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DOI:
[10.1002/erv.2555](https://doi.org/10.1002/erv.2555)

Document Version
Peer reviewed version

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Citation for published version (APA):

Collantoni, E., Solmi, M., Gallicchio, D., Santonastaso, P., Meneguzzo, P., Carvalho, A. F., Stubbs, B., Clementi, M., Pinato, C., Forzan, M., Cassina, M., Fontana, F., Piva, I., Siani, R., Salvo, P., Tenconi, E., Veronese, N., Correll, C. U., & Favaro, A. (2017). Catechol-O-Methyltransferase (COMT) Val158Met Polymorphism and Eating Disorders: Data From a New Biobank and Meta-Analysis of Previously Published Studies. *European eating disorders review : the journal of the Eating Disorders Association*, 25(6), 524-532.
<https://doi.org/10.1002/erv.2555>

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Text: 4,584 / 7000 words

Abstract: 150 /150 Words

Tables: 2

Figures: 2

Catechol- *O*-methyltransferase (COMT) val158met polymorphism and eating disorders: Data from a new biobank and meta-analysis of previously published studies

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ABSTRACT

Objectives. We investigated whether catechol-*O*-methyltransferase (COMT) val158met polymorphism is associated with Eating Disorders (ED).

Methods. We conducted a systematic literature search of studies published until January 15,2017 and added data from the Italian '*Biobanca Veneta per i Disturbi Alimentari*' biobank(BIO.VE.D.A.), performing a meta-analysis comparing COMT val158met genotype and allele frequencies in EDs, and AN or BN patients vs. controls.

Results. Ten studies plus BIO.VE.D.A. (ED: n=920, controls: n=261 controls) with 3,541 ED patients (AN=2,388; BN=233) and 3,684 controls were included. There were no significant group differences in COMT val158met alleles and genotypes frequencies between patients and controls, for all EDs pooled together (range of odds ratios (ORs): 0.96-1.04, p-values: 0.46-0.97, $I^2=0\%$) and when analyzing separately patients with AN (ORs: 0.94-1.04, p-values: 0.31-0.61, $I^2=0\%$) or BN (ORs: 0.80-1.09, p-values: 0.28-0.64, $I^2=0-44\%$).

Conclusions. Meta-analyzing data from 11 studies and 7,225 subjects, results show that COMT val158met polymorphism is not associated with EDs.

Key words: polymorphism; anorexia nervosa; bulimia nervosa; Catechol- O-methyltransferase (COMT); val158met.

INTRODUCTION

Eating disorders (EDs) are severe psychiatric conditions characterized by a frequently disabling course and associated with high rates of comorbid psychopathology (Solmi, Veronese, et al., 2016), medical complications (Shuttleworth, Sharma, Lal, & Allan, 2016) (Solmi, Veronese, et al., 2016) and specific neuropsychological profiles (Treasure, Claudino, & Zucker) (Van den Eynde et al., 2011) .

In the last decades, major advances have been made in the understanding of the neurobiology of EDs, with increasing knowledge in their pathophysiology (Veronese et al., 2015), genetic and epigenetic profiles (Zeynep Yilmaz, Hardaway, & Bulik, 2015), structural and functional brain alterations (Collantoni et al., 2016) (Frank, 2015) and executive functioning impairment (Tenconi et al., 2010). Since dopamine is implicated in appetite regulation, eating and motor behaviors, emotional functioning and cognitive processes, the literature paid a great deal of attention to the possible role of this neurotransmitter in the pathophysiology of EDs.

In particular, the dysregulation of fronto-striatal dopaminergic circuit has been considered a key factor in explaining the affective and cognitive alterations observed in anorexia nervosa (AN) and bulimia nervosa (BN) patients, since these neural pathways support self-regulatory capacities and reward-based learning (Berner & Marsh, 2014) (Kaye, Fudge, & Paulus, 2009). The role of genes implicated in dopaminergic prefrontal signaling and metabolism is therefore of particular interest in EDs, and has been investigated in several studies.

Among the genes involved in dopamine prefrontal metabolism catechol-*O*-methyltransferase (COMT) appears to play a pivotal role in the modulation of fronto-striatal networks because it seems to have an important role in the modulation of neurocognitive functioning (Savitz, Solms, & Ramesar, 2006). The val158met is by far the most studied COMT polymorphism, as it modifies the thermal stability of the gene and thus its enzymatic activity, with complex consequences on cognitive operations influenced by DA signaling (Dickinson & Elvevåg, 2009).

The relationship between DA tone in the prefrontal cortex and PFC-dependent cognitive performance is characterized by an inverted U-shape, which may be determined by differential effects of D1 and D2 receptor binding (Bilder, Volavka, Lachman, & Grace, 2004). In particular, in the presence of the COMT Met allele DA levels in the prefrontal cortex increase and the resulting higher tonic D1 stimulation leads to beneficial effects on the stability of mental representations but at the cost of disadvantageous consequences on cognitive flexibility and working memory update abilities. Conversely, the COMT Val allele is associated with decreased DA concentrations and a low D1/high D2 state, which is associated with greater behavioral flexibility but also to higher impulsivity and risky decision making (Bilder et al., 2004).

The study of the val158met COMT genotype in EDs is particularly interesting since the effects of the COMT enzyme are influenced by estrogen levels. Estrogens inhibit COMT mRNA expression, reducing the effect of the COMT enzyme activity and of the COMT genotype in women compared with men (Harrison &

Tunbridge, 2008; Jacobs & D'Esposito, 2011). Since estrogen levels decrease greatly during starvation, underweight patients with anorexia nervosa represent a unique opportunity to study the interaction between estrogen levels and the COMT genotype.

Several studies have investigated the relationship between AN and the COMT Val158Met polymorphism, while less data are available about BN. The most recent meta-analysis on COMT genotype and ED was based on literature searches conducted up to April 2011 (Brandys et al., 2012). However, since then additional studies have explored the potential association between EDs and COMT, and studies evaluating the relevance of COMT genotype in BN have not been meta-analyzed to date. Therefore, the aim of the present meta-analysis was to test whether COMT val158met polymorphism is associated with ED as a broad category, or specifically with AN or BN, summarizing all published evidence and adding novel data from the '*Biobanca Veneta per i Disturbi Alimentari*' biobank (BIO.VE.D.A) (Solmi, Gallicchio, et al., 2016).

METHODS

'Biobanca Veneta per i Disturbi Alimentari' (BIO.VE.D.A.) data

The Bio.Ve.D.A. sample included 920 life-time cases of AN (n=562) and/or BN (n=358) according to DSM-5 criteria (A.P.A., 2013), and 261 healthy controls (HC). These patients were recruited from five Eating Disorder Units of the Veneto region, Italy. The Bio.Ve.D.A. project is funded by the Veneto Region and its main aim is to establish a genetic biobank for EDs. The following inclusion criteria were used: a life-time diagnosis of AN or BN according to DSM-5, age >14 years old, patients' and parental (if less than 18 years old) informed consent. The study was approved by local hospital Ethics Committee. The following exclusion criteria were applied: organic comorbidity, or major psychiatric comorbidity (bipolar disorder, schizophrenia, major depressive disorder). All participants underwent saliva or blood sampling to collect DNA, which was extracted from 200µl of whole peripheral blood, using High Pure PCR Template Preparation Kit (Roche Diagnostics GmbH), or from 500µl of saliva with Oragene•DNA/saliva Kit (DNA Genotek Inc.) according to the manufacturer's instructions.

Procedures for genomic DNA extraction and for the COMT val158met polymorphism analysis have been described previously (Favaro et al., 2013).

Meta-analysis

Search strategy

We conducted an electronic literature search in PubMed and SCOPUS from data base inception until January 15th, 2017 for studies investigating COMT val158met genotype or alleles frequencies in EDs and a control group. The following search key was used: ("eating disorders"[MeSH Terms] OR ("eating"[All Fields] AND "disorders"[All Fields]) OR "eating disorders"[All Fields] OR "anorexia nervosa" OR "bulimia nervosa" OR "binge eating disorders") AND ("COMT"[All Fields] OR ("transferases"[MeSH Terms] OR "transferases"[All Fields] OR "transferase"[All Fields])). Equivalent search terms were used in Scopus. Reference lists of included articles and those relevant to the topic were hand-searched for identification of additional potentially relevant articles.

Study selection

Included were only peer-reviewed studies that i) included patients diagnosed with EDs according to DSM-5 criteria; ii) reported COMT val158met genotype or allele frequencies in patients with EDs and a control group. Previous reviews and meta-analyses were full-text read to identify further studies. No language restrictions were applied.

Data extraction and quality assessment

Two authors (E.C. and D.G.) independently extracted data from selected studies into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by consensus with a third author (A.F.). The

following information was extracted: (i) study population characteristics (e.g., sample size, demographics, diagnostic criteria and subtype of AN or BN, comorbidities, medications, anthropometric data); (ii) genotype or allele frequencies in patients and controls; (iii) quality indicators used for the STROBE assessment; and (iv) Hardy-Weinberg equilibrium. Whenever studies had the same authors or affiliation or close publication year, we contacted authors to verify that data were not referring to the same sample. Whenever genotype or allele frequencies were not available, we contacted authors to ask for unpublished data at least twice. We ran the following comparisons within patients and within controls: i) Met/Met, Val/Val, and Val/Met genotype frequency differences between AN, BN, or EDs and HC; ii) Val and Met frequency differences between AN, BN, or EDs and HC.

The Newcastle-Ottawa Scale (Wells, 2013) was used to assess the quality of the included studies.

Meta-analysis

We meta-analyzed comparisons reported in at least two studies, in order to provide the maximum number of meta-analyzable outcomes.

The meta-analysis was performed using Review Manager Version 5.3 for Windows (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre). When combining studies, the random effects model (DerSimonian & Laird, 1986) was used to account for study heterogeneity. For dichotomous data, Odds Ratio (OR) with its 95% confidence interval (CI) was used. Heterogeneity was assessed with the Cochran Q and I^2 statistics for each analysis, with $I^2 \geq 50$ indicating high heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Publication bias was assessed via visual inspection of funnel plots and Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997), with Comprehensive Meta-Analysis (CMA). In order to perform a sensitivity analysis and test for publication bias, we performed the trim and fill procedure to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric around the (new) effect size (Duval & Tweedie, 2000).

We included BIO.VE.D.A. group data in the meta-analysis. Hardy-Weinberg equilibrium was tested in each study separately with both χ^2 test and relative excess heterozygosity test (REH) (Ziegler, Van Steen, & Wellek, 2011). Finally, we tested the pooled REH from all included studies using a random effects model, which is a more appropriate tool than the χ^2 test to test HWE in meta-analyses (Ziegler et al., 2011).

RESULTS

Search results (fig 1)

We identified 354 studies through our electronic search, plus three additional references from the hand-searched bibliography of relevant papers. After duplicate removal, the title and abstract of 312 papers were screened, and 292 were excluded. We assessed full text of 20 papers, and excluded ten additional references for different reasons specified in figure 1. Finally we included in the meta-analysis ten studies (Brandys et al., 2012; Dmitrzak-Weglarz M, 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim, Kim, & Kim, 2010; Mikolajczyk, Grzywacz, & Samochowiec, 2010; Peng et al., 2016; Pinheiro et al., 2010; Z. Yilmaz, Kaplan, Zai, Levitan, & Kennedy, 2011), plus data from BIO.VE.D.A.

Characteristics of included studies (table 1)

The main features of the included studies are summarised in Table 1. Overall, we analyzed data from 3,541 patients with EDs, and 3,684 controls not affected by any ED. Among the patients with EDs, 2,950 had a lifetime diagnosis of AN and 591 had a lifetime diagnosis of BN. The mean age was 23.4±5.9 years for ED patients, and 25.1±6.2 for controls, the mean BMI was 17.03±2.7 Kg/m² for patients (lowest mean BMI=15.6±3.3 Kg/m² based on 3 studies), and 20.2±1.5 Kg/m² for controls. Seven studies only included patients with AN, one study included patients with BN, and three studies included both patients with AN and BN. Only one study reported data about life-time comorbidity, and one study reported information about concomitant medication treatment. In all studies, the COMT genotype was in Hardy-Weinberg Equilibrium, except one where such information was not reported.

All studies compared patients with ED with non-affected healthy controls (sisters of patients in one study). Eight studies defined ED according to DSM-IV criteria (A.P.A., 2000), while BIO.VE.DA data defined ED according to DSM-5 (A.P.A., 2013), and one study each used ICD-10 (W.H.O., 1992) or EDE-Q (Fairburn & Beglin, 1994) criteria.

Quality of included studies (table 1)

Overall, the quality was high, with seven out of eleven studies meeting all quality criteria, three studies missing one, and one study missing two features instead (table 1).

Meta-analysis (table 2, fig. 2)

All results of the meta-analyses comparing patients with control groups are reported in Table 2. Considering EDs as a unique group (11 studies, 3541 patients and 3684 controls), neither COMT val158met allele nor genotype frequencies were different compared with controls (range of ORs: 0.96-1.04, p-values: 0.46-0.97, I²=0%). The same was true in patients with AN (10 studies, 2950 patients, 3521 controls; range of ORs: 0.94-1.04, p-values: 0.31-0.61, I²=0%), and in patients with BN (4 studies, 591 patients, 566 controls; range of ORs: 0.80-1.09, p-values: 0.28-0.64, I²=0-44%).

Details of the comparative meta-analysis of Val allele distribution between patients with ED and controls is represented in figure 2.

Publication Bias

Funnel plot visual inspection and Egger's regression test showed the presence of publication bias (1.54, 95%CI 0.46-2.51; $p=0.003$) for val/val genotype frequency comparative meta-analysis. However, the trim and fill procedure substantially confirmed our results, since looking for missing studies both to the left and to the right of the pooled effect size resulted in no difference in genotype frequency between the two groups.

DISCUSSION

Due to the importance of dopamine signaling for normal human behavior, the COMT val158met SNP is one of the most studied genetic variants in psychiatry (Schacht, 2016), and its role in influencing cognitive and executive performances has been assessed in several studies (Bruder et al., 2005; Goldberg et al., 2003; Scheggia, Sannino, Scattoni, & Papaleo, 2012). Given the importance of dopamine metabolism in limbic and executive-associative pathways, and the involvement of striatal and prefrontal circuits in the pathophysiology of EDs, we aimed to meta-analytically evaluate whether the COMT val158met genotype differed between ED patients and controls, as this would point to specific pathophysiologic underpinnings of EDs and could possibly point to novel treatment approaches.

However, according to our analyses, there was no signal that COMT val158met polymorphisms are associated with AN or BN. Moreover, results were very homogenous and, although publication bias was present, results did not change after trim and fill procedure. Our results are consistent with those of the previous meta-analysis conducted by Brandys and colleagues, that rejected the hypothesis of an association between rs4680 and AN (Brandys et al., 2012). In addition, our meta-analysis also shows the absence of a significant association with BN, or ED as a combined category. BIO.VE.D.A. data, which represent the second largest database analyzed up to now considering AN diagnosis and the largest considering BN, were similarly consistent with the results of the other studies included in the meta-analysis. The fact that less studies investigated COMT polymorphisms in BN, compared with AN, is consistent with the more limited neurobiological characterization of BN and with a less homogeneous description of its neuropsychological functioning (Degortes, Tenconi, Santonastaso, & Favaro, 2016; Van den Eynde et al., 2011). Moreover, the absence of an association between COMT val158met genotype and ED mirrors similar results for the serotonin transporter 5-HTTLPR polymorphism, another monoamine modulating single polymorphism as previously reported (Rozenblat et al., 2017; Solmi, Gallicchio, et al., 2016).

Despite the possible role of COMT val158met polymorphism in influencing executive functioning and prefrontal connectivity in AN (Favaro et al., 2013), this genetic variant does not seem to represent a risk factor for the development of EDs. Favaro et al hypothesized that, due to the estrogens effects, COMT effects on cognitive functioning might be observable only in acute underweight AN patients (Favaro et al., 2013). From this perspective, it would be useful to explore the complex interaction between this genetic variant and estrogen levels not only with regards to the risk of developing an ED, but also as a factor involved in the maintenance of low BMI and lack of remission. Despite the current negative results, we suggest that the influence that COMT val158met genotype can exert on fronto-striatal functioning in ED and its consequences on clinical features, such as treatment response, should be further characterized by specific studies that investigate estrogen levels and executive functioning as possible mediators of outcome in EDs.

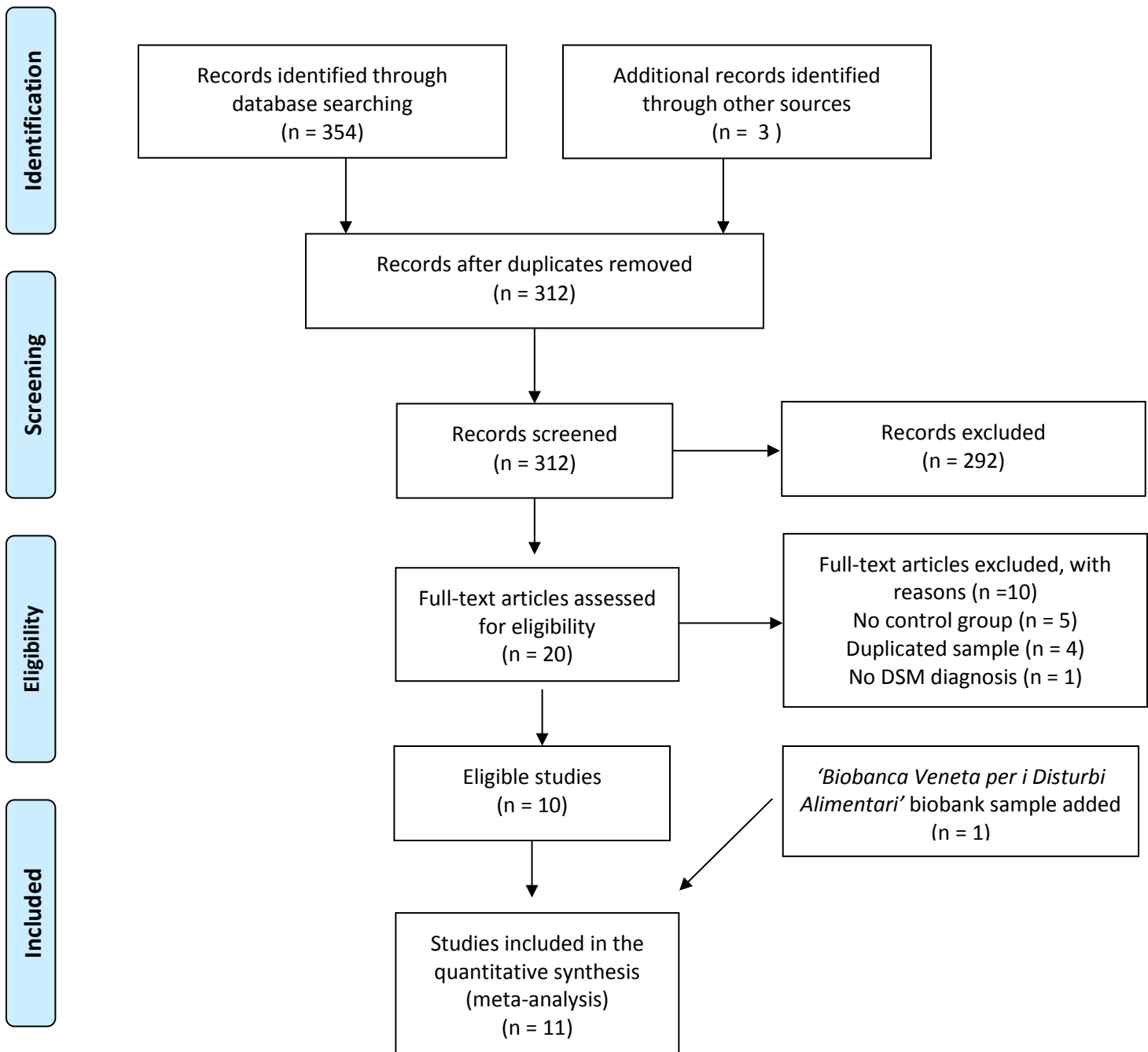
The present study has both strengths and limitations that need to be taken into consideration when interpreting its results. First, one of the strengths is the inclusion of data from the BIO.VE.D.A. biobank,

which provided the largest sample of patients affected by BN that has been investigated regarding the COMT val158met polymorphism and the second largest sample of patients diagnosed with AN. Second, the BIO.VE.D.A. sample was free from major psychiatric comorbidities (bipolar disorder, schizophrenia, major depressive disorder), removing the possibility of potential biases due to other major psychiatric disorders. Third, this is the first meta-analysis about the association between COMT val158met polymorphism and BN. The paucity of data about the role of this genetic variant in the etiology and in cognitive and executive features of BN points to the need of more studies that investigate these topics. Fourth, our meta-analysis added 4 studies, and 2356 subjects compared to the last meta-analysis that focused on AN only. Last but not least, our results showed low heterogeneity and lacked indication for publication bias, both when pooling EDs together and when analyzing AN and BN separately, which increases the confidence in our conclusions.

Several limitations should also be mentioned. First, we acknowledge the lack of studies, which consider the presence of comorbid psychiatric disorders. Second, only few studies included non-Caucasian patients. Thus, our results may not be representative of specific ethnic groups. For example, although studies in a Chinese Han population (Peng et al, 2016) and in Korean subjects (Kim et al, 2010) also failed to find significant differences in COMT genotype between patients with EDs and HC, two studies (with an overlapping sample) conducted in an Israeli sample did report a significant association between rs4680 and AN. Nevertheless, overall, the results were consistent and homogenous. Third, frequently control groups were simply defined as not being affected by ED, without clear exclusion of other organic or psychiatric diseases. Finally, only the BIO.VE.D.A. used the new diagnostic criteria using DSM-5, yet ED criteria do not vary greatly and this variation is unlikely to have influenced the results to a relevant degree.

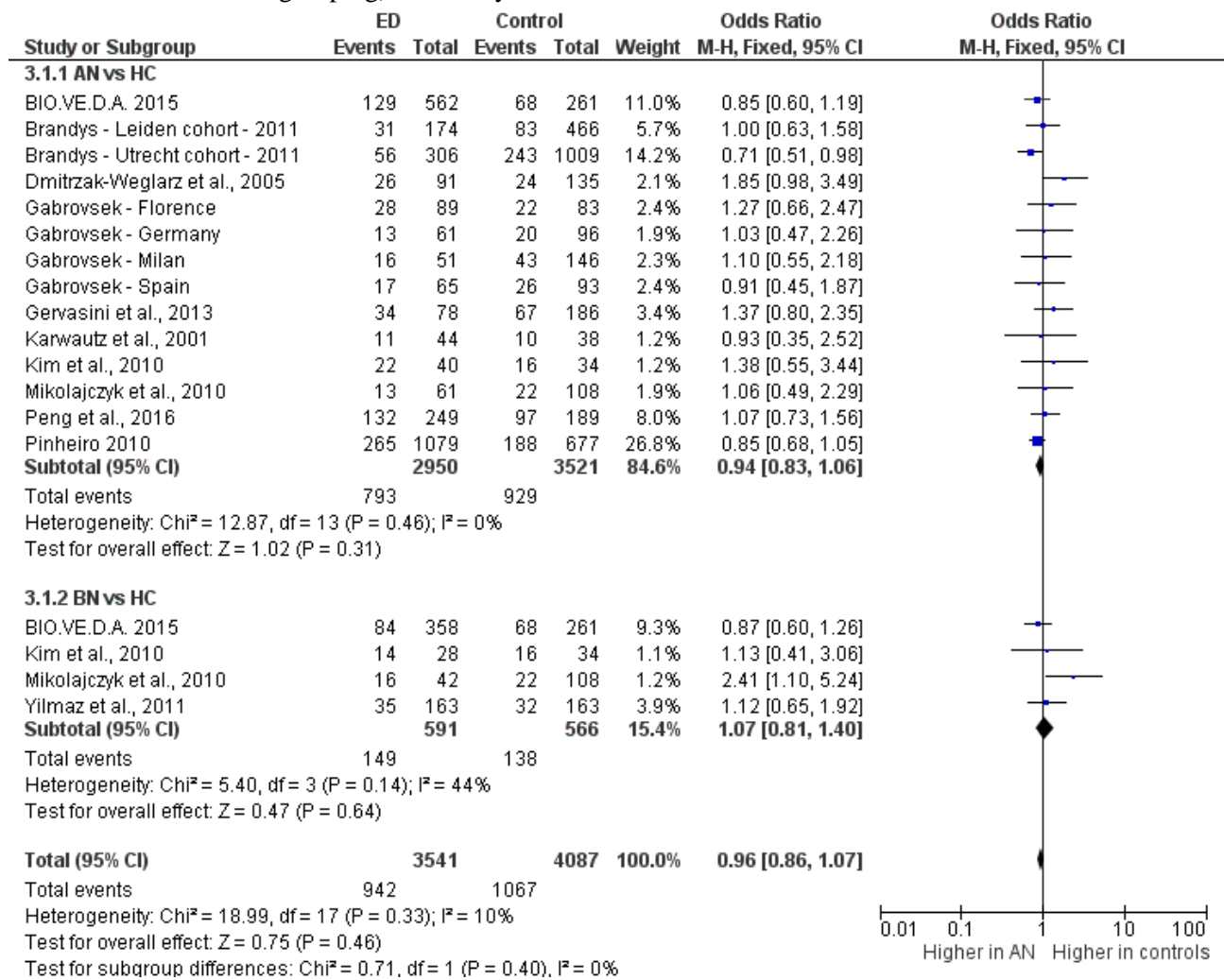
In conclusion, in this largest and most comprehensive meta-analysis to date, consistently no association was found between COMT val158met polymorphisms and ED, AN, or BN. Other genetic associations with ED, in general, and AN and BN, in particular, need to be investigated.

Figure 1. Flow-chart from literature search to study inclusion in meta-analysis.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Fig 2. Comparative meta-analysis of val/val genotype frequency in eating disorders (with anorexia nervosa and bulimia nervosa subgrouping) vs healthy controls*.



Legend: *: controls have been reported twice for studies including AN and BN and actual total control number is 5,684; AN: anorexia nervosa; BN: bulimia nervosa; ED: eating disorders.

Table 1. Characteristics of BIO.Ve.D.A. sample and included studies assessing catechol- *O*-methyltransferase val158met polymorphism in eating disorders vs controls.

Study/ Country	ED diagnostic criteria	HC Group	N AN/BN	N HC group	Age AN/BN	Age HC	BMI AN/BN (Kg/ m ²)	BMI HC (Kg/ m ²)	Lowest BMI ever AN/BN	Lowest BMI ever HC	Onset Age (yrs)	Measurement Method	Lifetime co-morbidity	Medications	Personality or Symptom Scale or other Clinical Data	Genotype in Hardy-Weinberg Equilibrium	NOS
BIO.Ve.D.A. group. 2016 Italy	DSM-5	Non affected controls	AN 562, BN 358	261	AN 24.9±9, BN 26.5±8.4	-	AN 15.5±1.6, BN 22.1±4.1	21.3±2.4	-	-	AN 18.3±5.9, BN 17.9±5.1	Saliva/blood, PCR	-	-	-	Yes	9
Gabrovsek et al. 2004 Multicentric: Italy (Florence and Milan), Spain, UK, Austria, Germany, Slovenia	DSM IV	Non affected controls	AN 266 (251 F, 5 M)	418	-	-	ED: 14.5±0.3	-	AN-BP: 16.1±3.5 AN-R: 14.3±2.1	-	ED: 18.3±4.3 AN-BP: 17.5±4.6 AN-R: 17.4±4.6	Cheek swabs, blood, PCR-RFLP, ARMS assay	-	-	-	Yes	8
Mikolajczyk et al. 2010 Poland	ICD 10	Non affected controls	AN 61 BN 42	108	ED: 22.45±3.85 AN: 22.07±3.76 BN: 23.00±3.95	22.85±3.71	ED: 16.84±3.56 AN: 15.05±2.54 BN: 19.41±3.27	20.65±1.25	-	-	-	Blood, PCR-RFLP	-	-	EDI TCI	Yes	9
Kim et al. 2010 Korea	EDE-Q	Non affected controls	AN 40 BN 28	34	AN 22.78±7.23 BN 23.00±3.21	22.65±3.57	AN 16.67±2.60 BN 20.66±2.65	21.52±1.68	AN 14.60±1.51 BN 18.12±2.19	20.19±1.52	AN 18.55±4.59 BN 20.07±2.99	PCR, blood	-	19 AN: SSRI 15 BN: SSRI	WAIS-IQ; TMT (Part A+PartB) VST; FTT; BDI; STAI; K-MOCI	Yes	9

Yilmaz et al. 2011 Canada	DSM IV	Non affected controls	BN 163	163	-	-	-	-	-	-	-	Blood High-salt Method	ADHD	-	SCID-1 EDE 12 WURS	Yes	9
Brandys et al. 2012* Netherlands	DSM IV	Non affected controls	AN 480	1475	25.6+- 7.1	23.4 ±12. 1	15.3±2.3	22.6±14. 1	-	-	-	Mass Spectro metry	-	-	-	Yes	9
Gervasini et al. 2013 Spain	DSM IV	Non affected controls	AN 78	186	26±7.4	22.18 ±6.1 3	17.60±2. 33	22.13±3. 45	-	-	17.16±5. 11	Blood	-	-	EDI-2 SCL-90R	Yes	9
Peng et al., 2016 China	DSM IV	Non affected controls	AN 249	189	19.09± 4.72	22.76 ±3.3 0	-	-	-	-	-	Blood	-	-	-	Yes	7
Pinheiro et al., 2010 Multicentric, primarily European	DSM IV	Non affected controls	AN 1079	677	27.1±8. 8	26.3 ±8.3	14.7±2.5 4	22.1±1.8	-	-	-	-	-	-	-	Yes	9
Dmitrzak- Weglarz et al., 2005 Poland	DSM IV	Non affected controls	AN 91	135	18.5 ±3.2	34.9 ±10	-	-	-	-	-	-	-	-	-	Yes	8
Karwautz et al., 2001 UK	DSM IV	Non affected controls (control were sisters of the probands)	AN 44	38	-	27.4 ± 2.2	-	22.4 ± 3.8	13.1±2.2	-	15.3±3.2	-	-	-	-	-	8
11 studies	DSM-IV: n=8, DSM- 5=1, ICD-10: n=1 EDE- Q: n=1	Non affected controls	3541(AN= 2950; BN= 591)	3684	23.4±5. 9; AN: 23±6.2; BN 24.2 ± 5.2	25.1 ±6,2	17,03± 2.7; AN: 15,9±4,9 ; BN: 20,7±3,3	22,1±5,8	15,61±,3 AN:14.5 ± 10.2; BN:18.1 ±2.2	20.2+- 1.5	17.8±4,5 ; AN:17.4 ±4.4 ; BN: 19±4	Blood: n=7; NA=3; Mass Spectro metry: n=1;	ADHD: n= 1	N=1 (19 AN: SSRI 15 BN: SSRI)	Yes: n=4 No: n=7	Yes: n=10, NR: n=1	8.5± <u>0.7</u>

Legend: *: study provided data from two samples; AN: anorexia nervosa; BDI: Beck Depression Inventory; BIO.Ve.D.A.: biobanca veneta per i disturbi del comportamento alimentare – Veneto region biobank for eating disorders; BMI: body mass index; BN: bulimia nervosa; DSM: diagnostic and statistical manual; EDE: Eating Disorders Examination Interview; EDI: Eating Disorders Inventory; FTT: Finger Tapping Test; HC = healthy control; ICD: international classification of diseases; K-MOCI: Korean Version of Maudsley Obsessive Compulsive Inventory; NOS: Newcastle-Ottawa Scale; SCID-1: Structural Clinical Interview for DMS-IV for Axis I disorders; SCL-90R: Symptom Checklist 90 Revised; SSRI: selective serotonin reuptake inhibitors; STAI: State and Trait Anxiety Inventory; TCI: Temperament and Character Inventory; TMT: Trail Making Test; VST: Visual Span Test; WAIS-IQ: Wechsler Adult Intelligent Scale; WURS: Wender Utah Rating Scale.

Table 2: Results of the meta-analysis comparing COMT val158met in patients with eating disorders, anorexia nervosa and bulimia nervosa vs. controls

Table 2. Comparative meta-analysis of catechol-*O*-methyltransferase (COMT) val158met polymorphism frequency in eating disorders vs healthy controls.

Comparison	Number of studies	Studies	Participants (patient vs. HC) or alleles	Statistical Method	Effect estimate	Heterogeneity (I ²)
EDs * (AN and BN) vs. controls						
<i>Val allele</i>	11	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010; Yilmaz et al., 2011	7082 vs 8174	Odds ratio (M-H, random, 95% CI)	0.99 [0.92, 1.06]; P=0.67 -	0%
<i>Met allele</i>	11	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010; Yilmaz et al., 2011	7082 vs 8174	Odds ratio (M-H, random, 95% CI)	1.02 [0.95, 1.09]; P=0.58	0%
<i>Val/Val</i>	11	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010; Yilmaz et al., 2011	3541 vs 4087	Odds ratio (M-H, random, 95% CI)	0.96 [0.86, 1.07]; P=0.46	10%
<i>Val/Met</i>	11	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010; Yilmaz et al., 2011	3541 vs 4087	Odds ratio (M-H, random, 95% CI)	1.04 [0.94, 1.14]; P=0.48	0%
<i>Met/Met</i>	11	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010; Yilmaz et al., 2011	3541 vs 4087	Odds ratio (M-H, random, 95% CI)	1.00 [0.90, 1.12]; P=0.97	0%
AN Vs. controls						
<i>Val allele</i>	10	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010	5900 vs 7042	Odds ratio (M-H, random, 95% CI)	0.97 [0.90, 1.04]; P=0.36	0%
<i>Met allele</i>	10	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al.,	5900 vs 7042	Odds ratio	1.04 [0.96, 1.12];	0%

Table 2: Results of the meta-analysis comparing COMT val158met in patients with eating disorders, anorexia nervosa and bulimia nervosa vs. controls

Comparison	Number of studies	Studies	Participants (patient vs. HC) or alleles	Statistical Method	Effect estimate	Heterogeneity (I ²)
		2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010		(M-H, random, 95% CI)	P=0.32	
<i>Val/Val</i>	10	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010	2950 vs 3521	Odds ratio (M-H, random, 95% CI)	0.94 [0.83, 1.06]; P=0.31	0%
<i>Val/Met</i>	10	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010	2950 vs 3521	Odds ratio (M-H, random, 95% CI)	1.03 [0.93, 1.14]; P=0.61	0%
<i>Met/Met</i>	10	BIO.VE.D.A. group; Brandys et al., 2011; Dmitrzak-Weglarz et al., 2005; Gabrovsek et al., 2004; Gervasini et al., 2013; Karwautz et al., 2001; Kim et al., 2010; Mikolajczyk et al., 2010; Peng et al., 2016; Pinheiro et al., 2010	2950 vs 3521	Odds ratio (M-H, random, 95% CI)	1.03 [0.91, 1.17] P=0.61	0%
BN vs. Controls						
<i>Val allele</i>	4	BIO.VE.D.A. group ; Kim et al., 2010; Mikolajczyk et al., 2010; Yilmaz et al., 2011	1182 vs 1132	Odds ratio (M-H, random, 95% CI)	1.09 [0.92, 1.29]; P=0.32	27%
<i>Met allele</i>	4	BIO.VE.D.A. group ; Kim et al., 2010; Mikolajczyk et al., 2010; Yilmaz et al., 2011	1182 vs 1132	Odds ratio (M-H, random, 95% CI)	0.93 [0.79, 1.10]; P=0.39	0%
<i>Val/Val</i>	4	BIO.VE.D.A. group ; Kim et al., 2010; Mikolajczyk et al., 2010; Yilmaz et al., 2011	591 vs 566	Odds ratio (M-H, random, 95% CI)	1.07 [0.81, 1.40]; P=0.64	44%
<i>Val/Met</i>	4	BIO.VE.D.A. group ; Kim et al., 2010; Mikolajczyk et al., 2010; Yilmaz et al., 2011	591 vs 566	Odds ratio (M-H,	1.07 [0.85, 1.36]; P=0.55	0%

Table 2: Results of the meta-analysis comparing COMT val158met in patients with eating disorders, anorexia nervosa and bulimia nervosa vs. controls

Comparison	Number of studies	Studies	Participants (patient vs. HC) or alleles	Statistical Method	Effect estimate	Heterogeneity (I ²)
				random, 95% CI)		
<i>Met/Met</i>	4	BIO.VE.D.A. group ; Kim et al., 2010; Mikolajczyk et al., 2010; Yilmaz et al., 2011	591 vs 566	Odds ratio (M-H, random, 95% CI)	0.80 [0.53, 1.21]; P=0.28	0%

*Legend: *: in EDs analyses HCs have been computed twice for studies including both AN and BN. Actual maximum total control number is 5,684; AN: anorexia nervosa; BN: bulimia nervosa; ED: eating disorders; HC: healthy controls.*

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