but not Val/Val genotype *vs.* Met/Met genotype. A super dominance model (Val/Val genotype + Met/Met genotype *vs.* Val/Met genotype) analysis also revealed similar results. Furthermore, a subgroup analysis of both Asians and Caucasians also suggest a trend similar to the total population. Surprisingly, only male MDD patients had a higher proportion of Met allele carriers, compared with the Val/Val genotype. In the first episode subgroup, the ">44" age group had a high

proportion of Met allele carriers and the Val/Met genotype in MDD patients over the Val/Val genotype. However, in the "<25" group, the proportion of Met/Met genotype was higher than the Val/Val genotype; but the Val/Met genotype did not show any association with MDD. Again, this subgroup analysis had a disadvantage of having a small sample size. Therefore, to effectively understand this association in different subgroups, a larger sample size would be required.

Based on these two different meta-analyses, we conclude that Met allele carriers obviously had a higher risk of BPD and MDD in some subgroups due to the altered regulation of dopamine (DA) levels. Bousman *et al.*, [35], suggested that subjects homozygous for APS haplotype (which contains Met at rs4680) had the lowest COMT activity, while subjects with two copies of LPS or HPS (which contain Val at rs4680) had the highest activity. This suggests that Met allele carriers could increase the risk of MD [11].

Another probable explanation of the increased risk of MD with the Val/Met genotype could be anti-heterosis. Heterosis occurs when subjects heterozygous for an allele have a different phenotype from homozygotes. This concept was originally applied to crop genetics in the context of hybrid vigor; however, at present, heterosis is increasingly being recognized in humans [36, 37]. There have been studies that linked heterosis to COMT gene Val158Met polymorphism, where heterozygous alleles have a significant advantage against schizophrenia aggression. It is worth mentioning that the meta-analysis results of this study were different, since heterozygotes have a significant anti-heterosis advantage in BPD and MDD.

In parallel, some potential limitations of the included data sets in this study should be considered before making any concrete judgment on the overall relevance of the current study. First, gene-gene and gene-environment interaction could not be analyzed due to the unavailability of relevant data. Second, populations included in this meta-analysis were primarily comprised of Asians and Caucasians. Lack of data from other ethnic groups may mislead the overall findings. Third, the study scale in some subgroups of the present meta-analysis was not large enough such as gender, different disease subtypes and age. Fourth, our study only included English and Chinese articles. Despite these limitations, all studies included in this meta-analysis clearly met our selection criteria. Genetic model comparisons were used to evaluate MD risk with COMT rs4680 polymorphism. Furthermore, subgroups analysis based on ethnicity, MD type and study scale provided better knowledge on COMT rs4680 polymorphism and MD risk.

In summary, our study confirms that COMT rs4680Met allele carriers increase the risk of MD, which is consistent with previous findings. However, some subgroups did not show similar patterns; and this may be due to the small sample size. Analyzing data from other ethnic groups with a larger sample size would be necessary to establish a final concrete statement on COMT rs4680 polymorphism and MD risk.

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## Disclosure of conflict of interest

None.

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