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THE INFLUENCE OF 5-HTTLPR, COMT VAL158MET POLYMORPHISM, ADVERSE LIFE EVENTS, ANXIETY, IMPULSIVITY AND NEUROTICISM ON EATING DISORDER SYMPTOMATOLOGY

Master's thesis

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Contents

Abstract

The aim of this study was to examine the effect of 5-HTTLPR and COMT Val158Met polymorphism, anxiety, impulsivity, neuroticism and adverse life events on abnormal eating behaviors among 25-year-old women. This study is based on ECPBHS (Estonian Children Personality, Behaviour and Health Study) older cohort data. Participants answered to State and Trait Anxiety Inventory (STAI), Barrat Impulsiveness Scale (BIS-11), NEO-PI Estonian version, Eating Disorder Inventory -2 (EDI-2). The sample was genotyped for 5-HTTLPR and COMT Val158Met polymorphism.

The main finding of the current study is that the influence of neuroticism on eating disorder symptomatology is mediated mainly by trait anxiety. This study shows consistent effects of neuroticism through trait anxiety on bulimic symptoms, body dissatisfaction and drive for thinness. Neuroticism through impulsivity influences only bulimic symptoms.

Trait anxiety can be seen as a stable trait predisposing people toward higher levels of eating disorder symptomatology.

Kokkuvõte

5-HTTLPR, COMT Val158Met polümorfism, negatiivsed elusündmused, neurootilisus, ärevus ja impulsiivsus söömishäire sümptomaatika mõjutajatena

Magistritöö eesmärgiks oli uurida 5-HTTLPRi, COMT Val158Met polümorfismi, ärevuse, impulsiivsuse, neurotismi ning negatiivsete elusündmuste mõju häirunud söömiskäitumise väljakujunemisele 25-aastastel naistel. Magistritöö põhineb Eesti Laste Isiksuse, Käitumise ja Tervise Uuringu (ELIKTU) vanema kohordi andmetel. Osalejatelt koguti andmed elukäigu, ärevuse (STAI), impulsiivsuse (BIS-11) ning isiksuseomaduste kohta (NEO-PI). Andmed söömishäirete sümptomaatika kohta saadi *Eating Disorder Inventory -2* (EDI-2) abil. Osalejatel määrati 5-HTTLPR ning COMT Val158Met genotüüp.

Antud tööst selgub, et neurotismi mõju söömishäirete sümptomaatikale on vahendatud püsiärevuse poolt. Antud tööst tuleb välja sarnane mõju nii buliimilistele sümptomitele, kehaga rahulolematusele kui kõhnuseihalusele. Neurotismi mõju on vahendatud ka impulsiivsuse poolt, kuid mõju on oluline vaid buliimilistele sümptomitele.

Püsiärevust võib näha kui faktorit, mis soodustab häirunud söömiskäitumise väljakujunemist.

Introduction

Eating disorders

Eating disorders are persistent disturbances of eating behavior or behavior intended to control weight (Fairburn & Walsh, 2002). These complex illnesses most often strike during adolescence or young adulthood and are more common among females than males. (Herzog, Franko, & Cable, 2008)

People with eating disorders share some common symptoms. They are occupied with negative thoughts and intense emotions about their body size and shape. They adopt unhealthy weight control practices and other abnormal eating habits, taking these measures to a dangerous extreme. (Herzog et al., 2008)

According to The Diagnostic and Statistical Manual of Mental Disorders, Text Revision, eating disorders are classified as anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS) (American Psychiatric Association [DSM-IV-TR], 2000). In International Classification of Diseases Version 10 (World Health Organization [ICD-10], 1992) eating disorders are classified under behavioral syndromes that are associated with physiological disturbances and physical factors together for example with sleep and sexual disorders. Eating disorders refer to a group of conditions defined by abnormal eating habits and involve 8 disorders in ICD-10. Besides AN and BN other eating disorders classified in ICD-10 are atypical anorexia nervosa, atypical bulimia nervosa, binge eating associated with other psychological disturbances, vomiting associated with other psychological disturbances, other eating disorders, eating disorder unspecified. (ICD-10, 1992)

Diagnostic criteria for anorexia nervosa (DSM-IV-TR, 2000) involve desire to maintain weight at or above a minimally normal weight for age and height or maintaining weight at less than 85 percent normal; intense fear of gaining weight or becoming fat, even though underweight; disturbance in experience of body weight or shape, or undue influence of body weight or shape on self-evaluation, or denial of the seriousness of current low body weight; amenorrhea in postmenarcheal females, defined as the absence of three consecutive menstrual cycles in girls or women who have started having periods.

Diagnostic criteria for bulimia nervosa include recurrent episodes of binge eating which are characterized both by consuming larger than normal amounts of food and by feeling out of control while bingeing; recurrent inappropriate compensatory behavior to prevent weight gain (e.g. excessive exercise, fasting, vomiting); and being “unduly

influenced" by body shape and weight (DSM-IV-TR, 2000). There are two subtypes of bulimia, purging and non-purging (Rumney, 2009).

Eating Disorder Not Otherwise Specified (EDNOS) is a category for patients who do not meet the above-mentioned criteria for any specific eating disorders (DSM-IV-TR, 2000).

Disordered eating is an important problem in today's society. Statistics show that more than 8 million people in the United States suffer from eating disorders, and many more have substantially abnormal eating habits that don't meet the formal criteria for classification as illness (Herzog et al., 2008). Estimated number of individuals with disordered eating behavior in European Union is currently considered to be 1.2 million (Wittchen & Jacobi, 2005).

It is difficult to establish accurate prevalence rates for eating disorders but epidemiological studies assessing eating disorder prevalence show that lifetime prevalence for anorexia nervosa is 0.3-0.9%, bulimia nervosa 1-1.5% and for binge eating disorder 1-3.5% (Hoek & van Hoeken, 2003; Hudson, Hiripi, Pope, & Kessler, 2007). In Estonia, the current prevalence of eating disorders in women is 0.7% for restrictive anorexia nervosa (AN-R), 1.4% for bulimia nervosa purging type (BN-P), 1.8% for binge eating disorder (BED) and 3.8% for EDNOS. The prevalence of eating disorders in men is 0.5% for BED and 0.5% for EDNOS (Akkermann, 2010).

Many ED patients have other mental health problems at the same time. Depressive symptoms and anxiety features are particularly common among individuals with disordered eating behavior since most patients meet criteria for one or more mood or anxiety disorders (Fairburn, 2008).

Risk factors

Despite the lack of clarity in eating disorders prevalence, it is clear that they impact the quality of life. Low treatment success for eating disorders (Steinhausen, 2002) and high mortality rate (Uher, 2009) are some of the main reasons why it is important to learn more about risk factors so practitioners could detect high risk individuals and prevent them from developing eating disorders.

It has been estimated that fewer than 50% of AN patients achieve full recovery, 33% improve and 20% remain chronically ill. Also, 33% of those who recover relapse (Herzog & Eddy, 2007). Only 1/3 of anorexic patients and about 6% of subjects with BN receive mental health care (Hoek & van Hoeken, 2003).

It is important to note that many patients may not meet full diagnostic criteria for a diagnosis of eating disorder but they will exhibit significantly disordered eating. Patients with disordered eating patterns who do not meet eating disorder criteria are still at risk for complications (Walsh, Wheat, & Freund, 2000). Disordered eating behavior disables physical health and psychosocial functioning (Fairburn & Walsh, 2002).

One thorough meta-analysis listed risk factors that include such factors as female gender, Caucasian race, childhood eating and digestive problems, anxiety, over concern with weight and shape, body dissatisfaction/negative body image, high drive for thinness, sexual abuse and other adverse life events (for a review please see Jacobi, Hayward, de Zwaan, Kraemer, & Stewart Agras, 2004).

Stice (2002) identified several risk factors which are important for the onset and maintenance of the disorders and these are for example body dissatisfaction, negative affect, and maladaptive coping skills. Mazzeo & Bulik (2009) stated the importance of genes as ED risk factors.

Adverse life events

Stressful life events are classified as risk factors for eating disorders and it is found that sexual abuse increases the risk at most (Jacobi et al., 2004). Though, it has been shown that there are a number of other stressful life events to increase the risk of disordered eating behavior (Loth, van den Berg, Eisenberg, & Neumark-Sztainer, 2008). Both clinical studies and population based studies show the connection between eating disorders and stressful life events (Loth et al., 2008; Schmidt, Tiller, Blanchard, Andrews, & Treasure, 1997; Welch, Doll, & Fairburn, 1997). Problems with sexuality predispose to anorexia (Schmidt et al., 1997) and BN patients experience more negative life events before the onset of the disorder as compared to AN patients (Welch et al., 1997).

It has been found recently that the combination of low social support and multiple negative life events predict bulimic symptoms but not restrictive eating or anxiety or mood symptoms (Bodell, Smith, Holm-Denoma, Gordon, & Joiner, 2011).

Garfinkel et al (1995) argued that childhood adversities may lead to several forms of affective disorders and eating disorders psychopathologies by reducing self-esteem and magnifying one’s sense of helplessness and body dissatisfaction.

Anxiety

Anxiety is a displeasing feeling of fear and concern (Davidson, 2008). It is long acting, future focused, broadly focused towards a diffuse threat, and promoting caution while approaching a potential threat (Sylvers, Lilienfeld, & LaPrairie, 2011).

Adverse life events can cause distress. Distress tolerance or anxiety management is a construct related to appraisal and coping processes (Folkman & Lazarus, 1980). High avoidance of affect and low acceptance and management of problems are negative components of distress tolerance associated with anxiety and disordered eating attitudes (Corstorphine, Mountford, Tomlinson, Waller, & Meyer, 2007).

Anxiety is common among individuals with ED patients (Bulik, Sullivan, & Kendler, 2002) as compared to healthy individuals. Eating disorders are highly comorbid with affective disorders, anxiety disorders and personality disorders (Godart, Flament, Perdereau, & Jeammet, 2002; Mitchell, Specker, & de Zwaan, 1991). It has been shown that also individuals with subclinical eating disorders show more anxious and depressive symptoms (Touchette et al., 2011).

Pallister & Waller (2008) suggested three potential explanations for the comorbidity between anxiety and eating disorders - anxiety could be a risk factor for ED or itself may cause anxiety, or these disorders may have common shared vulnerabilities.

It is not clear how anxiety is linked to disordered eating behavior although recent study by Kaye, Bulik, Thornton, Barbarich, & Masters (2004) have shown that anxiety disorders tend to precede the development of eating disorders.

Impulsivity

According to Eysenck, Pearson, Easting, & Allsop (1985) impulsivity is a dimensional personality trait which leads to behaving without stopping to think.

Patients with bulimia nervosa have been found to have higher global impulsivity scores using Barrett‘s Impulsivity Scale, than the nonclinical population and patients with anorexia nervosa restrictive subtype (Rosval, Steiger, Bruce, Israël, Richardson, & Aubut, 2006). BN has been associated with high impulsivity by Kemps & Wilsdon (2010) as well.

Jacobi et al. (2004) found that impulsive behaviour among bulimic patients is related to decreased serotonin levels in central nervous system, the same results have been shown by Steiger et al. (2001) as well. Yet, Racine, Culbert, Larson, & Klump (2009) did not find any associations between impulsivity, 5-HT genes and binge eating disorder.

Neuroticism

According to McCrae & Costa (1990) personality traits are enduring dimensions of individual differences in tendencies to show consistent patterns of thoughts, feelings, and actions. These traits are basic tendencies, rooted in biology that can resist the influences of environment (Allik & McCrae, 2002).

It has been shown that out of Big Five personality traits (for a full review see Costa & McCrae, 1992) neuroticism and extraversion affect disordered eating the most (Brookings & Wilson, 1994). Neuroticism is defined as the propensity to experience negative emotions (Eysenck, Eysenck, & Barret, 1985). Neuroticism includes emotions like irritability, sadness, anxiety, worry, hostility, self-conscientiousness, and vulnerability - all of these are correlated to one another (Costa & McCrae, 1992).

Persons with high neuroticism scores are more likely than other persons to develop anxiety and depression following negative life events (Jacobs, Kenis, Peeters, Derom, Vlietinck, & van Os, 2006). Recently Dahl et al. (2012) confirmed that individuals with disordered eating behavior report more depressive and anxious feelings and neuroticism.

Negative urgency, the tendency to act rashly when distressed, appears to be a particularly important risk factor for binge eating behavior (Fischer, Smith, & Cyders, 2008).

Positive associations between neuroticism and eating disorders have also been demonstrated (Bulik et al., 2002; Cassin & von Ranson, 2005). For example Podar (2010) showed very strong correlations between EDI-2 subscales and neuroticism and suggested that it is possible to consider eating disorder symptoms as an aspect of neurotic personality dispositions.

Serotonin transporter gene promoter region polymorphism (5-HTTLPR)

There is growing evidence that genetic variants contribute to the pathogenesis of eating disorders. It has been suggested that there are a number of genes that code for proteins that influence traits that index vulnerability to these disorders (Mazzeo & Bulik, 2009).

People with eating disorders have disturbances in neurotransmitting regulations that involve serotonin and dopamine system and that can be conditioned by genes (Mikolajczyk, Grzywacz, & Samochowiec, 2010) Thus it is important to study the genes underlying these neurotransmitters regulation.

It has been suggested that serotonin transporter gene is a good candidate gene for eating pathology. Human serotonin transporter is encoded by one gene (SLC6A4) in chromosome 17 (Gelernter, Pakstis, & Kidd, 1995). The serotonin transporter gene mediates

sodium dependent presynaptic reuptake of serotonin, thus terminating serotonergic neurotransmission.

The short or s-allele has been associated with trait anxiety (Lesch et al., 1996; Sen et al., 2004), affective instability (Lesch & Mössner, 1998; Steiger et al., 2005) and greater amygdale reactivity to emotion-related stimuli (Hariri et al., 2002).

Several lines of evidence indicate that disturbances of 5-HT neurotransmission contribute to various expressions of eating pathology, but in many studies no allelic differences in 5-HTTLPR have been found (Hinney et al., 1997; Lauzurica et al., 2003; Monteleone, Tortorella, Castaldo, & Maj, 2006; Rybakowski, Slopien, Dmitrzak-Weglarz, Czerski, Rajewski, & Hauser, 2006; Steiger et al., 2005; Sundaramurthy, Pieri, Gape, Markham, & Campbell, 2000; Urwin, Bennetts, Wilcken, Beumont, Russell, & Nunn, 2003).

Some studies have associated long or l-allele with bulimic symptoms (Matsushita, Nakamura, Nishiguchi, & Higuchi, 2002; Monteleone, Tortorella, Castaldo, & Maj, 2006) and overweight (Fumeron, Betoulle, Aubert, Herbeth, Siest, & Rigaud, 2001). Also, it has been found that s-allele (especially s/s genotype) is more frequent in individuals with anorexia nervosa (Fumeron et al., 2001; Matsushita, Suzuki, Murayama, Nishiguchi, & Hishimoto, 2004). S-allele, and especially the s/s genotype increases the risk for affective instability and symptom severity in disordered eating behavior (Akkermann, Nordquist, Oreland, & Harro, 2010).

Catechol-O-methyltransferase (COMT) gene Val158Met polymorphism

In the frontal regions of the brain, serotonin is theorized to contribute to regulating dopamine: when serotonin levels decrease, dopamine levels rise, and vice versa (Kapur & Remington, 1996; Sasaki-Adams & Kelley, 2001). Catechol-O-methyltransferase (COMT) is largely responsible for the metabolism of dopamine and norepinephrine in the prefrontal cortex (Enoch, Waheed, Harris, Albaugh, & Goldman, 2009). The role of COMT in dopamine metabolism has led to investigation of its variants in the etiology of numerous psychiatric disorders including psychotic, affective and anxiety disorders (Funke et al., 2005).

The catechol-O-methyltransferase (COMT) gene encodes the COMT enzyme responsible for degrading catecholamines, including dopamine and norepinephrine, particularly in frontal areas of the brain (Matsumoto et al., 2003). To date, one of the most studied variants of the COMT gene has been the G/A single nucleotide polymorphism resulting in valine–methionine substitution at codon 158 (Val158Met; rs4680). Functional studies have identified the Val158Met polymorphism as a marker of trimodal function (Chen

et al., 2004), leading to high (Val/Val), intermediate (Val/Met), and low (Met/Met) enzyme activities.

The Met allele has been associated with more anxious, cautious personality (Enoch, Xu, Ferro, Harris, & Goldman, 2003). Met allele has been associated with mood as well as anxiety disorders (Hosak, 2007). On the other hand the study based on selected cases and controls from a large twin cohort found the Val allele to predict both higher neuroticism and risk for anxiety disorders and major depression (Hettema et al., 2008). Some studies show marginal (Eley et al., 2003) or no associations between COMT genotype and personality traits (Ishii et al., 2007).

Val allele has been associated with increased risk for eating disorders (Mikolajczyk, Smiarowska, Grzywacz, & Samochowiec, 2006). Val/val genotype increases the risk of bulimia nervosa (Mikolajczyk et al., 2010). Though there are studies showing that there is no association between COMT-rs4680 and eating disorders (Gabrovsek et al., 2004; Yilmaz et al., 2011).

Yilmaz and colleagues (2011) suggested that while the Met allele may be associated with BN in general, the presence of the Val-allele, associated with high COMT enzyme activity, may serve as a risk factor for a subgroup of BN probands with ADHD symptoms.

One study concerning both candidate genes (serotonin transporter gene and COMT gene) showed that carriers of at least one Met-allele of the COMT gene had significantly higher total scores of the EDI-2. Carriers of the s-allele of the 5-HTTLPR had significantly higher scores of the EDI-2 drive for thinness and body dissatisfaction subscales (Frieling et al., 2006).

Interaction between genes and environment

Several studies show interaction effect of 5-HTTLPR variations and adverse life events on depression (Caspi et al., 2003; Cervilla et al., 2007; Kendler, Kuhn, Vittum, & Prescott, 2005; Wilhelm et al., 2006), although Gillespie, Whitfield, Williams, Heath, & Martin (2005) found no interaction effect between 5-HTT gene polymorphism and life events on depression. S-allele carriers have greater and longer lasting reactions to fearful stimuli (Armbruster, Moser, Strobel, Tilman, Kirschbaum, Lesch, & Brocke 2009).

Our previous study showed that the effect of the 5-HTTLPR on binge eating and on drive for thinness was moderated by adverse life events and sexual abuse in particular (Akkermann, Kaasik, Kiive, Nordquist, Oreland, & Harro, 2012).

It has been recently shown that childhood adverse experience is moderated by the COMT genotype in a way that Met allele carriers who have experienced childhood adverse life events have higher risk of developing severe alcohol dependence compared to individuals homozygous for the Val allele (Schellekens, Franke, Ellenbroek, Cools, de Jong, Buitelaar, & Verkes, 2012).

Aim of the study

Based on previous findings, the study was conducted to examine the relationship between 5-HTTLPR and COMT Val158Met polymorphisms adverse life events, neuroticism, anxiety, impulsivity and disordered eating behavior and attitudes.

Method

Participants

The study is based on the sample of the European Youth Heart Study (EYHS) which was first conducted in Estonia in 1998/1999, then complemented with psychology module and incorporated into the longitudinal Estonian Children Personality, Behavior and Health Study (ECPBHS). Sample formation is described in detail by Harro et al. (2001) study. This sample represents the proportion of certain aged urban and rural girls and boys living in one county at the time of sampling. The main unit of sampling was a school. Out of 54 schools that agreed to participate were selected 25 schools using cluster sampling. Of each sampled school all of the selected aged students were asked to participate and written consent was given by children and their parents.

This study is based on the data of the older cohort who participated in the study in 1998 (N = 593, mean age 15.4 years, SD = 0.6 years), 2001 (N = 417, mean age 18.3, SD = 07 years) and 2008 (mean age 24.7, SD = 0.7, N = 541). Data about female subjects was used, men were excluded due to the low prevalence of disordered eating in men. Subjects completed several questionnaires in laboratory setting, descriptive statistics are presented in table 1. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu. The study was conducted in accordance with the Declaration of Helsinki.

Table 1

Descriptive statistics of the sample

Measure	Mean	SD	Min result	Max result
Bulimia	1.31	2.15	0	15
Drive for Thinness	3.48	4.24	0	18
Body Dissatisfaction	7.31	7.10	0	27
Neuroticism	93.76	24.24	39	160
State anxiety (STAI-S)	33.13	9.93	20	75
Trait anxiety (STAI-T)	41.69	11.13	22	71
Impulsivity (BIS-11)	56.56	8.56	36	82
Adverse life events	2.47	2.44	0	10

Genotyping of the 5-HTTLPR and COMT Val158Met polymorphism

Genomic DNA extraction from venous blood and genotyping was carried out in Department of Neuroscience, Pharmacology, University of Uppsala, Sweden.

The alleles at the 5-HTTLPR locus were amplified from genomic DNA using polymerase chain reaction (PCR) as described previously by Harro et al. (2001).

DNA was extracted from venous blood with QIAamp DNA Midi kit (Qiagen, Hilden, Germany). COMT Val158Met polymorphism (rs4680) genotyping reactions were performed in a total volume of 20 μl with 10-50 ng of template DNA. The real-time polymerase chain reaction was performed with primers and fluorescent probes obtained from Applied Biosystems (Foster City, CA, USA) Custom TaqMan SNP Genotyping Assays. PCR reaction components and final concentrations were as follows: 1:5 5xHOT FIREPol Probe qPCR Mix Plus (ROX) (SolisBiodyne) and 1:20 80xTaqMan Primers Probe (F 5' - CCCAGCGGATGGTGGAT -3'; R 5' –CAGGCATGCACACCTTGTC –3'; Reporter 1 – TTCGCTGGCATGAAG (VIC); Reporter 2 –TCGCTGGCGTGAAG (FAM)). Reactions were performed on the ABI 7500 Real-Time PCR system and the amplification procedure consisted of an initial denaturation step at 95°C for 15 minutes and 40 cycles of 95°C for 15 seconds and 60°C for 1 minute. All genotyping reactions were carried out in duplicates and extra negative controls were added to each reaction plate. No inconsistencies occurred. Genotypes were found to be in the Hardy-Weinberg equilibrium.

Measures

Eating Disorders Inventory – 2 (EDI-2) (Garner, 1991), Estonian version (Podar et al., 1999) three subscales – drive for thinness (DT), bulimia (B) and body dissatisfaction (BD) –

were used to assess eating behavior and attitudes. Information about disordered eating behavior was collected in 2008. The drive for thinness subscale measures concern and preoccupation with dieting and weight gain, the bulimia subscale measures the tendency to think about and engage in episodes of binge eating and body dissatisfaction subscale measures dissatisfaction with the overall shape and with the size of those parts of the body that are of greatest concern to those with eating disorders (i.e. stomach, hips, thighs, buttocks). These subscales have been shown to be most directly related to eating-disordered behavior (Hurley et al., 1990).

Anxiety was measured by Estonian version of State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983; Kreegipuu, 1997). The data were collected in 2008.

Personality factors were measured in 2001 by NEO Personality Inventory (NEO-PI) (Costa & McCrae, 1985) adapted Estonian version (Pulver, Allik, Pulkkinen, & Hämäläinen, 1995). This model consists of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.

Estonian version of Barratt Impulsiveness Scale (BIS-11) (Paaver et al., 2007; Patton et al., 1995) was used to measure impulsivity in 2008. In data analysis was used the total score of BIS-11.

Participants completed a comprehensive list about their life events, which was composed by Department of Public Health in University of Tartu. In the list there were 23 questions about adverse life events such as physical and mental violence, sexual abuse, trauma etc. Events were recorded dichotomously – present or not present during lifetime. Data about adverse life events was collected in the second study wave in 2001.

Data analysis

Statistical analysis was made using SPSS version 17.0 and STATA version 12. Current analysis is based on previous studies. Descriptive statistics and dispersion analysis were carried out using SPSS Statistics. The author performed path analysis using least squares method to show the associations between 5-HTTLPR, COMT Val158Met polymorphism, adverse life events, neuroticism and the moderating effect of anxiety and eating disorders. All the necessary assumptions were met and diagnostics are shown in appendix.

Results

Genotypes

In our sample 333 women were genotyped for 5-HTTLPR. S-allele carriers were grouped into one group since genetic studies have shown that s/s and s/l genotypes are similar and both different from l/l homozygotes (Lesch et al., 1996). There were 134 (40%) l-homozygous and 199 (60%) s-allele carrier women.

332 women were genotyped for COMT gene - 67 (20%) were Val-homozygotes, 171 (52%) Val/Met heterozygotes and 94 (28%) Met-homozygotes. In the data analysis all three allelic versions were analyzed separately.

Adverse life events

The subjects were ranked ordered and then divided into three equal groups based on percentiles with each group consisting of 33.33% of total cases: individuals with no adverse life events, individuals with few (1-2 events) and moderate (three or more) history of adverse life events.

No statistically significant differences between 5-HTTLPR s-allele carriers and l/l homozygotes concerning the number of adverse life events, $F(1,227) = 0.15$, $p = .70$, were observed. Statistically significant differences between COMT Val158Met allelic variants on the frequency of adverse life events, $F(2,226) = 2.99$, $p = .05$, were shown. Post hoc comparisons using the Fisher LSD test revealed that Val/Met heterozygous individuals had experienced less adverse life events as compared to Val/Val ($p < .05$) and Met/Met ($p < .05$). homozygotes.

Anxiety

5-HTTLPR was not associated with trait anxiety (STAI-T) mean scores, $F(1,200) = 0.22$, $p = .64$, nor state anxiety (STAI-S), $F(1,200) = 0.27$, $p = .61$ mean scores. COMT genotype was not associated with trait and state anxiety.

Groups based on different levels of adverse life events (as described above) had statistically different levels of trait anxiety, ANOVA main effect of adverse life events on trait anxiety was proven at $p = .02$, $F(2,226) = 3.87$. Post hoc comparisons using the Fisher LSD test revealed that individuals who had experienced three or more adverse life events had higher trait anxiety mean scores compared to individuals who had experienced one or two

adverse life events ($p < .05$). The group with no history of adverse life events did not differ from other two groups regarding anxiety mean score ($p > .05$).

These kind of associations were present regarding state anxiety as well, ANOVA main effect of adverse life events on state anxiety was proven at $p = .03$, $F(2,227) = 3.75$. Post hoc comparisons using the Fisher LSD test revealed that individuals who had experienced three or more adverse life events had higher state anxiety mean scores compared to other two groups (individuals with no history of adverse life events, $p < .05$, and individuals who had experienced one or two adverse life events in the past, $p < .05$). The group with no history of adverse life events did not differ statistically significantly ($p > .05$) from the group with one or two adverse life events.

Impulsivity

According to one way ANOVA neither the 5-HTTLPR allelic variants based groups nor COMT genotype based groups differed in levels of impulsivity ($p = .48$ and .38, respectively). Impulsivity was not associated to previously experienced adverse life events ($p = .30$). There was a significant positive correlation between impulsivity and trait anxiety scores ($r = .39$, $p < .001$).

Neuroticism

5-HTTLPR had no effect on neuroticism $F(1,214) = 0.10$, $p = .75$. ANOVA main effect of COMT genotype on trait anxiety was near significant at $p = .07$, $F(2,213) = 2.67$. Post hoc comparisons using the Fisher LSD test revealed that Val/Met heterozygotes had lower levels of neuroticism compared to Val/Val homozygotes ($p = .03$). Met/Met homozygotes did not differ statistically significantly ($p > .05$) from two other groups.

Neuroticism was correlated with higher levels of reported adverse life events at the age of 18 ($r = .26$, $p < .001$). There was a significant positive correlation between impulsivity and neuroticism scores ($r = .39$, $p < .001$) as well.

Disordered eating behavior

5-HTTLPR allelic variations and COMT Val158Met genotype were not associated with either EDI-2 drive for thinness, $p > .05$, or bulimia scores, $p > .05$. Influence of 5-HTTLPR on body dissatisfaction was not statistically significant, $F(1,264) = 3.36$, $p = .07$, but there was a tendency that s-allele carriers were more satisfied with their body as

compared to l/l homozygotes according to post hoc comparisons using the Fisher LSD test. COMT genotype was also associated with EDI-2 body dissatisfaction score, $F(2,263) = 4.25$, $p = .02$. Post hoc comparisons using the Fisher LSD test revealed that Val/Met heterozygotes had lower body dissatisfaction scores compared to Val/Val ($p < .05$) and Met/Met homozygotes ($p = .06$). Met/Met homozygotes did not differ statistically significantly ($p > .05$) from Val/Val homozygotes.

Adverse life events had near significant ANOVA main effect on EDI-2 bulimia, $F(2,223) = 2.59$, $p = .08$, drive for thinness $F(2,218) = 2.87$, $p = .06$, and body dissatisfaction $F(2,218) = 2.55$, $p = .08$ score. Post hoc comparisons using the Fisher LSD test revealed that regarding drive for thinness, individuals who had experienced three or more adverse life events had higher drive for thinness mean scores compared to other two groups (individuals with no history of adverse life events, $p < .05$, and individuals who had experienced one or two adverse life events in the past, $p < .05$). The group with no history of adverse life events did not differ statistically significantly ($p > .05$) from the group with one or two adverse life events regarding drive for thinness. Same kinds of tendencies were seen regarding bulimia and body dissatisfaction but these were not statistically significant.

Trait anxiety (low, medium, high score) was associated with bulimia, $F(2,216) = 20.22$, $p < .001$, drive for thinness, $F(2,210) = 17.94$, $p < .001$, and body dissatisfaction, $F(2,211) = 12.20$, $p < .001$, mean scores. Post hoc comparisons using the Fisher LSD test revealed in all three cases at $p < .05$ that the groups with higher trait anxiety had higher EDI-2 bulimia, drive for thinness and body dissatisfaction scores. All three groups differentiated from each other.

Impulsivity was associated with bulimia, $F(2,176) = 4.85$, $p = .01$) but not with drive for thinness ($p = .17$) and body dissatisfaction ($p = .23$). Post hoc comparisons using the Fisher LSD test revealed that individuals with high impulsivity had higher bulimia scores comparing to individuals with low ($p = .01$) and medium ($p = .01$) impulsivity. Individuals who had low or medium scores in impulsivity did not differ from each other regarding bulimic symptomatology.

Interaction effect between genes and environment

There was no interaction effect of the 5-HTTLPR and adverse life events on EDI-2 bulimia subscale scores, $p = .55$, drive for thinness, $p = .20$, and body dissatisfaction, $p = .37$, respectively.

There was no interaction effect of the COMT genotype and adverse life events on EDI-2 subscales as well, all of the significance values were higher than .60.

Because univariate ANOVA showed no interaction effect of genes and adverse life events on EDI-2 subscales the gene x environment interaction was not included to the following pathway regression analysis.

Pathway regression analysis

The author made path analysis for three EDI-2 subscales – bulimia, drive for thinness, body dissatisfaction. The parameters of following pathway models (Fig. 1-6) were estimated by STATA 12 by using pathreg command ("Introduction to STATA", 2007). The command carries out necessary regression analysis for estimation of standardized coefficients by using ordinary least squares regression estimates. The fulfillment of regression model assumptions were tested and analyzed by diagnostic tests for each sub-regression model of pathway regression models. Path regression analysis tables and diagnostics are presented in appendix. Categorical (genetic) variables were incorporated in models as *dummy* (as described by Wooldridge, 2002) variables. Each pathway regression model consists of two regression models.

EDI-2 Bulimia subscale

By modeling the direct and indirect (through trait anxiety – STAI-T) effects of 5-HTTLPR, adverse life events and neuroticism on EDI-2 bulimia subscale only the indirect effects of neuroticism through trait anxiety (STAI-T) were statistically significant ($\beta = .53$; $p < .05$). Also the direct effect of trait anxiety on bulimia subscale was confirmed ($\beta = .45$; $p < .05$) while also controlling for direct effects of 5-HTTLPR, adverse life events and neuroticism on bulimia result of which none itself was statistically significant ($p > .05$). Still it can be seen that standardized errors of predicted variable of predicted variables STAI-T ($\varepsilon 1 = .84$) and bulimia ($\varepsilon 1 = .88$) were substantial. It can be concluded that the predictive power of variables and relationships modeled by pathway model is quite low.

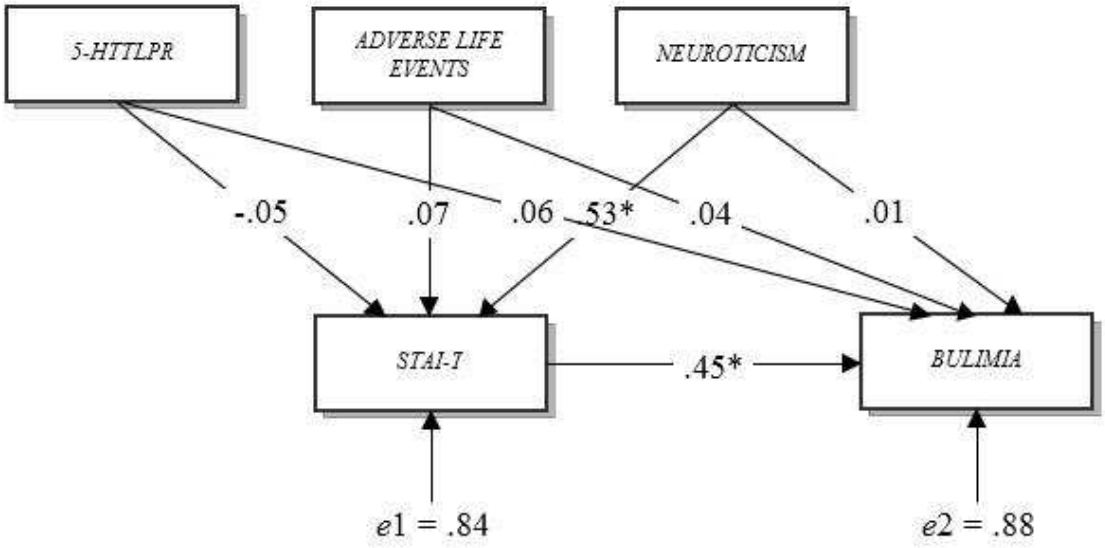

Figure 1. Direct and indirect (through trait anxiety) effects of 5-HTTLPR, adverse life events and neuroticism on EDI-2 bulimia subscale.

Next, the author included COMT gene Val158Met polymorphism to the model instead of 5-HTTLPR as it is shown in figure 2. In this model we have chosen Val/Val genotype to be the base group as benchmark group, that is, the group against which comparisons are made (as described in Wooldridge, 2002). By modeling the direct effect and indirect effect through trait anxiety of COMT gene Val158Met polymorphism, adverse life events and neuroticism on EDI-2 bulimia subscale only the indirect effects of neuroticism through trait anxiety were statistically significant ($\beta = .52$; $p < .05$). Also the direct effect of trait anxiety on bulimia subscale was confirmed ($\beta = .44$; $p < .05$) while also controlling for direct effects of COMT gene Val158Met polymorphism, adverse life events and neuroticism on bulimia subscale result of which none was statistically significant ($p > .05$). Similarly to previous model, here are substantial standardized errors of predicted variable of predicted variables STAI-T ($\varepsilon 1 = .84$) and bulimia ($\varepsilon 1 = .88$). It can be concluded that the predictive power of variables and relationships between them modeled by pathway model is quite low.

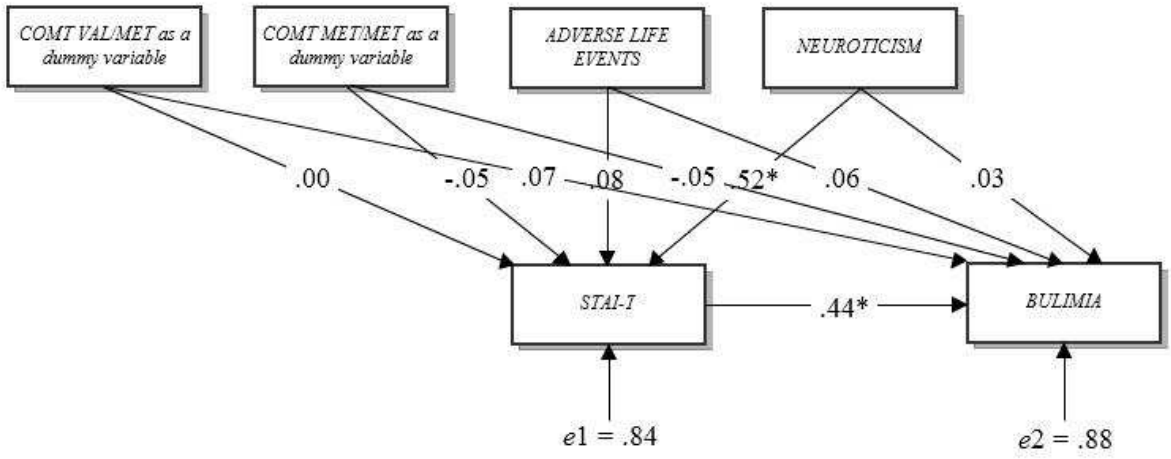

Figure 2. Direct and indirect (through trait anxiety) effects of COMT gene polymorphism, adverse life events and neuroticism on EDI-2 bulimia subscale.

EDI-2 Drive for Thinness subscale

Similar to first two models, the effects were the same regarding drive for thinness (Figure 3). The indirect effects of neuroticism through trait anxiety (STAI-T) were statistically significant ($\beta = .53$; $p < .05$) on drive for thinness result. Also the direct effect of trait anxiety on drive for thinness subscale was confirmed ($\beta = .43$; $p < .05$) while also controlling for direct effects of 5-HTTLPR, adverse life events and neuroticism on drive for thinness subscale of which none was statistically significant ($p > .05$). Standardized errors of predicted variable of predicted variables STAI-T ($\varepsilon 1 = .84$) and drive for thinness ($\varepsilon 1 = .91$) were substantial. The predictive power of variables and relationships between them modeled by pathway model is quite low.

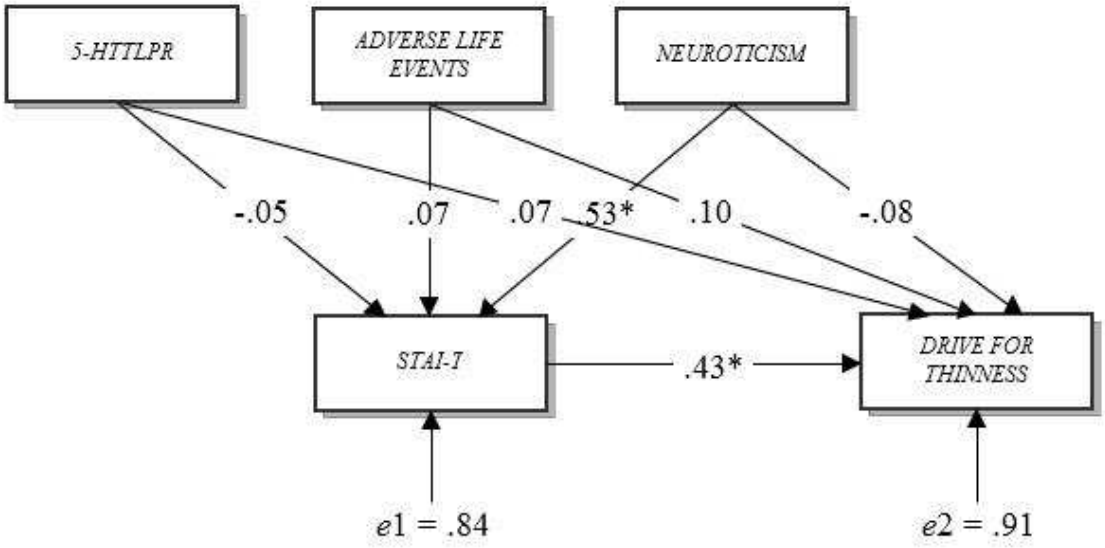

Figure 3. Direct and indirect (through trait anxiety) effects of 5-HTTLPR, adverse life events and neuroticism on EDI-2 drive for thinness subscale.

We included COMT gene Val158Met polymorphism to the model instead of 5-HTTLPR as it is shown in figure 4. By modeling the direct effect and indirect effect through trait anxiety of COMT gene polymorphism, adverse life events and neuroticism on EDI-2 drive for thinness subscale only the indirect effects of neuroticism through trait anxiety were statistically significant ($\beta = .52$; $p < .05$). Also the direct effect of trait anxiety on drive for thinness subscale was confirmed ($\beta = .42$; $p < .05$) while also controlling for direct effects of COMT gene polymorphism, negative life events and neuroticism on symptomatology scale of bulimia of which none was statistically significant ($p > .05$). Standardized errors are substantial.

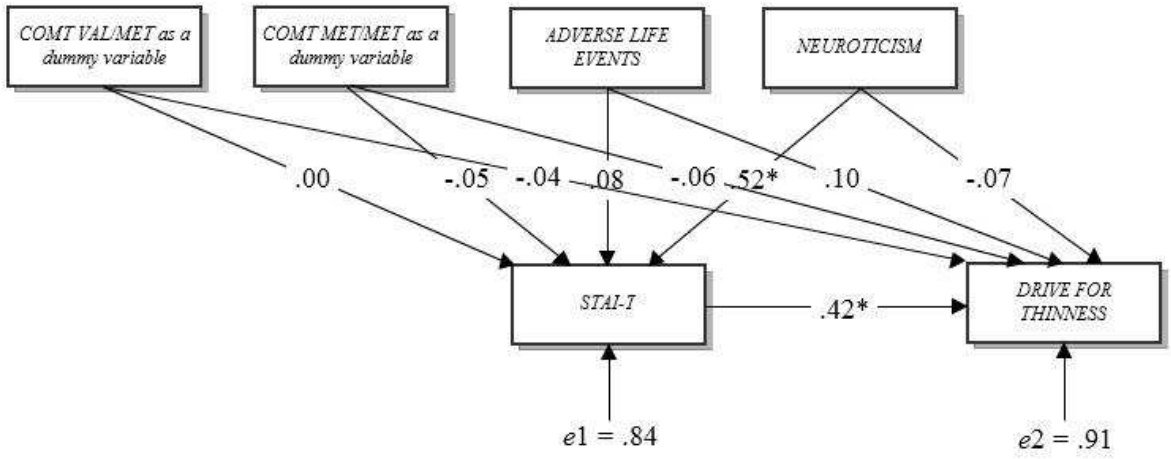

Figure 4. Direct and indirect (through trait anxiety) effects of COMT gene polymorphism, adverse life events and neuroticism on EDI-2 drive for thinness subscale.

EDI-2 Body Dissatisfaction subscale

Figure 5 shows similar results that neuroticism influences body dissatisfaction statistically significantly (β = .53; $p < .05$) through trait anxiety which itself influences body dissatisfaction (β = .34; $p < .05$). In this model, adverse life events had nearly significant direct effect on body dissatisfaction result (β = .14; $p = .06$).

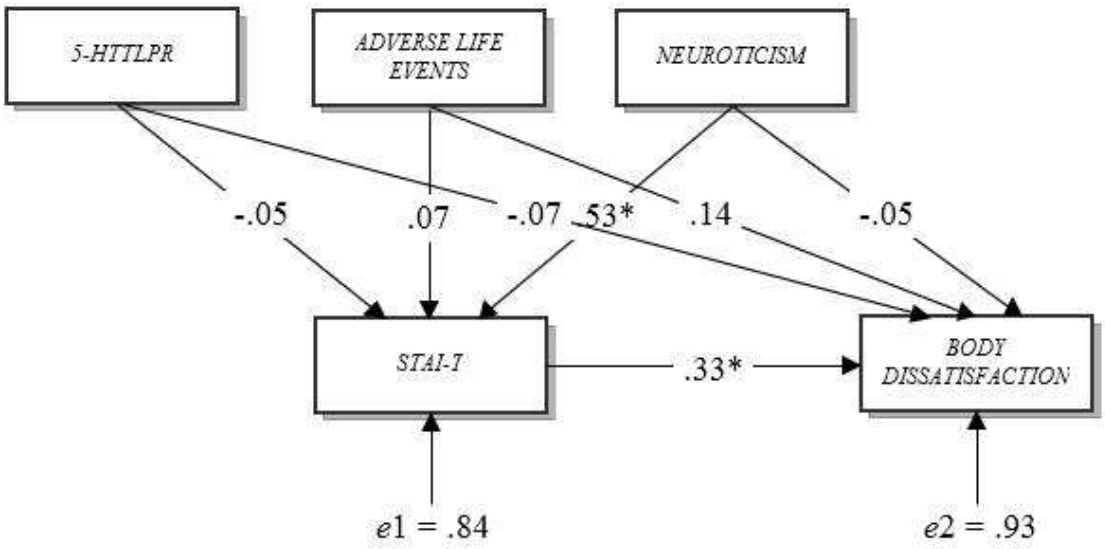

Figure 5. Direct and indirect (through trait anxiety) effects of 5-HTTLPR, adverse life events and neuroticism on EDI-2 body dissatisfaction subscale.

Figure 6 shows that COMT gene Val158Met polymorphism, adverse life events and neuroticism did not affect body dissatisfaction directly but neuroticism influences statistically significantly through trait anxiety.

By modeling the direct effect and indirect effect via trait anxiety of COMT gene Val158Met polymorphism, adverse life events and neuroticism on EDI-2 body dissatisfaction subscale only the indirect effects of neuroticism through trait anxiety were statistically significant ($\beta = .52$; $p < .05$). Also the direct effect of trait anxiety on body dissatisfaction subscale was confirmed ($\beta = .34$; $p < .05$) while also controlling for direct effects of COMT gene polymorphism, negative life events and neuroticism on body dissatisfaction of which none was statistically significant ($p > .05$). In this model the tendency of direct effect of adverse life events on body dissatisfaction can be seen ($p = .09$). Also COMT genotype effect, where Val/Met heterozygous individuals had lower body dissatisfaction scores as compared to Val/Val homozygotes. The same results were observed by dispersion analysis as well. There are substantial standardized errors of predicted variables STAI-T ($\varepsilon 1 = .84$) and bulimia ($\varepsilon 1 = .92$). It can be concluded that the predictive power of variables and relationships between them modeled by pathway model is quite low.

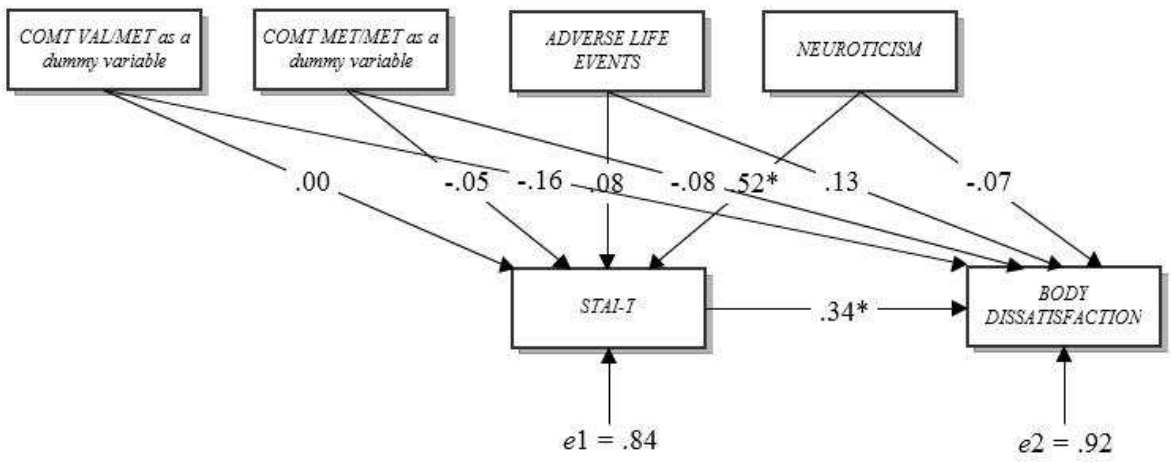

Figure 6. Direct and indirect (through trait anxiety) effects of COMT gene polymorphism, adverse life events and neuroticism on EDI-2 body dissatisfaction subscale.

It should be concluded that all six models (Fig. 1-6) acted the same way by modeling the direct and indirect (through trait anxiety) effects of 5-HTT or COMT gene Val158Met polymorphism, adverse life events and neuroticism on EDI-2 bulimia, drive for thinness and

body dissatisfaction subscales. Only the indirect effects of neuroticism through trait anxiety (STAI-T) were statistically significant. Also the direct effect of trait anxiety was confirmed in each model while controlling for direct effects of gene polymorphisms, adverse life events and neuroticism on eating disorder. Because all the pathway regression models presented above showed substantial size of error terms it can be concluded that the predictive power of variables and relationships between them modeled by pathway models is quite low.

Impulsivity and EDI-2 Bulimia subscale

Based on the findings that bulimic patients tend to be more impulsive as compared to healthy individuals the author conducted pathway regression analysis to show the effect of impulsivity on disordered eating behavior. Models regarding impulsivity and bulimic symptomatology are presented in appendix. Similarly to anxiety models impulsivity models acted the same way by modeling the direct and indirect (through impulsivity) effect of 5-HTTLPR and COMT Val158Met polymorphism, adverse life events and neuroticism on EDI-2 bulimia scores. Although the author formed the models regarding three EDI-2 subscales - bulimia, drive for thinness and body dissatisfaction - the model was correctly specified according to Ramsey RESET test only when looking for associations between impulsivity and bulimic symptoms (fig. 7). This is in accordance with ANOVA results.

In the model including 5-HTTLPR, adverse life events, neuroticism, impulsivity and bulimia (fig. 7), only the effect of neuroticism on impulsivity was statistically significant ($\beta = .35$; $p < .05$). The direct effect of impulsivity on bulimia was not statistically significant ($\beta = .17$; $p = .05$). Standardized errors were even more substantial as compared to models including trait anxiety and the predictive power was lower than in previous models.

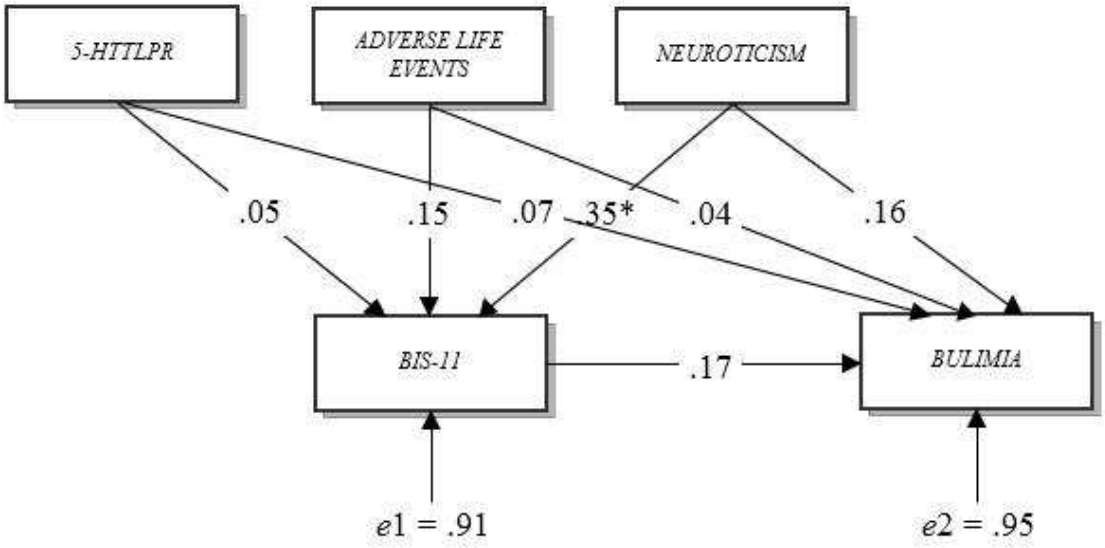

Figure 7. Direct and indirect (through impulsivity) effects of 5-HTTLPR, adverse life events and neuroticism on EDI-2 bulimia subscale.

In the model including COMT Val158Met polymorphism, only the indirect effect of neuroticism through impulsivity on bulimia scores was statistically significant (β = .35; p < .05) (Fig. 8) It should be said that adverse life events had a tendency to affect impulsivity (β = .14, p = .08). The direct effect of impulsivity (β = .19; p < .05) was confirmed while controlling for direct effects of COMT gene polymorphisms, adverse life events and neuroticism on bulimia of which none was statistically significant. The direct effect of COMT Val158Met polymorphism was also confirmed – Met/Met homozygotes had decreased EDI-2 bulimia scores as compared to Val/Val homozygotes (β = -.21, p < .05). Effect was not seen comparing Val/Val homozygotes to Val/Met heterozygotes (p = .38). Standardized errors were even more substantial as compared to models including trait anxiety.

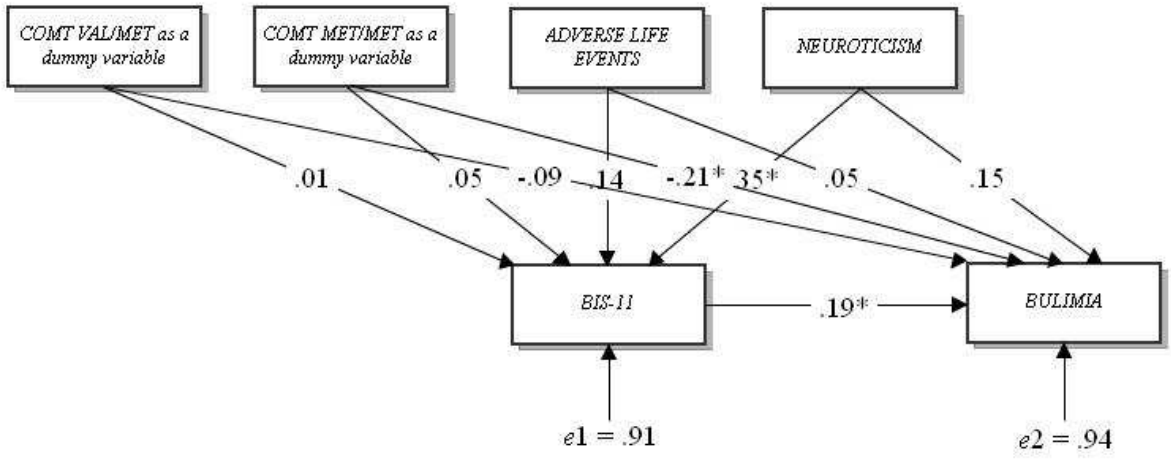

Figure 8. Direct and indirect (through impulsivity) effects of COMT Val158Met polymorphism, adverse life events and neuroticism on EDI-2 bulimia subscale.

Discussion

This study showed no 5-HTTLPR or COMT Val158Met polymorphism main effects on eating disorder symptoms regarding EDI-2 bulimia and drive for thinness scores. These results are consistent with number of previous findings (Gabrovsek et al., 2004; Hinney et al., 1997; Lauzurica et al., 2003; Urwin et al., 2003; Yilmaz et al., 2011). Although we found that both genetic polymorphisms are associated with body dissatisfaction. The tendency that s-allele carriers are less dissatisfied with their body weight and shape as compared to l/l homozygotes was contrary to general theory. These results are somewhat inconsistent with previous findings by Fumeron et al. (2001) who found that s-allele is more frequent among AN patients. Although AN patients are satisfied with their body size and weight, body dissatisfaction can be seen as the most important predisposing factor for eating disorders.

Very recent meta-analysis showed that across the studies there are homogeneous findings that COMT Val158Met polymorphism is not associated with AN (Brandys et al., 2012). This study showed no associations between COMT Val158Met polymorphism and drive for thinness – one of the most important components of AN – and therefore can confirm previous findings. On the other hand we found that body dissatisfaction is affected by Val158Met polymorphism. We found the tendency that Val/Met heterozygotes had lower neuroticism scores compared to Val/Val and Met/Met homozygotes (p = .07), no associations between COMT Val158Met genotype and impulsivity were found. It would be possible to

consider body dissatisfaction as an aspect of neurotic personality disposition as it was previously suggested by Podar (2010).

We did not find any associations between 5-HTTLPR and neuroticism nor impulsivity. Yet, it has been shown in meta-analysis that 5-HTT gene could be a good candidate gene in neuroticism, though the demonstrated effects are small (Schinka, Busch, & Robichaux-Keene, 2004). These results should be evaluated carefully because possible weak genetic components would need more substantial sample size to be statistically significantly distinguishable.

It has been shown in number of previous works that adverse life events are strongly related to disordered eating behavior (Pike, Wilfley, Hilbert, Fairburn, Dohm, & Stiegel-Moore, 2006; Risch et al., 2009; Welch et al., 1997). This study is consistent with previous findings. The frequency of adverse life events in the past was associated with eating disorder symptomatology at age of 25. Results were near significant regarding bulimic symptoms, body dissatisfaction and drive for thinness. Individuals with no history of adverse life events and individuals with few adverse life events do not differ from each other regarding body dissatisfaction, bulimia and drive for thinness. This was statistically significant regarding drive for thinness and same kind of tendencies were seen regarding body dissatisfaction and bulimic symptoms as well.

Previously we have reported the interaction effect of 5-HTTLPR and adverse life events on disordered eating behavior among ECPBHS younger cohort (Akkermann et al. 2012). This effect was confirmed also by Stoltenberg, Anderson, Nag, & Anagnopoulus (2012) who found that female s-allele carriers who were exposed to higher levels of childhood trauma reported significantly higher mean numbers of eating problems. This effect was not repeated in the current analysis based on ECPBHS older cohort. Adverse life events alone had an effect on eating disorder symptomatology but there was no interaction effect between adverse life events and 5-HTTLPR or COMT Val158Met polymorphism. We could hypothesize that there is an age-related vulnerability to adverse life events. In this case our sample consists of young women who reported about their previous adverse life events at the age of 18 years and the effect of adverse life events was considered at the age of 25 years. Our previous data was collected among teenage girls reporting about their experienced adverse life events at the age of 15 and the effect was considered at the age of 18. Younger girls may be more affected by experienced adverse life events. It should also be noted that older cohort reported less adverse life events experienced in the past as compared to younger cohort. It could be that adverse experiences moderated by genetic factors lead to disordered

eating behavior in some people when they have experienced adverse life events frequently. In this sample the group with most adverse life events had experienced 3-10 events compared to younger cohorts 6-18 events (Akkermann et al., 2012). Caspi et al. (2003) showed that 5-HTTLPR moderating effect of adverse life events on depression becomes particularly important when individuals had experienced more than 4 adverse life events.

To our best knowledge the current study is the first to explore mediating effect of trait anxiety and impulsivity among above mentioned genetic polymorphisms, adverse life events, neuroticism and disordered eating.

It has been shown previously that adverse life events (Loth et al., 2008; Schmidt et al., 1997; Welch et al., 1997), anxiety (Bulik et al., 2002; Mitchell et al., 1991), neuroticism (Brookings & Wilsdon, 1994; Dahl et al., 2012), 5-HTTLPR (Matsushita et al., 2002; Monteleone et al., 2006), COMT Val158Met polymorphism (Mikolajczyk et al., 2006; Mikolajczyk et al., 2010) can be seen as risk factors for eating disorders. Since EDI-2 bulimia, drive for thinness and body dissatisfaction subscales are most directly related to disordered eating behavior (Hurley et al., 1990), the author conducted pathway regression analysis taking into account all of these risk factors to show the relationship between these factors and disordered eating behavior. It is important to note that same kind of models were made regarding bulimia, drive for thinness and body dissatisfaction subscales and the results were the same all across the models. The author showed that eating disorder symptomatology is affected directly by trait anxiety. The effect of neuroticism through trait anxiety is statistically significant but has no direct effect on eating disorder symptomatology. These models show that different eating disorder symptomatology is affected by the same way directly by trait anxiety and by neuroticism through trait anxiety.

It is important to note that these path regression models acted the same way regarding all three EDI-2 subscales, so all of the main symptoms of eating disorders are affected in a similar way. The construct of control has been linked to anxiety, and it has been conceptualized as anxious perception of low control over external threats and emotional reactions. (Sassaroli, & Ruggiero, 2011) Perception of control is a general attitude involving not only eating and body weight and shape but also external events and internal feelings as well, such feelings may cause anxiety. To regain the feeling of control, individuals with ED commonly focus on eating and body size. (Sassaroli, & Ruggiero, 2011).

Is anxiety a cause or an effect of disordered eating behavior? Pallister & Waller (2008) suggested three potential explanations for the comorbidity between anxiety and eating disorders - anxiety could be a risk factor for ED or itself may cause anxiety, or these

disorders may have common shared vulnerabilities. Models of current study show that anxiety is a risk factor for eating disorders. All in all the results from this study as well results from previous research argue in favor of connection between symptomology of eating disorders and trait anxiety.

It is hypothesized that if a person is not very distress tolerant then she can develop eating disorders. In the current study adverse life events were associated with trait anxiety as was shown by dispersion analysis. In path regression analysis regarding neuroticism and 5-HTTLPR of COMT Val158Met genotype besides adverse life events the effect was not significant any more. This argues in favor to hypothesis that the level of anxiety cannot be explained away as a result of differences of environment between subjects. Rather anxiety can be seen as stable trait predisposing people toward higher levels of eating disorder related symptomology. The hypothesis was also supported by fact that trait anxiety was strongly influenced by personality dimension neuroticism that has been shown to be quite stable across life (Allik & McCrae, 2002).

We did not report that trait anxiety is influenced by 5-HTTLPR and COMT Val158Met polymorphism. The main finding of current study is that although it has been suggested that neuroticism affects disordered eating behavior directly (Bulik et al., 2002; Cassin & von Ranson, 2005; Fischer, Smith, & Cyders, 2008) we found that the influence is important only through trait anxiety. Our study has shown that trait anxiety and neuroticism are significantly related to eating disorders symptomology. So the author suggests that further studies targeting candidate genes for eating disorders should consider including the genes related to constructs of neuroticism and trait anxiety.

It has been shown that impulsivity is particularly associated with BN (Kemps & Wilsdon, 1994; Rosval et al., 2006). This study showed that EDI-2 bulimia subscale mean scores were associated with impulsivity. These kinds of associations were not present regarding body dissatisfaction or drive for thinness. Further, the author conducted pathway regression analysis adding 5-HTTLPR or COMT Val158Met polymorphism, adverse life events, neuroticism to the model together with impulsivity and EDI-2 bulimia subscale results to the model. This model showed that neuroticism affects bulimic symptomatology through impulsivity when genetic polymorphism of COMT Val158Met was included in the model. The effect of impulsivity on bulimic symptoms was not statistically significant when 5-HTTLPR was part of the model. Other factors besides impulsivity and neuroticism did not affect bulimic symptomatology directly or through impulsivity either when considering COMT Val158Met polymorphism or 5-HTTLPR effect in the model. These models are not

optimal for modeling influences on drive for thinness and body dissatisfaction because there are no significant associations between these variables.

We showed that impulsivity had significant effect on bulimic symptoms only when COMT Val158Met genotype was present in a model. This could be explaned by the hypothezis that inhibitory control is sensitive to dopamine function. Congdon, Constable, Lesch, & Canli (2009) found that COMT Met-allele carriers compared to Val/Val homozygotes had greater activation during inhibition.

This study supports the kind of treatment for ED where it is important to target the underlying vulnerability cognitions and anxiety as suggested by Pallister & Waller (2008). Anxiety has been linked to the construct of control. The perception of low control over external threats and emotional reactions increases anxiety. To regain the feeling of control, individuals with ED commonly focus on eating and body size (Sassaroli, & Ruggiero, 2011).

The findings from current study hint that practitioners should investigate eating problems among individuals with mood and anxiety disorders as suggested previously by Touchette et al. (2011).

In this study we used nonclinical sample and therefore it is unclear whether the kind of relationships would extend to individuals with clinical eating disorders and this should be examined in the future.

Another limitation of this study is our sample. The author was able to analyze only disordered eating symptomatology not diagnosed cases because of low incidence of diagnosed eating disorders. Future studies should investigate the applicability of these kinds of models among clinical population. Also it should be important to examine how some protective factors (for example social support) change the pathways to eating disorder symptoms.

Conclusion

This study shows no 5-HTTLPR or COMT Val158Met polymorphism effect on disordered eating behavior regarding bulimic symptoms and drive for thinness. Body dissatisfaction was influenced by both polymorphisms.

The main finding of current study is that although it has been suggested that neuroticism affects disordered eating behavior directly we found that the influence is mediated mainly by trait anxiety and modestly by impulsivity. Neuroticism seems to be

particularly important personality factor to affect impulsivity, anxiety and eating disorders as well through these factors.

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Appendix

Analysis regarding EDI-2 Bulimia subscale

Table 1

Pathway Analysis

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
5-HTTLPR (l/l vs s-allele carriers)	-1.25	1.51	-0.83	.41	-.05
Negative life events	0.34	0.31	1.12	.27	.07
Neuroticism	0.24	0.03	7.88	.00	.53
Constant	20.68	3.70	5.58	.00	.
n = 169	R^2 = .30	sqrt (1 - R^2) = .84			

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
STAI-T	0.09	0.02	5.42	.00	.45
5-HTTLPR (l/l vs s-allele carriers)	0.27	0.31	0.86	.39	.06
Negative life events	0.04	0.06	0.59	.56	.04
Neuroticism	0.00	0.00	0.15	.89	.01
Constant	-2.96	0.83	-3.59	.00	.
n = 169	R^2 = .22	sqrt (1 - R^2) = .88			

Table 2

Pathway Analysis

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
COMT Val/Met as dummy variable	0.07	1.84	0.04	.97	.00
COMT Met/Met as dummy variable	-1.35	2.18	-0.62	.54	-.05
Negative life events	0.38	0.31	1.23	.22	.08
Neuroticism	0.24	0.03	7.75	.00	.52
Constant	18.93	3.38	5.60	.00	.
n = 169	R^2 = .30	sqrt (1 - R^2) = .84			

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
STAI-T	0.08	0.02	5.29	.00	.44
COMT Val/Met as a dummy variable	0.28	0.37	0.75	.45	.07
COMT Met/Met as a dummy variable	-0.27	0.45	-0.62	.54	-.05
Negative life events	0.05	0.06	0.79	.43	.06
Neuroticism	0.00	0.01	0.33	.74	.03
Constant	-2.70	0.75	-3.59	.00	.
n = 169	R^2 = .23	sqrt (1 - R^2) = .88			

Analysis regarding Drive for Thinness

Table 3

Pathway Analysis

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
5-HTTLPR (l/l vs s-allele carriers)	-1.25	1.51	-0.83	.41	-.05
Negative life events	0.34	0.31	1.12	.27	.07
Neuroticism	0.24	0.03	7.88	.00	.53
Constant	20.68	3.70	5.58	.00	.
n = 169	R^2 = .30	sqrt (1 - R^2) = .84			

Drive for Thinness	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
STAI-T	0.17	0.03	5.07	.00	.43
5-HTTLPR (l/l vs s-allele carriers)	0.65	0.64	1.01	.31	.07
Negative life events	0.18	0.13	1.38	.17	.10
Neuroticism	-0.01	0.02	-0.89	.38	-.08
Constant	-3.55	1.71	-2.07	.04	.
n = 169	R^2 = .18	sqrt (1 - R^2) = .91			

Table 4

Pathway Analysis

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
COMT Val/Met as a dummy variable	0.07	1.84	0.04	.97	.00
COMT Met/Met as a dummy variable	-1.35	2.18	-0.62	.54	-.05
Negative life events	0.38	0.31	1.23	.22	.08
Neuroticism	0.24	0.03	7.75	.00	.52
Constant	18.94	3.38	5.60	.00	.
n = 169	R^2 = .30	sqrt (1 - R^2) = .84			

Drive for Thinness	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
STAI-T	0.16	0.03	4.95	.00	.42
COMT Val/Met as a dummy variable	-0.34	0.78	-0.44	.66	-.04
COMT Met/Met as a dummy variable	-0.63	0.93	-0.68	.50	-.06
Negative life events	0.18	0.13	1.35	.18	.10
Neuroticism	-0.01	0.02	-0.84	.40	-.07
Constant	-2.09	1.57	-1.33	.19	.
n = 169	R^2 = .18	sqrt (1 - R^2) = .91			

Analysis regarding EDI-2 Body Dissatisfaction

Table 5

Pathway Analysis

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
5-HTTLPR (l/l vs s-allele carriers)	-1.25	1.51	-0.83	.41	-.05
Negative life events	0.34	0.31	1.12	.27	.07
Neuroticism	0.24	0.03	7.88	.00	.53
Constant	20.68	3.70	5.58	.00	.
n = 169	R^2 = .30	sqrt (1 - R^2) = .84			

Body Dissatisfaction	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
STAI-T	0.22	0.06	3.83	.00	.33
5-HTTLPR (l/l vs s-allele carriers)	-1.01	1.13	-0.90	.37	-.07
Negative life events	0.44	0.23	1.90	.06	.14
Neuroticism	-0.01	0.03	-0.55	.58	-.05
Constant	0.37	3.02	0.12	.90	.
n = 169	R^2 = .14	sqrt (1 - R^2) = .93			

Table 6

Pathway Analysis

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
COMT Val/Met as a dummy variable	0.07	1.84	0.04	.97	.00
COMT Met/Met as a dummy variable	-1.35	2.18	-0.62	.54	-.05
Negative life events	0.38	0.31	1.23	.22	.08
Neuroticism	0.24	0.03	7.75	.00	.52
Constant	18.94	3.38	5.60	.00	.
n = 169	R^2 = .30	sqrt (1 - R^2) = .84			

Body Dissatisfaction	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
STAI-T	0.23	0.06	3.92	.00	.34
COMT Val/Met as a dummy variable	-2.35	1.37	-1.72	.09	-.16
COMT Met/Met as a dummy variable	-1.38	1.62	-0.85	.40	-.08
Negative life events	0.40	0.23	1.71	.09	.13
Neuroticism	-0.02	0.03	-0.82	.41	-.07
Constant	0.89	2.74	0.33	.75	.
n = 169	R^2 = .15	sqrt (1 - R^2) = .92			

Diagnostics

To test the fulfillment of regression model assumptions all the regression models of pathway regression models were carried out separately and then analyzed by appropriate diagnostic tests to check for multicollinearity by using TOL and VIF statistics, heteroskedasticity by using Breusch-Pagan test and model specification errors in terms of omitted variables by using Ramsey RESET test.

Regression model with error terms without constant variation across the range of factor variables (heteroskedasticity) can cause the erroneous estimations of standard error estimates of regression model parameters. Having erroneous model parameter's standard error estimates can cause wrong results in statistical test of statistical significance of model parameters. In models with detected heteroskedasticity new model with robust standard error estimates adjusted to heteroskedasticity was calculated in order to estimate the statistical significance of model parameters.

All such separate regression models satisfy the assumption of nonexistence of multicollinearity determined by comparing obtained TOL and VIF values against critical values (VIF > 5; TOL < 0.20). Also all such separate regression models meet the between the number of observations (n) and number of parameters in model (k) n > k.

Table 7

Regression analysis using least squares method

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
5-HTTLPR (l/l vs s-allele carriers)	-1.25	1.51	-0.83	.41	-4.22	1.73
Neuroticism	0.24	0.03	7.88	.00	0.18	0.30
Negative life events	0.34	0.31	1.12	.27	-0.26	0.95
Constant	20.68	3.70	5.58	.00	13.37	28.00

n = 169 R^2 = .30 (Adjusted R^2 = .29) Root MSE = 9.46
$F(3,165) = 23.87$, $p = .00$

Ramsey RESET test using powers of the fitted values of STAI-T

HO: model has no omitted variables
$F(3,162) =$ .69
Prob > F .56

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance
Variables: fitted values of STAI-T
χ^2 (1) = .00
Prob > χ^2 .97

Regression model analyzing the relationship between dependent variable STAI-T and factor variables 5-HTTLPR, negative life events and neuroticism (Table 7) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 30% of variance seen in dependent variable STAI-T. Only the factor variable neuroticism and constant of model were shown to be statistically significant ($p < .05$).

The diagnostic tests show that no specification errors in terms of omitted variables and heteroskedasticity in significance levels $p < .05$ can be shown.

Table 8

Regression analysis using least squares method

STAI-T	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
COMT Val/Met as a dummy variable	0.07	1.84	0.04	.97	-3.57	3.70
COMT Met/Met as a dummy variable	-1.35	2.18	-0.62	.54	-5.66	2.97
Neuroticism	0.24	0.03	7.75	.00	0.18	0.30
Negative life events	0.38	0.31	1.23	.22	-0.23	1.00
Constant	18.94	3.38	5.60	.00	12.26	25.62

n = 169 R^2 = .30 (Adjusted R^2 = .29) Root MSE = 9.49
$F(4,164) = 17.77$, $p = .00$

Ramsey RESET test using powers of the fitted values of STAI-T

HO: model has no omitted variables
$F(3,161)$ = .18
Prob > *F* .91

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance
Variables: fitted values of STAI-T
χ^2 (1) = .10
Prob > χ^2 .76

Regression model analyzing the relationship between dependent variable STAIT-T and factor variables COMT gene Val158Met polymorphism dummy variables, negative life events and neuroticism (Table 8) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 30% of variance seen in dependent variable STAI-T. Only the factor variable Neuroticism and constant of model were shown to be statistically significant ($p < .05$).

The diagnostic tests show that no specification errors in terms of omitted variables and heteroskedasticity in significance levels $p < .05$ can be shown.

Table 9

Regression analysis using least squares method

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.09	0.02	5.42	.00	0.05	0.12
5-HTTLPR (l/l vs s-allele carriers)	0.27	0.31	0.86	.39	-0.34	0.87
Neuroticism	0.00	0.01	0.15	.89	-0.01	0.02
Negative life events	0.04	0.06	0.59	.56	-0.09	0.16
Constant	-2.96	0.83	-3.59	.00	-4.60	-1.33

n = 169 R^2 = .22 (Adjusted R^2 = .20) Root MSE = 1.93
$F(4,164) = 11.43$, $p = .00$

Ramsey RESET test using powers of the fitted values of Bulimia

HO: model has no omitted variables
$F(3,161)$ = .55
Prob > *F* .65

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Bulimia	
χ^2 (1) =	70.31
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable bulimia and factor variables 5-HTTLPR, negative life events, STAI-T and neuroticism (Table 9) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 22% of variance seen in dependent variable Bulimia. Only factor variable STAI-T and constant of model were shown to be statistically significant ($p < .05$).

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table 10). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 10

Corrected regression analysis using robust standard errors

Bulimia	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.09	0.02	3.73	.00	0.04	0.13
5-HTTLPR (l/l vs s-allele carriers)	0.27	0.30	0.88	.38	-0.33	0.86
Neuroticism	0.00	0.01	0.16	.87	-0.01	0.01
Negative life events	0.04	0.07	0.49	.63	-0.11	0.19
Constant	-2.96	0.82	-3.63	.00	-4.58	-1.35

n = 169 R^2 = .22 Root MSE = 1.93
$F(4,164) = 8.58$, $p = .00$

Table 11

Regression analysis using least squares method

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.08	0.02	5.29	.00	0.05	0.12
COMT Val/Met as a dummy variable	0.28	0.37	0.75	.45	-0.46	1.02
COMT Met/Met as a dummy variable	-0.28	0.45	-0.62	.54	-1.15	0.60
Neuroticism	0.00	0.01	0.33	.74	-0.01	0.02
Negative life events	0.05	0.06	0.79	.43	-0.08	0.18
Constant	-2.70	0.75	-3.59	.00	-4.18	-1.21

n = 169 R^2 = .23 (Adjusted R^2 = .20) Root MSE = 1.93
$F(5,163) = 9.47$, $p = .00$

Ramsey RESET test using powers of the fitted values of Bulimia

HO: model has no omitted variables	
$F(3,160)$ =	.78
Prob > F	.51

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Bulimia	
χ^2 (1) =	65.21
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable bulimia and factor variables COMT gene Val158Met polymorphism dummy variables, negative life events, STAI-T and neuroticism (Table 11) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 23% of variance seen in dependent variable Bulimia. Only factor variable STAI-T and constant of model were shown to be statistically significant ($p < .05$).

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table 12). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 12

Corrected regression analysis using robust standard errors

Bulimia	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.08	0.02	3.67	.00	0.04	0.13
COMT Val/Met as a dummy variable	0.28	0.47	0.61	.55	-0.64	1.20
COMT Met/Met as a dummy variable	-0.28	0.45	-0.61	.54	-1.17	0.62
Neuroticism	0.00	0.01	0.36	.72	-0.01	0.02
Negative life events	0.05	0.08	0.62	.53	-0.11	0.21
Constant	-2.70	0.61	-4.42	.00	-3.90	-1.49

n = 169 R^2 = .23 Root MSE = 1.93
$F(5,163) = 7.74$, $p = .00$

Table 13

Regression analysis using least squares method

Drive for Thinness	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.17	0.03	5.07	.00	0.10	0.23
5-HTTLPR (l/l vs s-allele carriers)	0.65	0.64	1.01	.31	-0.62	1.92
Neuroticism	-0.01	0.02	-0.89	.38	-0.04	0.02
Negative life events	-.01	0.13	1.38	.17	-0.08	0.44
Constant	-3.55	1.72	-2.07	.04	-6.94	-0.16

n = 169 R^2 = .18 (Adjusted R^2 = .16) Root MSE = 4.02
$F(4,164) = 9.03$, $p = .00$

Ramsey RESET test using powers of the fitted values of Drive for Thinness

HO: model has no omitted variables	
$F(3,161)$ =	.27
Prob > F	.84

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Drive for Thinness	
χ^2 (1) =	23.86
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable drive for thinness and factor variables 5-HTTLPR, negative life events, STAI-T and neuroticism (Table 13) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 18% of variance seen in dependent variable drive for thinness. Only factor variable STAI-T and constant of model were shown to be statistically significant ($p < .05$).

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table

14). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 14

Corrected regression analysis using robust standard errors

Drive for Thinness	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.17	0.04	3.95	.00	0.08	0.25
5-HTTLPR (l/l vs s-allele carriers)	0.65	0.65	1.00	.32	-0.64	1.94
Neuroticism	-0.01	0.02	-0.71	.48	-0.05	0.02
Negative life events	0.18	0.15	1.22	.22	-0.11	0.47
Constant	-3.55	1.59	-2.23	.03	-6.69	-0.41

n = 169 R^2 = .18 Root MSE = 4.02
$F(4,164) = 7.22$, $p = .00$

Table 15

Regression analysis using least squares method

Drive for Thinness	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.16	0.03	4.95	.00	0.10	0.23
COMT Val/Met as a dummy variable	-0.34	0.78	-0.44	.66	-1.90	1.21
COMT Met/Met as a dummy variable	-0.64	0.93	-0.68	.50	-2.48	1.20
Neuroticism	-0.01	0.02	-0.84	.40	-0.04	0.02
Negative life events	0.18	0.13	1.35	.18	-0.08	0.44
Constant	-2.09	1.57	-1.33	.19	-5.20	1.02

n = 169 R^2 = .18 (Adjusted R^2 = .15) Root MSE = 4.04
$F(5,163) = 7.05$, $p = .00$

Ramsey RESET test using powers of the fitted values of Drive for Thinness

HO: model has no omitted variables	
$F(3,160)$ =	.39
Prob > F	.76

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Drive for Thinness	
χ^2 (1) =	26.07
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable drive for thinness and factor variables COMT gene Val158Met polymorphism dummy variables, negative life events, STAI-T and neuroticism (Table 15) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 18% of variance seen in dependent variable drive for thinness. Only factor variable STAI-T ($p < .05$) was shown to be statistically significant.

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table 16). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 16

Corrected regression analysis using robust standard errors

Drive for Thinness	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.16	0.04	3.83	.00	0.08	0.25
COMT Val/Met as a dummy variable	-0.34	0.85	-0.40	.69	-2.02	1.33
COMT Met/Met as a dummy variable	-0.64	0.89	-0.72	.48	-2.39	1.12
Neuroticism	-0.01	0.02	-0.68	.50	-0.05	0.02
Negative life events	0.18	0.16	1.15	.25	-0.13	0.49
Constant	-2.09	1.54	-1.36	.18	-5.13	0.95

n = 169 R^2 = .18 Root MSE = 4.04
$F(5,163) = 5.73$, $p = .00$

Table 17

Regression analysis using least squares method

Body Dissatisfaction	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.22	0.06	3.83	.00	0.11	0.34
5-HTTLPR (l/l vs s-allele carriers)	-1.01	1.13	-0.90	.37	-3.24	1.22
Neuroticism	-0.01	0.03	-0.55	.58	-0.07	0.04
Negative life events	0.44	0.23	1.90	.06	-0.02	0.89
Constant	0.37	3.02	0.12	.90	-5.59	6.32

n = 169 R^2 = .14 (Adjusted R^2 = .12) Root MSE = 7.06
$F(4,164) = 6.54$, $p = .00$

Ramsey RESET test using powers of the fitted values of Body Dissatisfaction

HO: model has no omitted variables
$F(3,161)$ = 1.85
Prob > F .14

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Body Dissatisfaction	
χ^2 (1) =	5.77
Prob > χ^2	.02

Regression model analyzing the relationship between dependent variable body dissatisfaction and factor variables 5-HTTLPR, negative life events, STAI-T and neuroticism (Table 17) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 14% of variance seen in dependent variable body dissatisfaction. Only factor variable STAI-T ($p < .05$) was shown to be statistically significant ($p < .10$).

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table 18). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 18

Corrected regression analysis using robust standard errors

Body Dissatisfaction	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.22	0.06	3.74	.00	0.11	0.34
5-HTTLPR (l/l vs s-allele carriers)	-1.01	1.19	-0.85	.40	-3.36	1.33
Neuroticism	-0.01	0.03	-0.49	.62	-0.07	0.04
Negative life events	0.44	0.26	1.70	.09	-0.07	0.95
Constant	0.37	2.92	0.13	.90	-5.40	6.13

n = 169 R^2 = .14 Root MSE = 7.06
$F(4,164) = 6.44$, $p = .00$

Table 19

Regression analysis using least squares method

Body Dissatisfaction	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.23	0.06	3.92	.00	0.11	0.34
COMT Val/Met as a dummy variable	-2.35	1.37	-1.72	.09	-5.04	0.35
COMT Met/Met as a dummy variable	-1.38	1.62	-0.85	.40	-4.58	1.83
Neuroticism	-0.02	0.03	-0.82	.41	-0.07	0.03
Negative life events	0.40	0.23	1.71	.09	-0.06	0.86
Constant	0.89	2.74	0.33	.75	-4.52	6.30

n = 169 R^2 = .15 (Adjusted R^2 = .12) Root MSE = 7.04
$F(5,163) = 5.70$, $p = .00$

Ramsey RESET test using powers of the fitted values of Body Dissatisfaction

HO: model has no omitted variables	
$F(3,160)$ =	2.24
Prob > F	.09

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Body Dissatisfaction	
χ^2 (1) =	7.91
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable body dissatisfaction and factor variables COMT gene Val158Met polymorphism dummy variables, negative life events, STAI-T and neuroticism (Table 19) was estimated by F-statistic to be statistically significant ($p < .05$) and described 15% of variance seen in dependent variable Body dissatisfaction. Only factor variable STAI-T ($p < .05$) was shown to be statistically significant ($p < .10$).

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table 20). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 20

Corrected regression analysis using robust standard errors

Body Dissatisfaction	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
STAI-T	0.23	0.06	3.85	.00	0.11	0.34
COMT Val/Met as a dummy variable	-2.35	1.61	-1.45	.15	-5.53	0.84
COMT Met/Met as a dummy variable	-1.38	1.78	-0.77	.44	-4.90	2.15
Neuroticism	-0.02	0.03	-0.75	.45	-0.08	0.04
Negative life events	0.40	0.27	1.47	.14	-0.14	0.93
Constant	0.89	2.88	0.31	.76	-4.79	6.57

n = 169 R^2 = .15 Root MSE = 7.04
$F(5,163) = 6.24$, $p = .00$

Analysis regarding 5-HTTLPR / COMT Val158Met polymorphism, adverse life events, neuroticism, impulsivity and EDI-2 Bulimia results

Table 21

Pathway Analysis

BIS-11	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
5-HTTLPR (l/l vs s-allele carriers)	0.87	1.44	0.60	.55	.05
Negative life events	0.54	0.28	1.90	.06	.15
Neuroticism	0.13	0.03	4.35	.00	.35
Constant	41.79	3.61	11.59	.00	.
n = 140	R^2 = .18	sqrt (1 - R^2) = .91			

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
BIS-11	0.04	0.02	1.93	.06	.17
5-HTTLPR (l/l vs s-allele carriers)	0.29	0.33	0.89	.37	.07
Negative life events	0.13	0.06	0.46	.65	.04
Neuroticism	0.01	0.01	1.79	.08	.16
Constant	-2.80	1.16	-2.42	.02	.
n = 140	R^2 = .09	sqrt (1 - R^2) = .95			

Table 22

Pathway Analysis

BIS-11	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
COMT Val/Met as dummy variable	0.11	1.75	0.07	.95	.01
COMT Met/Met as dummy variable	1.15	2.06	0.56	.58	.05
Neuroticism	0.13	0.03	4.33	.00	.35
Negative life events	0.51	0.29	1.76	.08	.14
Constant	42.88	3.28	13.09	.00	.
n = 140	R^2 = .18	sqrt (1 - R^2) = .91			

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**Beta**
BIS-11	0.04	0.02	2.11	.04	.19
COMT Val/Met as a dummy variable	-0.35	0.39	-0.89	.38	-.09
COMT Met/Met as a dummy variable	-0.98	0.46	-2.12	.04	-.21
Neuroticism	0.01	0.01	1.63	.11	.15
Negative life events	0.04	0.07	0.57	.57	.05
Constant	-2.02	1.11	-1.82	.07	.
n = 140	R^2 = .12	sqrt (1 - R^2) = .94			

Diagnostics

Table 23

Regression analysis using least squares method

BIS-11	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
5-HTTLPR (l/l vs s-allele carriers)	0.87	1.44	0.60	.55	-1.97	3.70
Negative life events	0.54	0.28	1.90	.06	-0.02	1.10
Neuroticism	0.13	0.03	4.35	.00	0.07	0.19
Constant	41.79	3.61	11.59	.00	34.66	48.92

n = 140 R^2 = .18 (Adjusted R^2 = .16) Root MSE = 8.16
$F(3,136) = 9.68$, $p = .00$

Ramsey RESET test using powers of the fitted values of BIS-11

HO: model has no omitted variables	
$F(3,133)$ =	.16
Prob > F	.92

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of BIS-11	
χ^2 (1) =	.21
Prob > χ^2	.65

Regression model analyzing the relationship between dependent variable BIS-11 and factor variables 5-HTTLPR, negative life events and neuroticism (Table 23) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 16% of variance seen in dependent variable BIS-11. Only the factor variable neuroticism and constant of model were shown to be statistically significant ($p < .05$). The effect of negative life events was near significant ($p = .06$).

The diagnostic tests show that no specification errors in terms of omitted variables and heteroskedasticity in significance levels $p < .05$ can be shown.

Table 24

Regression analysis using least squares method

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
BIS-11	0.04	0.02	1.93	.06	0.00	0.08
5-HTTLPR (l/l vs s-allele carriers)	0.29	0.03	0.89	.37	-0.35	0.94
Negative life events	0.03	0.06	0.46	.65	-0.10	0.16
Neuroticism	0.01	0.01	1.76	.08	0.00	0.03
Constant	-2.80	1.16	-2.42	.02	-5.08	-0.51

n = 140 R^2 = .09 (Adjusted R^2 = .07) Root MSE = 1.86
$F(4,135) = 3.44$, $p = .01$

Ramsey RESET test using powers of the fitted values of Bulimia

HO: model has no omitted variables	
$F(3,132)$ =	.92
Prob > F	.43

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Bulimia	
χ^2 (1) =	21.52
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable bulimia and factor variables 5-HTTLPR, negative life events, BIS-11 and neuroticism (Table 24) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 9% of variance seen in dependent variable Bulimia. Constant of the model was shown to be statistically significant ($p < .05$). Factor variable BIS-11 ($p = .06$) and neuroticism ($p = .08$) was shown to be near significant.

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table

25). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 25

Corrected regression analysis using robust standard errors

Bulimia	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
BIS-11	0.04	0.02	2.06	.04	0.00	0.07
5-HTTLPR (l/l vs s-allele carriers)	0.29	0.28	1.04	.30	-0.26	0.85
Negative life events	0.03	0.07	0.42	.68	-0.11	0.17
Neuroticism	0.01	0.01	1.98	.05	0.00	0.03
Constant	-2.80	1.06	-2.64	.01	-4.89	-0.70

n = 140 R^2 = .09 Root MSE = 1.86
$F(4,135) = 4.67$, $p = .00$

Table 26

Regression analysis using least squares method

BIS-11	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
COMT Val/Met as a dummy variable	0.11	1.75	0.07	.95	-3.34	3.57
COMT Met/Met as a dummy variable	1.15	2.06	0.56	.58	-2.92	5.21
Neuroticism	0.13	0.03	4.33	.00	0.07	0.20
Negative life events	0.51	0.29	1.76	.08	-0.06	1.08
Constant	42.88	3.28	13.09	.00	36.40	49.36

n = 140 R^2 = .18 (Adjusted R^2 = .15) Root MSE = 8.19
$F(4,135) = 7.22$, $p = .00$

Ramsey RESET test using powers of the fitted values of BIS-11

HO: model has no omitted variables	
$F(3,132)$ =	.11
Prob > F	.96

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of BIS-11	
χ^2 (1) =	.19
Prob > χ^2	.66

Regression model analyzing the relationship between dependent variable impulsivity (BIS-11) and factor variables COMT gene Val158Met polymorphism as dummy variable, negative life events, BIS-11 and neuroticism (Table 26) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 18% of variance seen in dependent variable BIS-11. Constant of the model was shown to be statistically significant ($p < .05$). Factor variable neuroticism ($p < .05$) was shown to be significant.). Negative life events ($p = .08$) was shown to be near significant.

The diagnostic tests show that no specification errors in terms of omitted variables and heteroskedasticity were confirmed.

Table 27

Regression analysis using least squares method

Bulimia	**Coef.**	**Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
BIS-11	0.04	0.02	2.11	.04	0.00	0.08
COMT Val/Met as a dummy variable	-0.35	0.39	-0.89	.38	-1.12	0.43
COMT Met/Met as a dummy variable	-0.98	0.46	-2.12	.04	-1.89	-0.06
Neuroticism	0.01	0.01	1.63	.11	0.00	0.03
Negative life events	0.04	0.07	0.57	.57	-0.09	0.17
Constant	-2.02	1.11	-1.82	.07	-4.20	0.17

n = 140 R^2 = .12 (Adjusted R^2 = .08) Root MSE = 1.84
$F(5,134) = 3.57$, $p = .00$

Ramsey RESET test using powers of the fitted values of Bulimia

HO: model has no omitted variables	
$F(3,131)$ =	1.48
Prob > F	.22

Breusch-Pagan / Cook-Weisberg test for heteroskedasticity

HO: Constant variance	
Variables: fitted values of Bulimia	
χ^2 (1) =	31.47
Prob > χ^2	.00

Regression model analyzing the relationship between dependent variable bulimia and factor variables COMT gene Val158Met polymorphism as dummy variable, negative life events, BIS-11 and neuroticism (Table 27) was estimated by *F*-statistic to be statistically significant ($p < .05$) and described 12% of variance seen in dependent variable Bulimia. Only factor variable BIS-11 and dummy variable COMT Val158Met Met/Met allele ($p < .05$). Constant of model was not statistically significant.

The diagnostic tests show that no specification errors in terms of omitted variables but heteroskedasticity was confirmed by Breusch-Pagan test ($p < .05$). New regression model with heteroskedasticity adjusted parameter's standard error parameters was calculated (Table 12). No change in terms statistically significant factors was seen after calculating a model with robust standard error estimates.

Table 28

Corrected regression analysis using robust standard errors

Bulimia	**Coef.**	**Robust Std. Err.**	**t**	**P > | t |**	**95% Conf. Interval**	
BIS-11	0.04	0.02	2.14	.04	0.00	0.08
COMT Val/Met as a dummy variable	-0.35	0.54	-0.64	.52	-1.41	0.72
COMT Met/Met as a dummy variable	-0.98	0.52	-1.87	.06	-2.01	0.06
Neuroticism	0.01	0.01	1.84	.07	0.00	0.02
Negative life events	0.04	0.08	0.48	.63	-0.12	0.19
Constant	-2.02	0.91	-2.23	.03	-3.81	-0.22

n = 140 R^2 = .12 Root MSE = 1.84
$F(5,134) = 4.16$, $p = .00$

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/Kadri Kaasik/