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# Catechol *O*-Methyltransferase (COMT) *VAL158MET* Functional Polymorphism, Dental Mercury Exposure, and Self-Reported Symptoms and Mood

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## Abstract

Associations were evaluated between a functional single nucleotide polymorphism (Val158Met) in the gene encoding the catecholamine catabolic enzyme catechol *O*-methyltransferase (COMT), dental mercury exposure, and self-reported symptoms and mood among 183 male dentists and 213 female dental assistants. Self-reported symptoms, mood, and detailed work histories were obtained by computerized questionnaire. Spot urine samples were collected and analyzed for mercury concentrations to evaluate recent exposures, whereas a chronic mercury exposure index for all subjects was created from the work histories. COMT polymorphism status was determined using a polymerase chain reaction (PCR)-based assay. Scores for current, recent, and chronic self-reported symptom groups and six self-reported mood factors were evaluated with respect to recent and chronic mercury exposure and COMT polymorphism status. Multiple regression analysis controlled for age, socioeconomic status, tobacco and alcohol use, self-reported health problems, and medications. Separate evaluations were conducted for dentists and dental assistants. No consistent patterns of association between either urinary mercury concentration or the chronic index of mercury exposure and any category of symptoms were observed. However, consistent and significant associations were found between increased symptoms and the COMT polymorphism involving the double allelic substitution (full mutation) compared to subjects with no substitutions. Associations with mood were limited to polymorphism status among female dental assistants, and were observed for four of six mood factors and overall mood score. These findings extend evidence of genetic factors potentially affecting human susceptibility to the toxic effects of mercury and other environmental chemicals.

Potentially severe neurological deficits have historically been associated with occupational exposures to high levels of elemental mercury ($Hg^0$) (Albers et al., 1988; Langworth et al., 1992; Piikivi et al., 1984; Piikivi & Hanninen, 1989). More recent studies of lower levels of

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$Hg^0$ exposure have also reported associations with neurological deficits (Clarkson et al., 2003; Langworth et al., 1997; Ritchie et al., 2002). Adverse neurobehavioral effects have now been correlated with elemental mercury exposures in the range of those experienced by the general U.S. population (Bittner et al., 1998; Echeverria et al., 1995, 1998). In evaluating issues surrounding susceptibility to the neurological effects of $Hg^0$ at such low levels of exposure, it becomes necessary to take into account other biological causes for these effects, in particular, polymorphisms among genes that are known to influence the same neurobehavioral functions that are adversely impacted by $Hg^0$ exposure. In this regard, studies in an established cohort of occupationally exposed dental professionals have previously evaluated polymorphisms of genes influencing the production of coproporphyrinogen oxidase (CPOX)(Woods et al., 2005; Echeverria et al., 2006; Heyer et al., 2006), brain-derived neurotropic factor (BDNF) (Heyer et al., 2004; Echeverria et al., 2005), and the serotonin transporter gene promoter region (5-HTTLPR) (Heyer et al., 2008). CPOX was the first polymorphism studied, as it, along with $Hg^0$, impacts the biosynthesis of heme, a likely mitigating factor in neurological signaling and neuronal functions (Chernova et al., 2007). BDNF and 5-HTTLPR were similarly evaluated because of their known direct impact on mood and behavior (Heyer et al., 2004, 2008). Independent and additive, although not interactive (i.e., synergistic), effects were associated with $Hg^0$ and each of these polymorphisms.

Catechol *O*-methyltransferase (COMT) is an important enzyme in the methylation of endogenous and exogenous catechol compounds, including catecholamine neurotransmitters such as dopamine, norepinehprine, and epinephrine, as well as catechol estrogens (Weinshilboum et al., 1999). A common guanine to adenine missense variant of the COMT gene (Lachman et al., 1996) produces a transcriptional substitution of methionine for valine at codon 108/158 depending upon whether the soluble (codon 108) or membrane-bound (codon 158) form of the enzyme is being encoded (Weinshilboum et al., 1999). *Met158* displays a three- to fourfold decrease in COMT enzymatic activity compared to *val158* (Lachman et al., 1996). The alleles are codominant in that heterozygous individuals possess COMT enzyme activity that is midway between that of homozygous individuals (Weinshilboum et al., 1999). There is genetic variation in the prevalence of COMT polymorphisms, with Caucasians having approximately 50% high activity *val158 alleles*, African-American somewhat higher, and Asians around 70–80% (Weinshilboum et al., 1999).

The greater activity of the wild-type *val158* form of COMT accounts for increased catabolism and reduced levels of these catecholamine neurotransmitters and estrogens compared to the *met158* gene product. A number of authors (Malhotra et al., 2002; Bruder et al., 2005; de Frias et al., 2004, 2005; Reuter et al., 2005; Goldberg et al., 2003), but not all (Stefanis et al., 2004; O'Hara et al., 2006; Tsai et al., 2003), demonstrated that cognitive function, particularly on more complex tasks, improves in proportion to the increased availability of neurotransmitters associated with the *met158* allelle. On the other hand, the *met158* allelle was associated with heightened affective response to negative stimuli (Smolka et al., 2005, 2007; Drabant et al., 2006; Montag et al., 2008) and increased pain responses accompanied by reduced coping ability (Zubieta et al., 2003; Diatchenko et al., 2005). Personality traits such as sensation seeking have been associated with the *Val158* allele (Lang et al., 2007; Tsai et al., 2004) primarily among women, while the *Met158* allele was correlated with harm avoidance (Hashimoto et al., 2007; Enoch et al., 2003) and anxiety (Stein et al., 2005).

In the present study, the independent and combined effects of $Hg^0$ exposure and the COMT *Val158Met* polymorphism were evaluated in dental professionals with prolonged occupational $Hg^0$ exposure. This article focuses on self-reported symptoms as assessed using a standardized list of self-reported symptoms, and on mood as categorized using the Profile of Mood States (POMS), as described later. A separate report will describe the effects of this COMT

polymorphism on neurobehavioral performance outcomes in relation to $Hg^0$ exposure in this cohort.

## Materials and Methods

### The Study Population

Associations between allelic variants of the COMT gene for the *Val158Met* single nucleotide polymorphism, dental mercury exposure, and self-reported mood and symptoms were evaluated among male dentists and female dental assistants in Washington State from our established cohort of occupationally exposed subjects. Dentists were identified from the registry of the Washington State Dental Association, and our initial contact included a short eligibility questionnaire and a request for a spot urine sample. Among the 1488 respondents who met our study criteria, mean urinary mercury concentrations (HgU) were 2.5 μg/L (range 0–67). A random stratified (based upon HgU concentrations) sample of 261 dentists (all male) was contacted, and 183 dentists (70%) had sufficient information, including COMT polymorphism data, for inclusion in our current study. A full description of the recruitment methods and eligibility criteria was previously published (Heyer et al., 2004; Woods et al., 2005). As previously described, dental assistants (all females) were recruited independently from the practices of the participating dentists to provide a similar range of dental office $Hg^0$ exposures. Four hundred potential dental assistant subjects were contacted, and 213 (53%) had sufficient data for inclusion in the current study. The institutional review boards of Battelle and the University of Washington approved the study protocol. All subjects gave written consent prior to participating in the study. Following completion of the study, subjects were informed of their urinary mercury levels but not of genotype, in accordance with University of Washington Human Subjects protocol.

### Data Collection

Testing was conducted at a central location, but some participants were tested at their offices due to distance from our test facility or for reasons of convenience. Participating subjects took a breath alcohol test prior to additional testing, and provided an approximately 50-ml spot urine sample for mercury analysis. Buccal cells were harvested from the inner cheek of each subject to provide DNA for genetic testing. Other test procedures included completing a computerized questionnaire (Neuroquest) and a computerized behavioral test battery, the Behavioral Evaluation for Epidemiologic Studies (BEES) (Echeverria et al., 2002). In addition, various paper-and-pencil and stand-alone neurological tests were administered. This study focuses on results of self-reported mood and symptoms, while the results of our neurobehavioral testing will be reported separately. Neuroquest collects information on demographics and personal habits, use of vitamins and supplements, medical and pregnancy histories, work histories, a symptoms checklist (45 symptoms), and a computerized version of the Profile Of Mood States (POMS) (McNair et al., 1971) to measure current mood. Medical conditions are grouped into categories, including (1) physical injury, (2) major operations, (3) digestive problems, (4) circulation problems, (5) sensory problems, (6) kidney problems, (7) endocrine problems, (8) immune problems, (9) brain-related problems, and (10) emotional problems. Yes/no information was collected on the presence of any condition, the presence of specific or “other” conditions, and the current use of medications for any of these conditions within each category.

### COMT *Val158Met* Genotyping

Genotyping was performed at the Functional Genomics Laboratory of the Center for Ecogenetics and Environmental Health at the University of Washington. A 5′-nuclease TaqMan Detection System-based assay was developed to discriminate G/A alleles of a single nucleotide polymorphism at codon 158 of the COMT gene. Primers and dual-labeled allele specific probes were designed through Assays-by-Design Service-SNP Genotyping by Applied

Biosystems Inc.(Foster City, CA). The polymerase chain reaction (PCR) primers were 5′-CGAGAT-CAACCCCGACTGT -3′ (sense) and 5′-CAGGCATGCA-CACCTTGTC -3′ (antisense). Each TaqMan MGB probe consisted of an oligonucleotide labeled both with a particular 5′ reporter dye and a 3′ nonfluorescent quencher. The probes for this assay were 5′-6 FAM-TCGCTGGCATGAAG-MGBNFQ-3′ and 5′-VIC-TTTCGCTGGCGTGAAG-MGBNFQ-3′. Amplification was performed by initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 s and annealing at 60°C. End-point analysis was performed on ABI 7900 sequence detection system (Applied Biosystems Inc., Foster City, CA) to determine the genotypes. Appropriate positive controls consisting of DNA aliquots representing wild-type/wild-type, wild-type/mutant, and mutant/mutant genotypes (characterized by DNA-sequencing) and a negative control (no DNA) were included in each assay performed. In addition, 10% of the identified alleles were randomly re-analyzed and compared to previous analyses for quality control of this genotyping assay.

## Mercury Exposure Scores

Analysis of total mercury in urine samples was performed using continuous-flow, cold-vapor spectrofluorometry, as previously described (Pingree et al., 2001). Urine samples were analyzed in triplicate and the geometric mean of the three analyses was computed as the Hg concentration of the sample. Urinary Hg levels were calculated as micrograms per liter of urine (μg/L). Urinary concentrations of $Hg^0$ are considered to reflect exposure over the last few months. Thus, recent mercury exposure was characterized using the natural log transformation of the spot concentrations. This transformation is used as it is considered to have a better linear association with adverse effects. The value 1 was added to the concentration before the transformation to create a lower bound of 0 and avoid having large differences in the log-transformed value associated with small differences in urinary concentrations of less than 1 μg/L.

Our chronic measure of mercury exposure was described in previous reports (Heyer et al., 2004; Echeverria et al., 2005) and is based upon subjects' work histories. Estimates of mercury exposure are calculated using the product of the reported average number of mercury amalgam fillings or removals performed weekly and the duration of the job. This product was then weighted by a time-period factor (1 = 1992, 1.5 = 1985–1992, 1.75 = 1972–1982, 2.0 = 1970) based upon historically measured urinary mercury levels in dental populations. The square root of the resulting sum was taken across all jobs to remove a very skewed tail that would impact analysis. Further, the result for age, an important covariate, was adjusted to remove substantial covariance.

## Symptoms Scores

Self-reported symptoms were obtained through a computerized symptom checklist of our design that is described elsewhere (Heyer et al., 2004). This checklist distinguishes between current (today) and recent (over the past 3 mo) symptoms. Recent symptoms are further classified by their duration, allowing the definition of chronic symptoms. A total of 45 symptoms are included, but only 27 are used to define the current checklist, as they evaluate activities over time (e.g., “write notes to remind myself”). Current symptoms were scored for intensity (range 0–4), while recent symptoms were scored using the product of their intensity and frequency (0–20). Chronic symptoms were defined as those recent symptoms lasting at least 1 yr. Thus, chronic symptoms are statistically tied to recent symptoms, and should not be considered totally independent.

In order to reduce the number of symptom variables in these analyses, 12 a priori symptom groups were created, each assigned a score equal to the highest (maximum) individual symptom score within that group. This “maximum” score was used to avoid very high scores associated

with subjects who "globalized" their symptom reporting. In addition, three individual symptom questions were selected to use independently of their group because they seemed to capture the full concept of the symptom group (these included memory, confusion, and depression). These are reported as their group name with "1 variable" attached.

The 12 symptom groups are: memory, confusion, depression, anxiety, coordination, mood, headache, parasthesias, muscle symptoms, stomach symptoms, skin symptoms, and lung symptoms. With the single variable scores, in total 15 symptom outcomes, which are not necessarily statistically independent, were evaluated.

## Mood Scores

Mood scores were obtained by a computerized version of the Profile of Mood States (POMS) questionnaire (McNair et al., 1971). The POMS has 65 questions and provides 6 mood factor scales. These include Tension-Anxiety (9 questions, score range 0–32), Depression-Dejection (15 questions, score range 0–60), Anger-Hostility (12 questions, score range 0–48), Vigor-Activity (8 questions, score range 0–32), Fatigue-Inertia (7 questions, score range 0–28), and Confusion-Bewilderment (7 questions, score range 0–24). These scores are derived from oblique factors and are thus somewhat correlated with one another. The Vigor-Activity score is negatively correlated with all the other scores. An overall score can be calculated by adding the first five scores and subtracting the Vigor-Activity score.

## Statistical Analyses

As in our previous reports regarding studies with this dental professional cohort (Heyer et al., 2004, 2008; Woods et al., 2005; Echeverria et al., 2005, 2006), results for the (male) dentists and (female) dental assistants are analyzed and reported separately. This decision is based on the differences in the measures of $Hg^0$ exposure, age structures, education and training, and symptom reporting profiles for these two groups (Table 1). Cross-sectional regression analyses were conducted using SPSS (version 16.0 for Windows). A data file was constructed that contained all symptom and mood scores, measures of exposure to elemental mercury (both current and chronic), the COMT genotype status, and covariates. Potential covariates evaluated in the analyses included demographic, dietary, and medical history variables. Final regression analyses included evaluation of both "base" and "full" models for both symptoms and mood outcomes. The base model includes age, race, dummy variables for the heterozygous (V/M) and full mutation (M/M) polymorphism of COMT, and the appropriate $Hg^0$ exposure variables —either natural log (ln) urinary mercury concentration (lnHgU) or the chronic mercury exposure index. Subjects with wild-type (V/V) genotype are the base group in the COMT analysis, and had dummy variables set to zero. A count variable for COMT (based on the *Met158* allele count of 0, 1, or 2) was tested, but only the results for mood where an allelic dose response was observed are reported. Our full model includes the base model plus potentially all the variables listed in Table 2. These additional variables were tested for inclusion in the model by employing backward deletion using a conservative elimination *p* value of 0.2 (Budtz-Jorgensen et al., 2007).

In analyzing cross-sectional data for mood and symptom reporting, it is often difficult to make a causal inference about whether the value of a covariate represents a true risk factor for the outcome being measured or is itself a result of the mood or symptom being modeled. Thus, for example, drinking may cause depression, or depression may lead to drinking. Because it is difficult to make such a priori decisions for the many covariate–outcome combinations, caution was taken in regard to overcontrolling in the analyses. In this regard, results are reported for both the "base" and "full" models, and their differences are evaluated as appropriate.

## Results

The final cohort for this analysis comprised 183 male dentists and 213 female dental assistants. Owing to a few cases with partially missing data, symptoms are analyzed for 181 males and 211 females, and mood is analyzed for 183 males and 211 females. The distributions of the continuous exposure variables and covariates used in the analysis are presented in Table 1, and the dichotomous exposure variables and covariates are in Table 2. Compared to the male dentists, it can be seen that the female dental assistants are younger (mean = 35.7 vs. 48.7 years), have lower vocabulary scores—a measure of training and education (8.2 vs. 10.6), and have considerably lower incomes (mean = $51,000 vs. $103,000). The female dental assistants are more likely to have a physical impairment and report a history of emotional, endocrine, and immune system problems. The dentists are more likely to report a history of cancer and physical problems. On the other hand, both genders are predominantly Caucasian, have similar drinking patterns (modest), and have similar distributions of the COMT polymorphism. While, as planned, dental office predicts the urinary mercury (HgU) concentrations for dentists and dental assistants, dentists had significantly higher exposures to mercury as measured by both HgU and the chronic exposure index.

Table 3 shows the descriptive data for the outcome variables of interest—mood and symptom scores. It is interesting to note that in every case (except for the POMS vigor score, which is scaled in the opposite direction), the female dental assistants have higher mean scores—usually considerably so— for both symptoms and mood, demonstrating more frequent reporting. Within each gender, symptom reporting is highest for depression, anxiety, and memory problems. However, among dentists, there are low reported levels for symptoms of muscles and coordination, symptoms that would directly impact their work. The data from these three tables support our decision to analyze the dentist and dental assistant populations separately.

Table 4 shows the results of regression analyses modeling symptom scores. To make the table easier to read, only symptoms with significant results in either the base or full model are reported (with other results being not listed or shaded out). The impact of the full model covariates can be estimated by comparing results between the two models. In almost all cases the full model increases the significance of the exposure being evaluated, indicating that it is unlikely that we are overcontrolling for the covariates in the full model.

Table 5 shows the results of regression analyses modeling mood. There were no significant associations between mood and either HgU concentrations or the chronic index of mercury exposure. However, COMT was significantly associated with three of the five mood scales as well as with the overall mood score, but only among dental assistants. As before, in almost all cases, the association was strongest in the full model, indicating a lack of overcontrolling.

### Recent Mercury Exposure and Symptoms (Table 4)

Recent mercury exposure, as indicated by HgU, was primarily correlated with symptoms among female dental assistants. Symptoms of confusion, as measured by either a single or grouped response, were increased among females for today's symptoms, but decreased for recent symptoms. There was no association with chronic symptoms. It is of interest that the unexpected inverse correlations of recent mercury exposure (HgU) with recent symptoms of confusion were significant only in the base model. This is one of the rare cases where the full model was not as strong as the base model, and may indicate that these correlations in the unexpected direction reflect the exposure-related distributions of the covariates. Moodiness and stomach symptoms were also significantly correlated with exposure, but limited to today's symptoms and with only moderate strength.

The single significant association between HgU and symptoms among male dentists was for recent skin symptoms. This association reached marginal significance in the full model, but was not significant in the base model. There was no counterpart for female dental assistants.

### Chronic Mercury Exposure and Symptoms (Table 4)

As previously observed, the majority of significant associations with chronic mercury exposure are among female dental assistants. Both recent and chronic symptoms of coordination and skin are positively associated with the chronic index. In addition, headache "today," but not recent or chronic headache, was also associated with chronic Hg exposure. Among male dentists, similarly isolated "today" symptoms for anxiety and headache were positively associated with the chronic index, while chronic lung symptoms were negatively associated. On a prima facie basis, it was determined that these isolated associations for "today" symptoms with chronic Hg exposure are less than convincing in terms of supporting a biologically plausible basis for a chronic $Hg^0$ effect.

### COMT Polymorphisms and Symptoms (Table 4)

There is an interestingly consistent but unexpected dichotomy observed in the data between associations with symptoms and heterozygous versus the full mutation polymorphism of COMT. The literature generally describes an allele–dose affect of the COMT polymorphism, with observed effects for full mutation (M/M) being similar to, but stronger than, those for heterozygous (V/M). In our analyses all significant associations observed between heterozygous polymorphisms and symptoms are negative—in the unexpected direction—suggesting an improved effect of the COMT V/M on the symptoms in question. In contrast, all significant associations observed between the full mutation and symptoms are positive—in the expected direction—suggesting a substantially worsening of the effect. The complete consistency of this division, the fact that it was observed among *both* male and female subjects, and the high significance of many of the observed associations make it unlikely that this dichotomy might be due to chance or unmeasured characteristics of the subjects. Thus, data indicate that subjects with only one *met158* allele (heterozygous) have reduced symptoms compared to subjects with none ("wild-type" subjects with two *val158* alleles who are our baseline in these analyses), whereas subjects with two *met158* alleles (full mutation) have consistently increased symptoms compared to our baseline (wild-type) group. Notably, there is no overlap of symptoms with significant associations between these two variant groups. For heterozygous COMT, decreased symptoms of depression, headache, and muscles among females and decreased skin symptoms among males were observed. In contrast, for the full mutation, increased symptoms of confusion among both males and females, along with increased symptoms of coordination and skin among males, were noted. While males in both heterozygous and full mutation groups report significant associations with skin, the heterozygous genotype is associated with recent and chronic symptoms, and the full mutation is associated only with "today" symptoms.

### COMT Polymorphism and Mood (Table 5)

The pattern of associations between COMT genotype and mood is much more consistent with patterns reported in the literature. In the present study these associations are confined to females, and all demonstrate the allelic dose-response mentioned above. This is demonstrated in the significant associations obtained when using a linear variable representing the number of *met158* alleles (0, 1, or 2) for each subject. Four of six mood factors had significant associations observed, i.e., tension, depression, fatigue, and confusion. Furthermore, the consistency of the association between COMT genotype and general mood was demonstrated by the generally enhanced significance of the association with the combined overall mood score.

### Interactions Between Mercury Exposure and COMT Polymorphism

Several symptoms with significant effects were associated with both mercury exposure and the COMT polymorphism. A gender- and symptom-specific overlap is noted with recent mercury exposure (HgU) and the COMT full mutation for recent symptoms of confusion (both one variable and grouped) among females. Interestingly, these symptoms are the same as those that were significant only in the base model for HgU, and may therefore be influenced by the distribution of the covariates.

## Discussion

No internally consistent associations between mercury exposure and self-reported symptoms were found in this study. This finding is consistent with those described in previous reports on this cohort, in which specific correlations contingent upon the genetic polymorphisms under evaluation were observed (Heyer et al., 2004, 2008). This result is not unexpected, as the $Hg^0$ exposures that were evaluated are quite low, and the effects of the specific polymorphisms under investigation impact neurobehavioral functions in different ways. In the present study, the positive correlations observed between recent mercury exposure (HgU) and confusion among dental assistants and between the chronic $Hg^0$ exposure index and anxiety among dentists were previously observed in our evaluations controlling for polymorphisms of both BDNF (Heyer et al., 2004) and 5-HTTLPR (Heyer et al., 2008) within this same cohort. Similarly, the associations between coordination and skin symptoms and the chronic index among dental assistants, and the inverse association between lung symptoms and our chronic $Hg^0$ index among dentists were previously noted, attesting to the consistency of these findings (Heyer et al., 2004). In the present study, there is no clear grouping of symptoms associated with mercury exposures while controlling for the COMT *Val158Met* polymorphism.

The dichotomous findings of significantly decreased symptoms associated with the heterozygous COMT but significantly increased symptoms associated with the full COMT mutation are intriguing. As noted earlier, there is no overlap of symptom categories with significant associations between these two allelic groups, mimicking the varied impacts of the *Val158Met* alleles described in the literature cited earlier. The high consistency of this dichotomy greatly reduces the likelihood of this observation being due to chance or unmeasured characteristics of the subjects within wild-type versus heterozygous allelic groups. Further evaluation of this observation in other populations will therefore be required to resolve this issue.

Few associations were observed between mood and mercury exposures in the present studies. However, associations with mood were consistently noted among female dental assistants in our evaluations of polymorphisms of BDNF, 5-HTTLPR, and now COMT. While associations among the POMS subscales have varied, the combined overall score has consistently shown strong associations with these polymorphisms. In the case of COMT, the observed associations are supported by reports showing impacts on affective response to occur primarily among females (Lang et al., 2007; Tsai et al., 2004; Enoch et al., 2003; Stein et al., 2005). Although no consistent patterns of association between mood and mercury exposure were observed in the present study, the findings do not preclude the likelihood that the *Val158Met* COMT polymorphism predisposes to increased susceptibility to the adverse neurobehavioral effects of mercury or other agents and may therefore serve to define subpopulations with increased sensitivity to this outcome.

In conclusion, the Neuroquest computerized self-reported symptom severity checklist and the computerized POMS mood scale were shown to be sensitive to the *Val158Met* COMT polymorphism in dental professionals with prolonged occupational exposure $Hg^0$. Most associations between symptoms and low-level mercury exposures seen in this study seem to

be modified by genetic variations known to impact neurobehavioral functions, e.g., polymorphisms of BDNF, 5-HTTLPR, and COMT. These polymorphisms independently affect symptoms and have been consistently seen to impact mood, especially among female participants. These findings contribute to growing body of evidence of genetic factors affecting human susceptibility to the adverse effects of mercury and possibly other environmental chemicals.

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**TABLE 1**

Continuous Exposure Variable and Covariate Descriptives

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| **Exposure variables** | **Range** | **Mean** | **SD** | **Range** | **Mean** | **SD** |
| Urinary mercury (μg/L)—unlogged | 0–15.57 | 2.39 | 2.08 | 0–10.30 | 1.82 | 1.88 |
| Chronic Hg index—age adjusted | 0–119.7 | 28.8 | 18.37 | 0–66.0 | 20.1 | 10.83 |
| Covariates | | | | | | |
| Age at evaluation | 28.28–65.90 | 48.67 | 7.74 | 19.27–65.07 | 35.65 | 8.84 |
| Vocabulary score | 7–11 | 10.60 | .95 | 3–11 | 8.20 | 2.03 |
| Income in $1000's | 25–800 | 168.01 | 103.14 | 7–250 | 51.19 | 31.44 |
| Alcohol drinks in last 12 hours | 0–8 | 1.98 | .61 | 0–6 | 1.62 | 0.90 |
| Alcohol drinks/week | 0–20 | 3.59 | 3.95 | 0–20 | 2.39 | 2.98 |
| Number of allergies | 0–3 | 0.20 | 0.49 | 0–3 | 0.29 | 0.55 |

## TABLE 2

Dichotomous Exposure Variable and Covariate Descriptives

| | Males | | Females | |
|---|---|---|---|---|
| **Exposure variables** | ***n*** | **%** | ***n*** | **%** |
| WT(V/V) | 49 | 26.9 | 60 | 28.7 |
| Het(V/M) | 80 | 44.0 | 88 | 42.1 |
| Mut(M/M) | 53 | 29.1 | 61 | 29.2 |
| Covariates | | | | |
| Caucasian | 175 | 96.2 | 181 | 86.6 |
| Have physical impairment | 10 | 5.5 | 17 | 8.1 |
| Medical history of: | | | | |
| Cancer | 17 | 9.3 | 7 | 3.3 |
| Emotional problems | 8 | 4.4 | 20 | 9.6 |
| Sensory problem | 24 | 13.2 | 25 | 12.0 |
| Physical problem | 112 | 61.5 | 93 | 44.5 |
| Endocrine problems | 9 | 4.9 | 17 | 8.1 |
| Respiratory problems | 22 | 12.1 | 31 | 14.8 |
| Digestive problems | 37 | 20.3 | 46 | 22.0 |
| Immune system problems | 5 | 2.7 | 17 | 8.1 |
| Major operations | 104 | 57.1 | 110 | 52.6 |

**TABLE 3**

Outcome Variable Descriptives

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| **Outcome variable** | **Range** | **Mean** | **SD** | **Range** | **Mean** | **SD** |
| POMS Mood Score | | | | | | |
| Tension | 0–26 | 5.35 | 4.22 | 0–27 | 8.03 | 5.39 |
| Depression | 0–35 | 3.26 | 5.37 | 0–37 | 5.33 | 6.63 |
| Anger | 0–38 | 3.93 | 5.06 | 0–32 | 5.73 | 5.55 |
| Vigor | 6–32 | 19.38 | 4.97 | 1–29 | 14.84 | 5.90 |
| Fatigue | 0–24 | 5.21 | 4.58 | 0–25 | 7.27 | 5.21 |
| Confusion | 0–14 | 3.12 | 2.72 | 0–18 | 4.76 | 3.37 |
| Overall total | −32–118 | 1.49 | 21.34 | −23–100 | 16.28 | 25.42 |
| Symptoms Today Score | | | | | | |
| Depression one variable | 0–2 | .11 | .35 | 0–3 | .25 | .62 |
| Confusion one variable | 0–2 | .10 | .33 | 0–3 | .39 | .64 |
| Headache | 0–2 | .13 | .39 | 0–4 | .38 | .796 |
| Anxiety | 0–4 | .39 | .66 | 0–4 | .61 | .85 |
| Moody | 0–3 | .08 | .34 | 0–3 | .25 | .56 |
| Depression | 0–3 | .44 | .69 | 0–4 | .74 | .85 |
| Confusion | 0–3 | .13 | .40 | 0–3 | .48 | .69 |
| Coordination | 0–3 | .06 | .31 | 0–4 | .18 | .52 |
| Parasthesias | 0–3 | .13 | .40 | 0–4 | .28 | .67 |
| Muscle | 0–3 | .03 | .26 | 0–4 | .21 | .59 |
| Stomach | 0–3 | .15 | .43 | 0–4 | .42 | .77 |
| Skin | 0–4 | .31 | .67 | 0–4 | .93 | 1.03 |
| Lung | 0–4 | .19 | .58 | 0–4 | .40 | .74 |
| Recent Symptoms Score | | | | | | |
| Depression one variable | 0–12 | .82 | 1.53 | 0–16 | 2.09 | 3.14 |
| Memory one variable | 0–12 | 1.22 | 1.95 | 0–16 | 2.03 | 2.94 |
| Confusion one variable | 0–6 | .46 | 1.00 | 0–20 | 1.66 | 2.62 |
| Headache | 0–12 | 1.30 | 1.69 | 0–20 | 3.41 | 3.65 |

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| **Outcome variable** | **Range** | **Mean** | **SD** | **Range** | **Mean** | **SD** |
| Anxiety | 0–16 | 2.78 | 2.87 | 0–20 | 5.16 | 4.80 |
| Moody | 0–9 | .91 | 1.61 | 0–20 | 2.72 | 3.43 |
| Depression | 0–16 | 3.00 | 3.36 | 0–20 | 5.99 | 5.03 |
| Confusion | 0–12 | .71 | 1.64 | 0–20 | 1.90 | 2.77 |
| Memory | 0–20 | 3.00 | 3.62 | 0–20 | 4.04 | 4.17 |
| Coordination | 0–12 | .27 | 1.38 | 0–20 | 1.80 | 3.67 |
| Parasthesias | 0–12 | .71 | 1.77 | 0–20 | 1.56 | 3.07 |
| Muscle | 0–12 | .28 | 1.24 | 0–16 | 1.34 | 2.59 |
| Stomach | 0–12 | 1.28 | 1.73 | 0–20 | 3.24 | 3.47 |
| Skin | 0–12 | 1.12 | 2.16 | 0–20 | 3.69 | 4.72 |
| Lung | 0–9 | .77 | 1.52 | 0–16 | 1.82 | 2.94 |
| Chronic Symptoms Score | | | | | | |
| Depression one variable | 0–12 | .72 | 1.51 | 0–16 | 1.63 | 2.87 |
| Memory one variable | 0–12 | 1.20 | 1.96 | 0–16 | 1.71 | 2.79 |
| Confusion one variable | 0–6 | .45 | 1.00 | 0–20 | 1.38 | 2.51 |
| Headache | 0–12 | 1.08 | 1.66 | 0–20 | 3.09 | 3.77 |
| Anxiety | 0–16 | 2.19 | 2.77 | 0–20 | 4.17 | 4.58 |
| Moody | 0–8 | .71 | 1.39 | 0–20 | 2.49 | 3.34 |
| Depression | 0–16 | 2.85 | 3.37 | 0–20 | 5.23 | 5.16 |
| Confusion | 0–12 | .60 | 1.40 | 0–20 | 1.63 | 2.67 |
| Memory | 0–20 | 2.96 | 3.65 | 0–20 | 3.76 | 4.21 |
| Coordination | 0–12 | .20 | 1.07 | 0–20 | 1.32 | 3.22 |
| Parasthesias | 0–12 | .65 | 1.76 | 0–20 | 1.18 | 2.69 |
| Muscle | 0–12 | .24 | 1.23 | 0–16 | 1.00 | 2.32 |
| Stomach | 0–12 | 1.14 | 1.73 | 0–20 | 3.06 | 3.44 |
| Skin | 0–12 | 1.00 | 2.12 | 0–20 | 3.40 | 4.77 |
| Lung | 0–6 | .55 | 1.28 | 0–12 | 1.50 | 2.73 |

**TABLE 4**

Self-Reported Symptoms, Mercury Exposure, and COMT Polymorphism

| | | Males (*n* = 181) | | | | Females (*n* = 211) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Base model | | Full model | | Base model | | Full model | |
| **Exposure** | **Symptom group/duration** | **Beta** | **Sig.** | **Beta** | **Sig.** | **Beta** | **Sig.** | **Beta** | **Sig.** |
| Natural log of urinary mercury adjusted for COMT | Confusion–one variable | | | | | | | | |
| | Today | | | | | .157 | *.069* | .224 | **.008** |
| | Recent | | | | | (−.788)[†] | **.022** | (−.571)[†] | *.082* |
| | Confusion–grouped variables | | | | | | | | |
| | Today | | | | | .167 | *.073* | .214 | **.019** |
| | Recent | | | | | (−769) | **.036** | (−.481) | *.163* |
| | Moody–grouped variables | | | | | | | | |
| | Today | | | | | .150 | **.046** | .161 | **.033** |
| | Stomach–grouped variables | | | | | | | | |
| | Today | | | | | .186 | *.064* | .215 | **.031** |
| | Skin–grouped variables | | | | | | | | |
| | Recent | .369 | *.244* | .562 | .044 | | | | |
| Age-standardized chronic mercury index adjusted for COMT | Coordination–grouped variables | | | | | | | | |
| | Recent | | | | | .519 | **.037** | .351 | *.134* |
| | Chronic | | | | | .462 | **.031** | .502 | **.016** |
| | Anxiety–grouped variables | | | | | | | | |
| | Today | .099 | *.051* | .106 | **.030** | | | | |
| | Headache–grouped variables | | | | | | | | |
| | Today | .061 | **.038** | .070 | **.012** | .131 | **.015** | .132 | **.016** |
| | Skin–grouped variables | | | | | | | | |
| | Recent | | | | | .708 | **.033** | .833 | **.007** |
| | Chronic | | | | | .664 | **.048** | .733 | **.019** |
| | Lung–grouped variables | | | | | | | | |
| | Chronic | (−.184) | *.053* | (−.196) | **.030** | | | | |
| COMT–Het(V/M) | Depression–grouped variables | | | | | | | | |
| | Today | | | | | (−.294) | **.036** | (−.277) | **.045** |

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| | | Males (*n* = 181) | | | | Females (*n* = 211) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Base model | | Full model | | Base model | | Full model | |
| **Exposure** | **Symptom group/duration** | **Beta** | **Sig.** | **Beta** | **Sig.** | **Beta** | **Sig.** | **Beta** | **Sig.** |
| | Headache–grouped variables | | | | | | | | |
| | Today | | | | | (−.369) | **.006** | (−.370) | **.005** |
| | Muscle–grouped variables | | | | | | | | |
| | Today | | | | | (−.184) | *.052* | (−.209) | **.022** |
| | Skin–grouped variables | | | | | | | | |
| | Recent | (−.887) | **.025** | (−.999) | **.005** | | | | |
| | Chronic | (−.943) | **015** | (−1.076) | **.001** | | | | |
| COMT–Mut(M/M) | Confusion–one variable | | | | | | | | |
| | Recent | | | | | .948 | **.050** | 1.059 | **.023** |
| | Chronic | | | | | .821 | *.076* | .890 | **.049** |
| | Coordination-grouped variables | | | | | | | | |
| | Recent | .554 | *.099* | .675 | **.028** | | | | |
| | Confusion–grouped variables | | | | | | | | |
| | Today | .164 | **.009** | .182 | **.002** | | | | |
| | Recent | .681 | **.016** | .835 | **.001** | | | | |
| | Chronic | .477 | **.029** | .537 | **.006** | | | | |
| | Skin-grouped variables | | | | | | | | |
| | Today | .151 | *.266* | .289 | **.020** | | | | |

*Note.* Only gender-specific categories with significant associations are shown; beta values represent the strength of the association between 0 and 100%. Boldface numerals indicate significant ($p < .05$); italicized numerals indicate not significant (shown for comparison between base and full models); parentheses indicate a negative association (reduced symptoms associated with exposure); †, also has significant association with COMT-Mut.

**TABLE 5**

Mood and COMT Polymorphism

| | Males (*n* = 181) | | | | Females (*n* = 211) | | | |
|---|---|---|---|---|---|---|---|---|
| | Base model | | Full model | | Base model | | Full model | |
| **Mood score/polymorphism** | **Beta** | **Sig.** | **Beta** | **Sig.** | **Beta** | **Sig.** | **Beta** | **Sig.** |
| POMS Mood–Tension Score | | | | | | | | |
| COMT - Het | | | | | 1.264 | *.157* | .987 | *.243* |
| COMT - Mut | | | | | 2.264 | **.019** | 2.496 | **.007** |
| Linear | | | | | 1.130 | **.019** | 1.250 | **.007** |
| POMS Mood–Depression Score | | | | | | | | |
| COMT - Het | | | | | .835 | *.459* | .596 | *.581* |
| COMT - Mut | | | | | 2.381 | *.053* | 2.452 | **.037** |
| Linear | | | | | 1.140 | *.062* | 1.217 | **.040** |
| POMS Mood–Fatigue Score | | | | | | | | |
| COMT - Het | | | | | 1.987 | **.025** | 1.856 | **.027** |
| COMT - Mut | | | | | 1.661 | *.083* | 2.279 | **.014** |
| Linear | | | | | 0.843 | *.078* | 1.140 | **.013** |
| POMS Mood–Confusion Score | | | | | | | | |
| COMT - Het | | | | | .755 | *.187* | .706 | *.201* |
| COMT - Mut | | | | | 1.336 | **.032** | 1.392 | **.021** |
| Linear | | | | | 0.655 | **.034** | 0.694 | **.021** |
| POMS Mood–Overall Score | | | | | | | | |
| COMT - Het | | | | | 7.019 | *.097* | 6.579 | *.097* |
| COMT - Mut | | | | | 10.344 | **.025** | 12.565 | **.004** |
| Linear | | | | | 5.210 | **.022** | 6.046 | **.005** |

*Note*. Only gender-specific categories with significant associations are shown; beta values represent the strength of the association between 0 and 100%. Boldfaced numerals indicate significant ($p < .05$); italicized numerals indicate not significant ($p > .05$; values are shown for comparison between base and full models).