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ORIGINAL RESEARCH

The role of *COMT* gene Val108/158Met polymorphism in suicidal behavior: systematic review and updated meta-analysis

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Background: It is accepted that there is a genetic factor that influences the risk of suicidal behavior. The *catechol-O-methyltransferase* (*COMT*) gene, especially the Val108/158Met polymorphism, has been associated with suicide; however, no conclusive outcome has been attained. Therefore, the aim of the present study was to assess the role of *COMT* Val108/158Met in suicidal behavior throughout an updated meta-analysis.

Methods: We performed an online search using PubMed and Web of Science (up to March 2017). Our systematic review included case-control studies of individuals who attempted suicide and completed suicide. We tested allelic, homozygous, heterozygous, dominant, and recessive inheritance models. The meta-analysis was performed in accordance with the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results: The meta-analysis comprised 17 studies, which included 3,282 cases and 3,774 controls, and showed that when evaluating the overall population, the Val108/158Met polymorphism of *COMT* was not associated with suicidal behavior in any of the inheritance models; however, the subanalyses showed that this polymorphism exhibits a risk factor in males and a protective effect in females. Additionally, it conveyed a risk factor in Asian populations when using the allelic (OR 1.25; CI: 1.04–1.51) and recessive models (OR 1.32; CI: 1.03–1.68).

Conclusion: Our updated meta-analysis suggests a possible association between *COMT* Val108/158Met and suicidal behavior in Asian populations. However, in view of the small number of studies, these results should be considered exploratory. We recommend that more studies be performed with larger samples.

Keywords: suicide, epidemiology, mental health, risk factors

Introduction

Suicidal behavior (SB) is a complex phenotype with biological, genetic, and environmental risk factors involved.[1,2] Several arguments show that psychiatric disturbances are major contributing factors in SB; however, genetic predisposition has been strongly considered to be a contributory factor in SB,[3,4] and evidence indicates that SB is modulated by a number of gene variants.[2,4] The majority of investigations have focused on genes that codify proteins of different neurotransmitter systems, such as dopamine transporter, serotonin transporter, the two isoforms of tryptophan hydroxylase, the serotonin receptors family, and catechol-*O*-methyltransferase (*COMT*).[2,5,6]

The *COMT* gene has been repeatedly explored in SB. COMT is one of the major enzymes involved in catecholamine degradation. Its gene is located on chromosome 22q11.1-11.2, and more than 4,000 polymorphisms have been identified (https://www.genecards.org/).[7–12] Human *COMT* contains a common functional polymorphism,

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G>A substitution in exon 4, which changes the amino acid at codon 108 (Val108Met) in soluble COMT or position 158 (Val158Met) in the membrane-bound COMT protein.[13–16] It has been observed that the COMT enzyme that contains valine has a relatively higher activity than the COMT enzyme that contains methionine.[17–21] This allele seems to be codominant with heterozygote enzyme activity following midway between the homozygous alleles.[13–16]

During the last few decades, many studies have analyzed the role of *COMT* and SB, with contradictory results. For instance, Ohara et al[22] reported, in 1996, that there was no association between *COMT* and suicide, while the group of Pivac et al[23] reported, in 2011, an association between *COMT* Val/Val genotype and suicide in nonalcoholic suicide completers. In addition, other studies have shown that the genotype that encodes the more active COMT enzyme (Val/Val) is more frequent in suicide attempters than in healthy subjects used as controls.[24] However, other reports have found no overall difference in allele/genotype frequency distribution between cases and controls but have found that the Met allele was more frequent among violent suicide attempters.[25] Several studies suggest that the Val108/158Met polymorphism of the *COMT* gene plays a role in numerous psychiatric disorders[26–32] but have not obtained conclusive results about a relationship between SB and the *COMT* gene. Therefore, meta-analytic techniques that summarize all data available and assess sample size effects as well as publication bias can provide results with a major statistical power.[7,14,33–36] Up to 2011, three meta-analyses had evaluated the association between the *COMT* gene and suicide;[7,33,37] however, five more recently published studies have contributed more information to understand the complexity of the genetic background of SB. Given the importance of the *COMT* gene in SB, we performed an updated meta-analysis and systematic review to further explore the hypothesis of the genetic predisposition of the Val108/158Met *COMT* polymorphism in SB.

Materials and methods

The systematic review and meta-analysis were conducted in light of the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses. This study had been previously registered in PROSPERO (PROSPERO 2017 CRD42017070229). As no human participants or animals had been recruited, ethical approval was not required.

Literature search strategy

To identify relevant articles, we performed an online search through PubMed and Web of Science, up to March 2017, using as keywords "*COMT* gene AND suicide," "rs4680 AND suicide," and "Val108/158Met AND suicide."

Inclusion/exclusion criteria

Relevant studies had to fulfill the following criteria: 1) studies with a case-control or cohort design; 2) studies evaluating the association between rs4680 *COMT* variant and suicide; 3) studies published in English and in peer-reviewed journals; 4) the genotype frequency distribution had to be cited or could be calculated; and 5) studies containing sufficient information to calculate ORs. The articles were excluded when 1) they were found to contain overlapping data, 2) the number of null and wild genotypes could not be ascertained, and 3) family members had been included in the case group because their analyses were based on linkage consideration.

Data extraction

The general information extracted from the articles included the following: first author, year of publication, country (area) of origin, study design, source of control groups (case-control studies), sample size, genotyping methods, diagnostics, methods used for the diagnostics matching variables, genotype and allele frequency distributions, and outcome findings. This key information was extracted in consensus by Hernández-Díaz and González-Castro.

Statistical analysis

The meta-analysis was carried out with the use of the Comprehensive Meta-Analysis Version 2.0 software (Biostat Inc., Englewood, NJ, USA). The analysis was performed using five genetic models (allele, dominant, recessive, homozygous, and heterozygous). For each model, the OR and 95% CI were calculated, and the results are presented as the random effects model of meta-analysis. The presence of heterogeneity was indicated when the P-value of the Q test <0.1 or $I^2>50\%$. The OR estimates for each study were used to analyze the fixed effects model (the Mantel–Haenszel method) when there was no evidence of statistical heterogeneity. Otherwise, the random effects model (the DerSimonian and Laird method) was considered. The Galbraith plot and sensitivity analysis were used to search for published studies with heterogeneity, and the meta-analysis was performed again after these published studies were excluded. The χ^2 test was used to define whether the gene frequency distribution was in Hardy Weinberg Equilibrium (HWE); the studies with a $P<0.5$ were considered out of the HWE; therefore, they were excluded from the meta-analysis. Subgroup analyses based on location and ethnicity (Asian and European), gender (males and females), and individuals with suicide attempt (SA) were also completed. Finally, a meta-regression based on age was performed.

The power of the study was calculated as previously reported elsewhere.[38] Using an effect size d=0.20 and 14 studies with 140 patients per group, we obtained a power of 0.99.

Quality assessment

The quality assessment of each study was performed using the Newcastle–Ottawa Quality Assessment Scale (NOS). A NOS $>$6 was considered a high-quality study. Any disparity about the NOS scores was resolved in consultation with a third reviewer.

Publication bias and sensitivity analyses

In addition, sensitivity and publication bias of the studies were evaluated. The sensitivity analysis was done by eliminating one study at a time. Begg's test and Egger's test were used to evaluate publication bias of the included studies; $P<0.5$ was considered statistically significant.

Results

Studies included

Ninety-three studies were first identified; after reviewing titles, abstracts, and compliance with the inclusion criteria, 17 studies were enrolled in this meta-analysis. A flowchart describing the inclusion/exclusion of the individual studies is displayed as Figure 1. The included studies were published between 1998 and 2016. Of these 17 studies, six evaluated European populations, six evaluated Asian descendants, three used a mixed population, and two evaluated American individuals. The genotype and frequency distributions are presented in Table 1. The studies of Schosser et al,[32] Baud et al,[24] and Sun et al,[36] were excluded from all the analyses because their control groups presented a HWE P-value $<$0.05.

Overall findings

In the overall population, after discarding the studies of Nedic et al,[11] and Ono et al,[21] (because the sensitivity and heterogeneity analyses indicated that they favored the presence of heterogeneity between studies), the association between the Val108/158Met *COMT* polymorphism and susceptibility to suicide was evaluated in 3,282 cases and 3,774 controls. No significant association was observed in any of the comparisons: allele model (OR =1.05; 95% CI =0.95–1.18; *Z P*-value =0.29), homozygous (OR =1.15, 95% CI =0.94–1.42, *Z P*-value =0.16), heterozygous (OR =1.06, 95% CI =0.91–1.24, *Z P*-value =0.43), dominant (OR =1.15, 95% CI =0.97–1.37, *Z P*-value =0.10), and recessive model (OR =1.10, 95% CI =0.95–1.28, *Z P*-value =0.18). The Egger's test and Begg's funnel did not evidence publication bias; Figure 1. Our results are presented in Table 2.

Regarding the meta-regression based on age, the overall population analysis revealed a point estimate slope of 0.0183 and a *P*-value of 0.222 (Figure 2).

Subgroup analysis

Asian populations

Five studies were included to investigate the association between the Val108/158Met *COMT* polymorphism and SB in Asian populations. We used allelic, homozygous, heterozygous, dominant, and recessive models and did not find any association; however, when we discarded the studies that favored heterogeneity, we found a slight association in the allelic (OR =1.25, 95% CI =1.04–1.51, *Z P*-value =0.01) and recessive (OR =1.32, 95% CI =1.03–1.68, *Z P*-value =0.02) models; Figure 3 and Table 2.

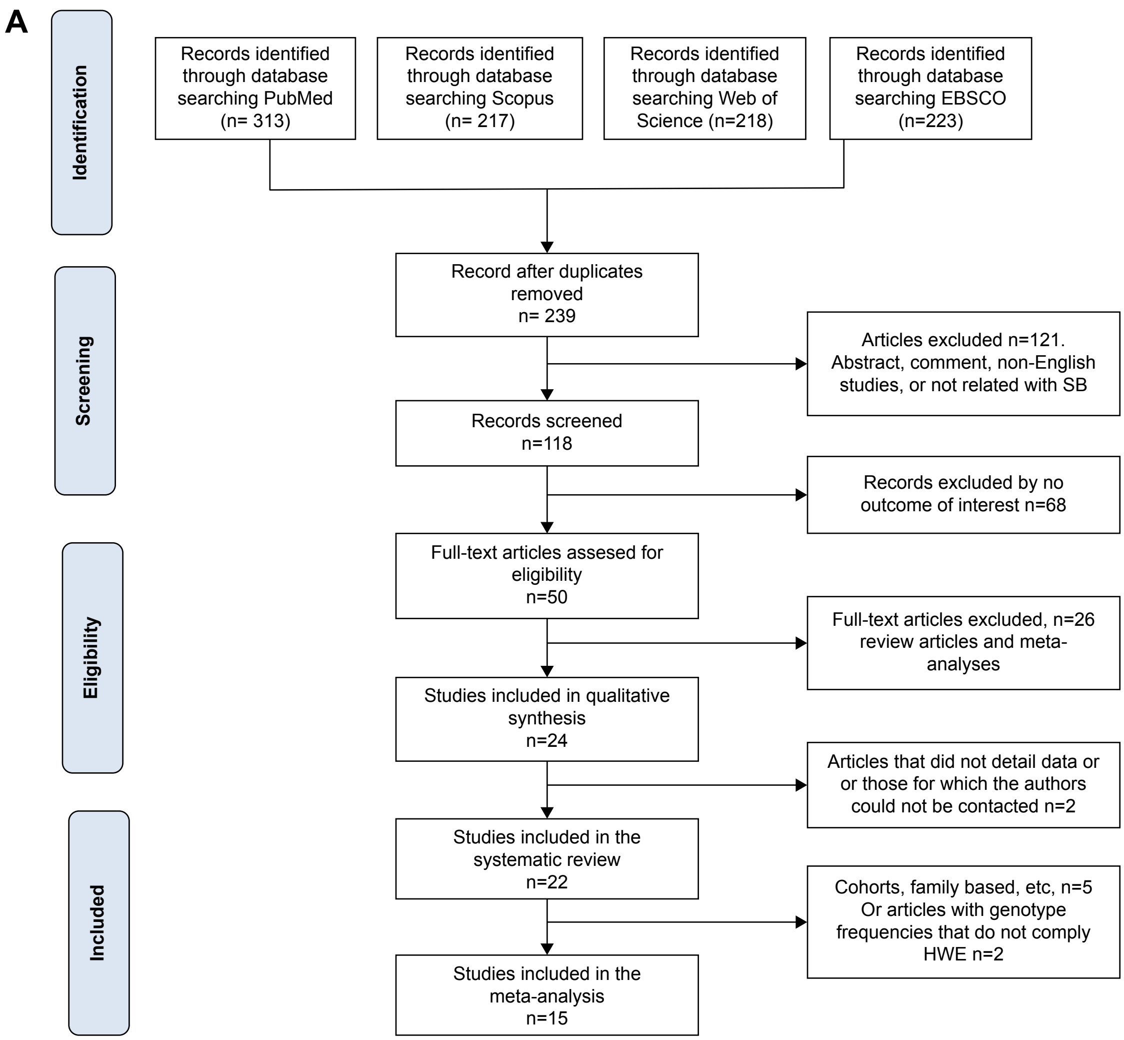
European populations

Subsequently, using five articles, we performed an analysis of European populations. In the absence of heterogeneity, no statistical association was observed in any of the models used: allele (OR =1.00; 95% CI =0.86–1.17; *Z P*-value =0.95), homozygous (OR =1.01, 95% CI =0.74–1.37, *Z P*-value =0.93), heterozygous (OR =0.86, 95% CI =0.67–1.11, *Z P*-value =0.25), dominant (OR =1.06, 95% CI =0.81–1.40, *Z P*-value =0.64), and recessive (OR =0.94, 95% CI =0.73–1.21, *Z P*-value =0.65) models; Figure 1 and Table 2.

Suicide attempters

Finally, to better comprehend the role of the *COMT*108/158 polymorphism, we performed a subgroup analysis using 11 studies that had evaluated suicide attempters. We still found the same negative results, even when we excluded one study that supported heterogeneity: allelic (OR =1.11; 95% CI =0.99–1.23; *Z P*-value =0.05), homozygous (OR =1.22; 95% CI =0.97–1.55; *Z P*-value =0.08), heterozygous (OR =1.03; 95% CI =0.86–1.23; *Z P*-value =0.71), dominant (OR =1.19; 95% CI =0.98–1.44; *Z P*-value =0.07), and

A



B

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Liou et al,[45] 2001	1.347	0.355	5.106	0.438	0.661
Rujescu et al,[25] 2003	0.828	0.483	1.419	–0.688	0.492
Du et al,[39] 2014	1.039	0.406	2.656	0.080	0.936
Ono et al,[21] 2004	0.850	0.404	1.788	–0.428	0.668
Russ et al,[31] 2000	0.583	0.169	2.014	–0.852	0.394
Pivac et al,[23] 2011	1.198	0.726	1.977	0.708	0.479
Tovilla-Zárate et al,[33] 2011	1.438	0.688	3.007	0.966	0.334
Lee and Kim[27] 2011	1.211	0.577	2.542	0.506	0.613
Zalsman et al,[47] 2008	1.684	0.841	3.369	1.471	0.141
Antypa et al,[46] 2016	1.428	0.711	2.869	1.001	0.317
Ohara et al,[20] 1998	0.207	0.032	1.337	–1.655	0.098
Chen et al,[8] 2014	2.297	1.065	4.953	2.121	0.034
Calati et al,[7] 2011	1.011	0.507	2.016	0.032	0.974
	1.158	0.942	1.424	1.395	0.163

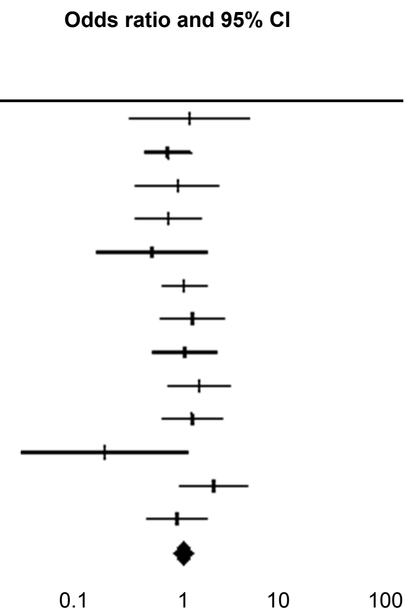


Figure 1 (*Continued*)

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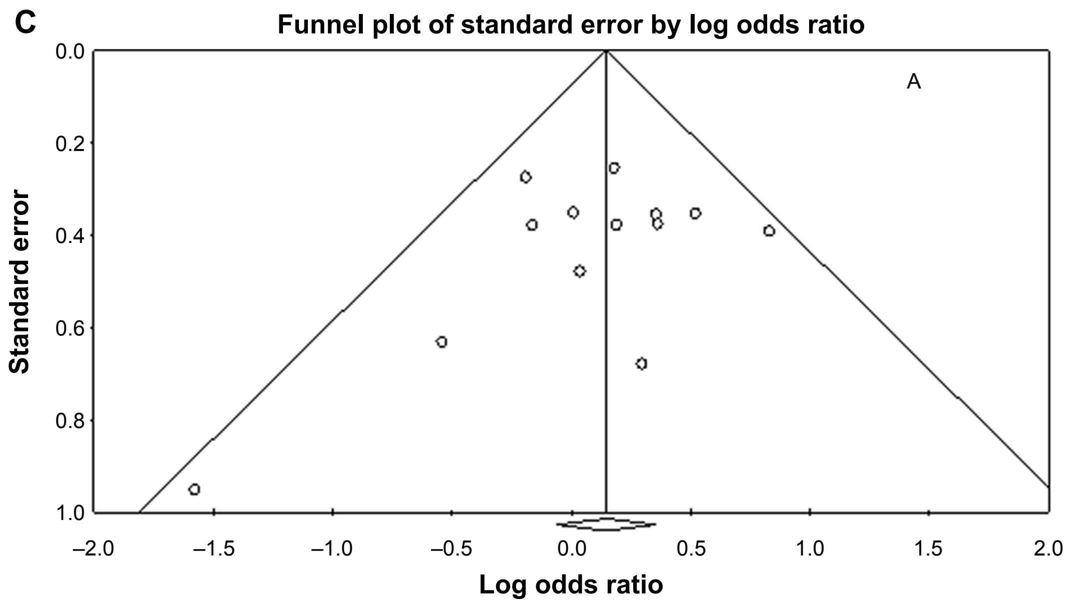


D

Study name	Statistics for each study				
	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Liou et al,[45] 2001	1.222	0.330	4.530	0.300	0.764
Rujescu et al,[25] 2003	0.783	0.510	1.203	–1.117	0.264
Du et al,[39] 2014	0.962	0.429	2.153	–0.095	0.924
Ono et al,[21] 2004	1.095	0.538	2.229	0.251	0.802
Russ et al,[31] 2000	0.741	0.252	2.178	–0.545	0.585
Pivac et al,[23] 2011	1.339	0.901	1.990	1.443	0.149
Tovilla-Zárate et al,[33] 2011	1.622	0.833	3.159	1.421	0.155
Lee and Kim[27] 2011	1.033	0.509	2.095	0.091	0.928
Zalsman et al,[47] 2008	1.346	0.784	2.313	1.077	0.281
Antypa et al,[46] 2016	1.204	0.665	2.180	0.614	0.539
Ohara et al,[20] 1998	0.462	0.114	1.867	–1.084	0.278
Chen et al,[8] 2014	2.097	0.990	4.441	1.934	0.053
Calati et al,[7] 2011	1.231	0.695	2.179	0.712	0.476
	1.157	0.971	1.379	1.634	0.102

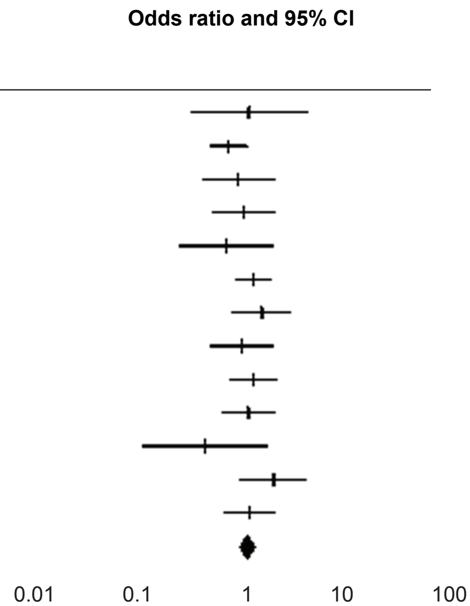


Figure 1 Procedures and data analysis.
Notes: (**A**) Flowchart showing study inclusion and exclusion details. (**B**) Forest plot of a homozygous model in the overall population. (**C**) Begg's funnel plot analysis of publication bias in homozygous models in the overall population. (**D**) Forest plot of a dominant model in European populations.

recessive (OR =1.12; 95% CI =0.96–1.31; *Z P*-value =0.13) models; Figure 3 and Table 2.

Male group analysis

Because of the possible influence that gender could have over the psychopathology of suicide, we evaluated the role of the *COMT* polymorphism in males. The analysis revealed an association when heterogeneity was absent in the allelic (OR=1.29; 95% CI=1.04–1.60; *Z P*-value=0.01), homozygous (OR =1.54; 95% CI =1.04–2.28; *Z P*-value =0.02), heterozygous (OR =1.67; 95% CI =1.17–2.38; *Z P*-value =0.001), and dominant (OR =1.66; 95% CI =1.18–2.31; *Z P*-value =0.001) models; Table 2 and Figure 4.

Female group analysis

Similarly, we explored the involvement of the *COMT* gene variants in suicide in females. Here too, we found an association when heterogeneity was absent in the allelic (OR =0.74;

Table 1 Systematic review of the genetic association of Val66Met and SB, characteristics of the studies included

First author	Location	Diagnosis instrument	SB cases	Number of		Mean age		Male/female		Cases			Controls			HWE		NOS
				Cases	Control	Cases	Control	Cases	Control	V-V	V-M	M-M	V-V	V-M	M-M	Cases	Controls	
Ohara et al,[20] 1998	Japan	DSM-IV	SA	115	135	38.5	–	60/55	–	2	7	3	58	59	18	0.54	0.62	4
Nolan et al,[12] 2000	USA, Finland	DSM-IV, DSM-III-R	SA	148	–	42.35	–	42.35	–	44	66	38	–	–	–	–	–	4
Russ et al,[31] 2000	USA	DSM-IV	SI	51	51	38	41	32/19	28/23	12	28	9	16	26	7	0.39	0.56	8
Liou et al,[45] 2001	Taiwan	DSM-IV	SA	62	188	36.7	38.6	26/36	97/91	36	23	3	98	79	11	0.77	0.45	5
Rujescu et al,[25] 2003	Germany	DSM-IV	SA	149	328	40	46	53/96	149/179	35	69	45	78	167	83	0.41	0.82	8
de Luca et al,[26] 2005	Canada	SCID I	SA	336	–	35.36	–	128/208	–	–	–	–	–	–	–	–	–	4
Ono et al,[21] 2004	Japan		SC	163	169	47.9	47.115	112/51	114/55	68	79	16	90	61	18	0.38	0.13	8
de Luca et al,[13] 2006	Canada	SCID I	SA	92	178	42.6	40.6	68/24	129/49	–	–	–	–	–	–	–	–	4
Baud et al,[24] 2007	Switzerland, France	STAXI	SA	427	185	38.7	46.08	125/302	130/55	124	218	85	34	107	44	0.55	0.03*	8
Zalsman et al,[47] 2008	USA	DSM-IV axis-I and II	SA	486	119	41.6	41.2	209/277	78/41	27	67	25	34	114	53	0.20	0.05	5
Perroud et al,[29] 2010	Switzerland, France	DIGS and MINI	SA	875	–	–	–	256/619	–	252	387	183	–	–	–	–	–	4
Nedic et al,[11] 2011	Croatia	DSM-IV	–	82	311	50.465	50.74	59/23	253/58	9	38	35	76	170	65	0.78	0.09	7
Pivac et al,[23] 2011	Slovenia	–	SA	356	198	48.9	47.1	–	–	78	197	81	45	97	56	0.05	0.88	7
Tovilla-Zárate et al,[33] 2011	Mexico	DSM-IV axis-I and II	SA	105	236	30.5	34.5	55/50	132/104	34	58	13	80	112	44	0.15	0.68	6
Calati et al,[7] 2011	Germany	SCID I and SCID II	SA	111	289	39.3	45.2	43/68	123/166	23	56	19	79	144	66	0.22	0.98	7
Lee and Him,[27] 2011	Korea	DSM-IV	SA	197	170	33.5	36.2	70/127	85/85	94	85	18	69	85	16	0.84	0.23	7
Schosser et al,[32] 2012		MINI and HAM-D	SI/SA	68	150	50.75	–	68/182	–	20	33	15	29	93	29	0.81	0.005	7
Du et al,[39] 2014	Hungary	DSM-IV	SC	49	72	64.5	48.915	35/14	46/26	16	19	14	22	30	20	0.15	0.16	8
Chen et al,[8] 2014	Taiwan	DSM-IV	SA	187	386	32.4	34.3	11/176	168/218	100	78	9	179	170	37	0.25	0.81	6
Pasi et al,[28] 2015	India	DSM-IV and C-SSRS	SA	25	–	–	–	20:05	–	13	23	4	–	–	–	–	–	4
Sun et al,[36] 2016	People's Republic of China	DSM-IV-TR axis-I	SA	369	369	44.1	43.9	117/252	117/252	218	129	22	193	161	15	0.66	0.005	7
Antypa et al,[46] 2016	Belgium	DSM-IV	SA	213	240	45.99	48.88	63/150	148/192	32	44	23	38	69	39	0.31	0.51	7

Notes: Data not available is indicated with "–". Statistical significance is indicated with "*".
Abbreviations: SB, suicidal behavior; V-V, Val-Val; V-M, Val-Met; M-M, Met-Met; DSM, Diagnostic and Statistical Manual of Mental Disorders; SCID, Structured Clinical Interview for DSM-IV; STAXI, State-Trait Anger Expression Inventory; DIGS, Diagnostic Interview for Genetic Studies; HAM-D, Hamilton Depression Rating Scale; C-SSRS: Columbia-Suicide Severity Rating Scale.

Table 2 Meta-analysis results comparing inherence models between cases and controls

Model	Number of studies	Heterogeneity	Random effects, OR (CI 95%)	*Z P*-value	I^2	Q test *P*-value	Egger's test *P*-value
Overall population							
Allelic	14	Large	0.98 (0.84–1.14)	0.85	59.84	0.00	0.12
	13	Absent	1.05 (0.95–1.18)	0.29	19.94	0.24	0.13
Homozygous	14	Large	1.01 (0.74–1.37)	0.93	52.07	0.01	0.33
	13	Absent	1.15 (0.94–1.42)	0.16	0.00	0.46	0.31
Heterozygous	14	Moderate	0.96 (0.80–1.15)	0.68	29.48	0.14	0.18
	12	Absent	1.06 (0.91–1.24)	0.43	0.00	0.52	0.12
Dominant	14	Large	1.03 (0.79–1.34)	0.80	53.88	0.00	0.97
	13	Absent	1.15 (0.97–1.37)	0.10	0.00	0.60	0.62
Recessive	14	Moderate	0.97 (0.80–1.18)	0.80	43.70	0.04	0.08
	12	Absent	1.10 (0.95–1.28)	0.18	0.00	0.49	0.48
Asian populations							
Allelic	5	Large	1.02 (0.77–1.35)	0.86	62.20	0.03	0.27
	3	Absent	**1.25 (1.04–1.51)**	**0.01**	0.00	0.83	0.65
Homozygous	5	Moderate	1.14 (0.65–2.02)	0.63	42.90	0.13	0.34
	4	Absent	1.32 (0.84–2.05)	0.21	11.62	0.33	0.92
Heterozygous	5	Large	0.98 (0.65–1.46)	0.92	63.99	0.02	0.42
	4	Absent	1.22 (0.93–1.60)	0.14	9.05	0.34	0.14
Dominant	5	Absent	1.20 (0.81–1.78)	0.35	3.37	0.38	0.43
Recessive	5	Large	1.01 (0.68–1.50)	0.95	66.03	0.01	0.35
	3	Absent	**1.32 (1.03–1.68)**	**0.02**	0.00	0.99	0.30
European populations							
Allelic	5	Large	0.86 (0.65–1.15)	0.32	72.72	0.00	0.58
	4	Absent	1.00 (0.86–1.17)	0.95	0.00	0.77	0.89
Homozygous	5	Large	0.76 (0.44–1.31)	0.33	69.43	0.01	0.42
	4	Absent	1.01 (0.74–1.37)	0.93	0.00	0.80	0.93
Heterozygous	5	Absent	0.86 (0.67–1.11)	0.25	0.00	0.55	0.68
Dominant	5	Large	0.84 (0.52–1.38)	0.50	77.60	0.00	0.79
	4	Absent	1.06 (0.81–1.40)	0.64	15.75	0.31	0.89
Recessive	5	Moderate	0.84 (0.62–1.12)	0.24	29.24	0.22	0.38
	4	Absent	0.94 (0.73–1.21)	0.65	0.00	0.92	0.73
Suicide attempters							
Allelic	11	Large	1.01 (0.85–1.21)	0.84	65.25	0.00	0.26
	10	Absent	1.11 (0.99–1.23)	0.05	7.35	0.37	0.22
Homozygous	11	Large	1.05 (0.73–1.51)	0.78	61.35	0.00	0.50
	10	Absent	1.22 (0.97–1.55)	0.08	6.16	0.38	0.64
Heterozygous	11	Absent	1.03 (0.86–1.23)	0.71	18.37	0.26	0.07
Dominant	11	Large	1.05 (0.77–1.44)	0.74	64.00	0.00	0.84
	10	Absent	1.19 (0.98–1.44)	0.07	1.57	0.42	0.99
Recessive	11	Moderate	1.04 (0.84–1.27)	0.69	41.02	0.07	0.03
	10	Absent	1.12 (0.96–1.31)	0.13	0.73	0.43	0.10
Males							
Allelic	7	Large	1.00 (0.69–1.43)	0.99	79.31	0.00	0.83
	5	Absent	**1.29 (1.04–1.60)**	**0.01**	16.96	0.30	0.74
Homozygous	7	Large	1.07 (0.54–2.13)	0.83	69.29	0.00	0.65
	6	Absent	**1.54 (1.04–2.28)**	**0.02**	0.00	0.61	0.50
Heterozygous	7	Large	1.20 (0.64–2.27)	0.55	71.69	0.00	0.84
	6	Absent	**1.67 (1.17–2.38)**	**0.00**	0.00	0.52	0.51
Dominant	7	Large	1.17 (0.60–2.24)	0.63	76.26	0.00	0.84
	6	Absent	**1.66 (1.18–2.31)**	**0.00**	0.00	0.76	0.32
Recessive	7	Large	0.91 (0.56–1.48)	0.71	76.07	0.00	0.63
	4	Absent	1.04 (0.70–1.53)	0.83	24.20	0.23	0.52
Females							
Allelic	7	Moderate	0.83 (0.66–1.03)	0.09	28.30	0.21	0.02
	6	Absent	**0.74 (0.59–0.92)**	**0.00**	0.00	0.70	0.26
Homozygous	7	Absent	**0.57 (0.37–0.87)**	**0.01**	0.00	0.86	0.54
Heterozygous	7	Absent	**0.64 (0.43–0.95)**	**0.02**	0.00	0.48	0.88
Dominant	7	Absent	**0.60 (0.41–0.88)**	**0.00**	0.00	0.67	0.92
Recessive	7	Absent	0.86 (0.63–1.18)	0.36	28.65	0.21	0.03
	6	Absent	**0.71 (0.51–0.98)**	**0.03**	0.00	0.93	0.33

Note: The data in bold means association.

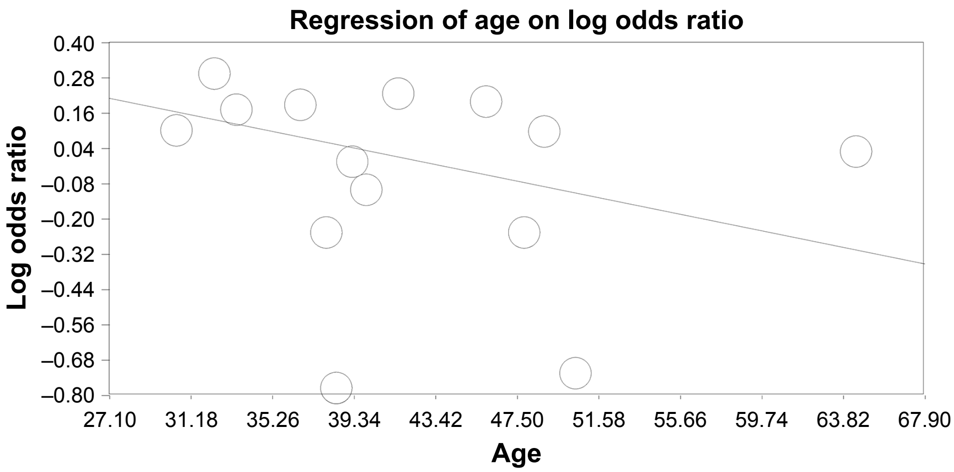


Figure 2 Meta-regression analysis based on mean age.

95% CI =0.59–0.92; *Z P*-value =0.001), homozygous (OR =0.57; 95% CI =0.37–0.87; *Z P*-value =0.01), heterozygous (OR =0.64; 95% CI =0.43–0.95; *Z P*-value =0.02), dominant (OR =0.60; 95% CI =0.41–0.88; *Z P*-value =0.001), and recessive (OR =0.71; 95% CI =0.51–0.98; *Z P*-value =0.03) models; Table 2 and Figure 4.

Sensitivity analysis

We conducted a sensitivity analysis to evaluate the stability of our results by removing each study at a time. However, no obvious changes were observed, and this confirmed that our results were stable under the five genetic models for the *COMT* Val108/158Met polymorphism.

Discussion

Some studies support the idea that there are neurobiological and genetic risks to developing SB, but the results have been inconsistent. The inconclusive results might be due to the use of small samples and differences in ethnicity.[13,39] Therefore, our aim was to further understand the effect of the *COMT* polymorphism in healthy individuals and suicide attempters by undertaking a systematic review and an updated meta-analysis. The current meta-analysis investigated the effect of the *COMT* Val108/158Met polymorphism in SB in global and subgroup analyses divided into ethnicities (Asians and Europeans), suicide attempters, and gender.

The global analysis showed no effect of the *COMT* polymorphism and SB in the overall population (using 14 high-quality studies); even though we used five different models, we did not observe any statistical association. On the contrary, in 2007, a meta-analysis that evaluated six studies showed a significant association between the *COMT* Val108/158Met polymorphism and SB; however, when one study at a time was removed from the analysis, the relationship between *COMT* and SB was no longer significant.[14]

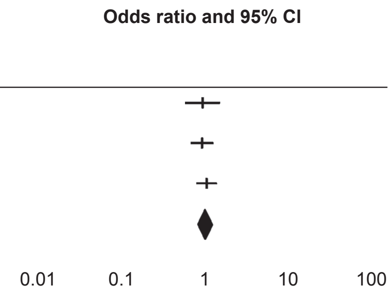
Furthermore, when we divided the populations by location and ethnicity (Asians and Europeans), we observed an association between the Val108/158 polymorphism and SB in Asian individuals, but not in Europeans; however, it is noteworthy that statistical significance was seen only after we excluded heterogeneity and only after three studies remained; therefore, this sample size was too small to give conclusive results. We therefore recommend that more studies be undertaken in order to reach a conclusion about this relationship. The discrepancy observed among the outcomes can be explained as follows: the frequency distribution of the Val and Met alleles might be dependent on ethnicity, genetic architecture, as well as the combination of behavioral and environmental risk factors, assignment of a higher or lower risk of developing SB to a particular location or sample.[17,25]

Furthermore, we performed, with the five models previously indicated, another subanalysis using researches that studied only suicide attempters and observed no association. However, it has been seen that the etiology of SB is multifactorial, including biological and genetic factors that differ in each particular SB (risk of suicide, suicide ideation, SA, or completed suicide); therefore, to reach definitive conclusions, it is necessary to take this multifactorial characteristic into consideration.[14,40]

The negative association we observed in the global analysis agrees with the meta-analyses by Tovilla-Zárate et al[33] and Calati et al,[7] who also obtained negative results in the pooled ORs in the overall populations. On the other hand, the study of Sadeghiyeh et al,[41] published in 2017,

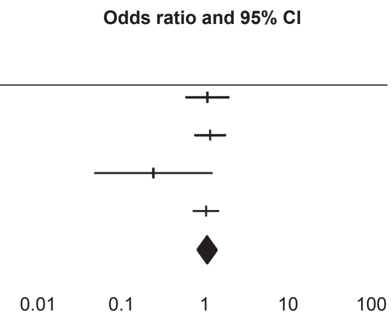
A

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Liou et al,[45] 2001	1.203	0.749	1.933	0.764	0.445
Lee and Kim,[27] 2011	1.184	0.869	1.613	1.068	0.286
Chen et al,[8] 2014	1.338	1.014	1.766	2.060	0.039
	1.257	1.040	1.519	2.365	0.018



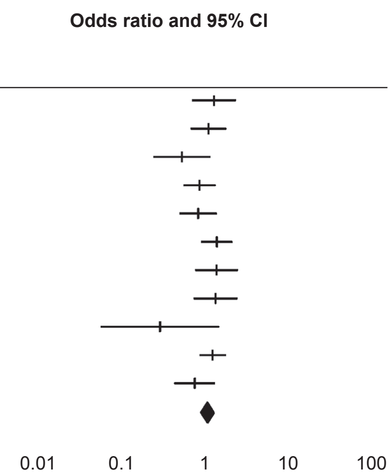
B

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Liou et al,[45] 2001	1.262	0.692	2.302	0.758	0.449
Lee and Kim,[27] 2011	1.362	0.884	2.099	1.402	0.161
Ohara et al,[20] 1998	0.291	0.058	1.458	–1.502	0.133
Chen et al,[8] 2014	1.218	0.847	1.750	1.063	0.288
	1.223	0.935	1.602	1.468	0.142



C

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Liou et al,[45] 2001	1.262	0.692	2.302	0.758	0.449
Rujescu et al,[25] 2003	1.086	0.667	1.768	0.332	0.740
Nedic et al,[11] 2011	0.530	0.244	1.150	–1.606	0.108
Pivac et al,[23] 2011	0.853	0.550	1.325	–0.706	0.480
Tovilla-Zárate et al,[33] 2011	0.821	0.492	1.369	–0.757	0.449
Lee and Kim[27]	1.362	0.884	2.099	1.402	0.161
Zalsman et al,[47] 2008	1.351	0.750	2.434	1.002	0.316
Antypa et al,[46] 2016	1.321	0.722	2.414	0.903	0.366
Ohara et al,[20] 1998	0.291	0.058	1.458	–1.502	0.133
Chen et al,[8] 2014	1.218	0.847	1.750	1.063	0.288
Calati et al,[7] 2011	0.749	0.429	1.307	–1.018	0.309
	1.034	0.864	1.237	0.362	0.717



D

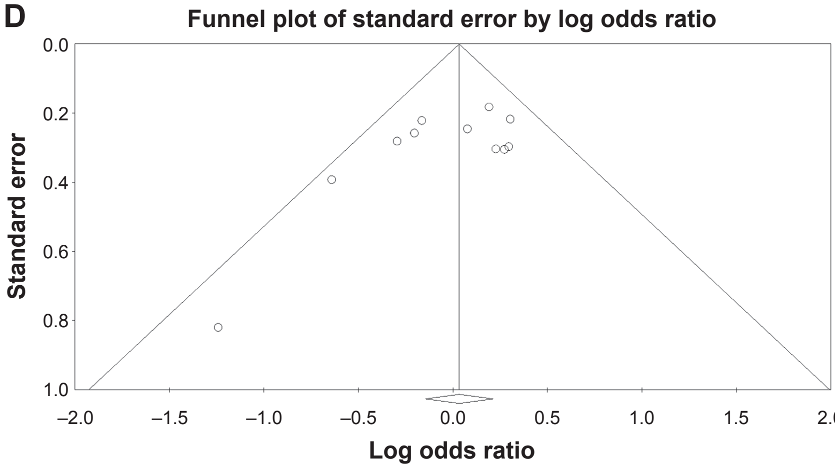
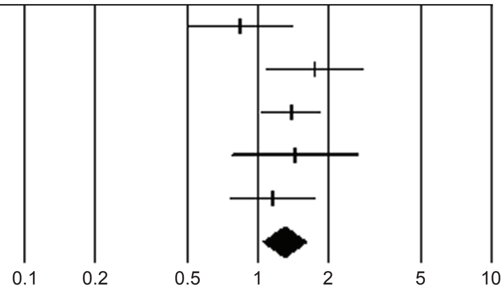


Figure 3 Data analysis.

Notes: (**A**) Forest plot of allelic model in Asian populations. (**B**) Forest plot of the recessive model in Asian populations. (**C**) Forest plot of the heterozygous model in suicide attempters. (**D**) Begg's funnel plot analysis of publication bias in the heterozygous model in suicide attempters.

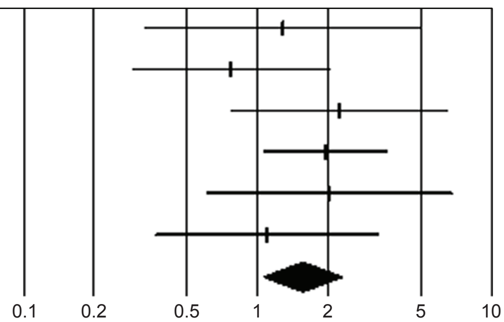
A

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Ohara et al,[20] 1998	0.838	0.497	1.412	–0.665	0.506
Lee and Kim,[27] 2011	1.750	1.086	2.820	2.298	0.022
Pivac et al,[23] 2011	1.386	1.030	1.864	2.159	0.031
Du et al,[39] 2014	1.438	0.768	2.689	1.136	0.256
Sun et al,[36] 2016	1.149	0.753	1.754	0.646	0.518
	1.293	1.042	1.603	2.338	0.019



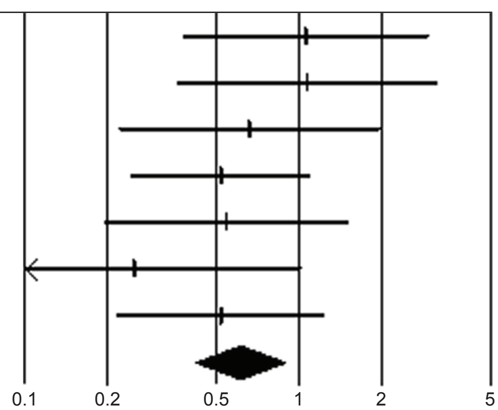
B

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Ohara et al,[20] 1998	1.280	0.330	4.959	0.357	0.721
Ono et al,[21] 2004	0.771	0.289	2.055	–0.521	0.603
Lee and Kim,[27] 2011	2.236	0.765	6.534	1.471	0.141
Pivac et al,[23] 2011	1.947	1.052	3.605	2.120	0.034
Du et al,[39] 2014	2.022	0.602	6.787	1.140	0.254
Sun et al,[36] 2016	1.094	0.364	3.289	0.160	0.873
	1.546	1.047	2.282	2.193	0.028



C

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Ohara et al,[20] 1998	1.055	0.375	2.971	0.101	0.919
Ono et al,[21] 2004	1.070	0.358	3.197	0.121	0.904
Lee and Kim[27] 2011	0.659	0.221	1.970	–0.746	0.455
Pivac et al,[23] 2011	0.517	0.243	1.100	–1.713	0.087
Nedic et al,[11] 2011	0.543	0.195	1.509	–1.171	0.242
Du et al,[39] 2014	0.250	0.061	1.019	–1.934	0.053
Sun et al,[36] 2016	0.518	0.216	1.245	–1.471	0.141
	0.608	0.418	0.885	–2.601	0.009



D

Study name	Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Ohara et al,[20] 1998	0.619	0.300	1.278	–1.297	0.195
Ono et al,[21] 2004	0.927	0.433	1.987	–0.194	0.846
Lee and Kim[27]	0.795	0.459	1.379	–0.815	0.415
Pivac et al,[23] 2011	0.600	0.287	1.255	–1.357	0.175
Nedic et al,[11] 2011	0.471	0.122	1.826	–1.088	0.276
Du et al,[39] 2014	0.662	0.140	3.123	–0.521	0.603
	0.711	0.516	0.980	–2.085	0.037

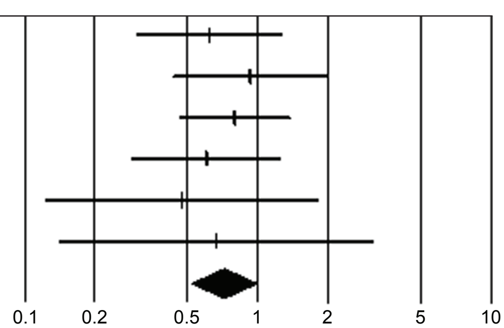


Figure 4 Forest plot in the (**A**) male group in the allelic model, (**B**) male group in the homozygous model, (**C**) female group in the dominant model, (**D**) female group in the recessive model.

showed that the *COMT* 158G/A (COMT Val158Met) polymorphism was associated with suicide susceptibility only in females.[7,14,33] Following this sense, we performed an analysis by gender; the evaluation of males using the five genetic models proposed previously revealed that Val could be a risk factor for suicide in males. Regarding the group of females, we observed a protective effect of the Val allele of *COMT* polymorphism, which is similar to the findings observed by Sadeghiyeh et al,[41] namely, a risk effect of the Met allele in homozygous and recessive models in the female group. However, we recommend increasing the sample size in features studies in order to increase the power to detect small effects of the polymorphism.

We emphasize that the main strength of our study in comparison with previous meta-analyses published is the number of cases and controls included. Kia-Keting et al[14] used 519 cases and 933 controls, Calati et al,[7] 1,324 cases and 1,415 controls, and Tovilla-Zárate et al,[33] 2,723 cases and 1,886 controls. An additional meta-analysis by Sadeghiyeh et al[41] involved 2,353 suicide attempters and 2,593 controls. Meanwhile, we compared 3,282 cases and 3,774 controls. Therefore, our study has more power to detect the small effects of the polymorphism.

Our study has some limitations. First, despite the sample size we used (a large number of cases and controls), our sample is not as large as the ones evaluated in other reports that have studied psychiatric disorders such as schizophrenia or bipolar disorder.[42–44] Second, we did not analyze the endophenotypes of SB. Hence, because of the available data, we could evaluate only SA, apart from SB. This is an important limitation because it has been reported that SA, suicide ideation, and death by suicide could have differences in the etiology. Third, we did not analyze environmental or biological factors that influence SB, although analyses of all variants should be performed.[21,45]

Conclusion

To sum up, our outcomes revealed a possible association of the *COMT* Val108/158 polymorphism with SB. In males, *COMT* Val108/158 increased the risk of SB, whereas in females, *COMT* Val108/158 exhibited a protective factor against SB. Also, *COMT* Val108/158 could be a risk factor in Asian individuals. Because of the limitation of the study, we recommend that more studies be undertaken using larger samples.

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Disclosure

The authors report no conflicts of interest in this work.

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