Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2009 March 5; 150B(2): 209–218. doi:10.1002/ajmg.b.30789.

Emotional Symptoms in Children: The Effect of Maternal Depression, Life Events, and COMT Genotype

Jonathan Evans^{1,*}, Ke Xu², Jon Heron³, Mary-Anne Enoch², Ricardo Araya¹, Glyn Lewis¹, Nic Timpson⁴, Simon Davies¹, David Nutt¹, and David Goldman²

¹Academic Unit of Psychiatry, University of Bristol, Cotham House, Cotham Hill, Bristol, UK

²Laboratory of Neurogenetics, National Institute on Alcoholism and Alcoholism, NIH, Rockville, Maryland ³ALSPAC, Department of Social Medicine, University of Bristol, Bristol, UK ⁴Department of Social Medicine, University of Bristol, Bristol, UK

Abstract

Early adversity predicts anxiety and depression but variation in response to adversity is not understood. We investigated whether association between early adversity and emotional symptoms in young children differs according to variation of the *COMT* gene. The main outcome measure was the emotionality subscale of the Strengths and Difficulties Questionnaire (SDQ) completed by mothers for 8,431 children aged 6–7 years old in the Avon Longitudinal Study of Parents and Children. Adversity measures included exposure to maternal postpartum depressive symptoms and adverse life events for children. DNA from the children was genotyped for five *COMT* polymorphisms including the *COMT* Val158Met locus. Maternal depression increased the odds of high emotionality in the children, (OR 1.99, 95% CI 1.73–2.29, $P < 0.001$) as did life events score, (OR 1.21 for each s.d. increase in life event score, 95% CI 1.15–1.27, $P < 0.001$). There was no main effect of Val158Met genotype on emotional symptoms (OR for effect of each copy of the methionine allele was 1.04, 95% CI 0.97–1.10, $P = 0.284$). The relationship between adversity and emotional symptoms did not vary by genotype ($G \times E$ for maternal depression $\chi^2 = 3.17$, $P = 0.075$; $G \times E$ for life events $\chi^2 = 1.69$, $P = 0.430$). There was no main effect of *COMT* haplotype, nor was there an interaction with adversity. Early adversity predicts emotional symptoms in children aged 6–7 years. Although some studies indicate a role for *COMT* in emotionality, anxiety, and depression in adults, no direct effect or interaction of *COMT* genotype was observed in this large sample of young children.

Keywords

anxiety; depression; genotype; depression postpartum; catechol-*O*-methyltransferase; stress psychological; longitudinal studies

INTRODUCTION

Early adversity, such as exposure to maternal depression or to stressful life events, often precedes childhood emotional disorders, which in turn are frequently followed by major depression and anxiety disorders in adulthood [Brennan et al., 2000; Fombonne et al., 2001; Harrington, 2001; Kendler et al., 2003; Kessing et al., 2003]. However, it is a common observation that individuals vary in their sensitivity to adversity. One explanation for this is

innate variation in vulnerability (or conversely resilience), arises from the effects of alleles that have been transmitted to the child. The child's genotype may exert effects by, shaping environmental exposures themselves (gene–environment covariance) or, variation in response to the environment (gene–environment interactions). In fact both processes may operate. Twin studies of depression in adolescents have found that genetic variation not only correlates with environmental mediators of depression such as life events [Rice et al., 2003] but also interacts with them to increase the risk of depression [Silberg et al., 2001; Rice et al., 2003; Lau and Eley, 2008].

An innate vulnerability/resilience model implies that exposures to adversity are important, but insufficient in the causal pathway to emotional disorders. There is evidence to support such a model for major depression and anxiety disorders in adults, adolescents, and children where these disorders display moderate heritabilities [Kendler et al., 1995; Gjone et al., 1996; Rutter et al., 1999; Rice et al., 2002]. Furthermore, although genes contributing to anxiety and depression appear to act through multiple pathways, some of the vulnerability genes appear to specifically alter emotional responses to adverse life events [Kendler, 2005]. This is supported by evidence that a stressful life event is more likely to provoke a new episode of depression in individuals with greater genetically determined vulnerability [Kendler et al., 1995].

Consistent with a developmental vulnerability/resilience model, a polymorphism of the serotonin transporter gene appears to increase the risk of depression via a specific interaction with stressful life events experienced during childhood and young adulthood despite having no direct effect on behavior in the absence of earlier exposure [Caspi et al., 2003]. Investigating gene–environment interactions may help identify the etiological effects of genes in complex behavior and disease which might otherwise be obscured.

Like the serotonin transporter just discussed, catechol-*O*-methyltransferase (COMT) may also play a role in stress vulnerability. COMT has an important role in the metabolism of central nervous system catecholamines (dopamine, noradrenaline), catecholestrogens and catechol drugs. Removal of dopamine from the prefrontal cortex is twofold slower in COMT knockout mice showing the importance of this enzyme in central dopamine regulation [Yavich et al., 2007]. Individuals with the chromosome 22q11 microdeletion in the COMT gene have been reported to have a high frequency of disorders such as anxiety, OCD, and depression [Massat et al., 2005]. A common COMT polymorphism, Val158-Met, is responsible for a three to fourfold variation in enzyme activity [Weinshilboum et al., 1999; Chen et al., 2004]. The expression of alleles in the brain also varies according to the haplotype background. Haplotypes have been identified that are associated with high and with low expression of the Val158 allele [Zhu et al., 2004], and progress has been made in understanding the effects of other COMT loci on expression of the enzyme, via alteration of mRNA stability or translatability [Nackley et al., 2006]. To date, most studies have been performed with the Val158Met polymorphism alone, although haplotype analyses indicate that functional variants other than Val158Met may contribute to the relationship between COMT and anxiety [Stein et al., 2005]. The lower activity Met158 allele has been associated with greater response to stress in the form of unpleasant visual stimuli in emotion-modulating brain regions, including the limbic system and connected prefrontal areas and accounts for 38% of the variance in responses [Smolka et al., 2005]. The Met158 allele has been found to be associated with higher trait anxiety [Woo et al., 2002; Zubieta et al., 2003] OCD, panic disorder, and phobic anxiety [Karayiorgou et al., 1999; Woo et al., 2002; McGrath et al., 2004] but not with anxiety disorders as a group [Ohara et al., 1998] and may show sexual dimorphism in its effects on anxiety as several studies have found associations only in women [Enoch et al., 2003; Olsson et al., 2005; Stein et al., 2005]. As COMT is implicated in noradrenaline metabolism it therefore could be important in the HPA axis stress response which correlates with average basal noradrenaline activity [Young et al., 2005]. Low activity Met158 homozygous individuals have greater HPA axis response

to μ opioid receptor blockade [Oswald et al., 2004], thus COMT genotype may play an important role in the balance between emotional resilience and vulnerability to stress.

Given the potential role of COMT in stress vulnerability outlined above, any relationship between COMT and anxiety may arise from varying responses to stress exposure rather than direct effects. We thus chose to investigate this in a population sample using exposures to stress arising from common and clinically important adversities, maternal postnatal depression and stressful life events. We investigated maternal depression in the postpartum period as an adverse exposure because there is strong evidence of association with later mental health problems for children, which we have reported in this sample [Ramchandani et al., 2005]. Careful observational studies suggest that young infants are particularly sensitive to the effect of having a depressed mother [Cummings and Davies, 1994; Murray and Cooper, 1997; Ramchandani et al., 2005]. We investigated life events as a stress exposure as there is a well established link with the onset of depression and anxiety and evidence for a genetic vulnerability to this link [Kendler et al., 1995]. In this study we have set out to investigate whether maternal depressive symptoms and adverse life events lead to emotional symptoms in childhood, a precursor of later depression and anxiety, and whether this relationship varies according to the child's genotype including both the Val158Met polymorphism and *COMT* haplotype. We studied a large, community-based sample of children recruited as part of ALSPAC, the Avon Longitudinal Study of Parents and Children.

MATERIALS AND METHODS

Study Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) enrolled 14,541 women in the early stages of pregnancy and resident in Avon, England and 13,801 mothers remained in the study with 13,985 surviving offspring at 12 months. The women had an expected date of delivery between April 1, 1991 and December 31, 1992. Questionnaires were sent at regular intervals during pregnancy and following childbirth and biological samples were taken from parents and children including blood samples from which DNA was extracted [Golding et al., 2001].

Our starting sample consists of 8,511 children, whose parents returned the 81-month questionnaire providing data on emotional symptoms. COMT genotype data was available for 8,530 children, with complete data on maternal depression and genotype for 5,742 and for life events and genotype available for 5,670.

Ethical Approval and Consent

The study was approved by the ALSPAC Ethics Committee and National Health Service Research Ethics Committee. Parents who enrolled themselves and their children into ALSPAC gave written or verbal informed consent at enrolment to phenotypic and genotypic analyses, and they or the child were free to withdraw at any time.

Main Outcome—Emotional Symptoms

The Strengths and Difficulties Questionnaire (SDQ) [Goodman, 1997], is a widely used measure of childhood psychiatric symptoms that has been validated against more time-consuming instruments such as the Rutter scales [Elander and Rutter, 1996]. Correlation between the complete scale (parent completed) and Rutter scale (also parent completed) is high, with a coefficient of 0.78 for the emotionality subscale [Goodman, 1997]. Factor analysis has identified five dimensions measured by the SDQ: conduct problems, emotional symptoms, hyperactivity, peer problems and prosocial behavior. This factor structure has been confirmed in several different samples including a study from the Office of National Statistics in the UK

involving a nationwide epidemiological sample of 10,000 5- to 15-year olds [Goodman, 2001]. In this large sample the parent rated SDQ was also validated against DSM IV diagnoses derived by an interviewer. Using a cut off score of 4/5 on the parent rated emotional symptoms scale placed 10% of children in the high-risk group. This cut off gave a calculated sensitivity of 91%, a specificity of 54%, a positive predictive value of 21% and a negative predictive value of 98% for a DSM IV diagnosis of an anxiety disorder or depressive disorder [Goodman, 2001]. Although there may be a bias introduced by maternal mood when rating child's mood, this effect on other scales has been reported as small [Youngstrom et al., 1999].

The focus of the analyses in this article is on the emotional symptoms subscale of the SDQ as the main outcome measure. These questions concern behavior over the last 6 months. Mothers endorsed items as "not true," "somewhat true" or "certainly true," numerically scored as 0, 1, or 2. Five items form the emotionality subscale, yielding a maximum score of 10. The items are: "Often complains of headaches, stomach-aches or sickness," "Many worries, often seems worried" "Often unhappy, down-hearted or tearful" "nervous or clingy in new situations, easily loses confidence" and "many fears, easily scared."

Adversity Measures

Maternal depression—Mothers completed the Edinburgh Postnatal Depression Scale (EPDS), a self-report depression rating scale, at 18 and 32 weeks of pregnancy and at 8 weeks, 8 months, 21 months, and 33 months postnatally [Cox et al., 1987]. The EPDS focuses on the cognitive and affective features of depression rather than somatic symptoms. This scale was developed to screen for depression in women following childbirth but can be used either as a continuous score or to identify possible major depressive disorder when the score exceeds 12. There have been numerous validation studies and the sensitivity in relation to major depressive disorder varies between 100% and 68% and specificity between 96% and 93% [Shakespeare, 2001], comparable to other screening instruments [Lee et al., 2001]. The EPDS has also been validated for use outside the postnatal period with sensitivity of between 100% and 73% and specificity of between 87% and 82% for identifying major depression during pregnancy [Murray and Cox, 1990; Adouard et al., 2005].

We defined maternal postpartum depression as a score of > 12 on the EPDS at either eight weeks or 8 months postpartum. We chose these time points because our previous work found that parental mood in the early postnatal period has a strong effect on developmental outcomes [Ramchandani et al., 2005]. Information on earlier maternal depression was available based on response to the question "have you suffered from severe depression prior to this pregnancy."

Life events—Life events were measured using an adapted life event questionnaire completed by the mother who recorded whether the child had experienced each of 17 different upsetting events since 5 years of age. The items included in this questionnaire were taken from those recorded in previous studies [Brown and Harris, 1978; Barnett et al., 1983; Stephens et al., 2001]. The mother also rated the impact of the event on the child scored on a four point scale from "Yes and s/he was very upset" to "yes and s/he was not upset." These ratings were used to derive average impact scores for each of the 17 upsetting events. In order to investigate the effect of stressful life events on emotional symptoms we derived a total score based on 17 life events. Each of these 17 life events was weighted according to the average impact recorded by women who reported that their child had experienced the event. The purpose of this was to reduce bias in the rating of impact resulting from maternal mood and to more accurately measure stress exposure since the different events we recorded would not have equivalent impact.

Other data available included ethnicity, housing tenure, marital status of mother, highest educational level achieved by mother, crowding, maternal age at delivery and parity (number of previous births categorized as 0, 1, 2 or more).

Genotyping

Genomic DNA was extracted from peripheral blood. 5'-nuclease assays were used to genotype the *COMT* Val158Met polymorphism (rs4680, nt3099225) as well as four other SNPs within *COMT*: rs2097603 (nt3076132), rs6269 (nt309706), rs4818 (nt3099161), and rs165599 (nt3108931).

The principle of the 5'-nuclease assay is selective binding of allele-specific probes during DNA amplification, resulting in the nuclease-mediated liberation of an allele-specific fluorescent dye from proximity to the quencher dye that is also present on the probe. Primer/probe combinations were designed using Primer Express software (2.0) (ABI, Foster City, CA). DNA sequences were obtained from Gen Bank and the Celera Discovery System. Primer/probe sequences are listed in Table I. The total PCR reaction volume was 5 μ l, including 2.5 μ l Master Mixture (ABI), 100 nM of each probe, 900 nM forward primer and 900 nM reverse primer, and 5 ng DNA. PCR reactions were performed on 9700 Thermo Cyclers machines (ABI) using 384 well plates. Reaction conditions included 2 min at 50°C to activate Uracil DNA glycosylase (UNG) to control carry-over contamination, 10 min at 95°C to denature DNA, 1 min at 60–62°C for annealing depending on the SNP, and for a total of 40 cycles. Allele discrimination was performed in a Taqman 7900 machine. Two standards for each genotype including homozygotes 1 and 2 and the heterozygotes were confirmed by sequencing six genomic DNA samples using a 377 sequencer (ABI). Genotyping completion rate was 99%. Duplicate genotyping of 10% of samples yielded a genotyping error rate of 0.1% and there were no significant deviations from Hardy–Weinberg equilibrium (rs2097603, $\chi^2 = 0.24$, $P = 0.626$; rs6269, $\chi^2 = 1.56$, $P = 0.211$; rs4818, $\chi^2 = 1.46$, $P = 0.227$; rs4680, $\chi^2 = 1.72$, $P = 0.190$; rs165599, $\chi^2 = 0.26$, $P = 0.623$).

Statistical Analyses

For initial analyses we used proportional odds ordinal logistic regression models to investigate association of (1) maternal postpartum depression, (2) life events, and (3) *COMT* Val158Met (scored 0, 1, or 2 to indicate the number of Met alleles present) to emotionality subscale score. We grouped emotionality subscale scores into 5 categories (scores of 0, 1, 2, 3, and >3). With this grouping the assumption of proportional odds was met for the exposures we investigated.

Following the examination of direct associations we examined whether there was an interaction of *COMT* genotype and maternal postpartum depression on emotionality score within an ordinal logistic regression model. We repeated these analyses, testing for interaction between genotype and stressful life events. Within the ordinal logistic regression model we tested for interactions using the Chi-square statistics. We tested all models unadjusted, and for the model with maternal postpartum depression we examined the effect of adjusting for history of depression.

***COMT* haplotype**—Haplotypes were derived using PHASE [Stephens et al., 2001]. Three of five SNPs (rs6269, rs4818 and the val158met SNP—rs4680) were in strong linkage disequilibrium, with D' scores of >0.8. We were able to use LD patterns of several additional markers in this region available from Hapmap to infer that there are three major cladistically related haplotype groups, and this grouping was performed prior to linkage analyses. Each haplotype group contains at least one common haplotype, and rarer daughter haplotypes are differentiated from these common haplotypes by a single mutational event. Met158 was found on one haplotype group designated Met (freq = 0.49). Val158 was found on two haplotype

groups, designated Val_A (freq = 0.39) and Val_B (freq = 0.09). The three-locus haplotypes (rs6269-rs4818-rs4680) are Met: A-C-A, Val_A: G-G-G, Val_B: A-C-G and these have frequencies of 0.49, 0.39, and 0.09, respectively. The two Val haplotypes correspond to higher and lower expressing COMT genetic backgrounds [Bray et al., 2003; Zhu et al., 2004], Val_A being simultaneously the highest COMT enzyme activity, and highest mRNA expressing haplotype [Nackley et al., 2006]. Recently it has been shown that low expression of the Val_B haplotype is mediated via altered mRNA secondary structure, leading to its reduced translatability, and also Val_B may lead to effectively lower COMT enzyme activity than the Met allele such that Val_A is highest, Met intermediate, and Val_B lowest [Nackley et al., 2006]. The correspondence of these haplotypes to the Nackley pain sensitivity haplotypes is shown in Table II.

The three haplotype groups yield six diplotypes (Met/Met, Met/Val_A, Met/Val_B, Val_A/Val_A, Val_A/Val_B, Val_B/Val_B) which were investigated for linkage.

We conducted all analyses on the whole sample as well as separately for boys and for girls because there is evidence of sexual dimorphism in COMT activity and in the effect of the COMT gene on behavior.

RESULTS

As shown in Figure 1, two-thirds of 8,431 children aged 7–8 had few emotional symptoms, scoring 0–2 on the SDQ. However, 12.8% (1,079) had an SDQ score of four or higher, putting them in the high-risk group for anxiety and depressive disorders [Goodman, 2001]. Girls were more likely to experience emotional difficulties (Fig. 1). 13.8% (564) of girls scored four or higher compared to 11.9% (515) of boys $P = 0.009$ a risk difference of 1.89% (95% CI 0.47%, 3.32%).

Both maternal postpartum depression and adverse life events scores were assessed as different aspects of childhood adversity (Table III). Among 8,286 children who had data on SDQ and postpartum depression, 1077 (13%) had a mother with a depression score indicative of probable depressive disorder at 8 weeks or 8 months postpartum. And among 8,185 children with data on SDQ and life events, 5,644 (69.0%) children experienced at least one adverse life event sometime in the 21 months following the fifth birthday as reported by their mothers

Exposure to adversity (either maternal postpartum depression or life events) was significantly less common in children whose parents; owned their properties, were in their first marriage, or had use of a car, and was less common in children with older mothers. Exposure to maternal postpartum depression was more common in those children whose mothers; attained a lower educational level, were of higher parity or experienced overcrowding. Exposure to life events was slightly more common in girls and in children whose mothers were of lower parity. Thus maternal postpartum depression and adverse life events in childhood are both potential indicators, as well as predictors, of other childhood stressors.

COMT Genotype

There was no difference in COMT genotype or allele frequency by sex, mother's marital status, SES, mother's educational attainment or mother's mood. There were 444 (4.8%) children whose ethnicity was classified as "non-white" and 177 (1.9%) whose ethnicity was unknown and 8,671 classified as "white." In view of differences in population frequency of COMT alleles, non-White children were not included in further analyses.

There was no direct association of *COMT* Val158Met genotype on emotional symptoms experienced by children. The odds ratio for a "dose response" effect of each copy of the

methionine allele to increase number of emotional symptoms was 1.04 (95% confidence interval 0.97–1.10, $P = 0.284$). There was also no evidence of a difference in association by gender (χ^2 for gender interaction 0.43, $P = 0.513$; Table IV).

Maternal Depression and COMT Genotype

Children of mothers with postpartum depression were almost twice as likely to experience a higher level of emotional symptoms 7–8 years later (OR = 1.99, 95% confidence interval 1.73–2.29, $P < 0.001$). This association remained following adjustment for self-reported history of severe depression before pregnancy although the size of the effect diminished (OR 1.93, 95% confidence interval 1.65–2.25, $P < 0.001$). There was no evidence for a statistical interaction with child's sex. Val158Met genotype did not alter this relationship between maternal postnatal depression and emotional symptoms (Table V).

Life Events and COMT Genotype

We also observed a strong relationship between adverse life events experienced in the 21 months after the child's fifth birthday and emotional symptoms at aged 7–8 years. The odds ratio of experiencing a higher level of emotional symptoms, was 1.21 (95% confidence interval 1.15–1.27, $P < 0.001$, $n = 8,233$) for each standard deviation increase in adverse life event score. There was no significant interaction with child's sex. Association between life events and emotional symptoms did not vary according to Val158Met genotype (χ^2 for interaction 1.69, $P = 0.430$; Table V).

We created a dichotomous genotype variable by combining Val Met and Val Val genotype. This gives an interaction odds ratio for life events $\times$ emotional symptom score of 1.01 (95% confidence interval 0.9–1.14).

Analyses by Gender

Analyzing the sexes separately, we found association did not vary according to genotype between (1) maternal postpartum depression and emotional symptoms ($G \times E$ interaction for girls $\chi^2 = 3.99$, $P = 0.136$ and for boys $\chi^2 = 1.61$, $P = 0.448$) and (2) life events and emotional symptoms ($G \times E$ interaction girls $\chi^2 = 0.22$, $P = 0.896$ and for boys $\chi^2 = 2.10$, $P = 0.350$).

Haplotype Analyses

The effects of three cladistically related and functionally significant haplotype groups were compared: Met, which includes all Met158-carrying haplotypes, and Val_A and Val_B, which both carry the Val158 allele. These differ up to 25-fold in effect on COMT protein expression, such that the Val_B haplotype may be predictive of lowest COMT enzyme activity, with the Met haplotype functionally intermediate and Val_A highest [Nackley et al., 2006]. These haplotypes form six diplotypes of varying frequency. In this sample 8,666 children had data on all three SNPs required to generate the six diplotypes. The frequencies were Met/Met (2405, 27.7%), Met/Val_A (3471, 40%), Met/Val_B (797, 9.1%), Val_A/Val_A (1270, 14.6%), Val_A/Val_B (577, 6.6%), Val_B/Val_B (146, 1.7%).

There was no direct association of COMT diplotype on emotional symptoms and no differences when examining boys and girls separately (for interaction with gender $\chi^2 = 6.73$, $P = 0.241$). The relationship between maternal depression or life events and emotional symptoms for both sexes combined did not differ according to child's diplotype (for interaction with maternal depression $\chi^2 = 5.40$, $P = 0.37$ for interaction with life events $\chi^2 = 2.95$, $P = 0.708$; Table VI).

DISCUSSION

This is the largest study to investigate the relationship between the *COMT* Val158Met genotype and measures relating to anxiety and depression. It is the only study of which we are aware, to investigate the role of *COMT* on the emotionality of children, to examine the interaction of genotype with maternal postpartum depression and stressful life events, and to include in these analyses *COMT* haplotypes that capture additional functional variation at the *COMT* gene.

The main findings were a strong association between both maternal depressive symptoms and stressful life events with increased emotional symptoms in children, as reported by their mothers but no direct or $G \times E$ interaction between *COMT* genotype, either maternal depression or life events and emotional symptoms in these 7- to 8-year-old children. The large sample size means we have had the power to detect all but the very smallest interaction effects. We found an interaction odds ratios with a 95% confidence interval close to unity (0.9–1.14). By way of comparison the interaction odds ratio found in the Caspi et al. study [2003] for the interaction between a polymorphism of a different gene 5-HTT and number of life events was 1.35 (from Fig. 3). We can exclude an effect of *COMT* Val158Met genotype of similar magnitude on the relationship between stress and emotional symptoms in children.

Limitations

Although the sample size of our study was large, it may have been insufficient to achieve adequate power to detect a gene–environment interaction for the particular symptom clusters in these children [Clayton and McKeigue, 2001]. Haplotypes were cladistically grouped in a way that is also predictive of *COMT* function [Nackley et al., 2006], however the key Val_B/Val_B homozygous diplotype, which appears to be effectively lowest in enzyme expression [Nackley et al., 2006], has a frequency of approximately 1%, such that power is limited even in this large dataset. The power was reduced further when examining the data separately by gender. However, whilst small effects may be of etiological interest, they are less likely to be useful in developing interventions.

The children in this study were not interviewed in order to determine a psychiatric diagnosis. Although the questionnaire used has been validated against an interview based diagnostic measure it remains possible that any effect of *COMT* is restricted to a specific psychiatric disorder which could not be accurately measured in this study.

It is important to consider measurement error not only because it could reduce power but also because it is a potential source of bias. Assessment of childhood psychopathology in our study did not include a diagnostic interview. The mother rated their child's emotional symptoms. This raises the possibility of substantial bias resulting from concurrent maternal mood state. However the scale we used has good internal consistency and has been validated against diagnostic interview and is particularly good for depression and anxiety disorders [Goodman, 2001]. Furthermore it is unlikely the strong relationship we found between postpartum depression and child's anxiety symptoms could be entirely explained by a rating bias. In this regard, the strongest predictor of child emotionality at age 7–8 years was depression occurring in the immediate postpartum period rather than maternal depression that occurred antenatally or later and closer to the time that the mother rated the child's emotionality.

Biases may also arise in maternal ratings of children's exposure to stressful life events. There is some evidence that maternal mood correlates with likelihood of a mother reporting that stressful events occurred to her child. However, adverse events happening to children may also have an impact on mother's mood and depressed mothers may be more likely to encounter adversity such as marital problems or economic adversity. We found evidence of an association between depressed mood in the mother and the presence of reported life events for the child.

To reduce the bias of concurrent maternal mood we weighted child's stressful events by using average impact scores across the whole sample rather than the impact score rated by the child's own mother.

Interpretation

We found no direct or $G \times E$ interaction between *COMT* genotype and emotional symptoms in these 7- to 8-year-old children, even though the *COMT* Met158/Met158 genotype has previously been associated with higher levels of anxiety and amygdala emotional and pain/stress responses in adults [Woo et al., 2002; Smolka et al., 2005]. The Val158 allele is found on a different haplotype backgrounds that can influence level of expression, and potentially, *COMT* function [Bray et al., 2003; Zhu et al., 2004] and recently it has been clarified that the Val_B haplotype is lowest in functional expression due to an alteration in mRNA secondary structure that impairs its translatability [Nackley et al., 2006]. However, refining the analyses by taking into account *COMT* haplotype did not alter these conclusions. As *COMT* association to behavior was restricted to females in three previous studies [Enoch et al., 2003; Olsson et al., 2005; Stein et al., 2005] and because there is evidence for sexual dimorphism in *COMT* activity [Floderus and Wetterberg, 1981], we also examined effects separately by gender but found no differences. These analyses involved seven different tests of interaction which increased the possibility of at least one being positive by chance but this was not the case.

There are a number of reasons *COMT* might not be associated with emotional symptoms in children. One important explanation is the possibility of age specific action of gene polymorphisms. There have been several studies indicating that the heritability of anxiety and depression is weaker in childhood, becoming stronger for adolescents and adults [Rice et al., 2003]. However a study of more than 9,000 twin pairs estimated heritability of parentally rated anxious/depression at 67% in children aged 7 and found that heritability decreased with the age of the child [Boomsma et al., 2005]. It is possible that the genetic etiology of childhood depression and anxiety differs from these same behaviors in adolescence and adulthood. Children who are anxious and depressed are at greater risk of anxiety and depression as adults, as shown in a prospective study of 776 longitudinally followed adolescents in New York [Pine et al., 1998]. However, while most of the anxiety and depression occurring in young adults was preceded by problems in adolescence, most anxiety and depression in adolescent did not persist [Pine et al., 1998]. There are reasons for thinking there may be an age specific action of *COMT* in women. Enzyme activity is 20–30% lower in women than men and varies across the estrous cycle, at least in rats [Gallardo et al., 1997]. Estrogen may inhibit *COMT* gene transcription by blocking estrogen responsive elements in the promoter region [Jiang et al., 2003]. Pre-pubertal girls have low estrogen levels compared with adult women, although their estrogen levels are eightfold higher than in pre-pubertal boys [Klein et al., 1994]. However, it is not known whether these low prepubertal estrogen levels are sufficient to influence *COMT* activity.

The interplay between maternal depression, life event exposure for the child, the impact of these life events and child mood is complex. Some effects are bi-directional. Although later child symptoms cannot cause maternal postpartum depression they could result from another variable such as early temperament, which may have led to maternal postpartum depression. This is further complicated when investigating genetic associations as the mother and child share some genes. Some of these relationships are illustrated in Figure 2.

It is possible that any interaction with *COMT* Val158Met or the diplotypes is restricted to those children who were exposed to more severe adversity. The adverse events experienced in this study varied between death of a pet and death of a parent. Earlier $G \times E$ studies that have found effects, for example [Caspi et al., 2003], have generally included children who have experienced severe adverse events such as physical, emotional, or sexual abuse. Maternal

postpartum depression can vary in severity and chronicity and interactions with genes maybe restricted to those with the most severe depressions.

Despite other interpretations noted above, the most likely explanation for our findings is that whilst provisional findings indicate an effect of this genotype on pain related behavioral and neuroendocrine responses [Zubieta et al., 2003; Oswald et al., 2004; Diatchenko et al., 2006] these effects do not appear to have direct consequences for depression and anxiety in childhood nor influence response to life events.

In summary, in this large study of children aged between 6 and 7 years, maternal postpartum depression and recent adverse life events experienced by the child were strong predictors of emotional symptoms. However, these associations were not affected by genetic variation at *COMT*, a gene whose inherited functional variation has been linked to anxiety, depression, and stress response in adults. The *COMT* gene may not play a major role in determining vulnerability to depression and anxiety in childhood, but it remains possible that *COMT* may play a role in anxiety and depression occurring later in life.

ACKNOWLEDGMENTS

Core support for the Avon Longitudinal Study of Parents and Children (ALSPAC) is provided by the Medical Research Council, the Wellcome Trust, and the University of Bristol. This research was supported in part by the Intramural Research Program of the National Institute on Alcohol Abuse and Alcoholism, NIH. Dr. Goldman receives intramural funding through the National Institutes of Health and the National Institute on Alcoholism and Alcohol Abuse. The authors thank the families who took part in this study, the midwives for their help with recruitment, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The authors also thank Professor George Davey-Smith and Professor Jean Golding for comments on an earlier draft of this article.

Grant sponsor: Medical Research Council; Grant sponsor: Wellcome Trust;

Grant sponsor: University of Bristol; Grant sponsor: Intramural Research Program of the National Institute on Alcohol Abuse and Alcoholism, NIH.

REFERENCES

- Adouard F, Glangeaud-Freudenthal NMC, Golse B. Validation of the Edinburgh postnatal depression scale (EPDS) in a sample of women with high-risk pregnancies in France. *Arch Womens Ment Health* 2005;8:89–95. [PubMed: 15883653]
- Barnett B, Hanna EW, Parker G. Life events for obstetric groups. *J Psychosom Med* 1983;27:313–320.
- Boomsma DI, van Beijsterveldt CEM, Hudziak JJ. Genetic and environmental influences on anxious/depression during childhood: A study from the Netherlands Twin Register. *Genes Brain Behav* 2005;4:466–481. [PubMed: 16268991]
- Bray NJ, Buckland PR, Williams NM, Williams HJ, Norton N, Owen MJ, et al. A haplotype implicated in schizophrenia susceptibility is associated with reduced COMT expression in human brain. *Am J Hum Genet* 2003;73:152–161. [PubMed: 12802784]
- Brennan PA, Hammen C, Andersen MJ, Bor W, Najman JM, Williams GM. Chronicity, severity, and timing of maternal depressive symptoms: Relationships with child outcomes at age 5. *Dev Psychol* 2000;36:759–766. [PubMed: 11081699]
- Brown, GW.; Harris, TO. Social origins of depression a study of psychiatric disorder in women. New York: Free Press; 1978.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301:386–389. [PubMed: 12869766]
- Chen JS, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-o-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet* 2004;75:807–821. [PubMed: 15457404]

- Clayton D, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 2001;358:1356–1360. [PubMed: 11684236]
- Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression—Development of the 10-Item Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987;150:782–786. [PubMed: 3651732]
- Cummings EM, Davies PT. Maternal depression and child-development. *J Child Psychol Psychiatry* 1994;35:73–112. [PubMed: 8163630]
- Diatchenko L, Nackley AG, Slade GD, Bhalang K, Belfer I, Max MB, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain* 2006;125:216–224. [PubMed: 16837133]
- Elander J, Rutter M. Use and development of the Rutter parents' and teachers' scales. *Int J Methods Psychiatr Res* 1996;6:63–78.
- Enoch MA, Xu K, Ferro E, Harris CR, Goldman D. Genetic origins of anxiety in women: A role for a functional catechol-O-methyltransferase polymorphism. *Psychiatr Genet* 2003;13:33–41. [PubMed: 12605099]
- Floderus Y, Wetterberg L. The inheritance of human-erythrocyte catechol-O-methyltransferase activity. *Clin Genet* 1981;19:392–395. [PubMed: 7296929]
- Fombonne E, Wostear G, Cooper V, Harrington R, Rutter M. The Maudsley long-term follow-up of child and adolescent depression 1. Psychiatric outcomes in adulthood. *Br J Psychiatry* 2001;179:210–217. [PubMed: 11532797]
- Gallardo MG, Chiocchio SR, Tramezzani JH. Involvement of Catecholestrogens in the release of pituitary hormones. *Endocr Regul* 1997;31:19–28. [PubMed: 10931644]
- Gjone H, Stevenson J, Sundet JM, Eilertsen DE. Changes in heritability across increasing levels of behavior problems in young twins. *Behav Genet* 1996;26:419–426. [PubMed: 8771902]
- Golding J, Pembrey M, Jones R. ALSPAC-The Avon Longitudinal Study of Parents and Children—I. Study methodology. *Paediatr Perinat Epidemiol* 2001;15:74–87. [PubMed: 11237119]
- Goodman R. The strengths and difficulties questionnaire: A research note. *J Child Psychol Psychiatry* 1997;38:581–586. [PubMed: 9255702]
- Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;40:1337–1345. [PubMed: 11699809]
- Harrington R. Adolescent depression—Same or different? *Arch Gen Psychiatry* 2001;58:21–22. [PubMed: 11146754]
- Jiang H, Xie T, Ramsden DB, Ho SL. Human catechol-O-methyltransferase down-regulation by estradiol. *Neuropharmacology* 2003;45:1011–1018. [PubMed: 14573393]
- Karayorgou M, Sobin C, Blundell ML, Galke BL, Malinova L, Goldberg P, et al. Family-based association studies support a sexually dimorphic effect of COMT and MAOA on genetic susceptibility to obsessive-compulsive disorder. *Biol Psychiatry* 1999;45:1178–1189. [PubMed: 10331110]
- Kendler KS. "A gene for...": The nature of gene action in psychiatric disorders. *Am J Psychiatry* 2005;162:1243–1252. [PubMed: 15994704]
- Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, et al. Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry* 1995;152:833–842. [PubMed: 7755111]
- Kendler KS, Hettema JM, Butera F, Gardner CO, Prescott CA. Life event dimensions of loss, humiliation, entrapment, and danger in the prediction of onsets of major depression and generalized anxiety. *Arch Gen Psychiatry* 2003;60:789–796. [PubMed: 12912762]
- Kessing LV, Agerbo E, Mortensen PB. Does the impact of major stressful life events on the risk of developing depression change throughout life? *Psychol Med* 2003;33:1177–1184. [PubMed: 14580072]
- Klein KO, Baron J, Colli MJ, McDonnell DP, Cutler GB. Estrogen-levels in childhood determined by an ultrasensitive recombinant cell bioassay. *J Clin Invest* 1994;94:2475–2480. [PubMed: 7989605]
- Lau JY, Eley TC. Disentangling gene-environment correlations and interactions on adolescent depressive symptoms. *J Child Psychol Psychiatry* 2008;49:142–150. [PubMed: 18211276]

- Lee DTS, Yip ASK, Chiu HFK, Leung TYS, Chung TKH. Screening for postnatal depression: Are specific instruments mandatory? *J Affect Disord* 2001;63:233–238. [PubMed: 11246101]
- Massat I, Souery D, Del-Favero J, Nothen M, Blackwood D, Muir W, et al. Association between COMT (Val(158)Met) functional polymorphism and early onset in patients with major depressive disorder in a European multicenter genetic association study. *Mol Psychiatry* 2005;10:598–605. [PubMed: 15583702]
- McGrath M, Kawachi I, Ascherio A, Colditz GA, Hunter DJ, De Vivo I. Association between catechol-O-methyltransferase and phobic anxiety. *Am J Psychiatry* 2004;161:1703–1705. [PubMed: 15337664]
- Murray, L.; Cooper, PJ. Postpartum depression and child development. New York: Guilford Press; 1997.
- Murray D, Cox JL. Screening for depression during pregnancy with the Edinburgh Depression Scale (EPDS). *J Reprod Infant Psychol* 1990;8:99–107.
- Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynskiy O, Makarov SS, et al. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science* 2006;314:1930–1933. [PubMed: 17185601]
- Ohara K, Nagai M, Suzuki Y, Ochiai M, Ohara K. No association between anxiety disorders and catechol-O-methyltransferase polymorphism. *Psychiatry Res* 1998;80:145–148. [PubMed: 9754693]
- Olsson CA, Anney RIL, Lotfi-Miri M, Byrnes GB, Williamson R, Patton GC. Association between the COMT Val(158)Met polymorphism and propensity to anxiety in an Australian population-based longitudinal study of adolescent health. *Psychiatr Genet* 2005;15:109–115. [PubMed: 15900225]
- Oswald LM, McCaul M, Choi L, Yang XJ, Wand GS. Catechol-O-methyltransferase polymorphism alters hypothalamic-pituitary-adrenal axis responses to naloxone: A preliminary report. *Biol Psychiatry* 2004;55:102–105. [PubMed: 14706432]
- Pine DS, Cohen P, Gurley D, Brook J, Ma YJ. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry* 1998;55:56–64. [PubMed: 9435761]
- Ramchandani P, Stein A, Evans J, O'Connor TG. Paternal depression in the postnatal period and child development: A prospective population study. *Lancet* 2005;365:2201–2205. [PubMed: 15978928]
- Rice F, Harold G, Thapar A. The genetic aetiology of childhood depression: A review. *J Child Psychol Psychiatry* 2002;43:65–79. [PubMed: 11848337]
- Rice F, Harold GT, Thapar A. Negative life events as an account of age-related differences in the genetic aetiology of depression in childhood and adolescence. *J Child Psychol Psychiatry* 2003;44:977–987. [PubMed: 14531580]
- Rutter M, Silberg J, O'Connor T, Simonoff E. Genetics and child psychiatry: II—Empirical research findings. *J Child Psychol Psychiatry* 1999;40:19–55. [PubMed: 10102725]
- Shakespeare, J. Evaluation of Screening for Postnatal Depression against the NSC Handbook Criteria. London (UK): National Screening Committee; 2001.
- Silberg J, Rutter M, Neale M, Eaves L. Genetic moderation of environmental risk for depression and anxiety in adolescent girls. *Br J Psychiatry* 2001;179:116–121. [PubMed: 11483472]
- Smolka MN, Schumann G, Wrase J, Grusser SM, Flor H, Mann K, et al. Catechol-O-methyltransferase val(158)met genotype affects processing of emotional stimuli in the amygdala and prefrontal cortex. *J Neurosci* 2005;25:836–842. [PubMed: 15673663]
- Stein MB, Fallin MD, Schork NJ, Gelernter J. COMT polymorphisms and anxiety-related personality traits. *Neuropsychopharmacology* 2005;30:2092–2102. [PubMed: 15956988]
- Stephens M, Smith NJ, Donnelly P. A new statistical method for haplotype reconstruction from population data. *Am J Hum Genet* 2001;68:978–989. [PubMed: 11254454]
- Weinshilboum RM, Otterness DM, Szumlanski CL. Methylation pharmacogenetics: Catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu Rev Pharmacol Toxicol* 1999;39:19–52. [PubMed: 10331075]
- Woo JM, Yoon KS, Yu BH. Catechol O-methyltransferase genetic polymorphism in panic disorder. *Am J Psychiatry* 2002;159:1785–1787. [PubMed: 12359690]
- Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Mannisto PT. Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J Neurosci* 2007;27:10196–10209. [PubMed: 17881525]

- Young EA, Abelson JL, Cameron OG. Interaction of brain noradrenergic system and the hypothalamic-pituitary-adrenal (HPA) axis in man. *Psychoneuroendocrinology* 2005;30:807–814. [PubMed: 15896919]
- Youngstrom E, Izard C, Ackerman B. Dysphoria-related bias in maternal ratings of children. *J Consult Clin Psychol* 1999;67:905–916. [PubMed: 10596512]
- Zhu GS, Lipsky RH, Xu K, Ali S, Hyde T, Kleinman J, et al. Differential expression of human COMT alleles in brain and lymphoblasts detected by RT-coupled 5' nuclease assay. *Psychopharmacology* 2004;177:178–184. [PubMed: 15290009]
- Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu YJ, et al. COMT val(158)met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 2003;299:1240–1243. [PubMed: 12595695]

FIG. 1.

Frequency of emotional symptoms in children aged 7–8 years. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIG. 2.
Model for pathways from genes through adversity to childhood anxiety and depression.

TABLE IPrimer and Probe Sequences for Five *COMT* SNPs

SNP	Sequence
rs2097603	
Forward primer	5'-GCCGTGTCTGGACTGTGAGT-3'
Reverse primer	5'-GGGTTTCAGAATCACGGATGTG-3'
Probe T	5'-6FAM-AACAGACAGAAAAGTTTCCCTTCCCA-3'-TAMRA
Probe C	5'-VIC-CAGACAGAAAAGCTTCCCTTCCCAT-3'-TAMRA
rs6269	
Forward primer	5'-AGGCACAAGGCTGGCATTT-3'
Reverse primer	5'-CCACAGCCCCCTTGCT-3'
Probe G	5'-6FAM-TGCCCCTCTGCGAACACAAGG-3'-TAMRA
Probe A	5'-VIC-ACCTTGCCCCTCTGCAAACACAAG-3'-TAMRA
rs4818	
Forward primer	5'-GGGGGCTACTGTGGCTACT-3'
Forward primer	5'-TCAGGCATGCACACCTTGTC-3'
Probe C	5'-6FAM-CGAGGCTCATCACCATCGAGATCA-3'-TAMRA
Probe G	5'-VIC-CGAGGCTGATCACCATCGAGATCA-3'-TAMRA
rs4680 (Val158Met)	
Forward primer	5'-TCGAGATCAACCCGACTGT-3'
Reverse primer	5'-AACGGGTCAGGCATGCA-3'
Probe C	5'-6FAM-CCTTGTCTTCACGCCAGCGA-3'-TAMRA
Probe T	5'-VIC-ACCTTGTCTTCATGCCAGCGA-3'-TAMRA
rs165599	
Forward primer	5'-GCCAGGGGCACCTGTTAG-3'
Reverse primer	5'-CTGGCTGACTCCTCTTCGTTT-3'
Probe A	5'-6FAM-ACGACTGCCAGCCT-3'-TAMRA
Probe G	5'-VIC-ACGACTGCCGGCC-3'-TAMRA

TABLE II

COMT Haplotypes

Haplotype	rs6269-rs4818-rs4680	Nackley et al.	Frequency	Enzyme
Met	A-C-A	APS (average pain)	0.49	Intermediate
	G-G-A			
	G-C-A			
	A-G-A			
Val _A	G-G-G	LPS (low pain)	0.39	Highest
	G-C-G			
Val _B	A-C-G	HPS (high pain)	0.09	Lowest
	A-G-G			

TABLE III

Family Characteristics of Children Exposed to Maternal Postpartum Depression and Experiencing Life Events

	Maternal postpartum depression		Life events	
	Exposed, n (%)	χ^2 (P)	2 or more (%)	χ^2 (P)
Boys	14.4	0.29, 0.588	37.1	4.71, $P = 0.030$
Girls	14.1		39.5	
Mort/owned	12.3	115.8, $P < 0.001$	36.6	46.3, $P < 0.001$
Council	22.4		40.9	
Other rented	16.9		48.9	
First marriage	12.3	88.3, $P < 0.001$	36.6	40.1, $P < 0.001$
2nd + marriage	22.5		36.4	
Div/Sep/widowed	16.7		41.0	
Never married	17.8		46.2	
Use of car	13.3	73.0, $P < 0.001$	37.7	10.3, $P = 0.001$
No use of car	22.7		45.0	
<0 level ^a	17.5	44.6, $P < 0.001$	37.2	1.37, $P = 0.505$
0 level	12.6		37.8	
>0 level	12.8		38.8	
<1/room	12.9	85.1, $P < 0.001$	37.7	2.81, $P = 0.245$
1/room	17.7		40.1	
>1/room	24.2		40.6	
Maternal age				
<20	22.8	40.1, $P < 0.001$	55.1	84.7, $P < 0.001$
20–24	15.3		46.5	
25–29	13.2		39.1	
30–34	13.3		35.2	
35+	16.2		31.4	
Parity = 0	12.0	39.1, $P < 0.001$	41.4	30.6, $P < 0.001$
Parity = 1	15.3		35.8	
Parity = 2+	16.8		34.7	

^aNational examinations taken in the UK at the age of 16.

TABLE IV

Main Effect of the COMT Val158Met Polymorphism on Emotional Symptoms

Comparison	Full sample	Girls	Boys	Gender interaction (χ^2 , P)
Val/Val	1.00	1.00	1.00	
Met/Val	1.13 [1.01–1.27]	1.07 [0.90–1.26]	1.18 [1.01–1.39]	0.85, 0.655
Met/Met	1.08 [0.95–1.23]; $P = 0.122$	1.03 [0.86–1.24]; $P = 0.731$	1.13 [0.94–1.35]; $P = 0.128$	
“Dose” effect	1.04 [0.97–1.10]; $P = 0.284$	1.01 [0.92–1.11]; $P = 0.768$	1.06 [0.97–1.16]; $P = 0.220$	0.43, 0.513
N	5,838	2,822	3,016	

Figures are OR [95% CI].

TABLE V

Maternal Depression and Life Events in Relation to High Emotionality in Children: Interaction with COMT Val158Met Genotype

	Maternal depression		
	Unadjusted	Adjusted for history of depression before pregnancy	Life events (unadjusted)
Full sample	1.99 [1.73, 2.29]; $P < 0.001$	1.93 [1.65, 2.25]; $P < 0.001$	1.21 [1.15, 1.27]; $P < 0.001$
Met/Met	1.58 [1.17, 2.12]; $P = 0.002$	1.68 [1.21, 2.32]; $P = 0.002$	1.20 [1.08, 1.33]; $P < 0.001$
Val/Met	2.18 [1.79, 2.65]; $P < 0.001$	2.05 [1.64, 2.57]; $P < 0.001$	1.18 [1.10, 1.26]; $P < 0.001$
Val/Val	2.04 [1.57, 2.65]; $P < 0.001$	1.92 [1.43, 2.59]; $P < 0.001$	1.27 [1.16, 1.40]; $P < 0.001$
G $\times$ E interaction	$\chi^2 = 3.17, P = 0.075$	$\chi^2 = 1.27, P = 0.531$	$\chi^2 = 3.17, P = 0.075$

TABLE VI

Main Effect of Diplotype on Emotional Symptoms: Maternal Depression and Life Events in Relationship to High Emotionality in Children, Interaction with COMT Diplotype

Diplotype	Main effects of diplotype, ^a OR [95% CI] (N)	Diplotype level specific effects of postpartum depression, ^a OR [95% CI] (N)	Diplotype level specific effects of life events, ^a OR [95% CI] (N)
N (all diplotypes)	5,928	5,832	5,758
Met/Met	1.00 reference (1,651)	1.99 [1.54, 2.57]; $P < 0.001$ (1,616)	1.27 [1.16, 1.39]; $P < 0.001$ (1,603)
Met/Val _A	1.03 [0.92, 1.15] (2,354)	2.32 [1.86, 2.89]; $P < 0.001$ (2,319)	1.19 [1.11, 1.28]; $P < 0.001$ (2,290)
Met/Val _B	1.04 [0.87, 1.24] (547)	1.66 [1.06, 2.59]; $P = 0.027$ (538)	1.12 [0.98, 1.29]; $P = 0.107$ (531)
Val _A /Val _A	0.91 [0.78, 1.05] (883)	1.43 [0.98, 2.10]; $P = 0.066$ (873)	1.23 [1.08, 1.41]; $P = 0.002$ (851)
Val _A /Val _B	0.90 [0.74, 1.09] (398)	1.81 [1.07, 3.05]; $P = 0.026$ (386)	1.11 [0.91, 1.36]; $P = 0.312$ (383)
Val _B /Val _B	1.07 [0.74, 1.53] (100)	1.88 [0.66, 5.39]; $P = 0.240$ (100)	1.26 [0.89, 1.79]; $P = 0.186$ (100)
Global P -value	$P = 0.417$	NA	NA
Diplotype $\times$ exposure interaction (χ^2 , P)	NA	$\chi^2 = 5.40$, $P = 0.37$	$\chi^2 = 2.95$, $P = 0.71$

^aOR, odds ratio of higher emotional symptom score group for each s.d. increase in weighted life event score.