



Thyroid hormones and adult interpersonal violence among women with borderline personality disorder



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ABSTRACT

Elevated T3 levels have been reported in men with antisocial behavior. The aim of the present study was to investigate the relationship between thyroid hormones and expressed adult interpersonal violence in female patients with borderline personality disorder (BPD). Furthermore, expressed adult interpersonal violence in female BPD patients was compared to healthy female controls. A total of 92 clinically euthyroid women with BPD and 57 healthy women were assessed with the Karolinska Interpersonal Violence Scales (KIVS). Baseline thyroid function was evaluated by measuring plasma free and bound triiodothyronine (FT3 and T3), thyroxine (FT4 and T4), and thyroid-stimulating hormone (TSH) with immunoassays in patients. Plasma cortisol was also measured. Among females with BPD, expressed interpersonal violence as an adult showed a significant positive correlation with the T3 levels. The mean expression of interpersonal violence as an adult was significantly higher in BPD patients as compared to healthy controls. The multiple regression model indicated that two independent predictors of KIVS expressed interpersonal violence as an adult: T3 and comorbid diagnosis of alcohol abuse. Association between T3 levels and violent/aggressive behavior earlier reported exclusively in male samples may be valid also in females with BPD.

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1. Introduction

The risk of violent behavior is elevated in both individuals with personality disorders (Berman et al., 1998; Johnson et al., 2000; Coid et al., 2006) as well as in the context of hazardous drinking. Borderline personality disorder (BPD) has been associated with violent acts (Fountoulakis et al., 2008), especially if combined with antisocial personality disorder (Howard et al., 2008; Látalová and Praško, 2010), even though the association may not be that evident in all groups of BPD patients (Allen and Links, 2012). Impulsive aggression, a heritable trait (Olweus, 1979; Coccaro et al., 1993), is a core feature of “cluster B” personality disorders, particularly antisocial personality disorders as well as BPD.

Thyroid hormones, in relation to violent behavior, have been studied mostly in male forensic settings. Elevated mean T3 levels have been reported in young criminally active and institutionalized male recidivists, as compared to non-delinquent controls,

although the two groups did not differ in TSH levels (Levander et al., 1987). In line with that finding, young men with persistent criminal behavior had higher mean T3 levels, as compared to both men with previous but no current antisocial behaviors and controls (Alm et al., 1996). In addition, Stålenheim (2004) found positive associations between T3 levels and Psychopathic Check List scores of Detachment and Irritability, in a group of violent male criminal recidivists. Suicidal and violent behaviors are interlinked and may share common neurobiological underpinnings. We have reported that high scores on aggressiveness were associated with a low T3/T4 ratio in male suicide attempters (Sinai et al., 2009). Stress reactions have also been associated with the thyroid function (Kioukia-Fougia et al., 2002), and basal hypothalamic pituitary adrenal (HPA) axis activity has been reported to be negatively related to provoked aggressive behavior (Böhnke et al., 2010).

No prior study has assessed the association between thyroid hormones and expressed interpersonal violence in women. Studies in the general population have reported that men are more violent than women, but this has not been found to be the case among psychiatric inpatients (Krakowski and Czobor, 2004).

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The aim of the present study was to assess the relationship between thyroid hormones and expressed adult interpersonal violence in female patients with borderline personality disorder. Furthermore, we compared expressed adult interpersonal violence in female BPD patients with violence scores of female healthy volunteers. It is not known if the same kind of association between thyroid hormones and violent behavior, earlier reported in anti-social male populations, could be found in women with BPD and severe suicidal behavior. We hypothesized higher scores of expressed interpersonal violence in individuals with BPD, and that thyroid hormones and comorbid substance abuse would be associated with adult violent behavior in patients with BPD.

2. Methods

2.1. Study setting

The participants were recruited between 1999 and 2004 for a clinical psychotherapy trial: "Stockholm county council and Karolinska Institute Psychotherapy project for suicide-prone women" (SKIP). The SKIP project is a randomized controlled trial, comparing the efficacies of two forms of psychotherapy, and general psychiatric care (treatment as usual). Inclusion criteria were BPD diagnosis according to DSM-IV, a history of at least two suicide attempts (defined as a self-destructive act with some degree of intent to die), a fair capacity to communicate verbally and in writing in the Swedish language, and age between 18 and 50 years. Exclusion criteria were schizophrenia spectrum psychosis, melancholia, mental retardation, drug abuse and severe anorexia. The Regional Ethical Review Board in Stockholm approved the study protocol (Dnr. 95–283) and the participants gave their written informed consent to the study.

2.2. Participants

2.2.1. Patients

A total of 162 women with BPD were invited to take part in the SKIP project. Of these individuals, 14 declined to join the study, 41 were excluded due to not fulfilling inclusion criteria or to fulfilling exclusion criteria and one completed suicide before joining the study. Thus, out of 162 women, 106 (65%) took part in the SKIP study. The mean age of the patients was 29.5 years (S.D.=7.6; range 19–50). We obtained laboratory data for 97 of 106 individuals. 92 patients were euthyroid (TSH reference range: 0.4–3.5 mE/l, Karolinska University Hospital) and thus included in the statistical analyses. The study population has recently been described in more detail (Sinai et al., 2014). This SKIP-cohort is practically independent (except two patients who also participated in an earlier study; Sinai et al., 2009), and not overlapping with other clinical studies on suicide attempters. All self-rating scales were completed under the supervision of a research nurse. The participants were interviewed by a trained psychiatrist, using the SCID I research version interview to establish the DSM-IV diagnoses (First et al., 1997). Trained clinical psychologists established Axis II diagnoses by DIP-I-interviews (Ottosson et al., 1995). Ninety (98%) of the participants had at least one current Axis I psychiatric diagnosis. Among the Axis I diagnoses, 78 (85%) of the patients met the criteria for mood disorders (unipolar major depressive disorder, single episode or recurrent, bipolar disorder, depressed or dysthymic disorder), 76 (83%) for anxiety disorders. Fifty-two (57%) patients met the criteria of posttraumatic stress disorder (PTSD). Twenty-four (26%) had a comorbid eating disorder; of whom 16 (17%) with bulimia and 8 (9%) with anorexia nervosa. Eight women (9%) had a diagnosis of alcohol abuse. Fifty women had an additional personality disorder (PD); avoidant PD ($n=24$), paranoid PD ($n=15$), obsessive-compulsive PD ($n=12$), histrionic PD ($n=10$), dependent PD ($n=9$), narcissistic PD ($n=4$). Twenty-two (24%) women had three or more personality disorders. The criteria for conduct disorder were met in seven of the women. Medication records were obtained for 68 (74%) of the patients, of whom seven patients were medication free. Three patients were treated with lithium. The most frequent medications were venlafaxine ($n=12$), fluoxetine ($n=11$), sertraline ($n=9$) and citalopram ($n=4$). Two patients had a combination of two antidepressants. In the medical records, there were no prescriptions of thyroid supplementation, anti-arrhythmic medications or opioids.

2.2.2. Healthy controls

Fifty-seven healthy women were recruited for another study (Jokinen et al., 2010). They were screened by a psychiatrist to verify the absence of current mental disorder. The mean age for healthy volunteers was 39.4 years (S.D.=10.7; range, 18–54).

2.3. Neuroendocrine testing

Baseline thyroid function was evaluated by measuring plasma free and bound T3, T4 and TSH levels. Venous blood was drawn and immediately frozen in aliquots

at -70°C or below until analyzed. The samples were thawed and analyzed by immunoassays (Unicel Dxl 800 Beckman Coulter, for FT4, FT3 and TSH and AutoDelfia, for T4 and T3) in the year 2010. No prior thawing of the frozen plasma samples had been performed. The Karolinska University Laboratory in Solna, Stockholm, performed all analyses according to accredited routines. The reference range for TSH was: 0.4–3.5 (mE/l) and for T3 1.1–2.5 (nmol/l), Karolinska University Hospital. The intra-assay coefficient of variation (CV) for TSH was 3.85–5.56%, for FT4 2.74–4.4%, for FT3 5.1–6.6%, for T4 2.7–3.6% and for T3 2.9–3.1%. The interassay CV for TSH was 3.02–3.68%, for FT4 3.34–8.08%, for FT3 1.3–8%, for T4 1.4–2.2% and for T3 1.2–2.1%. Analytical interferences in thyroid hormone testing are estimated to occur in less than 0.1%, at the Karolinska University Laboratory. Cortisol CV was within the range 43 (15%)–690 (6%) nmol/l, analyzed by Modular Analytics 170, Roche Diagnostics, Switzerland. Pre-analytical variation was minimized by performing the venipuncture in a standardized manner for all participants, of which a great majority was sampled at noon.

2.4. Assessments of adult used interpersonal violence

The Karolinska Interpersonal Violence Scale (KIVS) (Jokinen et al., 2010) contains four subscales with direct questions with concrete examples of exposure to violence and expressed violent behavior in childhood (between 6 and 14 years of age) and during adult life (15 years or older). The ratings (0–5 for each subscale, in total maximum of 20) were completed by the interviewing trained psychiatrist during a structured interview, to gather a comprehensive lifetime trauma and victimization history, as well as history of lifetime expressed violent behavior. The KIVS scale has been validated against several other rating scales measuring aggression and acts of violence and the inter-rater reliability of the KIVS subscales was high ($r > 0.9$) (Jokinen et al., 2010). The KIVS-subscale used adult interpersonal violence, is shown in Table 1.

2.5. Statistical analysis

Group differences in expressed adult interpersonal violence were analyzed with the Mann–Whitney U test. Correlation analyses (Spearman's rho, two tailed test) were used to determine associations between the clinical ratings and the biological variables. The significance of association between the categorical variables comorbid alcohol diagnosis (current and/or remitted versus no lifetime alcohol diagnosis) and diagnosis of PTSD was tested with a χ^2 test. Based on the results of the bivariate analyses, the association between T3 and expressed interpersonal violence among patients was analyzed with multiple regression analysis, adjusted for age, cortisol, sample storage time, and comorbid alcohol diagnosis. The selected covariates showed significant correlations with either T3 levels (age, cortisol, sample storage time) or with expressed interpersonal violence (comorbid alcohol diagnosis).

The residual scatterplots were examined to check the assumptions of normality, linearity and homoscedasticity between the predicted dependent variable scores and errors of predictions, and the assumptions were deemed to be satisfied. Furthermore, the Durbin–Watson test statistic expressed no correlation in adjacent residuals. The alpha level was set on $p < 0.05$. Missing data was handled by pairwise exclusion in the statistical analyses, in order to preserve degrees of freedom. The statistical analysis was performed using the SPSS statistical software package (IBM, SPSS™, version 22).

3. Results

3.1. Clinical assessments

KIVS ratings for adult expression of interpersonal violence were available from 91 euthyroid participants with BPD and 57 healthy controls. The mean expression of interpersonal violence as an adult was significantly higher in BPD patients (mean=1.3, S. D.=1.3, median=1, range 0–4), as compared to healthy controls (mean=0.4, S.D.=0.8, median=0, range 0–3), $p=0.001$. None of the patients or the controls did score the highest level (KIVS score: 5) of expressed adult interpersonal violence. Among patients 23% reported score 3 or 4, in contrast to the controls, among whom only 2% scored on the same rating levels. KIVS ratings of expressed adult interpersonal violence in patients and healthy controls are depicted in Fig. 1. Since the patients were significantly younger than the controls ($t_{(d.f.=90,8)}=6.6$, $p=0.0001$), the correlations between age and the KIVS ratings of expressed violence as an adult were analyzed and found to be non-significant in both patients ($p=0.23$) and healthy controls ($p=0.89$). The mean total score of KIVS among the patients was 7.3 (S.D.=3.8, median=7,

Table 1

KIVS scores of used adult interpersonal violence were rated by the interviewing trained psychiatrist.

The KIVS score	The KIVS statements
0	No violence.
1	Slapped or spanked children on occasion. Shoved or shook partner or another adult.
2	Occasionally smacked partner or child. Fought when drunk.
3	Assaulted partner drunk or sober. Repeated corporal punishment of child. Frequent fighting when drunk. Hit someone when sober.
4	Instance of violent sexual abuse. Repeated battering/physical abuse of child or partner. Assaulted/attacked other persons frequently, drunk or sober.
5	Killed or caused severe bodily harm. Repeated instances of violent sexual abuse. Convicted of crime of violence.

range 0–19) and in healthy volunteers was 2.8 (S.D.=3.1, median=2, range 0–17).

Patients with BPD and comorbid diagnosis of alcohol abuse ($n=35$, remitted and/or current) reported significantly higher expressed interpersonal violence as an adult (mean KIVS score=1.74), as compared to patients with BPD and without comorbid alcohol abuse (mean KIVS score=1.0; $n=56$; $Z=-2.6$, $p=0.008$). Levels of expressed interpersonal violence as an adult did not differ between patients with or without comorbid diagnosis of PTSD ($Z=-1.8$, $p=0.07$). Current alcohol abuse was not more frequent among women with PTSD ($\chi^2=0.19$, $p=0.66$).

3.2. Association between neuroendocrine measures

Table 2 shows the correlations between the thyroid hormones and cortisol. T3 and FT3/FT4 showed a significant positive correlation with serum cortisol ($\rho=0.30$, $p=0.006$), ($\rho=0.21$, $p=0.05$).

3.3. Association between neuroendocrine measures and expressed interpersonal violence.

Table 2 shows the correlations between the hormone values and the KIVS scores. Among patients, expressed interpersonal violence as an adult showed a significant positive correlation with the T3 levels ($\rho=0.23$, $p=0.04$) (Fig. 2). The correlations between the other hormone parameters and expressed adult interpersonal violence were all non-significant. Therefore T3 was further analyzed in the multiple regression analysis. A multiple regression of expressed interpersonal violence as an adult as dependent variable and T3, age, cortisol, sample storage time and comorbid alcohol abuse diagnosis (current and/or remitted) as independent variables was performed. The overall model was significant ($F_{(5, 81)}=3.1$, $p=0.012$) with $R=0.41$, $R^2=0.17$ and adjusted $R^2=0.12$, which implies that the model accounted for 12% of the variance in expressed adult interpersonal violence.

Two independent variables were statistically significant predictors of KIVS expressed interpersonal violence as an adult: T3 ($p=0.03$) and comorbid diagnosis of alcohol abuse ($p=0.02$). The standardized value of β for T3=0.27 indicated that higher T3 levels were associated with higher scores of KIVS expressed adult interpersonal violence. In the final regression model, dropping the non-significant predictors (age, cortisol, and sample storage time), the overall model was significant ($F_{(2, 81)}=5.3$, $p=0.007$) and accounted for 10% of the variance of the expressed interpersonal violence as an adult.

4. Discussion

In this study we assessed the relationship between serum thyroid hormones and expressed adult interpersonal violence in 92 euthyroid female patients with borderline personality disorder. Furthermore, we compared the levels of expressed adult interpersonal violence in female BPD patients, with levels of adult interpersonal violence in healthy female controls. As hypothesized, the patients reported significantly higher levels of adult interpersonal violence as compared to healthy controls, which is in line

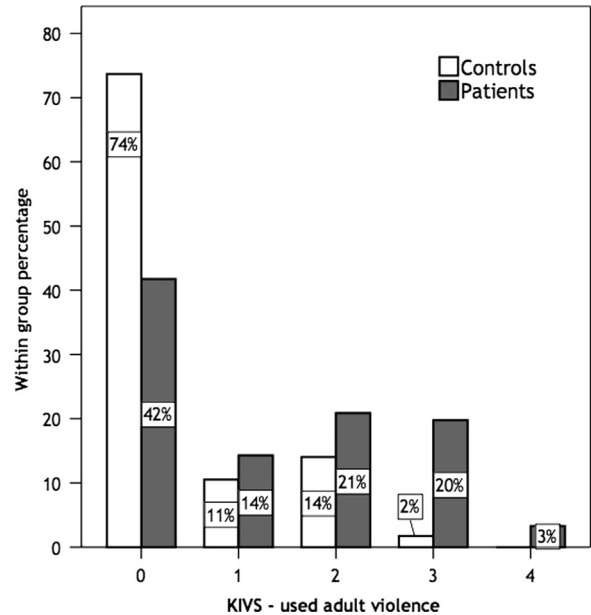


Fig. 1. Levels of expression of adult interpersonal violence among individuals with BPD and controls.

with earlier studies (Fountoulakis et al., 2008). It has been proposed that some subgroups of patients with BPD would be more prone to express violent behavior (Nestor, 2002). Factors apart from a diagnosis of BPD, such as: length of hospital stay, attachment style, number of prior suicide attempts, co-morbidity with other personality disorders (antisocial and psychopathic personality disorder) and co-morbid axis-I disorders, childhood abuse and childhood expression of violence, have been proposed to increase the risk of violence, especially in clinical or forensic populations (Allen and Links, 2012). In the current study, the patients had inclusion criteria of both BPD and at least two serious suicide attempts. Furthermore, they had a high degree of comorbidity with other personality disorders that may have contributed to the significantly higher levels of expressed adult interpersonal violence as compared to healthy controls.

In line with earlier studies (Krug et al., 2002; Foran and O'Leary, 2008; Heinz et al., 2011), we observed an association between the comorbidity with alcohol abuse and high levels of interpersonal violence as an adult. Interestingly, comorbidity with PTSD was not associated with higher levels of adult interpersonal violence in female patients with BPD. This is in line with a recent study of veterans reporting that PTSD alone was not related to violence and physical aggression, whereas co-occurring PTSD and alcohol abuse heightened the violence risk (Elbogen et al., 2014). However, there are also some studies reporting that PTSD is associated with both intimate partner violence in female veterans (Kirby et al., 2012), as well as physical aggression in general (Taft et al., 2005). We could not confirm these results in females with BPD.

Table 2

Hormone levels (TSH (mE/L), T3 (nmol/L), T3 (pmol/L), T4 (nmol/L), FT3 (pmol/L), FT4 (pmol/L), Cortisol (nmol/L)), and Spearman's correlation between hormones and KIVS subscale: adult expression of interpersonal violence, among women with BPD.

Variables	Mean (S.D.) Median (Range)	Correlation between cortisol and HPT-axis parameters	Correlation between KIVS adult used violence and hormone parameters
TSH	1.35 (0.67) 1.2 (0.4–3.5) n=92	0.17	–0.055
T3	1.9 (0.34) 1.9 (1.2–2.5) n=83	0.30**	0.23*
T4	103 (18) 104 (65–140) n=84	0.18	0.08
FT3	4.7 (0.7) 4.6 (3.1–7.1) n=92	0.20	0.17
FT4	9.6 (1.6) 9 (6–14) n=92	–0.08	0.07
T3/T4	0.02 (0.003) 0.02 (0.01–0.02) n=81	0.15	0.13
FT3/FT4	0.5 (0.1) 0.5 (0.34–0.89) n=92	0.21*	0.04
Cortisol	406 (193) 361 (140–1070) n=92		–0.04

* $p \leq 0.05$

** $p \leq 0.01$

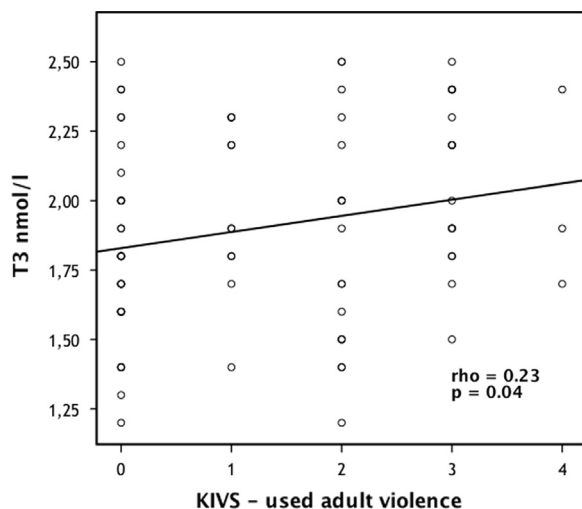


Fig. 2. Correlation of adult expression of interpersonal violence and T3 levels among patients.

The main finding of the study was a positive relationship between adult expression of interpersonal violence and serum T3 levels in female patients with BPD. To the best of our knowledge, this is the first study to report a positive association between T3 levels and expressed adult interpersonal violence in women with BPD.

Earlier studies reporting associations between thyroid hormone levels and violent behavior have focused on male delinquent cohorts. Higher mean T3 levels were found in young male criminally active institutionalized recidivists (Levander et al., 1987), as well as in male juvenile delinquents presenting persistent criminal behavior (Alm et al., 1996). In forensic male patients, high T3 levels were associated with criminality, psychopathy and cluster B disorders (antisocial and BPD) (Stälénheim et al., 1998), and diagnosis of conduct disorder (Ramklint et al., 2000). We have earlier reported an association between a low T3/T4 ratio and high aggressiveness in male but not in female suicide attempters (Sinai et al., 2009). Impulsive-aggressive traits are part of suicidal phenotype (Turecki, 2014). The neurobiological factors underlying or correlating with these developmental traits have not been fully characterized but there are a few promising leads. Impulsive aggressive and suicidal behaviors are associated with both low levels of serotonin and cholesterol (Brown et al., 1982; Moberg et al., 2011; Asellus et al., 2014). Our findings of HPT axis involvement in relation to aggressive personality traits or interpersonal violence in two distinct patient cohorts with suicidal behavior, as well as the earlier literature of HTP axis dysregulation in suicidal patients (Pompili et al., 2012), may indicate involvement of altered thyroid hormones in a clinical endophenotype characterized by impulsive, aggressive and suicidal behaviors. Early life adversities can be manifested through developmental dysregulation of behavior and personality traits. We have earlier published one article from this clinical cohort where we found lower FT3/FT4 ratio in women with BPD exposed to interpersonal violence in childhood (Sinai et al., 2014). Even though the data are cross-sectional, the findings fit well into the literature of traumatic early-life environment leading to behavioral phenotypes characterized by impulsive, aggressive and suicidal behaviors with distinct neurobiological underpinnings (Turecki, 2014).

In our study, female BPD patients who reported more adult interpersonal violence had significantly higher serum T3 levels also when adjusted for age, comorbid substance abuse, serum cortisol levels and sample storage time. Our finding indicates that the association between T3 levels and violent/aggressive behavior earlier reported exclusively in male populations, may also be present in females with BPD. Thus, our results may widen the generalizability of the findings of HPT-axis involvement in aggression dysregulation in both men and women with severe personality disorders. This may not be unexpected given the similarities in the symptoms, risk factors and clinical outcome of BPD and antisocial personality disorder. Gender may contribute to a different behavioral expression of underlying common impulsive traits in these personality disorders (Paris, 1997). In BPD, impulsive aggression may be associated with aberrant mentalizing capacities and rejection sensitivity (Ripoll et al., 2013). Interpersonal sensitivity may trigger both impulsive aggression as well as emotion dysregulation, the core features of BPD (Stanley and Siever, 2010).

This study sheds further light on the relationship of stress hormones and interpersonal violence. Thyroid hormones can be considered to be a slow reactive hormonal adaptor and the relationship to stressful events is known since long (Mandelbrote and Wittkower, 1955). We did not find a significant association between serum cortisol and expressed interpersonal violence. Stress is one of the most important promoters of aggression and basal HPA axis activity has been reported to be negatively related to provoked aggressive behavior (Böhnke et al., 2010). However, no clear relationship between basal HPA axis activity and aggressive behavior in humans has been established.

Our finding may stimulate speculations whether the individuals prone to express interpersonal violence have a certain hormonal profile, linked to a trait within the borderline spectra: impulsive aggression. The cross-sectional study design prevents us from drawing causal conclusions with regard to thyroid hormone

levels and adult violence. We cannot either exclude the possibility that violent behavior might also change the thyroid axis.

Among the gains of this study is the assessment of interpersonal violence with a structured interview in a euthyroid population (Dickerman and Barnhill, 2012). The questions in KIVS concerning expression of violence, focused on actual behavior, i.e. performed violent acts, and not on how the respondent felt about or perceived the incidences. Among the limitations of the study is the lack of HPT axis measures in the healthy control group, which would have broadened the understanding of the findings, however the range of both TSH and T3 levels of the patients were within reference range for the method used at the Karolinska University Laboratory. Further, we did not have collateral information of expressed violent acts in adult life; presumably occurring within close relationships. In addition, due to the inclusion criteria of at least two suicide attempts, this group may comprise a selected subgroup of BPD with more psychiatric burden. This inclusion criterion yielded a cohort with a rather homogenous pattern of suicidal behavior and more detailed information of characteristics of suicidal behavior was not obtained systematically during the study period, which can be seen as a limitation.

In summary, women with BPD reported more expressed adult interpersonal violence than healthy controls, and within the BPD group we found a significant positive relationship with adult expression of interpersonal violence and serum T3 levels, controlled for comorbid alcohol abuse.

Conflict of interests and funding

No conflicts of interests to declare for any of the co-authors. Funding for this study was provided by the Swedish Research Council (Project numbers: 5454; K2009-61 P-21304-04-4; K2009-61X-21305-01-1), Kalmar County Council and by the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

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