



## Epidemiology

## Trace elements among a sample of prisoners with mental and personality disorders and aggression: correlation with impulsivity and ADHD indices



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## ARTICLE INFO

## Keywords:

Zinc  
Copper  
Cadmium  
Aggressive behaviour  
Mental disorders  
Personality disorders

## ABSTRACT

**Objectives:** Mental, personality and substance use disorders are over represented among prisoners and aggressive individuals. The psychopathological and biological markers linked to mental functioning remain still unclear. In particular, the role of trace elements in mental illness is still matter of debate. Here, we investigated whether trace elements are correlated to specific psychopathological phenotype groups.

**Methods:** Axis I and II disorders, aggression, impulsivity, adult attention deficit/hyperactivity disorders (ADHD) indices and serum levels of zinc, copper and cadmium were evaluated in 160 male prisoners.

**Results:** Using latent class analysis we could subdivide prisoners into three distinct psychopathological classes: Class 1 characterized by low prevalence of aggression, personality disorders and substance abuse/dependence (alcohol, cannabis, cocaine); Class 2 represented by low prevalence of aggression and high prevalence of personality disorders and substance abuse/dependence; Class 3 defined by high prevalence of aggression, personality disorders and substance abuse/dependence. Serum levels of zinc were higher in Class 2 and 3 compared to Class 1. Moreover, Class 3 was associated with higher scores of impulsivity and ADHD indices.

**Conclusion:** Our results suggest that impulsivity but also adult ADHD indices are related to aggressive behaviour, and higher zinc levels are linked to personality disorders and addictions, but not to aggression.

## 1. Introduction

There is a significant high rate of mental, personality and substance use disorders among offenders and individuals who display aggressive behavior [1–6]. To date, the complex neurobiological mechanisms underlying mental and personality disorders, aggressive behavior, attention-deficit status as well as their link has not yet been completely elucidated through basic and clinical research. Neurotransmitter system impairments such as monoamines, GABA and glutamate, dysregulation of several receptor subunits, intracellular cascades, and/or other neuronal elements, neurosteroids, and nitric oxide have been shown to be implicated [7–9]. Several studies found that imbalances in the optimum levels of trace elements such as zinc, copper and cadmium are associated with many neurobehavioral consequences including aggression

[10–14], intellectual and learning disabilities [15,16], ADHD in children [16–18], Parkinson [19], Alzheimer [20] and depression [21]. However, these studies sometimes produced contrasting results and no indication on whether the observed differences represented a direct or causal relationship between trace elements status and psychiatric symptoms. Trace elements are key modulators of several biological processes and consequently alterations in their intake/body levels lead to pathological states [22–27]. In particular, copper is an important component of several metalloenzymes, including tyrosine hydroxylase and dopamine hydroxylase involved in the synthesis of dopamine and norepinephrine, respectively [28]. Zinc plays an important role in many biological processes such as the activity of more than 300 enzymes, the structure of several proteins, and the control of genetic expression [29]. In addition, it modulates the activity of several voltage-gated ion

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channels and transmitter receptors as well as the uptake of several neurotransmitters such as serotonin, dopamine, glutamate and histamine [30]. Cadmium is not regarded as essential to human life but instead is considered a toxic metal producing adverse health effects on human beings such as renal dysfunction, bone demineralization and cancer [31].

Between January 2007 and November 2009, we examined a sample of 160 male prisoners from a federal penitentiary in Montreal in which we evaluated Axis I and Axis II disorders, levels of impulsivity and aggression toward others and themselves, and attention-deficit/hyperactivity disorder (ADHD) indices. A blood sample was also withdrawn for the analysis of some trace elements. Specifically, we aimed to investigate whether serum concentration of zinc, copper and/or cadmium might be associated to specific psychopathology phenotypes. This hypothesis derived by the fact that, as above indicated, these trace elements are modulating the activity of several neurotransmitter systems such as serotonin, dopamine, and glutamate that are important modulators of mood and behavior [8,32,33].

## 2. Material and methods

### 2.1. Participants

Between January 2007 and November 2009, 321 male prisoners from a federal penitentiary in Montreal were invited to participate in our study. 246 accepted the invitation and among them, 186 agreed to undergo both a psychiatric assessment and a blood withdrawal. In 26 prisoners, the psychiatric assessment and/or the analysis of both three trace elements were not completed. Consequently, 160 prisoners were used in this study. All the participants were exposed to a homogenous diet, with daily limited choice among few different dishes per meal. Venous blood samples for the assay of trace elements were withdrawn between 8:00 and 10:00 a.m. after an overnight fasting, allowed to clot at room temperature and centrifuged at 3000g for 10 min. The obtained serum was then stored at  $-80^{\circ}\text{C}$ . All participants were informed about the risks and benefits of participation, and all provided written consent. The study was approved by the Ethical Review Boards of the Institut Philippe-Pinel de Montréal, McGill University and The Université du Québec à Trois-Rivières and has been conducted according to the principles expressed in the Declaration of Helsinki.

### 2.2. Psychiatric assessment

#### 2.2.1. AXIS I disorders

The presence of DSM-IV-TR AXIS I disorders was evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [34] administered by two professional raters who received a common training and showed very good inter-rater agreement (K values ranged from 0.918 to 1.000). Disorders assessed included life-time presence of mood disorders (major depressive disorder, depressive disorder not otherwise specified, dysthymia, bipolar disorder I or II, mood disorders due to drugs of abuse), anxiety disorders (panic disorder, generalized anxiety disorder, agoraphobia without panic disorder, specific phobia, social phobia, posttraumatic stress disorder, obsessive-compulsive disorder), psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychotic disorders due to drugs of abuse), eating disorders (anorexia nervosa, bulimia nervosa, binge-eating disorder), and pathological gambling. Moreover, substance abuse/dependence to alcohol, cannabis, stimulants, opioids, cocaine, and hallucinogens was assessed.

#### 2.2.2. AXIS II disorders

Presence or absence of Cluster B personality disorders (antisocial, borderline, histrionic and narcissistic) were evaluated using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) [35]. Inter-rater agreement for Axis II Disorders was also very high (K

values ranged from 0.868 to 0.932).

#### 2.2.3. Aggression against others

Violence and aggression were evaluated using the MacArthur Community Violence Instrument (MacVI) [36]. This self-reported instrument reports on lifetime prevalence of aggressive behavior at two severity levels. Severe aggressive behaviour corresponds to any assault using a weapon or resulting in injury, any threat with a lethal weapon use, or any sexual assault. Minor or general aggressive behaviour corresponds to simple assault without injury or weapon use [37].

#### 2.2.4. Self-harm

The rate and severity of self-injurious behaviors were estimated using the Lethality of Suicide Attempt Rating Scale (LSAR) [38]. It comprises a scale ranging from 0 to 10 at equal intervals to measure the severity (or lethal) events beyond the stated intention by the respondent. The LSAR scoring is based on the actual severity of the method used as well as the circumstances surrounding the event. Lifetime prevalence of suicide attempts was assessed with this scale.

#### 2.2.5. Impulsivity

The Barratt Impulsiveness Scale (BIS) was used to measure impulsivity. It is the most widely used self-report measure of impulsive personality traits which, in its latest version (BIS-11) [39], measures three *a priori* defined components of impulsiveness: cognitive (problems related to concentrating/paying attention), motor (fast reactions and restlessness) and non-planning impulsiveness (orientation towards the present rather than to the future) [40].

#### 2.2.6. Attention-deficit status

Conners' Adult ADHD Rating Scales (CAARS) were used to assess ADHD-related symptoms and behaviors [41]. This instrument quantifies ADHD indices across clinically significant domains and explores the manifestations of those symptoms. The CAARS version used in this study is the CAARS Self-Report: Short Version [42] that is comprised of 26 items and allowed us to assess the following subscales: A) Inattention/Memory Problems Subscale, B) Hyperactivity/Restlessness Subscale, C) Impulsivity/Emotional Lability Subscale, D) Problems with Self-Concept Subscale, E) ADHD Index.

### 2.3. Serum sample analysis

#### 2.3.1. Copper and zinc determination

Serum copper and zinc levels were determined using atomic absorption spectrometer (Spectr AA 55B, Varian, Agilent Technologies, Palo Alto, CA, USA).

Serum samples were diluted (1:4 and 1:5 for Cu and Zn, respectively) with ultradeionized water. Cu and Zn concentrations were established on the basis of three measurements for each sample.

#### 2.3.2. Cadmium determination

A graphite furnace atomic adsorption spectrometer (GFAAS) was used to quantify Cd in the serum. Samples were diluted (1:4) with ultradeionized water and a  $\text{PdNO}_3$  solution was used as modifier. Cd was determined with the standard addition method; all determinations were run in triplicate, and individual values were averaged.

The Autosampler system was used in the automix mode and with sample intake to the graphite tube of  $1\ \mu\text{l/s}$ . The total volume inserted in the tube was  $20\ \mu\text{l}$  ( $5\ \mu\text{l}$  of matrix modifier,  $10\ \mu\text{l}$  of sample, and  $5\ \mu\text{l}$  of standard solution). Samples analysis was carried out using a Varian AA240Z GFAAS equipment (Agilent Technologies, Palo Alto, CA, USA).

The data obtained were processed with nonlinear fitting software Sigmaplot 9.0 (Systat Software Inc., Chicago, IL, USA).

### 2.4. Statistics

Statistical analyses were performed using SAS version 9.3 (Cary, NC: SAS Institute Inc.). The relationship between continuous variables was examined by Spearman’s correlations. Differences in the levels of trace elements, impulsivity or attention-deficit status between latent classes were assessed using one-way ANOVA followed by the post hoc multiple comparisons using a Tukey-Kramer adjustment. When Spearman’s correlation coefficient analysis revealed a significant correlation between variables, ANCOVA followed by the post hoc multiple comparisons using a Tukey-Kramer adjustment were performed to qualify the relationships. Differences were considered significant at a  $p < 0.05$  level.

### 2.5. Latent class analysis

Given the complexity of our study population in terms of psychiatric/behavioral symptomatology and the high number of variables under examination that would require a higher number of subjects to perform multiple regression and/or logistic regression analyses, we first identified subgroups of prisoners with similar psychological/psychiatric features using a latent class analysis (LCA) [43]. Then, we examined whether the subgroups of prisoners presented differences in impulsivity, ADHD traits, and trace element serum levels and their possible correlation/association.

LCA is a statistical method used to determine homogeneous, mutually exclusive groups (called “classes”) that exist within a heterogeneous population. The PROC LCA software was used to estimate model parameters and the number of latent classes that best describe our population [43]. To select the appropriate number of classes, the goodness of fit statistics such as the likelihood-ratio  $G^2$  static, the Akaike Information Criterion (AIC), and the Bayesian Information Criterion (BIC), model parsimony and interpretation of class meaning were used [43]. The model expressing the lower likelihood-ratio  $G^2$ , AIC and BIC values is preferable [43]. The variables included in the model were: age and lifetime prevalence of mood and anxiety disorders, psychosis, substance abuse/dependence to alcohol, cannabis, stimulants, opioids, cocaine, and hallucinogens, severe and general aggressive behaviors, antisocial behavior, Axis II Cluster B disorder, and suicide attempts. Disorders or expressed behaviors with rates between 0 and 10% were not included in the LCA (psychosis, eating disorders, pathological gambling, sedative abuse/dependence, and borderline, histrionic and narcissistic personality disorders). The variable age was dichotomized based on the median value of the population (40 years old) and then coded 1 for age  $\leq 40$  or 2 for age  $> 40$  years. For the behavioral variables, 1 was used for absence and 2 for presence of the behavior. PROC LCA method allows covariates to be added to the basic model via multinomial logistic regression. The three subtraits of impulsivity according to BIS, the five subscales of CAARS, and zinc, copper and cadmium plasmatic levels were therefore included in the model as covariates since previous research has shown they are related to the main variables [8,32]. In doing so, we will also determine whether the covariates may be a predictor of class membership.

In order to examine possible differences in the levels of impulsivity, attention-deficit indices or trace elements between latent classes, each prisoner was assigned to a latent class based on the maximum-probability rule, which in turn gives the highest posterior probability of class membership for each individual.

## 3. Results

### 3.1. Demographics

Table 1 reports the demographic characteristics of the 160 participating prisoners. Half of the participants met criteria for lifetime presence of mood disorders as well as alcohol or cannabis abuse/

**Table 1**  
Clinical characteristics (lifetime diagnosis) of the prisoners (n = 160).

|   |                |
|---|----------------|
| Age, mean (SD)  | 40.5 ( ± 13.3) |
| <b>AXIS I disorders, No. (%)</b>  |                |
| Mood disorders  | 94 (58.8)      |
| Anxiety disorders   | 29 (18.1)      |
| Psychosis   | 8 (5.0)        |
| Pathological gambling   | 12 (7.5)       |
| Eating disorders  | 1 (0.6)        |
| Alcohol abuse/dependence  | 106 (66.3)     |
| Cannabis abuse/dependence   | 88 (55.0)      |
| Sedative abuse/dependence   | 12 (7.5)       |
| Stimulants abuse/dependence   | 45 (28.1)      |
| Opioids abuse/dependence  | 24 (15.0)      |
| Cocaine abuse/dependence  | 75 (46.9)      |
| Hallucinogens abuse/dependence  | 43 (26.9)      |
| <b>AXIS II disorders, No. (%)</b>   |                |
| Borderline personality disorder   | 3 (1.9)        |
| Histrionic personality disorder   | 0 (0)          |
| Narcissistic personality disorder   | 5 (3.1)        |
| Antisocial behavior   | 111 (69.4)     |
| Cluster B personality disorder  | 120 (74.4)     |
| <b>Hetero-aggression: MacArthur Community Violence Instrument, No. (%)</b>              |                |
| Severe aggressive behavior  | 80 (50.0)      |
| General aggressive behavior   | 108 (67.5)     |
| <b>Self-aggressive behavior: the Lethality of Suicide Attempt Rating Scale, No. (%)</b> |                |
| Suicide attempts  | 45 (28.1)      |

dependence. Slightly less than half of the sample (46.9%) had a diagnosis of lifetime cocaine abuse/dependence. Fully three quarters (74.4%) of prisoners presented a cluster B personality disorders and 69.4% an antisocial personality disorder. The other cluster B personality disorders displayed prevalence not higher than 5%. According to the MacArthur Community Violence Instrument, 50% of the prisoners had a severe aggressive behavior and 67.5% a general aggressive behavior lifetime. Nearly one third (28.1%) of participants reported at least one suicide attempt during their lifetime.

### 3.2. Latent class analysis (LCA)

In order to define homogeneous classes of prisoners based on their clinical characteristics, a LCA analysis was performed. (Table 1). According to the likelihood-ratio  $G^2$  static, the AIC, BIC, and entropy, a three-class model had the best statistical fit (Table 2) but also was the best model providing a substantive classification of distinct and well characterized psychiatric phenotypes. As shown in Table 3, class 1 accounted for 24%, class 2 for 12% and class 3 for 64% of the prisoners. Class 1 was composed by prisoners exhibiting low prevalence of aggressive behavior, axis II disorders and drugs or alcohol abuse/dependence. In turn, prisoners of class 2 showed low prevalence of aggressive behavior but high prevalence of axis II and drug and alcohol abuse/dependence. Finally, class 3 prisoners displayed high prevalence of aggressive behavior, axis II as well as drugs and alcohol abuse/dependence (Table 3).

Given that impulsivity, inattention and hyperactive-impulsive behaviors and trace elements have been shown to relate to psychiatric disorders, they were introduced into the model as covariates. Multinomial logistic regression analyses revealed that BIS-11 motor and

**Table 2**  
Fit indices for the latent class analysis.

| Model     | Log-likelihood | AIC    | BIC     | Entropy |
|-----------|----------------|--------|---------|---------|
| 2 classes | -1213.22       | 935.07 | 1024.25 | 0.99    |
| 3 classes | -1141.78       | 888.92 | 1024.23 | 0.87    |
| 4 classes | -1175.15       | 852.19 | 1033.62 | 0.93    |
| 5 classes | -1119.22       | 837.08 | 1064.64 | 0.91    |

**Table 3**  
Conditional probabilities from the three-class model.

| Item                        | Class 1 (n = 39, 24%)<br>Low aggressive behavior<br>Low Axis II<br>Low drugs abuse/dependence | Class 2 (n = 20, 12%)<br>Low aggressive behavior<br>High Axis II<br>High drugs abuse/dependence | Class 3 (n = 101, 64%)<br>High aggressive behavior<br>High axis II<br>High drugs abuse/dependence |
|-----------------------------|---|---|---|
| Age > 40 yr                 | <b>0.64</b>   | <b>0.69</b>   | 0.36  |
| Mood disorders              | 0.51  | 0.35  | <b>0.66</b>   |
| Anxiety disorders           | 0.20  | 0.05  | 0.20  |
| Alcohol dependence          | 0.34  | <b>0.66</b>   | <b>0.79</b>   |
| Cannabis dependence         | 0.14  | <b>0.79</b>   | <b>0.66</b>   |
| Stimulants dependence       | 0.06  | 0.00  | 0.42  |
| Opioids dependence          | 0.03  | 0.30  | 0.17  |
| Cocaine dependence          | 0.06  | <b>0.75</b>   | <b>0.57</b>   |
| Hallucinogens dependence    | 0.03  | 0.16  | 0.38  |
| Severe aggressive behavior  | 0.13  | 0.06  | <b>0.73</b>   |
| General aggressive behavior | 0.39  | 0.20  | <b>0.88</b>   |
| Antisocial behavior         | 0.03  | <b>0.69</b>   | <b>0.95</b>   |
| Axis II disorders           | 0.11  | <b>0.69</b>   | <b>0.96</b>   |
| Suicide lifetime prevalence | 0.11  | 0.30  | 0.34  |

Boldface indicates frequency greater than 60%.

**Table 4**  
Predictive group membership: multivariate logistic regression analysis results.

| Covariate                                 | 2 Log likelihood | df | Sig.          |
|---|------------------|----|---------------|
| BIS-11 Motor impulsiveness                | 6.06             | 2  | <b>0.0483</b> |
| BIS-11 Cognitive impulsiveness            | 3.40             | 2  | 0.1826        |
| BIS-11 Non planning impulsiveness         | 9.16             | 2  | <b>0.0102</b> |
| CAARS-A<br>Inattention/Memory Problems    | 0.68             | 2  | 0.7104        |
| CAARS-B<br>Hyperactivity/Restlessness     | 13.60            | 2  | <b>0.0011</b> |
| CAARS-C<br>Impulsivity/Emotional Lability | 16.38            | 2  | <b>0.0003</b> |
| CAARDS-D<br>Problems with Self-Concept    | 1.38             | 2  | 0.5009        |
| CAARS-E<br>ADHD Index                     | 9.85             | 2  | <b>0.0073</b> |
| Zinc serum levels                         | 12.75            | 2  | <b>0.0017</b> |
| Copper serum levels                       | 0.04             | 2  | 0.9810        |
| Cadmium serum levels                      | 3.34             | 2  | 0.1887        |

Boldface indicates covariates that are significant class membership predictors.

non planning impulsiveness, CAARS-B Hyperactivity/Restlessness, CAARS-C Impulsivity/Emotional Lability and CAARS-E ADHD Index and Zinc serum levels were the covariates predictive of class membership (Table 4).

### 3.3. BIS-11, CAARS scores and Trace elements serum levels

The next step was to determine if the three classes differed in term of BIS-11, CAARS scores and trace elements serum levels. Each prisoner was assigned to one of the three latent classes based on the highest posterior probability of class membership. A Spearman correlation analysis was also performed to examine whether in the whole population there was a correlation between trace elements serum levels, age, BIS-11 and CAARS scores that consequently needed to be considered. Age was weakly and negatively correlated to zinc serum levels ( $r = -0.237$ ,  $p = 0.003$ ) and BIS scores while positively correlated to

copper serum levels ( $r = 0.219$ ,  $p = 0.005$ ). Interestingly, cadmium serum levels were weakly and positively correlated with BIS-11 non-planning impulsiveness ( $r = 0.157$ ,  $p = 0.048$ ), CAARS-A Inattention/Memory Problems ( $r = 0.227$ ,  $p = 0.004$ ) and CAARS-E ADHD Index ( $r = 0.202$ ,  $p = 0.010$ ).

Fig. 1 displays class differences for BIS-11 (A) and CAARS (B) scores. Controlling for the factor age, prisoners belonging to class 3 showed high levels of impulsivity. Indeed, BIS-total score (ANCOVA:  $F_{2,156} = 10.16$ ,  $p < 0.001$ ) was significantly higher in class 3 than in class 1 ( $p = 0.01$ ) and 2 ( $p < 0.001$ ). No difference was found between class 1 and 2 (Fig. 1A) meaning that impulsivity is highly linked to aggressive behavior. Similar findings were obtained when analyzing the three a priori defined BIS-11 subtraits of impulsiveness (Fig. 1A). The levels of motor impulsiveness ( $F_{2,156} = 3.51$ ,  $p = 0.03$ ) were higher for prisoners of latent class 3 than those of latent class 2 ( $p = 0.02$ ), the levels of cognitive impulsiveness ( $F_{2,156} = 10.15$ ,  $p < 0.001$ ) were higher in class 3 compared to class 1 ( $p < 0.001$ ) and 2 ( $p = 0.002$ ), and the levels of non-planning impulsiveness ( $F_{2,155} = 4.53$ ,  $p = 0.01$ ) were higher in class 3 than in class 1 ( $p = 0.02$ ).

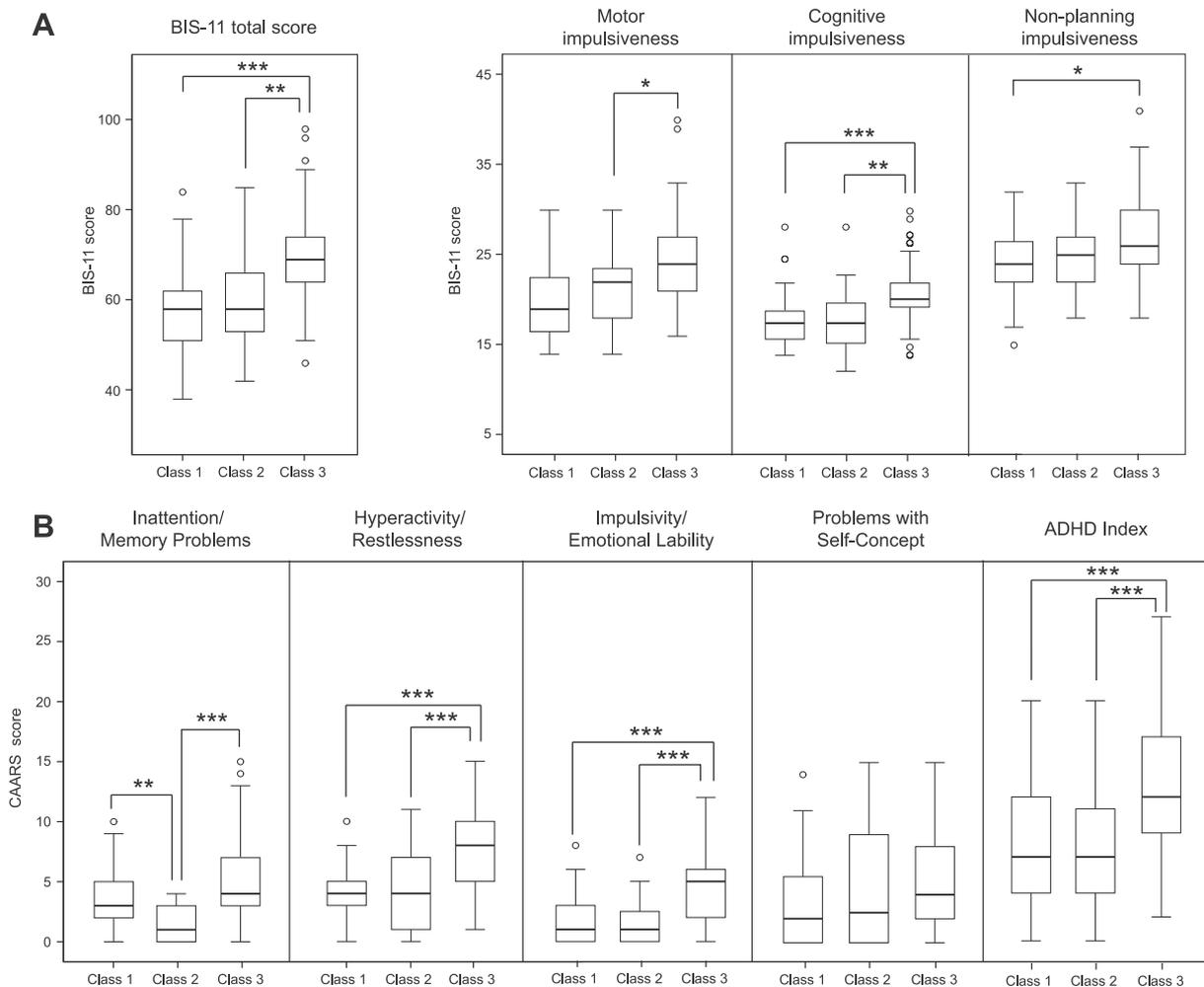
Notably, significant changes on CAARS subscales scores were also detected between the three classes (Fig. 1B). CAARS-A Inattention/Memory Problems scores ( $F_{2,156} = 13.65$ ,  $p < 0.001$ ) were lower in class 2 than in class 1 ( $p = 0.009$ ) and 3 ( $p < 0.001$ ). CAARS-B Hyperactivity/Restlessness ( $F_{2,155} = 10.47$ ,  $p < 0.001$ ) and CAARS-C Impulsivity/Emotional Lability ( $F_{2,156} = 19.05$ ,  $p < 0.001$ ) scores were higher in class 3 compared to class 1 and 2 ( $p < 0.001$ ). No difference between classes was found for CAARS-D Problems with Self-Concept, whereas CAARS-E ADHD Index ( $F_{2,156} = 13.60$ ,  $p < 0.001$ ) was significantly higher in prisoners belonging to class 3 than to class 1 ( $p < 0.001$ ) and 2 ( $p < 0.001$ ).

Controlling for age, differences in zinc serum levels between classes were computed using ANCOVA ( $F_{2,156} = 4.11$ ,  $P = 0.018$ ). As showed in Fig. 2, prisoners of class 1 showed lower zinc serum levels than those of class 2 ( $p = 0.01$ ) and 3 ( $p = 0.04$ ). No differences between classes were instead found for copper and cadmium serum levels (Fig. 2) as well as for the ratio copper/zinc, copper/cadmium and cadmium/zinc (data not shown).

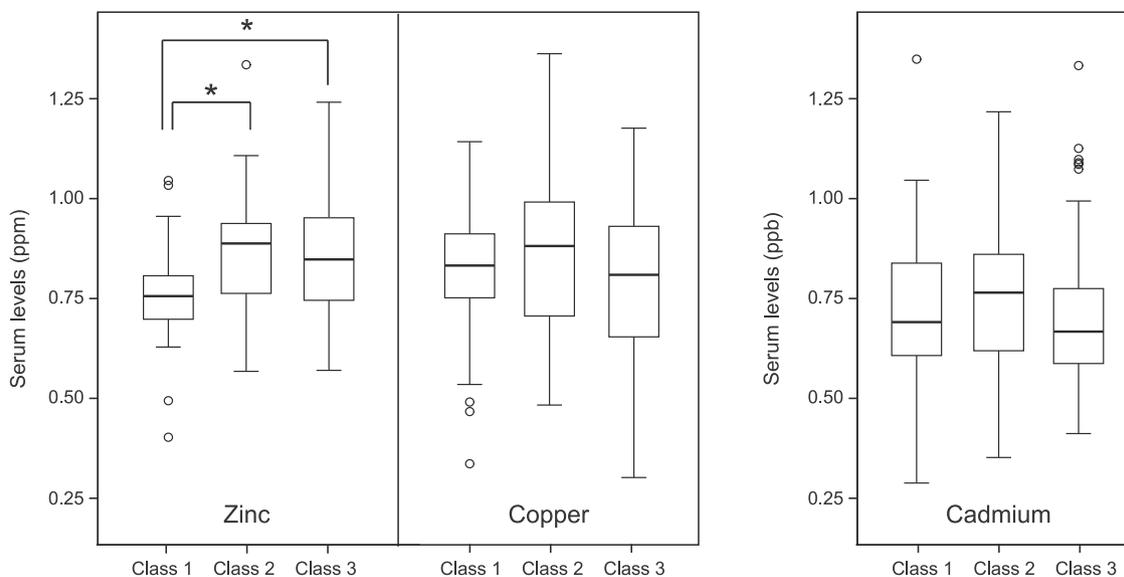
## 4. Discussion

In this study, we aimed at investigating whether a possible relationship between zinc, copper or cadmium serum levels and psychopathology was present in a prisoner population. We found that zinc was linked to the presence of personality disorders and addiction.

Since prisoners showed several co-morbidities, the sample could not be classified and examined according to single diagnostic categories. Therefore, we used LCA analysis to identify subgroups of prisoners with comorbidities. A three-class model led us to distinguish prisoners based on low or high prevalence of aggressive behavior, axis II cluster B disorders and alcohol and drugs abuse/dependence. Then, we have examined whether these psychopathological traits were associated to behavioural variables and trace elements serum levels. Our results indicate that Class 1 is composed by prisoners showing low prevalence of aggression, personality disorders and substance abuse/dependence to alcohol, cannabis, and cocaine, Class 2 by prisoners with low prevalence of aggression and high prevalence of personality disorders and substance abuse/dependence, and Class 3 by prisoners with high prevalence of aggression, personality disorders and substance abuse/dependence. We found that Class 3 is associated with higher impulsivity levels (BIS-11 scores) and CAARS scores, in particular those related to hyperactivity/restlessness, impulsivity/emotional lability and ADHD symptoms. Being Class 3 differentiated from Class 1 and 2 by the high prevalence of aggressive behaviour, we confirmed the already known close relationship between impulsivity and aggressive/violent behaviour [8,32,44]. In keeping with the epidemiology of mental and personality disorders in correctional settings literature [3,5,45–47], 75% of



**Fig. 1.** BIS-11 (A) and CAARS (B) scores in the three classes of prisoners. The boxplot represents observations from the 25th to the 75th percentile; the horizontal line within the box represents the median value. Lines outside the box represent the 10th and 90th percentiles. The outliers are displayed as individual points. \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , ANOVA or ANCOVA followed by Tukey–Kramer adjustment for multiple comparisons.



**Fig. 2.** Serum levels of zinc, copper and cadmium in the three classes of prisoners. The boxplot represents observations from the 25th to the 75th percentile; the horizontal line within the box represents the median value. Lines outside the box represent the 10th and 90th percentiles. The outliers are displayed as individual points. \*  $P < 0.05$ , ANCOVA followed by Tukey–Kramer adjustment for multiple comparisons.

prisoners included in our sample has a diagnosis of antisocial behavior, 66–67% of alcohol abuse/dependence and general aggressive behavior, and 58% of mood disorders.

As previously reported [48,49], the levels of impulsivity, measured by the total BIS-11 score, are inversely correlated with age. As reviewed by Moeller et al. [50], several studies have reported high levels of impulsivity in substance-dependent populations, but in our classes, the differences in impulsivity seem more linked to aggressive behavior than to substance abuse/dependence. Indeed, prisoners of class 2 (low prevalence of aggression) and 3 (high prevalence of aggression) share similar prevalence for alcohol, cocaine, cannabis and other substances abuse/dependence but different impulsivity levels.

It was quite unexpected to find that prisoners of Class 2 had lower CAARS scores than those of Class 3. Since the feature distinguishing Class 2 from Class 3 is aggressive behaviour, our results suggest -for the first time - that the different symptom dimensions of ADHD into adulthood are more strongly associated to aggressive behavior than other symptom dimensions such as substance abuse or antisocial personality traits. Consequently, adult ADHD symptom dimensions must be taken into consideration as a potential risk factor for aggressive behaviour.

Our results also indicate that serum levels of Zn were lower in Class 1 than in Class 2 and 3 prisoners. We can therefore speculate that the high levels of serum zinc in Class 2 and 3 are very likely a contributing factor or a consequence of the axis II cluster B disorders and/or drug and alcohol abuse/dependence. Cook et al. [51] found no difference in the plasmatic levels of zinc between alcoholics and controls, but out of 13 alcoholic males, three had abnormally high zinc levels. No correlation between zinc levels and alcohol intake was also reported by Karkkainen et al. [52]. However, as reviewed by McClain and Su, increased urinary zinc losses and depressed serum zinc levels are common in chronic alcoholics with or without liver disease [53]. Interestingly, in contrast with previous literature [54], González-Estecha et al. [55] found that bipolar patients display higher serum zinc levels with respect to controls, but they then observed that zinc levels were higher among those patients who declared cannabis and cocaine consumption. In healthy men who were tobacco consumers, higher zinc serum levels were found [56]. Similarly, high zinc levels were reported in confiscated heroin and cocaine samples [57,58]. In line with these findings, prisoners in class 2 and 3 presented high prevalence of cannabis and cocaine abuse/dependence, but we did not collect information related to tobacco consuming.

Cadmium is a toxic heavy metal of which environmental exposure in children as well as in adults has been associated to neurocognitive impairments that leads to a decreased performance in tasks requiring attention and perception [59,60]. Even if we did not assess possible sources of external cadmium intake, consistent with previous findings, we found that cadmium serum levels were positively correlated with measures of mental and cognitive functioning such as BIS-11 non-planning impulsiveness which assesses careful thinking and planning and enjoyment of challenging mental tasks [39], CAARS-A inattention/memory problems which are related to trouble concentrating and difficulty planning or completing tasks, and CAARS-E ADHD Index which identifies clinically significant levels of ADHD symptoms and thus individuals 'at risk' for ADHD [41]. Mental and personality disorders, aggressive behaviour and cognitive deficits are highly associated, but in most of the studies above presented and investigating a possible relationship between them and trace elements, only some of these psychopathological/behavioural variables were considered, and information on whether or not the others were excluded/not assessed was often missing. This fact may explain why several discrepancies are reported in literature.

One limitation of this study is that, given the large number of variables included and the relatively small sample size, we could not use a statistical approach employing a multivariate/logistic regression analysis. This approach could help establishing in a more direct way a

possible relationship between behavioural/psychiatric variables and trace elements.

A second limitation of the study is that we did not assess the prevalence of smoking cigarettes or nicotine dependence, a factor that may affect circulating trace elements. However, before 2014 when the participants were enrolled in this study, the percentage of prisoners smoking cigarettes in Canadian prisons has been indicated to be very high (> 80%) [61]. Consequently, given this high prevalence, this factor is likely to be equal among the three latent classes and thus not contributing to trace elements differences we observed.

Additional limitations of this study arise with regard to the lack of mechanism to understand the relationship between trace elements and the analyzed variables, the potential for selection bias among the participants, and a possible limited generalizability of the results to any other setting.

In conclusion, LCA yielded a three-subgroup model of the prisoners based on psychiatric disorders. Importantly, impulsivity, attention-deficit/hyperactivity and related behaviours and serum zinc levels are shown to be good predictors of class membership. In particular, impulsivity levels and attention-deficit/hyperactivity indices are predictors of prisoners with more prevalent aggressive behavior while serum zinc levels of prisoners who suffered from personality disorders and substance abuse/dependence. Further studies are needed to evaluate the link between aggression and adult ADHD indices and whether the increase in serum zinc levels may somehow influence personality disorders and cannabis/cocaine/alcohol abuse/dependence or is a consequence of these disorders.

### Competing interests

All authors declare that they have no competing interests.

### Acknowledgments

This study was supported by the Canadian Institutes of Health Research (CIHR). We thank Dr. Xianming Tan (Biostatistics Core Facility, Research Institute of the McGill University Health Centre) for statistical assistance. Authors also thank Dr Anne Crocker and Dr Gustavo Turecki for their participation in the project.

### References

- [1] L. Arseneault, T.E. Moffitt, A. Caspi, P.J. Taylor, P.A. Silva, Mental disorders and violence in a total birth cohort: results from the Dunedin Study, *Arch. Gen. Psychiatry* 57 (10) (2000) 979–986.
- [2] E.B. Elbogen, S.C. Johnson, The intricate link between violence and mental disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions, *Arch. Gen. Psychiatry* 66 (2) (2009) 152–161.
- [3] S. Fazel, J. Danesh, Serious mental disorder in 23000 prisoners: a systematic review of 62 surveys, *Lancet* 359 (9306) (2002) 545–550.
- [4] S. Fazel, M. Grann, Psychiatric morbidity among homicide offenders: a Swedish population study, *Am. J. Psychiatry* 161 (11) (2004) 2129–2131.
- [5] S. Fazel, K. Seewald, Severe mental illness in 33,588 prisoners worldwide: systematic review and meta-regression analysis, *Br. J. Psychiatry* 200 (5) (2012) 364–373.
- [6] S. Hodgins, M. Lalpalmé, J. Toupin, Criminal activities and substance use of patients with major affective disorders and schizophrenia: a 2-year follow-up, *J. Affect. Disord.* 55 (2–3) (1999) 187–202.
- [7] D.S. Charney, E.J. Nestler, P. Sklar, J.D. Buxbaum, *Neurobiology of Mental Illness*, Oxford University Press, 2013.
- [8] S. Comai, M. Tau, G. Gobbi, The psychopharmacology of aggressive behavior: a translational approach: part 1: neurobiology, *J. Clin. Psychopharmacol.* 32 (1) (2012) 83–94.
- [9] S.V. Faraone, J. Biederman, Neurobiology of attention-deficit hyperactivity disorder, *Biol. Psychiatry* 44 (10) (1998) 951–958.
- [10] P.F. Cromwell, B.R. Abadie, J.T. Stephens, M. Kyler, Hair mineral analysis: biochemical imbalances and violent criminal behavior, *Psychol. Rep.* 64 (1) (1989) 259–266.
- [11] L.A. Gottschalk, T. Rebello, M.S. Buchsbaum, H.G. Tucker, E.L. Hodges, Abnormalities in hair trace elements as indicators of aberrant behavior, *Compr. Psychiatry* 32 (3) (1991) 229–237.
- [12] M. Marlowe, H.G. Schneider, L.B. Bliss, Hair mineral analysis in emotionally disturbed and violence prone children, *Int. J. Biosoc. Med. Res.* 13 (2) (1991)

- 169–179.
- [13] R.O. Pihl, F. Ervin, Lead and cadmium levels in violent criminals, *Psychol. Rep.* 66 (3 Pt 1) (1990) 839–844.
- [14] W.J. Walsh, H.R. Isaacson, F. Rehman, A. Hall, Elevated blood copper/zinc ratios in assaultive young males, *Physiol. Behav.* 62 (2) (1997) 327–329.
- [15] M. Marlowe, J. Errera, J. Jacobs, Increased lead and cadmium burdens among mentally retarded children and children with borderline intelligence, *Am. J. Ment. Defic.* 87 (5) (1983) 477–483.
- [16] T. Ciesielski, J. Weuve, D.C. Bellinger, J. Schwartz, B. Lanphear, R.O. Wright, Cadmium exposure and neurodevelopmental outcomes in U.S. Children, *Environ. Health Perspect.* 120 (5) (2012) 758–763.
- [17] M.M. Mahmoud, A.A. El-Mazary, R.M. Maher, M.M. Saber, Zinc, ferritin, magnesium and copper in a group of Egyptian children with attention deficit hyperactivity disorder, *Ital. J. Pediatr.* 37 (2011) 60.
- [18] L.E. Arnold, R.A. DiSilvestro, Zinc in attention-deficit/hyperactivity disorder, *J. Child Adolesc. Psychopharmacol.* 15 (4) (2005) 619–627.
- [19] J.M. Gorell, C.C. Johnson, B.A. Rybicki, E.L. Peterson, G.X. Kortsha, G.G. Brown, R.J. Richardson, Occupational exposures to metals as risk factors for Parkinson's disease, *Neurology* 48 (3) (1997) 650–658.
- [20] T.J. Craddock, J.A. Tuszynski, D. Chopra, N. Casey, L.E. Goldstein, S.R. Hameroff, R.E. Tanzi, The zinc dyshomeostasis hypothesis of Alzheimer's disease, *PLoS One* 7 (3) (2012) e33552.
- [21] M. Maes, P.C. D'Haese, S. Scharpe, P. D'Hondt, P. Cosyns, M.E. De Broe, Hypozincemia in depression, *J. Affect. Disord.* 31 (2) (1994) 135–140.
- [22] C. Meplan, Trace elements and ageing, a genomic perspective using selenium as an example, *J. Trace Elem. Med. Biol.* 25 (Suppl. 1) (2011) S11–S16.
- [23] D. Wasko-Czopnik, L. Paradowski, The influence of deficiencies of essential trace elements and vitamins on the course of Crohn's disease, *Adv. Clin. Exp. Med.* 21 (1) (2012) 5–11.
- [24] H. Tapiero, K.D. Tew, Trace elements in human physiology and pathology: zinc and metallothioneins, *Biomed. Pharmacother.* 57 (9) (2003) 399–411.
- [25] R. Squitti, Metals in Alzheimer's disease: a systemic perspective, *Front. Biosci.* 17 (2012) 451–472.
- [26] D.B. Louria, M.M. Joselow, A.A. Browder, The human toxicity of certain trace elements, *Ann. Intern. Med.* 76 (2) (1972) 307–319.
- [27] S.A. Navarro Silvera, T.E. Rohan, Trace elements and cancer risk: a review of the epidemiologic evidence, *Cancer Causes Control* 18 (1) (2007) 7–27.
- [28] M. Arredondo, M.T. Nunez, Iron and copper metabolism, *Mol. Aspects Med.* 26 (4–5) (2005) 313–327.
- [29] S. Frassinetti, G. Bronzetti, L. Caltavuturo, M. Cini, C.D. Croce, The role of zinc in life: a review, *J. Environ. Pathol. Toxicol. Oncol.* 25 (3) (2006) 597–610.
- [30] J. Garcia-Colunga, D. Reyes-Haro, I.U. Godoy-Garcia, R. Miledi, Zinc modulation of serotonin uptake in the adult rat corpus callosum, *J. Neurosci. Res.* 80 (1) (2005) 145–149.
- [31] A. Bernard, Cadmium & its adverse effects on human health, *Indian J. Med. Res.* 128 (4) (2008) 557–564.
- [32] S. Comai, A. Bertazzo, J. Vachon, M. Daigle, J. Toupin, G. Côté, G. Turecki, G. Gobbi, Tryptophan via serotonin/kynurenine pathways abnormalities in a large cohort of aggressive inmates: markers for aggression, *Prog. Neuropsychopharmacol. Biol. Psychiatry* 70 (2016) 8–16.
- [33] M. Manchia, B. Carpiniello, F. Valtorta, S. Comai, Serotonin Dysfunction, Aggressive behavior, and mental illness: exploring the link using a dimensional approach, *ACS Chem. Neurosci.* 8 (5) (2017) 961–972.
- [34] M.B. First, M. Gibbon, R. Spitzer, J. Williams, User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version, SCID-I, Version 2, (1996).
- [35] M.B. First, M. Gibbon, User's guide for the structured clinical interview for DSM-IV axis II personality disorders: SCID-II, Amer Psychiatric (1997) Pub Incorporated.
- [36] J. Monahan, H.J. Steadman, E. Silver, P.S. Appelbaum, P.C. Robbins, E.P. Mulvey, L.H. Roth, T. Grisso, S. Banks, Rethinking Risk Assessment: the MacArthur Study of Mental Disorder and Violence, Oxford University Press, USA, 2001.
- [37] H.J. Steadman, E.P. Mulvey, J. Monahan, P.C. Robbins, P.S. Appelbaum, T. Grisso, L.H. Roth, E. Silver, Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods, *Arch. Gen. Psychiatry* 55 (5) (1998) 393–401.
- [38] K. Smith, R.W. Conroy, B.D. Ehler, Lethality of suicide attempt rating scale, *Suicide Life Threat. Behav.* 14 (4) (1984) 215–242.
- [39] J.H. Patton, M.S. Stanford, E.S. Barratt, Factor structure of the Barratt impulsiveness scale, *J. Clin. Psychol.* 51 (6) (1995) 768–774.
- [40] E.S. Barratt, Impulsiveness Subtraits: Arousal and Information Processing, in: J.T. Spence, C.E. Izard (Eds.), *Motivation, Emotion, and Personality*, Elsevier-North Holland, New York, 1985, pp. 137–146.
- [41] C. Conners, D. Erhardt, J. Epstein, J. Parker, G. Sitarenios, E. Sparrow, Self-ratings of ADHD symptoms in adults I: factor structure and normative data, *J. Atten. Disord.* 3 (3) (1999) 141–151.
- [42] K. Conners, *Conners' Adult ADHD Rating Scales (CAARS): for Use in Correctional Settings*, Multi-Health Systems, Toronto, 2004.
- [43] S.T. Lanza, L.M. Collins, D.R. Lemmon, J.L. Schafer, PROC LCA: a SAS procedure for latent class analysis, *Struct. Equ. Model.* 14 (4) (2007) 671–694.
- [44] A.D. Seroczynski, C.S. Bergeman, E.F. Coccaro, Etiology of the impulsivity/aggression relationship: genes or environment? *Psychiatry Res.* 86 (1) (1999) 41–57.
- [45] P.J. Kinsler, A. Saxman, Traumatized offenders: don't look now, but your jail's also your mental health center, *J. Trauma Dissociation* 8 (2) (2007) 81–95.
- [46] J. Brink, Epidemiology of mental illness in a correctional system, *Curr. Opin. Psychiatry* 18 (5) (2005) 536–541.
- [47] A.P. Mundt, R. Alvarado, R. Fritsch, C. Poblete, C. Villagra, S. Kastner, S. Priebe, Prevalence rates of mental disorders in Chilean prisons, *PLoS One* 8 (7) (2013) e69109.
- [48] F. Gerard Moeller, D.M. Dougherty, E.S. Barratt, V. Oderinde, C.W. Mathias, R. Andrew Harper, A.C. Swann, Increased impulsivity in cocaine dependent subjects independent of antisocial personality disorder and aggression, *Drug Alcohol Depend.* 68 (1) (2002) 105–111.
- [49] P. Smith, M. Waterman, N. Ward, Driving aggression in forensic and non-forensic populations: relationships to self-reported levels of aggression, anger and impulsivity, *Br. J. Psychol.* 97 (3) (2006) 387–403.
- [50] F.G. Moeller, E.S. Barratt, D.M. Dougherty, J.M. Schmitz, A.C. Swann, Psychiatric aspects of impulsivity, *Am. J. Psychiatry* 158 (11) (2001) 1783–1793.
- [51] C.C. Cook, R.J. Walden, B.R. Graham, C. Gillham, S. Davies, B.N. Prichard, Trace element and vitamin deficiency in alcoholic and control subjects, *Alcohol Alcohol.* 26 (5–6) (1991) 541–548.
- [52] P. Karkkainen, H. Mussalo-Rauhamaa, K. Poikolainen, J. Lehto, Alcohol intake correlated with serum trace elements, *Alcohol Alcohol.* 23 (4) (1988) 279–282.
- [53] C.J. McClain, L.C. Su, Zinc deficiency in the alcoholic: a review, *Alcohol. Clin. Exp. Res.* 7 (1) (1983) 5–10.
- [54] M.S. Mustak, T.S. Rao, P. Shanmugavelu, N.M. Sundar, R.B. Menon, R.V. Rao, K.S. Rao, Assessment of serum macro and trace element homeostasis and the complexity of inter-element relations in bipolar mood disorders, *Clin. Chim. Acta* 394 (1–2) (2008) 47–53.
- [55] M. Gonzalez-Estecha, E.M. Trasobares, K. Tajima, S. Cano, C. Fernandez, J.L. Lopez, B. Unzeta, M. Arroyo, F. Fuentenebro, Trace elements in bipolar disorder, *J. Trace Elem. Med. Biol.* 25 (Suppl. 1) (2011) S78–83.
- [56] P.A. Lopes, M.C. Santos, L. Vicente, M.O. Rodrigues, M.L. Pavao, J. Neve, A.M. Viegas-Crespo, Trace element status (Se, Cu, Zn) in healthy Portuguese subjects of Lisbon population: a reference study, *Biol. Trace Elem. Res.* 101 (1) (2004) 1–17.
- [57] T. Bora, M. Merdivan, C. Hamamci, Levels of trace and major elements in illicit heroin, *J. Forensic Sci.* 47 (5) (2002) 959–963.
- [58] Z. Zhang, J. Yang, H. Ouyang, Z. Li, Z. Chai, J. Zhu, J. Zhao, Z. Yu, J. Wang, Study of trace impurities in heroin by neutron activation analysis, *J. Radioanal. Nucl. Chem.* 262 (1) (2004) 295–297.
- [59] R.W. Thatcher, M.L. Lester, R. McAlaster, R. Horst, Effects of low levels of cadmium and lead on cognitive functioning in children, *Arch. Environ. Health* 37 (3) (1982) 159–166.
- [60] T. Ciesielski, D.C. Bellinger, J. Schwartz, R. Hauser, R.O. Wright, Associations between cadmium exposure and neurocognitive test scores in a cross-sectional study of US adults, *Environ. Health* 12 (2013) 13.
- [61] R. Collier, Prison smoking bans: clearing the air, *CMAJ* 185 (10) (2013) E474.