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Salivary cortisol and suicidal behavior – A follow-up study

Running title: Salivary cortisol and suicidal behavior

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Abstract

Introduction

Hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis is a common finding in Major Depressive Disorder. Similar studies on suicide attempters are less abundant, and the results are divergent. The main aim of the present study was to investigate HPA-axis parameters by the time of a suicide attempt and at follow-up in search for associations between HPA axis function and suicidal behavior.

Methods

Thirty-five suicide attempters and 16 non-suicidal controls were admitted to a psychiatric ward between the years of 1986 and 1992. Corticotrophin-releasing hormone (CRH) in cerebrospinal fluid and urinary cortisol were obtained for the suicide attempters. The patients were followed up approximately 12 years after the index admission. Cortisol was measured in saliva, and additional suicide attempts and current psychiatric symptoms were registered.

Results

At follow up, evening salivary cortisol was lower in suicide attempters compared to controls. Low cortisol levels at follow up were associated with severe psychiatric symptoms. Among women, repeated suicide attempts were associated with low morning and lunch salivary cortisol, and in this subgroup we also found significant correlations between salivary cortisol at follow up, and CRH as well as urinary cortisol at index.

Conclusion

We found evidence for an association between low HPA axis activity and suicidal behavior. This could be due to long lasting and severe psychiatric morbidity, which in turn has exhausted the HPA axis of these patients. The potential role of hypocortisolism should be given more attention in studies on suicidal patients.

Keywords

HPA axis; Salivary cortisol; Suicide attempt; Follow up; Major depressive disorder; Corticotrophin releasing hormone

1. Introduction

Finding biological measures in order to predict suicidal behavior is an important task in psychiatric research. Disturbances of the Hypothalamic-Pituitary-Adrenal (HPA) axis are well documented among patients suffering from psychiatric disorders, in particular Major Depressive Disorder (MDD) (Bao et al., 2008). The majority of studies indicate a hyperactivity of the HPA-axis in patients with an ongoing depression (Plotsky et al., 1998; Pariante, 2003; Claes, 2004). However, low HPA-axis activity has been suggested in depression with atypical features (Antonijevic, 2006), as well as in multiepisodic and chronic depressive disorders (Shah et al., 1998; Oldehinkel et al., 2001; Watson et al. 2002; Ehnvall et al., 2004). Among suicide attempters, patients with axis II personality disorders display lower cortisol levels than the ones without such a diagnosis (Westrin et al., 2003). There is also evidence of HPA-axis hypoactivity in the pathophysiology of stress- and fatigue related disorders (Heim et al., 2000).

In previous studies, our research group has reported lower levels of corticotrophin-releasing hormone (CRH) in cerebrospinal fluid (CSF) of suicide attempters with MDD, compared to non-MDD suicide attempters. Patients with repeated suicide attempts had lower CSF-CRH than non-repeaters (Traskman-Bendz et al., 1992). A subset of these patients was followed up after a mean of 7 months, and the CRH levels remained on an unchanged low level (Westrin, et al., 2001). We have also found a negative correlation between suicidal intent and post-dexamethasone cortisol levels in serum among suicide attempters with MDD, indicating an inverse relationship between suicidality and HPA axis-drive in this patient group (Lindqvist et al., In press). Low 24-hour urinary cortisol is associated with adverse events during early life in the same patient material (Sunnqvist et al., In press). In line with these results, studies from other groups also demonstrate that suicidal

patients may display decreased levels of cortisol (Secunda et al., 1986; Pfennig et al., 2005). However, in contrast some studies indicate that HPA-hyperactivity is associated with suicidal behavior (Lopez-Ibor et al., 1985; Westrin and Nimeus, 2003) and completed suicide (Yerevanian et al., 2004; Coryell et al., 2006; Jokinen et al., 2007). As evident from the above, there is abundant evidence of a disturbed HPA-axis activity in suicide victims and attempters, and there is a great need for a more detailed understanding of these changes.

The aim of the present study was therefore to investigate cortisol and CSF-CRH in suicide attempters in search for associations between HPA axis abnormalities and suicidal behavior – and this time in a long term follow up situation. Based on our previous findings, our main hypothesis was that HPA axis activity would remain low in suicide attempters with MDD. We also hypothesized that the severity of psychiatric symptoms would correlate negatively with salivary cortisol levels.

2. Methods

2.1 Index period

2.1.1 Suicide attempters

The 40 suicide attempters participating in the present study were originally admitted to the medical intensive care unit of the Lund University Hospital between the years of 1986 and 1992 (index-period). Within a few days, they were referred to a psychiatric ward of the Lund University hospital, specialized in mood disorders and suicidal behaviour. A suicide attempt was defined as: “situations in which a person has performed an actually or seemingly life threatening behavior with the intent of jeopardizing his/her life or to give the appearance of such intent, but which has not resulted in death” (Beck et al., 1972). The diagnoses were set according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (American

Psychiatric Association, 1987). Two psychiatrists set the diagnoses after a consensus discussion.

2.1.2 Sampling for biochemical analyses

At index, 16 of the 40 suicide attempters agreed to undergo lumbar puncture. Lumbar punctures were performed after a medication free period of 16 ± 7 days from admission to the psychiatric ward. Occasional doses of benzodiazepines were allowed during this period. Blood samples were screened for antidepressants, neuroleptics, and benzodiazepines on the day of the lumbar puncture. None of the patients had any detectable levels of antidepressants or neuroleptics, but benzodiazepines were detected in seven (41%) of the suicide attempters. Lumbar punctures were performed as previously described by Träskman-Bendz et al. (Traskman-Bendz et al., 1992). Twenty-four hour urine samples were collected during three consecutive days for 24 of the 40 suicide attempters.

2.1.3 Analyses of biochemical markers

CRH levels were determined in CSF using radioimmunoassays (RIA), as previously described (Traskman-Bendz et al., 1992). Cortisol was measured in 24-hour urine samples using a RIA (Orion Diagnostica Cat. No: 68548, Espoo, Finland). Three urine samples were collected on consecutive days, and the average of these values was used for statistical analysis.

2.2 Follow up

2.2.1 Patients and psychiatric evaluations

Follow up was conducted approximately 12 years after index admission (1999-2002). Sixty patients (40 suicide attempters and 20 non-suicidal controls) participated in the follow up. The sample of non-suicidal controls consisted of patients who received psychiatric inpatient care during the same time period (1986-1992) as the group of former suicide attempters, but had no history of suicide attempt prior to that time. The controls were matched with the suicide attempters at index according to diagnosis, time of hospitalisation, gender and age.

At follow up, the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1994) was used for diagnostics. All patients were assessed for Axis II personality disorders. Semi structured interviews were conducted by a psychiatrist and a resident of psychiatry, and included information on suicidal attempts during the follow up time, as well as assessments of current psychiatric symptoms. For the latter purpose the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al., 1978) was used. The CPRS consists of 65 items, rated from 0 to 3 defined points with halfsteps. The first 40 items are reported and the last 25 are observed by the psychiatrist. The reliability and validity of the CPRS have been proved (Jacobsson et al., 1978; Asberg and Schalling, 1979). The Montgomery – Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) is a subscale extracted from the CPRS. It contains 10 items that assess severity of depression, rated 0 – 6 points on each item. The MADRS has also been tested for validity and reliability (von Knorring and Strandman, 1978; Maurer et al., 1984).

Thirteen (37%) of the suicide attempters and eight (50%) of the controls received antidepressants, nine (26%) suicide attempters and four (25%) controls various somatic drugs, and 11 (31%) suicide attempters and 4 (25%) controls did not receive any medication. Two (6%) of the suicide attempters medicated with antipsychotics.

2.2.2 Salivary cortisol

A total of six salivary cortisol samples in Salivette tubes (Sarstedt, Nümbrecht, Germany) were collected from each subject over two days. Two samples were taken between 0600h and 0800h (morning cortisol), two samples between 1200h and 1400h (lunch cortisol), and two samples between 2000h and 2200h (evening cortisol). In the statistical analyses we used mean values from morning-, lunch- and evening cortisol.

The first two samples were taken in the hospital and the other samples by the patients at home. The patients were given written instructions concerning the sampling procedure, i.e. they were not to drink, eat or use tobacco thirty minutes before taking the sample. They were also instructed not to brush their teeth within an hour, or to rinse their mouth within 15 minutes before the procedure. The samples were kept at room temperature until all were taken and then sent to the laboratory for centrifugation and storage at -20°C.

Cortisol in saliva was determined with a RIA (Spectria Cortisol, Orion Diagnostica, Espoo, Finland). The coefficient of variation (within assay) of the method was 5,9 and 5,1 % at 7 and 32 nmol/l, respectively.

2.2.3 Exclusion criteria

Nine patients were excluded from the follow up study, due to the following reasons:

Systemic endocrinological disorders (N=3); One suicide attempter and one control patient underwent systemic corticosteroid treatment and one suicide attempter suffered from insulin-dependent diabetes mellitus.

Suicide attempt of a control subject during follow-up (N=3).

Three suicide attempters were excluded due to exceptionally elevated cortisol levels; One patient displayed values >100 nmol/l on two occasions. One patient had a mean cortisol value of 65 nmol/l, and one patient displayed values >1000 nmol/l on two occasions. Two of these patients were taking herbal medications and the third was a heavy smoker. Although we cannot completely exclude that the exceptionally high values were due to the patients' psychiatric conditions, they might be influenced by smoking and herbal medication, or due to errors in the assay. In a previous study, salivary cortisol values exceeding 44 nmol/l were considered non-physiological and therefore excluded (Peeters et al., 2003).

After checking for exclusion criteria, we included 51 (35 suicide attempters and 16 controls) patients in the study.

2.3 Ethical approval

The study was carried out at the Lund Suicide Research Centre at the Department of Psychiatry of Lund University Hospital. The Lund University Medical Ethics Committee has approved of the study, and all the patients gave a written informed consent to participate in the research program.

2.4 Statistical analysis

The Statistical Package for the Social Sciences (SPSS) program version 15.00 for Windows was used. The Kruskal-Wallis test was used for multiple comparisons and the Mann-Whitney U-test for groupwise comparisons, due to non-parametrical data and differences in number of subjects between groups. Correlations were calculated using Spearman's rho. One-tailed analyses were used for calculating correlations between psychiatric symptoms and cortisol.

Pearson's Chi-Square was used to compare proportions. Exact P-values are given in the statistical reports.

3. Results

3.1 Patient characteristics at index and follow up

Demographic and diagnostic characteristics of the patients are summarized in **Table 1**. The groups were balanced with respect to diagnosis and demographic characteristics at the index time period. There were no significant correlations between any of the HPA axis measurements and age at follow up.

Forty-three percent of the suicide attempters, and 50 percent of the controls did not fulfil the criteria for a psychiatric diagnosis at follow up. Among the suicide attempters, the prevalence of MDD was similar at index compared to follow up (34 % at follow up compared to 31% at index), while fewer of the controls were diagnosed with MDD at follow up (6 % at follow up compared to 44 % at index), perhaps reflecting a higher rate of clinical recovery over time in the group of non-suicidal controls. At follow up, there were no significant differences between suicide attempters and non-suicidal controls regarding prevalence of axis II personality disorders. Mann-Whitney U-tests showed no significant differences in morning (median 5.5 vs. 5.9, $P=0.670$), lunch (median 3.1 vs. 3.9, $P=0.224$), or evening (median 1.3 vs. 1.4, $P=0.529$) salivary cortisol between the patients who had received an axis II personality disorder and those who had not.

Sixteen of the suicide attempters had made one or more additional suicide attempts during the follow up period, and were denoted *repeaters*.

3.2 Salivary cortisol and history of suicide attempt

Kruskal-Wallis analysis of salivary cortisol at follow up revealed significant differences between suicide-attempters and non-suicidal controls during the three comparison time-points of the day. Subsequent Mann-Whitney's U-tests showed that evening cortisol was significantly lower in suicide-attempters (n=35) compared to non-suicidal controls (n=16) (median 1.3 vs. 1.9, $P=0.05$) (**Table 2**).

To investigate the impact of MDD on cortisol levels, the suicide-attempters were divided into those who had, versus had not, received an MDD diagnosis at either index or follow up. As expected, both MDD- (n=18) and non MDD suicide attempters (n=17) had significantly lower evening salivary cortisol than the non-suicidal controls (n=16) (Mann-Whitney's U-tests, $P=0.006$ and $P=0.044$ respectively). Among the three groups, suicide-attempters with MDD displayed the lowest evening cortisol (median, 1.2 vs. 1.4 for non-MDD suicide attempters and 1.9 for controls), although there was no statistically significant difference when this group was compared to the non-MDD suicide attempters (Mann-Whitney's U-tests, $P=0.246$). (**Table 3**).

There were no significant differences in salivary cortisol between repeaters and non-repeaters (**Table 4**).

Four patients were classified as violent suicide attempters at index according to the criteria described by Traskman and colleagues (Traskman et al., 1981), and there were no significant differences in any of the HPA axis measurements between them and the non-violent suicide attempters.

3.3 Gender differences

There were no significant differences between males and females regarding age, principal diagnosis, recovery at follow up, repeater/non-repeater or mean salivary cortisol levels. A significantly greater proportion of the women had a personality disorder according to DSM IV, Axis II (45% vs. 10 % for men, Pearson's Chi-Square, $P=0.011$).

When the groups were split based on gender, female repeaters ($N=12$) displayed significantly lower levels of cortisol in the morning (Mann-Whitney's U-test, median 4.3 vs. 8.1, $P=0.031$) and at lunch (Mann-Whitney's U-test, median 2.8 vs. 4.8, $P=0.02$) than female non-repeaters ($N=6$).

Furthermore, there were significant correlations between morning salivary cortisol at follow-up and CSF-CRH at index (Spearman's rho = 0.72, $N=9$, $P=0.03$), as well as urinary cortisol at index (Spearman's rho = 0.78, $N=13$, $P=0.002$) among women, as depicted in **Figures 1 and 2**. However, we found no such correlations in the group as a whole.

3.4 Cortisol and psychopathology

There were significant negative correlations between evening cortisol and total CPRS score (Spearman's rho = -0.33, $P=0.017$), reported CPRS score (Spearman's rho = -0.32, $P=0.020$), and MADRS score (Spearman's rho = -0.29, $P=0.030$). Morning cortisol correlated negatively with observed CPRS score (Spearman's rho = -0.31, $P=0.020$). Negative correlations, in this context, refer to an association between low cortisol levels and more severe psychiatric symptoms.

Twenty-three patients did not meet the criteria for any psychiatric diagnosis at follow up. Mann-Whitney's U-tests revealed no significant differences between these patients and the ones who received a psychiatric diagnosis at follow up (N=28), in morning (P=0.937), lunch (P=0.449), or evening (P=0.149) salivary cortisol.

4. Discussion

Summary

We found that evening cortisol was low in psychiatric patients with a history of at least one suicide attempt, as compared to psychiatric patients who had never attempted suicide.

Furthermore, female suicide attempters who had low CSF-CRH and urinary cortisol at the index suicide attempt, which took place around 12 years prior to the current follow-up, still displayed the lowest cortisol levels in our patient material. Females with repeated suicidal behavior had the lowest morning and lunch cortisol levels of all groups, significantly lower than non-repeaters. We also detected a negative correlation between CPRS- and MADRS scores and cortisol at the follow-up. This strengthens the evidence that the decreased HPA-axis activity is linked to a more severe psychiatric symptomatology in suicide attempters.

Taken together, we find evidence for a decreased HPA axis activity in patients with suicidal behavior compared to patients without a history of suicide attempts.

Limitations and strengths of the method

The measurement of cortisol in saliva has proven a valid and reliable reflection of the free fraction of cortisol (non-protein bound) in blood (Kirschbaum and Hellhammer, 1989; Kirschbaum and Hellhammer, 1994). The major advantage using this method is that the

sampling technique is non-invasive and can be performed in non-stressful conditions, without laboratory surroundings (Weibel, 2003). The method is widely used and reference intervals for the normal population exist. However, the correlative validity of salivary cortisol as a surrogate of free plasma cortisol has been under some debate (Levine et al., 2007). The method suffers from some disadvantages, including lack of compliance (Gutteling et al., 2005). In addition, saliva samples taken after eating or drinking substances with low pH may give falsely high cortisol values (Goodyer et al., 1996). Tobacco use may also interfere with the analysis (Badrick et al., 2007). We have been aware of these potential pitfalls of the method and used strict instructions to the patients to avoid them.

A gender difference with respect to morning cortisol levels has been reported in the general population (Van Cauter et al., 1996), and in addition we therefore performed the relevant statistical analyses on a gender basis.

Our results in relation to other studies

A study of the CSF-CRH levels in the same patient material at the index suicide attempt (12 years prior to this follow-up) found lower levels in patients with MDD compared to patients with other diagnoses. (Traskman-Bendz et al., 1992). That study also demonstrated that patients who had committed one or several suicide attempts prior to enrollment in the study (repeaters) displayed lower CSF-CRH levels than non-repeaters. The findings in our long-term follow-up study are in line with these earlier reports. However, the differences in cortisol between MDD- and non MDD suicide attempters did not reach significance in our study. This might be due to the relatively small number of patients in the follow-up material.

Results from other groups on the relationship between suicidal behaviour and HPA axis function have yielded divergent results, and to some extent employed different

methods. Lopez-Ibor and colleagues found that depressed suicidal patients were more likely to be nonsuppressors of cortisol, after a Dexamethasone Suppression Test (DST) (Lopez-Ibor et al., 1985). Similar findings were reported in a study by Westrin et al. (Westrin and Nimeus, 2003) where suicide attempters who were nonsuppressors of cortisol had higher scores on the Suicide Assessment Scale (SUAS) than suppressors, irrespective of psychiatric diagnosis. In contrast, no difference in HPA-axis function was detected when suicidal and non-suicidal depressed patients were compared using either the DST only (Brown et al., 1986), or the DST plus measurements of CSF-CRH and urinary cortisol (Roy, 1992). In line with the results of the present paper, some other studies have shown a relative hypoactivity of the HPA-axis in depressed patients manifesting suicidal behaviour and ideation (Secunda et al., 1986; Pfennig et al., 2005). In the more recent study by Pfennig and colleagues, the combined dexamethasone suppression/CRH stimulation test was used, which has been suggested to be more sensitive to changes in the HPA axis than the DST (Heuser et al., 1994). In this study, 310 patients with depressive syndromes were classified as “suicidal” or “non-suicidal”. The patients in the suicidal group had either attempted suicide prior to admission, or expressed suicidal ideation. The suicidal group showed a trend towards lower cortisol levels post dexamethasone, significantly lower cortisol response to CRH, and a trend toward a lower ACTH response to CRH. The lowest plasma cortisol and corticotrophin responses were found in the patients who recently attempted suicide. Interestingly, not only acute suicidal behaviour, but also a previous history of suicide attempts was associated with lower HPA axis activity. These findings are to a large extent in line with the results in our study.

Several other hormones and neuropeptides may interfere with the regulation of the HPA-axis (Swaab et al., 2005). We previously found reduced CSF levels of the hypothalamic peptide orexin in suicide attempters with MDD (Brundin et al., 2007). Orexins modulate the HPA axis by stimulating CRH-Adrenocorticotrophic Hormone (ACTH) secretion

(Spinazzi et al., 2006). Vasopressin-neurophysins, on the other hand, have not been found to affect the HPA-axis after a DST in suicide attempters (Pitchot et al., 2008).

As for the subgroup of patients with major depression, most results point towards an activation of the HPA-axis (Plotsky et al., 1998; Holsboer, 2000; Swaab et al., 2005), although studies are not unanimous. CSF-CRH has, in patients with MDD, been detected as high (Banki et al., 1992; Catalan et al., 1998), normal (Pitts et al., 1995), and low (Geraciotti et al., 1992). With relevance to the results in the present study, there is some evidence of low salivary cortisol levels in depressed patients compared to healthy controls. Salivary cortisol was measured before and after uncontrollable stressful events, and was found to increase in controls, while depressed patients exhibited the opposite pattern (Croes et al. 1993). Similar findings have been reported after negative life-events, where depressed patients displayed no increase in salivary cortisol, as opposed to healthy controls (Peeters et al. 2003).

Hypocortisolism- mechanisms

Low HPA axis activity, or hypocortisolism, is a relatively new phenomenon in stress research (Heim et al., 2000). Hypocortisolism has been reported in patients with stress related disorders, such as Chronic Fatigue Syndrome (CFS) (Wyller, 2007), fibromyalgia (Adler et al., 2002), Post Traumatic Stress Disorder (PTSD) (Ehlert et al., 2001), and depression with atypical features (Antonijevic, 2006). Since these disorders also share some symptoms (including enhanced stress sensitivity, pain, and fatigue), common underlying physiological abnormalities have been suggested (Heim, Ehlert et al. 2000). Alterations of the HPA axis, in terms of hypocortisolism, may lead to an overactive immune system, with an increased inflammatory response (Heim et al., 2000). Proinflammatory cytokines may be involved in

the generation of psychiatric symptoms common in the disorders mentioned above, as well as in the group of suicide attempters studied here.

The mechanisms behind hypocortisolism are yet to be understood. A developmental model has been suggested, where prolonged periods of stress (accompanied by initial HPA axis hyperdrive) are presumed to “wear out” the stress system, resulting in a switch into a hypoactive mode (Fries et al., 2005). This hypothesis is supported by data from animal studies (Houshyar et al., 2001), studies on patients in an experimental setting (Vingerhoets et al., 1996), as well as clinical observations of patients with stress related disorders (Van Houdenhove and Egle, 2004). This concept might also be applicable to affective disorders, since a neuroendocrinological distinction has been suggested in depression, based on chronicity and duration of illness. Patients with chronic MDD have more often a normal or low HPA activity than non chronic patients (Shah et al., 1998; Oldehinkel et al., 2001; Watson et al., 2002). In addition, it has been noted that MDD patients with multiple depressive episodes have lower HPA axis activity than patients with fewer depressive episodes (Ehnavall et al., 2004). One could speculate that the patients in our sample with a history of suicide attempt, had been subjected to longer periods of mental stress than the controls, hence their HPA axis showed a tendency towards a hypoactive mode. This notion is partly supported by the fact that MDD was more prevalent among suicide attempters than controls at follow up, although the groups were diagnostically balanced at index. It appears as if patients with suicidal behaviour are more prone to suffer from severe, and long lasting depressive syndromes, which in turn might lead to a hypoactive HPA axis.

Conclusions and implications

We found lower cortisol levels in suicide attempters compared to non-suicidal psychiatric patients and evidence that repeated suicidal behavior is associated with low cortisol. We had

no information on HPA axis activity of the non-suicidal controls at index. We can therefore not argue for a long-standing difference in HPA axis function between suicide attempters and controls, but conclude that a history of one or more suicide attempts is associated with lower cortisol levels in our material at follow-up.

The observation that HPA axis activity tends to remain low in suicidal patients after a long follow up period, raises the question of whether this hypofunction is a trait- rather than a state-related feature of the HPA axis in these patients. Previous studies on the HPA axis in psychiatric research have often focused on hyperactivity of the stress system. We believe that there is now some evidence that hypocortisolism might play a part in the pathophysiology of psychiatric disorders. Suicidal behavior and duration of symptoms are two factors that may be associated with this phenomenon, and further studies are warranted in order to elucidate the underlying mechanisms.

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Table 1. Demographic and diagnostic characteristics of the patients

Group	Suicide attempters (N=35)		Non-suicidal controls (N=16)	
Age at follow up, Mean (SD)	51 (10)		50 (9)	
Females, N (%)	18 (51)		11 (69)	
Males, N (%)	17 (49)		5 (31)	
Axis II personality disorder at follow up, N (%)	9 (26)		3 (19)	
Diagnosis, N (%)	Index	Follow-up	Index	Follow-up
MDD	11 (31)	12 (34)	7 (44)	1 (6)
Dysthymia	8 (23)	2 (6)	2 (13)	1 (6)
Adjustment Disorder	7 (20)	1 (3)	3 (19)	0 (0)
Substance Abuse Disorder	3 (9)	3 (9)	1 (6)	1 (6)
Psychotic Syndrome	2 (5)	0 (0)	0 (0)	0 (0)
Depression Not Otherwise Specified	3 (9)	0 (0)	2 (12)	0 (0)
Other diagnosis	1 (3)	2 (5)	1 (6)	5 (32)
No diagnosis	0 (0)	15 (43)	0 (0)	8 (50)

Table 2. Morning, lunch, and evening salivary cortisol levels for suicide attempters and controls at follow up.

Cortisol concentrations were measured in nmol/l, Median and Interquartile Range (IQR)

	Suicide attempters (N=35)	Non suicidal controls (N=16)	Significance (Mann-Whitney´s U-test)
Morning cortisol (Median, IQR)	5.4, 4.3-9.0	7.2, 5.3-13.6	P=0.231
Lunch cortisol (Median, IQR)	3.5, 2.3-4.7	4.1, 3.5-4.8	P=0.203
Evening cortisol (Median, IQR)	1.3, 1.1-1.9	1.9, 1.5-4.0	P=0.050

Table 3. Morning, lunch, and evening cortisol levels for controls, non MDD suicide attempters and MDD suicide attempters at follow up.

Cortisol concentrations were measured in nmol/l, Median and Interquartile Range (IQR)

	Non suicidal controls (N=16)	Non-MDD suicide attempters (N=17)	MDD suicide attempters (N=18)	Significance (Kruskal Wallis)
Morning cortisol (Median, IQR)	7.2, 5.3-13.6	5.5, 4.5-10.3	5.4, 3.3-8.7	P=0.411
Lunch cortisol (Median, IQR)	4.1, 3.5-4.8	3.6, 2.2-5.0	3.3, 2.3-4.6	P=0.402
Evening cortisol (Median, IQR)	1.9, 1.5-4.0	1.4, 1.2-2.1	1.2, 1.0-1.7	P=0.013

Table 4. Morning, lunch, and evening cortisol levels for controls, non-repeaters and repeaters at follow up

Cortisol concentrations were measured in nmol/l, Median and Interquartile Range (IQR)

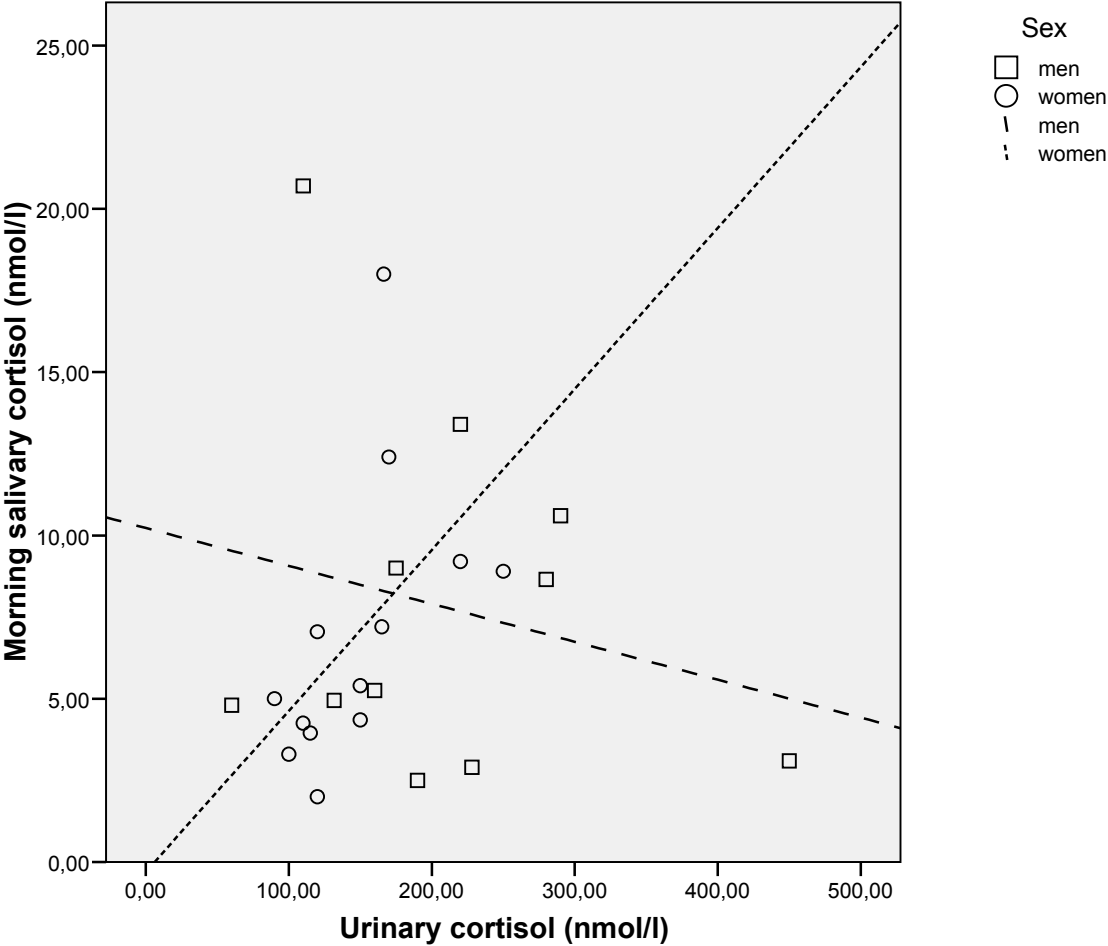
Suicide attempters who made one or more suicide attempt during follow up were denoted *repeaters*.

	Non suicidal controls (N=16)	Non repeaters (N=19)	Repeaters (N=16)	Significance (Kruskal Wallis)
Morning cortisol (Median, IQR)	7.2, 5.3-13.6	7.4, 4.9-9.8	5.1, 3.8-7.6	P=0.213
Lunch cortisol (Median, IQR)	4.1, 3.5-4.8	3.9, 2.3-4.9	2.9, 2.2-4.4	P=0.286
Evening cortisol (Median, IQR)	1.9, 1.5-4.0	1.3, 1.1-1.9	1.5, 1.1-2.0	P=0.016

Role of funding source

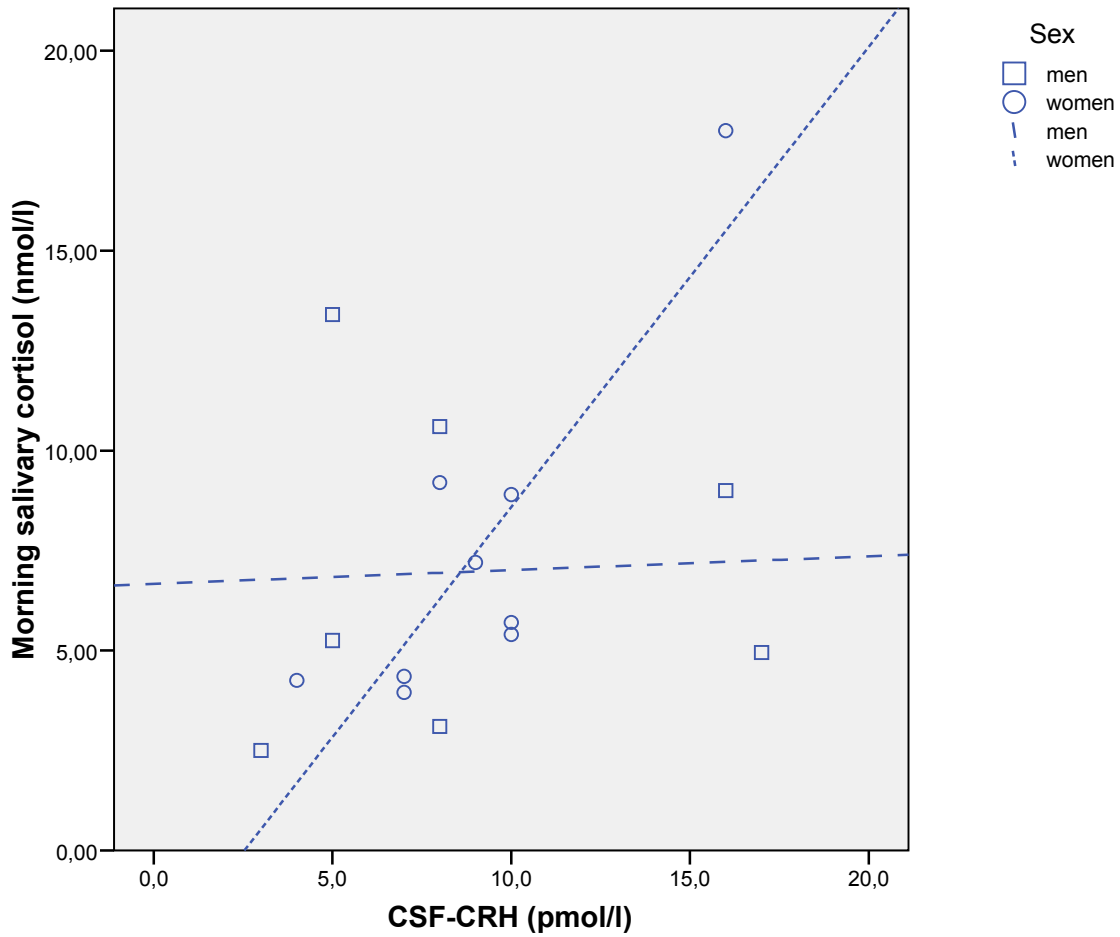
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Figure 2. Morning salivary cortisol at follow up versus urinary cortisol at index for men (N=11) and women (N=13)



Spearman's rho = 0.78, P=0.002 (women); -0.12, P=0.729 (men)

Figure 1. Morning salivary cortisol at follow up versus Cerebrospinal Fluid (CSF) - Corticotropin-Releasing-Hormone (CRH) for men (N=7) and women (N=9)



Spearman's rho = 0.72, P=0.03 (women); 0.13, P=0.79 (men)

Conflict of interest

None of the authors have any financial or personal relationships that could bias their work

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