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# Association of Val158Met polymorphism in *COMT* gene with attention-deficit hyperactive disorder
## An updated meta-analysis

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## Abstract

**Background:** The results of published articles on the relationship between the Val158Met polymorphism in the (Catechol-O-methyltransferase) *COMT* gene and the susceptibility of attention-deficit hyperactive disorder (ADHD) are controversial. We conducted an updated meta-analysis of case-control studies to assess the relationship between Val158Met polymorphism in *COMT* gene and ADHD susceptibility.

**Methods:** A comprehensive literature search was conducted to identify all the case-control studies on the relationship between the *COMT* gene Val158Met polymorphism and ADHD susceptibility. According to the heterogeneity test results among studies evaluated with $I^2$, the fixed effect model or random effect model was selected as the pooling method. Meta-regression as well as sensitive analysis were used to explore possible causes of between-study heterogeneity. The funnel plot and Harbord test were used to estimate publication bias.

**Results:** Finally, seventeen studies that met the inclusion criteria were included. The Val158Met genotype distributions of *COMT* gene in controls were in Hardy–Weinberg equilibrium in all studies. In general, there was no significant association between the *COMT* gene Val158Met polymorphism and ADHD susceptibility in dominant, recessive, and codominant models. The recessive genetic model ($I^2 = 60.8\%$) showed strong heterogeneity among studies, and still no significant association was found after sensitivity analysis. Subgroup analysis stratified by ethnicity (Asian and Caucasian) also showed that there was no significant association in the above-mentioned three models.

**Conclusions:** This updated meta-analysis indicated that the Val158Met polymorphism in the *COMT* gene may not be related to the risk of ADHD. Further researches are needed to confirm these results.

**Abbreviations:** ADHD = attention deficit hyperactivity disorder, CI = confidence interval, COMT = catechol-O-methyltransferase, FEM = fixed effect model, OR = odds ratio, REM = random effect model.

**Keywords:** attention deficit hyperactivity disorder (ADHD), catechol-O-methyltransferase (*COMT*), meta-analysis, polymorphism

## 1. Introduction

Studies have shown that catecholamines (including dopamine, norepinephrine and adrenaline) neurotransmitter metabolic pathway disorders was the neurobiochemical basis of attention-deficit

hyperactive disorder (ADHD).[1,2] Catechol-o-methyltransferase (COMT) is an important enzyme in the study of ADHD. It is the main degrading enzyme involved in the degradation of catecholamines in the cerebral cortex, which preferentially affects prefrontal cortical dopamine metabolism.[3,4] The gene encoding COMT is located on chromosome 22q11.2 and contains a functional polymorphism (rs4680). In the gene sequence of codon 158, a nucleotide change from guanine to adenine (G to A), resulting in substituting valine for methionine reduces the COMT enzyme activity three to four-folds.[5,6] Theoretically, a decrease in COMT enzyme activity associated with the Met allele may reduce the degradation of dopamine, leading to an increase in its concentration in the prefrontal cortex.[7] Given the importance of COMT in regulating dopamine, the Val158Met polymorphism of *COMT* gene may play a role in the onset of ADHD.

As respected, several studies have investigated the relationship between Val158Met polymorphism in *COMT* gene and ADHD susceptibility.[8–12] However, the results that have been published so far are contradictory. Although there have been previous meta-analyses of this association, previous meta-analyses were mostly limited to English language articles and the number of include case-control studies was relative limited.[13–16] Therefore, we conducted an updated meta-analysis to assess the role of the *COMT* gene Val158Met polymorphism in the susceptibility of ADHD, as well as to evaluate the potential between-study heterogeneity and explore the potential publication bias.

## 2. Methods

All analysis results of this study were based on previously published studies and therefore did not require ethical approval or patient consent.

### 2.1. Search strategy

We retrieved the English or Chinese literature published before March 2020 from the following databases: PubMed; EMBASE; CNKI (China National Knowledge Infrastructure); VIP (Database of Chinese Scientific and Technical Periodicals); CBM (China Biological Medical literature database); ISI (Web of Science). The following keywords

"attention-deficit hyperactive disorder" or "ADHD" and "Catechol-O-methyltransferase", "COMT" "Val158Met", "rs4680" "polymorphism", "mut*" and "varia*" were used for literature search. We also reviewed references of the included studies and review articles to identify other studies that were not captured by our database search. At the same time, we tried to contact the authors of the selected studies via emails and request them to provide any unpublished data.

### 2.2. Inclusion criteria

The inclusion criteria for the present meta-analysis were as follows:

(1) case-control study published as original study to evaluate the relationship between Val158Met polymorphism in *COMT* gene and ADHD susceptibility;
(2) the number of each genotype and allele in the case group and control group was provided or the study provided data that can count the number of each genotype.
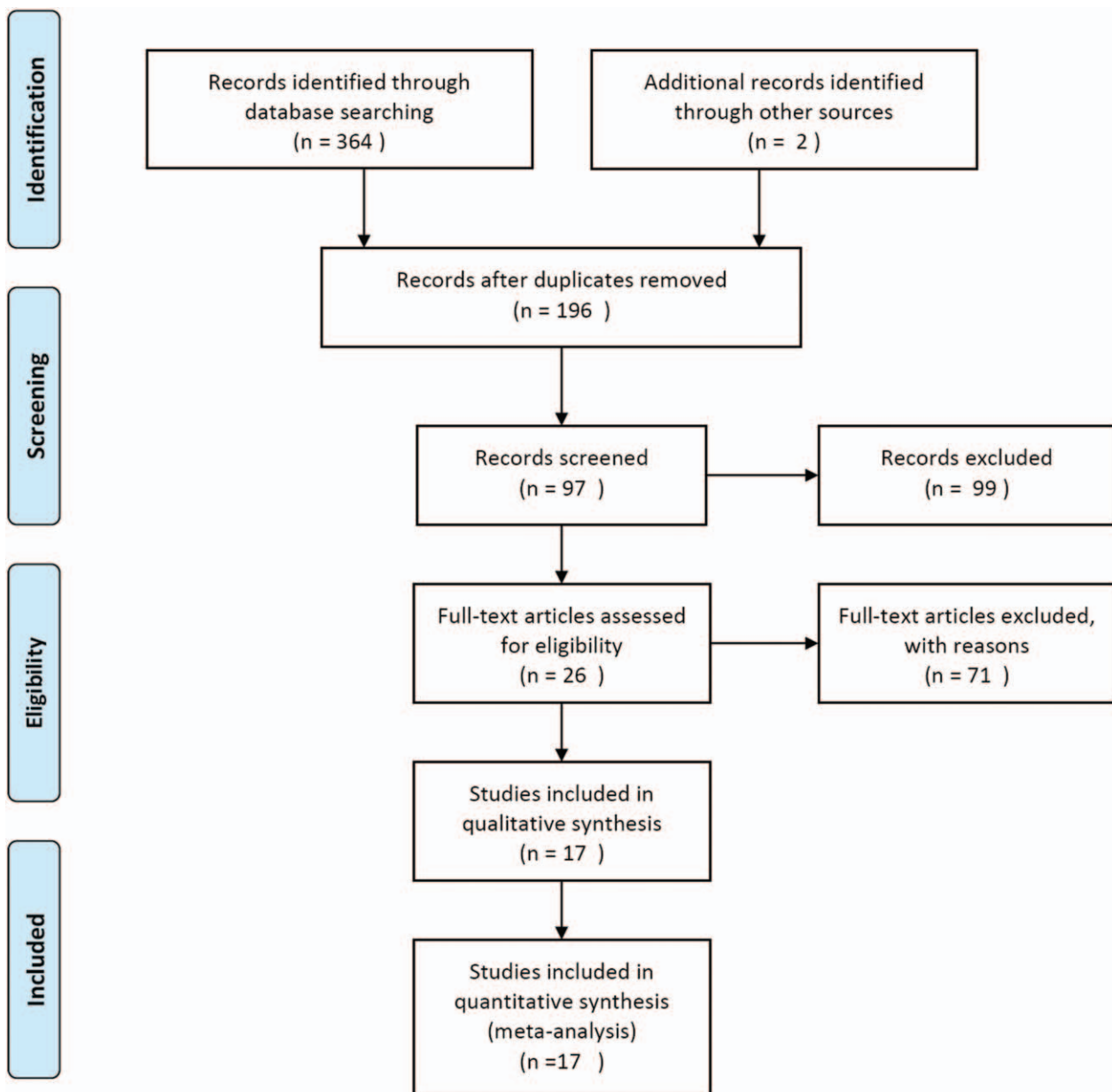


**Figure 1.** Flow chart of study identification and selection.

### Table 1

**Characteristics of COMT gene Val158Met polymorphism genotype distributions in studies included in this meta-analysis.**

| First author | Year | Country | Ethnicity | Numbers of Case/Control | Genotypes GG/GA/AA | | % of male (case/control) | Mean age (case/control) |
| | | | | | Case | Control | | |
|---|---|---|---|---|---|---|---|---|
| Qian QJ | 2003 | China | Asian | 317/194 | 158/140/24 | 99/78/17 | 86.8/Na | 10.4/Na |
| Zhang XN | 2003 | China | Asian | 117/105 | 67/41/9 | 60/40/5 | 79.5/77.1 | 10.5/14.5 |
| Gao XP | 2006 | China | Asian | 54/30 | 25/25/4 | 13/16/1 | 83.3/73.3 | 9.9/9.5 |
| Chen JF | 2007 | China | Asian | 100/100 | 59/34/7 | 53/39/8 | 85/85 | 10.8/10.1 |
| Kereszturi E | 2008 | Hungary | Caucasian | 173/284 | 49/87/37 | 53/151/80 | 87.3/Na | 9.1/Na |
| Song EY | 2009 | Korea | Asian | 60/100 | 33/27/0 | 65/29/6 | 81.7/Na | 9.3/Na |
| Halleland H | 2009 | Norway | Caucasian | 435/383 | 84/214/137 | 71/188/124 | 53.3/41.4 | 34.4/27.8 |
| Zhang YB | 2009 | China | Asian | 114/76 | 58/43/10 | 40/25/11 | 80.7/68.4 | 12.5/13.1 |
| Xiong ZG | 2011 | China | Asian | 110/90 | 64/42/4 | 56/26/8 | Na/Na | Na/Na |
| Das M | 2011 | India | Asian | 126/96 | 138/114* | 109/83* | 90.9/76.9 | 7.3/19.5 |
| Chiho Y | 2013 | Japan | Asian | 50/32 | 20/30† | 4/28† | 100/100 | 9.7/16.9 |
| Carpentier PG | 2013 | Netherlands | Caucasian | 176/500 | 51/125‡ | 154/346‡ | 47.7/49.4 | 37.1/59.4 |
| Perkovic MN | 2013 | Coratia+ Estonia | Caucasian | 650/157 | 134/311/205 | 43/88/26 | 100/Na | 13.5/15 |
| Perkovic MN | 2014 | Coratia | Caucasian | 102/128 | 31/71‡ | 18/110‡ | 100/100 | 9.2/16.9 |
| Biehl SC | 2014 | German | Caucasian | 35/35 | 7/18/10 | 10/17/8 | 57.1/45.7 | 3636.6 |
| Jin J | 2016 | China | Asian | 594/154 | 326/228† | 86/68† | 85/74 | 10.1/9.3 |
| Pekcanlar Aka | 2018 | Turkey | Caucasian | 34/50 | 13/17/4 | 20/20/10 | 94/90 | 14.2/14.3 |

COMT = Catechol-O-methyltransferase, Na = not available.
* We can only get the allele counts for A /G from the original study.
† We can only get the genotype counts for (GA+AA)/GG from the original study.
‡ We can only get the genotype counts for AA /(GG+GA) from the original study.

If a data from the same population was published more than once, we choose the most complete one. Otherwise, we will choose the most recent article. Two researchers independently reviewed all studies to confirm that all studies were eligible for inclusion in our meta-analysis. The disagreements between the two researchers were resolved by consensus with the third reviewer.

### 2.3. Data extraction

After reaching a consensus, two researchers separately extracted the data required for meta-analysis. The following information was extracted from each study: first author, publication year, country, ethnic origin of the study population, sample size, distributions of genotypes and alleles (data that can count the number of each genotype and allele), mean age, male sex percentage of case and control groups.

### 2.4. Statistical analysis

The χ2 test with exact probability method were used to analyze whether the genotype distribution of Val158Met *COMT* gene in all control groups deviated from Hardy Weinberg equilibrium (HWE). When $P < .05$, it was regarded as diverging from HWE. Use the reciprocal of variance as the weight to pool the logarithm of Odds Ratio (OR) with 95% confidence intervals (CI) to assess the strength of association of the Val158Met polymorphisms in *COMT* gene with risk of ADHD. We performed analysis for the polymorphism considering dominant (AA+GA vs GG), recessive (AA vs GA+GG), and codominant (A vs G) models, respectively. We used the $I^2$ of Higgins and Thompson to assess heterogeneity among studies.[17] $I^2$ ranged from 0% to 100% and reflects the percentage of variation (variance) caused by heterogeneity in the total variation (variance) of the study. When $I^2 > 50\%$, it is considered that there is substantial heterogeneity among studies[18] and the DerSimonian and Laird random effect model

### Table 2

**Pooled measures on the relations of COMT gene Val158Met polymorphism with ADHD risk.**

| Data | Population | Inherited model | Pooled OR (95% CI) | | $I^2$ (%) |
| | | | FEM | REM | |
|---|---|---|---|---|---|
| All relevant articles | Overall | Dominant | 1.002 (0.875–1.148) | 0.994 (0.834–1.184) | 32.5 |
| | | Recessive | 1.049 (0.893–1.233) | 1.032 (0.759–1.404) | 60.8 |
| | | Codominant | 1.018 (0.924–1.122) | 1.015 (0.885–1.163) | 40.1 |
| | Asian | Dominant | 1.013 (0.851–1.207) | 1.006 (0.828–1.223) | 14.4 |
| | | Recessive | 0.786 (0.527–1.174) | 0.786 (0.527–1.174) | 0.0 |
| | | Codominant | 0.999 (0.861–1.159) | 0.999 (0.861–1.159) | 0.0 |
| | Caucasian | Dominant | 0.985 (0.794–1.222) | 1.001 (0.686–1.461) | 59.4 |
| | | Recessive | 1.110 (0.931–1.323) | 1.188 (0.795–1.775) | 75.8 |
| | | Codominant | 1.033 (0.908–1.174) | 1.038 (0.758–1.422) | 78.4 |
| After sensitive analysis | Overall | Recessive | 0.935 (0.787–1.111) | 0.937 (0.720–1.219) | 38.7 |

ADHD = attention deficit hyperactivity disorder, Codominant model = A vs G, COMT = Catechol-O-methyltransferase, Dominant model = GA+AA vs GG, FEM = fixed effect model, Recessive model = AA vs GG +GA, REM = random effect model.

(REM) was used as the pooling method; and the fixed effect model (FEM) was adopted as the pooling method if $I^2 < 50\%$. Meta-regression with restricted maximum likelihood estimation to detect potential covariates (sex, age, publication year and ethnicity) that have an impact on between-study heterogeneity. Sex was indicated by ratio of male percent in case group to that in control group, while age was expressed by ratio of mean age in case group to that in control group and ethnicity was categorized as Asian and Caucasian. The 'leave one out' sensitivity analysis was carried out taking $I^2 > 50\%$ as the criteria to assess the key studies with substantial impact on heterogeneity among studies.[19] Funnel plots and Harbord test were used to investigate the publication bias among the included studies.[20] An analysis of influence was conducted,[21] which describes the stability of the pooled effect after removing a single study. If the point estimate of an individual study's omitted analysis is outside the 95%

confidence interval of the pooled effect, the influence is suspected to be excessive. Using ethnicity (categorized as Asian and Caucasian) as a grouping variable, a subgroup analysis of the relationship between COMT gene polymorphism and ADHD risk was conducted. All statistical analyses were performed with STATA version 12.0 (Stata Corporation, College Station, TX). All reported probabilities (P values) were two-sides and $P < .05$ was considered statistically significant.

## 3. Results

### 3.1. Characteristics of studies

The flow chart of study identification and selection is shown in Figure 1. The initial implementation of the search strategy yielded 366 potentially relevant citations. According to the predeter-
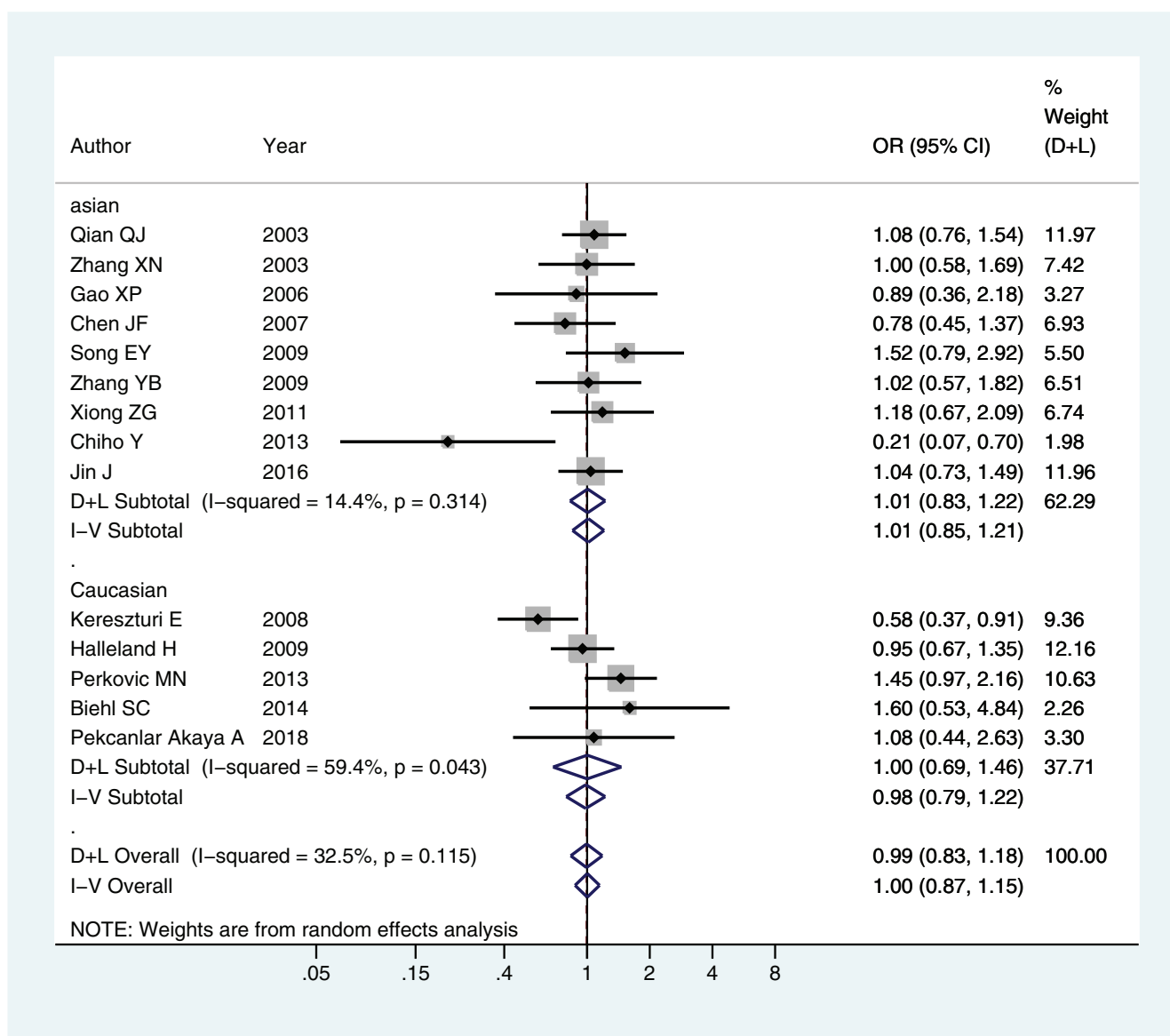


**Figure 2.** Forest plot of ORs for the association of COMT gene Val158Met polymorphism with ADHD risk in dominant model (GA+AA vs GG). The upper, middle, and lower panels are for Asian, Caucasian, and overall populations, respectively. Each panel contains both fixed (denoted as I-V) and random (denoted as D + L) effect model pooled ORs White diamond denotes the pooled OR. Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% CIs.

mined criteria, we identified 17 published articles[10,12,22–36] eligible for this meta-analysis on the relation of Val158Met polymorphism in *COMT* gene to ADHD risk. All the above mentioned seventeen articles were case-control design including 3274 ADHD cases and 2514 controls. General characteristics and the Val158Met genotype distributions in the articles included in this meta-analysis are shown in Table 1.

### 3.2. Quantitative synthesis

The results of the pooled analysis are summarized in Table 2. No study was deviated from HWE in controls. Overall, no association was found between Val158Met polymorphism and the risk of ADHD (FEM: OR = 1.002, 95% CI = 0.875–1.148; $I^2$ = 32.5%), recessive (REM: OR = 1.032, 95% CI = 0.759–1.404; $I^2$ = 60.8%) and codominant (FEM: OR = 1.018, 95% CI = 0.924–1.122; $I^2$ = 40.1%) models. In the subgroup analysis by ethnicity, none of the above-mentioned genetic models found significant correlations. Figure 2 showed pooled OR of overall and ethnicity subgroup in the dominant model.

### 3.3. Sources of heterogeneity and sensitive analysis

As seen in Table 2, strong evidence of heterogeneity among studies was demonstrated in the recessive inherited model ($I^2$ = 60.8%). Univariate meta-regression analysis was conducted using gender, age, publication year, and ethnicity as covariates. However, no covariate had a significant effect on heterogeneity among studies.

In the sensitivity analysis, one study published in 2013 that conducted by Perkovic MN was found to be the key contributor to between-study heterogeneity in the recessive model. After further excluding the article, the meta-analysis also showed no significant association of Val158Met polymorphism with the risk of ADHD (Fig. 3).

### 3.4. Influence analysis

After sensitivity analysis, no individual study was found to have excessive influence on the pooled effect. Figure 4 presented the result of influence analysis after sensitivity analysis of the recessive model.
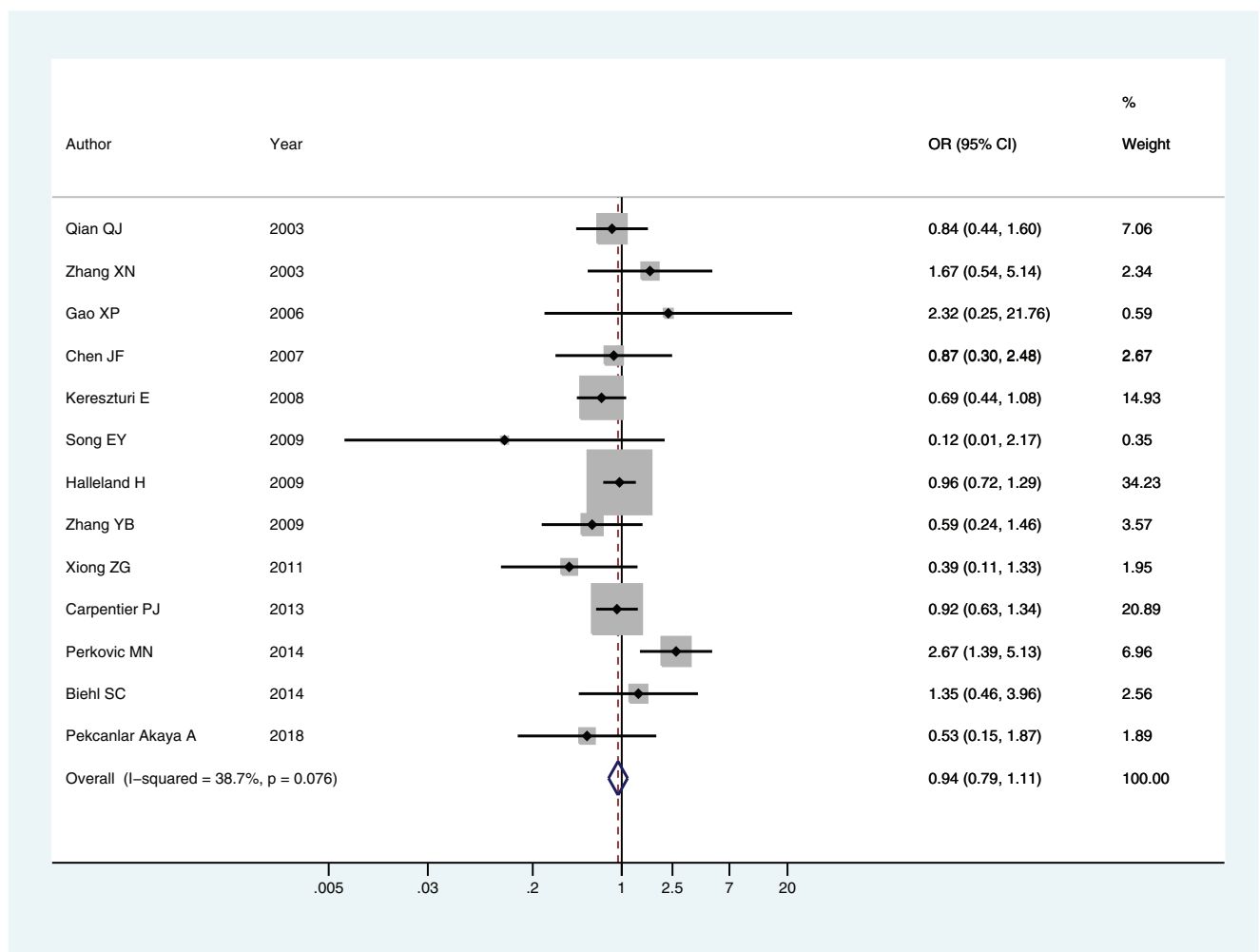


**Figure 3.** Forest plot of ORs for the association of COMT gene Val158Met polymorphism with ADHD risk in recessive model (AA vs GG+GA) of the fixed effect model pooled ORs. White diamond denotes the pooled OR. Black squares indicate the OR in each study, with square sizes inversely proportional to the standard error of the OR. Horizontal lines represent 95% CIs.

### 3.5. Publication bias

No significant publication bias was detected in dominant and codominant models. And for the recessive model, before and after sensitive analysis, no significant publication bias was detected. Figure 5 showed the funnel plot for publication bias after sensitivity analysis of the recessive model.

## 4. Discussion

Eisenberg et al[8] reported an association between *COMT* polymorphism and ADHD disorder in a group of Israeli nuclear families in 1999, however, they failed to replicate the finding in an independently recruited group in 2000.[37] Since then, there have been many related studies focused on the *COMT* gene polymorphism and ADHD risk. Nevertheless, results of subsequent studies are conflicting. Kereszturi et al's[25] study showed that the Val allele was more frequent in the ADHD group compared to the healthy population. Hong et al[38] found that compared with Val-homozygous adolescents, the white matter network of COMT Met-carriers was significantly weakened. In the study of Kabukcu et al,[39] the connection between the COMT val158met polymorphism and right cingulate hyperactivity disorder was first discovered, which affected brain development. However, no significant association was found between the *COMT* genotype and ADHD in Yatsuga et al's[31] study and Pekcanlar Akaya et al's[36] study. Also several meta-analysis[13–16] indicated no association between *COMT* val158met polymorphism and ADHD.

Different results may be considered due to the multifactorial nature of ADHD. Given the above-mentioned inconsistent results, an updated meta-analysis is the appropriate approach to obtain a more definitive conclusion regarding the role of *COMT* val158met polymorphism on ADHD. Our meta-analysis, based on seventeen articles including 3274 ADHD cases and 2514 controls allowed a much greater possibility of reaching reasonable and strong conclusions. Still, no significant association of the *COMT* val158met polymorphism with ADHD risk was found in the overall as well as subgroup analysis by ethnicity before and after sensitive analysis.

Heterogeneity among studies is common in meta-analysis of gene correlation studies.[40] The present meta-analysis also showed significant heterogeneity in recessive model. In different studies, an indeterminate number of characteristics (e.g., sex, age, publication year and ethnicity) could be the sources of between-study heterogeneity. Therefore, we used meta-regression and "leave one out" sensitivity analysis to explore the potentially important sources of between-study heterogeneity and reduce heterogeneity caused by both covariates and studies. We did not identify that any of the aforementioned covariates were important factors for between-study heterogeneity. Subgroup analysis by ethnicity also found no significant positive results in both Asian and Caucasian population. Although sex, age, publication year and ethnicity were not found to be sources of disease–effect heterogeneity in our meta-analysis, other genetic and environment variables and their possible interaction may be potential contributors to this disease–effect inconsistency. From this perspective, the lack of relevant study-level covariates information in the reported articles limited the more reliable assessment of sources of this heterogeneity. At the same time, other possible factors related to disease–effect diversity, such as differences in design quality and variations in genotyping, etc. could not be ruled out. The key contributor to between-study
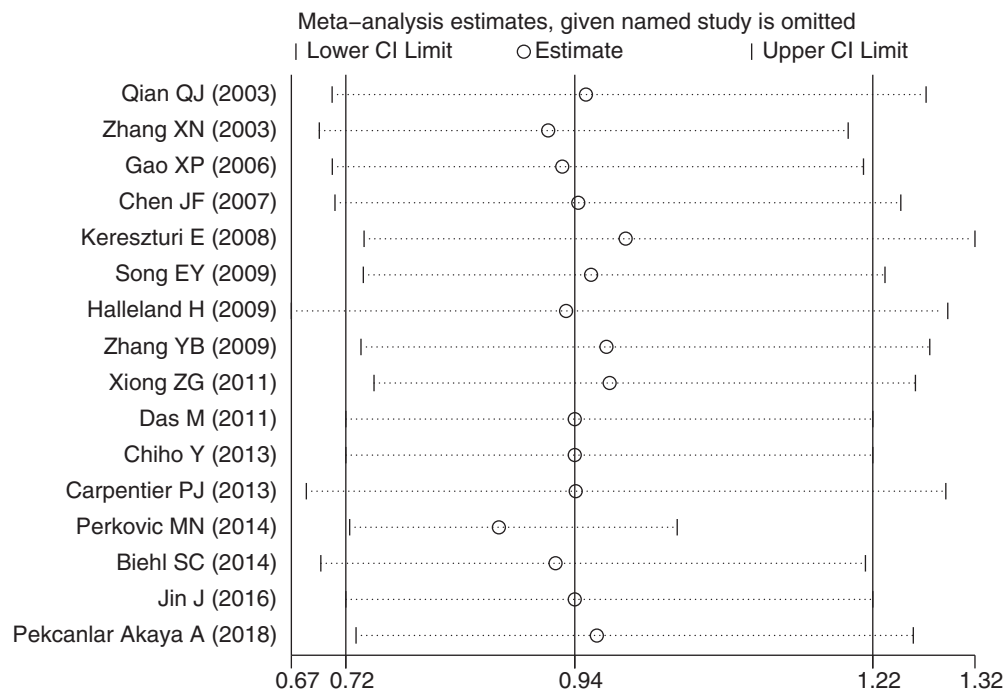


**Figure 4.** Analysis of influence of individual study on the pooled estimate in recessive model (AA vs GG+GA) of COMT gene Val158Met polymorphism after sensitive analysis in overall population. Open circle indicate the pooled odds ratio, given named study is omitted. Horizontal lines represent the 95% confidence intervals.
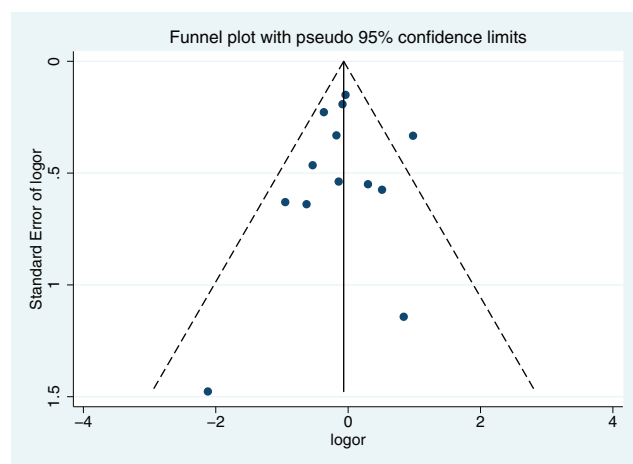
**Figure 5.** Funnel plot with pseudo 95% confidence limits for publication bias after sensitivity analysis in recessive model (AA vs GG+GA) after sensitive analysis.

heterogeneity assessed by the "leave one-out" sensitivity analysis was the one conducted by Perkovic MN et al[12] published in 2013. The heterogeneity caused by the study might lie in the subjects were sampled in two different countries (507 in Tartu, Estonia and 300 in Osijek, Croatia).

After sensitive analysis, no individual study was found to have excessive influence on the pooled effect as well as no publication bias was observed in all the above-mentioned models in the present meta-analysis. ADHD is a multifactorial disease that is affected by a variety of environmental and genetic factors. In this study, we simply explored the relationship between *COMT* gene Val158Met polymorphism and ADHD risk. The possible interactions between *COMT* gene Val158Met polymorphisms and other gene polymorphisms and also environmental factors need to be further explored in future research.

In conclusion, this meta-analysis suggested that there might be no association of the Val158Met polymorphism in *COMT* gene with ADHD risk. Since potential biases and confounding factors could not be ruled out completely in our meta-analysis, further better-design studies are needed to test our results.

## Author contributions

**Data curation:** Peipei Kang, Xiling Peng.
**Formal analysis:** Peipei Kang.
**Methodology:** Peipei Kang, Limei Luo.
**Writing – original draft:** Peipei Kang.
**Writing – review & editing:** Peipei Kang, Limei Luo, Xiling Peng, Yanhu Wang.

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