Chapter 6

Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease

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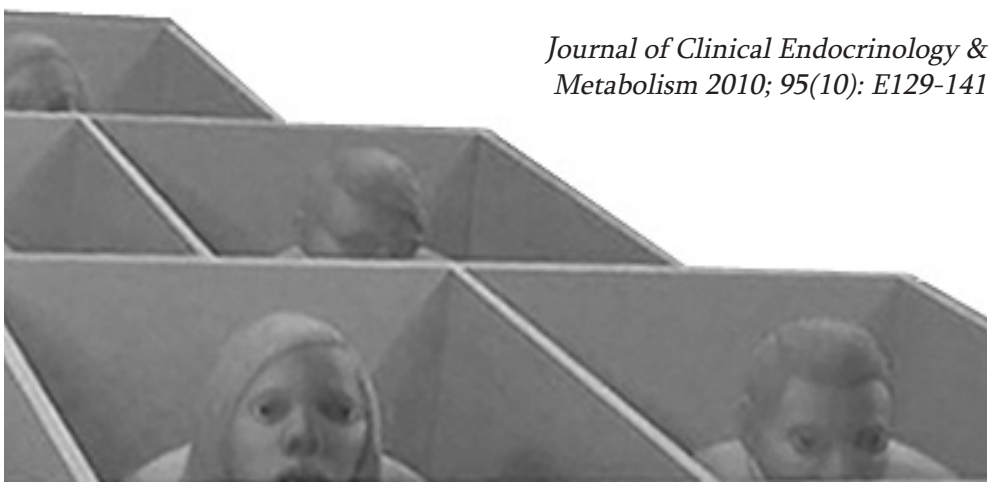

Abstract

Context and Objective: Psychopathology and maladaptive personality traits are often observed during the active phase of Cushing's disease (CD). We hypothesized that patients with long-term cure of CD show persistent psychopathology and maladaptive personality traits.

Design: Four questionnaires on frequently occurring psychopathology in somatic illnesses were used, including the Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale, and Mood and Anxiety Symptoms Questionnaire short-form. Personality was assessed using the Dimensional Assessment of Personality Pathology short-form (DAPPs).

Patients and Controls: We included 51 patients cured of CD (16% men, 53±13 yr) and 51 matched controls. In addition, we included 55 patients treated for nonfunctioning pituitary macroadenomas (55% men, 62±10 yr), and 55 matched controls.

Results: Mean duration of remission was 11 yr (range 1–32yr). Compared with matched controls, patients cured from CD scored significantly worse on virtually all questionnaires. Compared with nonfunctioning pituitary macroadenoma patients, patients treated for CD scored worse on apathy ($P<0.001$), irritability ($P<0.001$), anxiety ($P<0.001$), negative affect and lack of positive affect ($P<0.001$ on both scales), somatic arousal ($P<0.001$), and 11 of 18 subscales of the Dimensional Assessment of Personality Pathology short-form ($P<0.05$).

Conclusions: Patients with long-term cured CD show an increased prevalence of psychopathology and maladaptive personality traits. These observations suggest irreversible effects of previous glucocorticoid excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general. This may also be of relevance for patients treated with high doses of exogenous glucocorticoids.

Introduction

Patients with active Cushing's disease are exposed to excessive endogenous glucocorticoid levels, caused by ACTH-producingpituitaryadenomas.In these patients, psychopathology is often observed with major depression being the most common comorbid disorder, although mania and anxiety disorders have also been reported (1). After successful treatment of hypercortisolism, both physical and psychiatric signs and symptoms improve substantially (2, 3). However, these patients do not completely return to their premorbid level of functioning, and persistently impaired quality of life has been reported despite long-term cure (4). Furthermore, maladaptive personality traits were documentedafter treatment for Cushing's disease insome,but not all, studies (3, 5–7). Table 1 gives an overview of the current literature on psychopathology and personality traits in patients with Cushing's disease. Alarge number of studies in humans and animal models have documented that prolonged, increased endogenous or exogenous exposure to glucocorticoids may have longlasting adverse effects on behavioral and cognitive functions due to functional and, over time, structural alterations in specific brain target areas (8, 9). An important question is to what extent these adverse effects of glucocorticoids are reversible after withdrawal of glucocorticoid excess. At present, it is not clear whether, and to what extent, psychopathology and maladaptive personality traits persist after long-term cure of Cushing's disease. Therefore, our aim was to investigate psychopathology that is frequently present in patients with somatic illnesses and personality traits among long-term cured Cushing's disease patients, and compare them with matched controls. To exclude the possibility that pituitary adenomas and/or their treatment in general are associated with increased psychopathology or maladaptive personality traits, we also studied these parameters in patients previously treated for nonfunctioning pituitary macroadenomas (NFMA).

Table 1 Overview of studies on psychopathology and personality traits in patients with Cushing's disease

Author, year	Number of subjects	Gender (m/f)	Age yr (SD)	Active/treated	Methods	Outcomes
Cohen, 1980 (2)	29 Cushing's syndrome	7/22	42 (SD or range NA)	Almost all were seen during admission for diagnosis. A few were first seen immediately after surgery	Interviews. Detailed clinical history and an examination of mental state	Of all patients, 86% had distinct affective disorders. Twenty five patients suffered from depression, and one had manic and depressive episodes.
Starkman, 1981 (17)	35 Cushing's syndrome	7/28	35 (range 19-59)	Active	Semi-structured interview	Multiple psychiatric disturbances were found, including impairments in affect and vegetative functions. Low ACTH levels were associated with milder rather than pronounced depressed mood.
Haskett, 1985 (18)	30 Cushing's syndrome	6/24	37±11 (at time of diagnose)	6 untreated 24 treated (0-18 yrs before)	Schedule for affective disorders and schizophrenia-lifetime version of structured interview	83% of the patients met the criteria for an episode of affective disorder during the course of the disease. Patients frequently attempted to minimize or conceal psychiatric disturbance.
Starkman, 1986 (24)	23 Cushing's syndrome	5/18	37 (range 19-60)	Before and after treatment (2-72 months)	Semi-structured interview, Hamilton rating scale for depression	Depressed mood after treatment was significantly decreased in terms of decreased frequency compared to before treatment.
Sablowski, 1986 (6)	9 Cushing's disease 9 Acromegaly 6 Prolactinoma 24 Controls	NA	NA	Before and after surgery	Freiburger Personality Inventory, Gieβen test, State-trait-anxiety inventory	Pre-operative, there is a tendency to higher scores of trait-anxiety in pituitary patients compared to controls. This did not change after surgery. Furthermore, Cushing's disease patients seemed more nervous and restrained than acromegaly patients.
Loosen, 1992 (19)	20 Cushing's disease 20 major depressive disorder	1/19	39±11	Active	Structured clinical interview for DSM-III-R, Research diagnostic criteria, Family history research diagnostic criteria	79% of the patients received the diagnosis generalized anxiety disorder, 68% major depressive disorder, and 53% panic disorder.
Kelly, 1996 (20)	209 Cushing;s	47/162	39 (range 8-74)	Active	Clinical interview, Present	When Cushing's syndrome was diagnosed, 57% of

	syndrome 24 pituitary adenoma patients				State Examination, Hamilton rating scale for depression	the patients showed significant psychiatric illness, usually depression.
Kelly, 1996 (3)	43 Cushing's syndrome 24 acromegaly and prolactinoma	10/33	NA	Before and after treatment	Present state examination, Hamilton rating scale Crown-Crisp experiential index, Eysenck personality inventory	Present state examination: only 19% of the active Cushing's syndrome patients were normal, whereas 87% of the controls were normal. Depression and all scales of the Crown-Crisp improved after treatment. When patients were re-assessed after appropriate treatment, there was a significant decrease in neuroticism score but no change in extraversion.
Dorn, 1995 (21)	33 Cushing's syndrome 17 Matched hospitalized controls	5/28	36±9	Hypercortisolaemic during interview	Interviews, Atypical depression diagnostic scale, Hamilton rating scale, self-report instruments, medical records information	Anytime during the active phase, 67% of the patients had at least one diagnosis. Atypical depression was the most frequent finding (52%). The duration of CS was an important factor in predicting whether patients sought psychological intervention.
Dorn, 1997 (22)	33 Cushing's syndrome	5/28	36±9	Before and 3, 6, en 12 months after correction for hypercortisolism	Interviews, Atypical depression diagnostic scale, Hamilton rating scale, self-report instruments, medical records information	Before cure, 67% had significant psychopathology. After cure, overall psychopathology decreased to 54% at 3 months, 36% at 6 months, and 24% at 12 months. There was an inverse correlation between psychological recovery and baseline morning cortisol. Atypical depression remained the most frequent finding.
Sonino, 1998 (23)	162 Cushing's disease	38/124	38±13	Active	Paykel's clinical interview for depression	54% of the patients suffered from a major depressive disorder during the course of their illness. Depression was associated with older age, female sex, higher pretreatment urinary cortisol levels among others.
Flitsch, 2000 (29)	19 Cushing's disease 18 Acromegaly 11 NFMA	7/12	34±12	Before and after (6 months) transsphenoidal microsurgery	Semi-structured interview, Reiburger Personlichkeitsinventar, State-trait-anxiety-inventory, Rosenzweig	Most common psychopathological signs were excitability and depression. At least one of these signs was found in 12 out of 19 Cushing's disease patients. Six-eight months after surgery, majority of the

					picture frustration test, Befindlichkeitsskala, Giessener Beschwerdebogen	Cushing's disease patients (10 of 19) noticed an increase in physical well-being.
Sonino, 2006 (7)	24 Cushing's syndrome 24 Healthy matched controls	5/19	35±11	1-3 yrs in remission	Tridimensional personality questionnaire, Symptom rating test	No significant differences in personality dimensions between patients and controls. On the Symptom rating test, patients scored higher on anxiety, depression and psychotic symptoms compared to controls.
Sonino, 2007 (25)	Cushing's disease: 15 Other pituitary: 71 Non-pituitary: 60	uk	39 ± 12 (total sample)	Cured disease or in remission for >9 months <3 years	Structured clinical interview for DSM-IV, Diagnostic criteria for psychosomatic research, Psychosocial index, Medical outcomes study	Patients with Cushing's disease reported more stress and less well-being than controls. Twenty percent of the patients suffered from major depression, 33% from generalized anxiety disorder, and 47% of irritable mood.
Present study	67 Cushing's disease 67 Matched controls 55 NFMA 55 Matched controls	10/57	Cushing's disease: 53 (13) NFMA: 62 (10)	13±13 yrs in remission	Apathy Scale, Irritability Scale, Hospital Anxiety and Depression Scale (HADS), Mood and Anxiety Symptoms Questionnaire short-form (MASQ), and Dimensional Assessment of Personality Pathology short-form (DAPP)	Patients with cured Cushing's disease have an increased prevalence of psychopathology and maladaptive personality traits compared to matched controls and patients treated for NFMA. Compared to NFMA patients, the patients treated for Cushing's disease scored worse on apathy, irritability, negative affect and lack of positive affect, somatic arousal, and eleven out of eighteen maladaptive personality traits of the DAPP.

NA; not available, NFMA; non-functioning macro adenoma

Patients and Methods

Patients

We included four groups of subjects: 1) patients with long-term cure of Cushing's disease, and 2) gender-, age-, and education level-matched control subjects for these patients with previous Cushing's disease, 3) patients previously treated for NFMA, and 4) age-, gender-, and education level-matched control subjects for these patients previously treated for NFMA. The inclusion of these two separate control groups was necessary because patients with Cushing's disease and NFMA patients differ considerably with respect to age and gender distribution. We performed a clinical chart review of 85 patients who had been treated by transsphenoidal surgery if necessary followed by repeated surgery and/or postoperative radiotherapy. All were in remission of Cushing's disease at the time of the current study for at least 1yr. The long-term treatment outcome of these patients has been characterized and described in detail (10). We invited these patients to participate in the current study. Each patient was asked to provide a control person of comparable gender, age, and education level. Gender and education had to be the same, and age was allowed to differ maximally by 10 yr. Patients who did not respond were encouraged by phone to participate. Thirty-four patients (40%) refused to participate for several reasons including living outside The Netherlands, which implicated that the patients were not able to use the prepaid answer envelope to return the questionnaires. The other reasons were old age and/or debilitating disease. Fifty-one patients (60%) participated in the current study and completed all questionnaires. The clinical characteristics of the nonparticipants did not differ from those of the participants.

Cushing's disease had been diagnosed based on the clinical manifestations and positive biochemical tests including increased urinary excretion rates of free cortisol; decreased overnight suppression by dexamethasone (1mg); and, since 2004, elevated midnight salivary cortisol values in addition to non-suppressed ACTH levels. All patients had been treated by transsphenoidal surgery, if necessary, followed by repeated surgery and/or postoperative radiotherapy. Cure of Cushing's disease was defined by normal overnight suppression of plasma cortisol levels (<50nmol/l) after administration of dexamethasone (1mg) and normal 24h urinary excretion rates of cortisol (<220nmol/24h). Hydrocortisone independency was defined as a normal cortisol response to CRH or insulin-tolerance test (ITT). In addition, we invited 132 patients with NFMA treated previously by transsphenoidal surgery to participate in the study. The response rate was 94%. Fifty-five patients (42%) completed all questionnaires. There were no differences in clinical characteristics between participants and nonparticipants. Each patient was asked to provide a control person of comparable gender, age, and education level.

Pituitary function was assessed at yearly intervals in both patient groups. In patients cured of Cushing's disease who were glucocorticoid dependent after treatment, recovery of the pituitary-adrenal axis was tested twice a year. The dose of hydrocortisone was on average 20 mg/d divided into two to three dosages. After withdrawal of hydrocortisone replacement for 24h, a fasting morning blood sample was taken for the measurement of serum cortisol concentrations. Patients with serum cortisol concentration less than 120 nmol/l (blood samples obtained between 0800 and 0900 h) were considered to be glucocorticoid dependent, and hydrocortisone treatment was restarted. Patients with serum cortisol levels between 120 and 500 nmol/l were tested by ITT or CRH stimulation. In case the cortisol responses to these tests were less than 550 nmol/l, hydrocortisone treatment was restarted. In patients under the age of 70yr, GH-deficiency was assessed by ITT or combined GHRH-arginine test, after at least 2yr of remission of Cushing's disease. Patients with inadequate stimulation of GH by one of these tests were treated with recombinant human GH, aiming at IGF-I levels between 0 and +2 SD values. In addition, free T_4 and testosterone levels (in male patients) were assessed. If results were below the lower limit of the respective reference ranges, substitution with L-T_4 and/or testosterone was prescribed. In the case of amenorrhea and low estradiol levels in premenopausal women, estrogen replacement was provided.
Inclusion criteria for the current study were age older than 18yr and remission defined by strict biochemical criteria for at least 1yr. Patients with present or previous drug or alcohol abuse or with neurological disorders not related to Cushing's disease or NFMA were excluded. The protocol was approved by the Medical Ethics Committee and written informed consent was obtained from all subjects.

Questionnaires

Patients and controls were asked to complete questionnaires on psychopathology and personality at home and to return them in a prepaid envelope.

Apathy scale

Apathy was assessed using the Apathy Scale, which was designed at the Johns Hopkins School of Medicine (Baltimore, MD). The Apathy Scale consists of 14 questions on a four-point scale measuring the different features of apathy in the 2 wk before. The score for each item ranges from 0 (no apathetic behavior) to 3 (maximum intensity of apathetic behavior). The total score ranges from 0 to 42 points, with higher scores indicating greater apathy. A total score of 14 points or more is being used to characterize subjects as apathetic (11, 12).

Irritability scale
Irritability was assessed using the irritability scale that consists of 14 items on a four-point scale measuring different features of irritability in the 2 previous weeks. The total score ranges from 0 to 42 points, with higher scores indicating greater irritability. A total score of 14 points or more is being used to characterize subjects as irritable (12).

Hospital Anxiety and Depression Scale (HADS)
Anxiety and depression were assessed using the HADS that consists of 14 items on a four-point scale. Both anxiety and depression subscale scores range from 0 to 21 points. Higher scores indicate more severe anxiety and/or depression. A score greater than 8 points on one of the subscales is being used to characterize subjects as being anxious or depressed respectively (13, 14).

Mood and Anxiety SymptomsQuestionnaire shortform (MASQ-30)
The MASQ-30 consists of 30 items assessing symptoms that occur in mood and anxiety disorders subdivided into the three subscales of negative affect, lack of positive affect, and somatic arousal. The scores for each subscale ranges from 10 to 50, with higher scores indicating more severe negative affect, more lack of positive affect, or more somatic arousal. There are no formal cutoff scores (15).

Dimensional Assessment of Personality Pathology short-form (DAPPs)
The DAPPs consists of 136 items to assess personality traits, which are subdivided into 18 subscales: submissiveness, cognitive distortion, identity problems, affective lability, stimulus seeking, compulsivity, restricted expression, callousness, oppositionality, intimacy problems, rejection, anxiousness, conduct problems, suspiciousness, social avoidance, narcissism, insecure attachment, and self-harm. The score for each subscale differs with a maxima of 30–40 and higher scores indicating more pronounced maladaptive personality traits. There are no formal cut-off scores (16).

Statistical analysis

Data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL, USA). All data were presented as mean ± SD, unless mentioned otherwise. When data were missing, multiple imputation was used to impute the missing values. In the present study, this was not a major issue because only approximately 0.5% of the data were missing and therefore imputed. Ten different imputations were calculated and the pooled descriptives and P-values were used. The primary analysis comprised the comparison of the results between patients cured of Cushing's disease and their matched controls and between the patients with NFMA and their matched controls. Groups were compared using an independent-samples *t*

test. A χ^2 test was used in case of categorical data. Secondary analysis comprised the comparison of results of patients treated for Cushing's disease and patients treated for NFMA. Mean and SD scores for each questionnaire subscale were calculated for each control group, and subsequently Z-scores were calculated for each patient group in relation to their appropriate control group. Independent variables affecting psychopathology and personality in patients cured of Cushing's disease were explored by stepwise linear regression analysis. The standardized β-coefficients of this analysis were reported. The level of significance was set at $P \leq 0.05$.

Results

Sociodemographic and clinical characteristics

Patients cured of Cushing's disease and their matched controls

All patients (n=51) had been treated by transsphenoidal surgery, and 11 patients (22%) had been treated by additional radiotherapy because of persistent disease after surgery (Table 2). At the time of the current study, all patients were in remission and the mean duration of remission was 11±9yr (range 1–32yr, mode 3 and 5yr). Thirty-one patients (61%) were treated for some degree of pituitary insufficiency. Twenty-seven patients (53%) were substituted with hydrocortisone.

Patients treated for NFMA and their matched controls

All patients (n=55) had been treated by transsphenoidal surgery and 24 of these (43%) also by additional radiotherapy (Table 3). Mean duration of follow-up was 14±11yr (range 1–51yr, mode 4, 7, and 12yr). At the time of the current study, 51 patients (93%) were treated for pituitary insufficiency. Hydrocortisone substitution was used by 33 patients (60%).

Psychopathology

Patients cured of Cushing's disease versus their matched controls

Patients with long-term cure of Cushing's disease had a higher total score on the Apathy Scale ($t(85)=4.6$, $P<0.001$) and on the Irritability Scale ($t(77)=4.1$, $P<0.001$), compared with matched controls (Table 4). Patients also showed higher scores on the anxiety and depression subscales of the HADS ($t(82)=3.9$, $P<0.001$, and $t(78)=4.8$, $P<0.001$, respectively). On the MASQ-30, patients with long-term cured Cushing's disease scored higher on negative affect ($t(91)=3.5$, $P<0.001$) and somatic arousal ($t(78)=4.1$, $P<0.001$) and lower on positive affect ($t(95)=-3.7$, $P<0.001$). On the Apathy scale, 57% of the patients with Cushing's disease had a score of 14 or greater, and on the Irritability Scale, 31% of the patients had a score

Table 2 Clinical characteristics of patients cured of Cushing's disease and their matched controls

	Cushing's disease (n=51)	Matched controls (n=51)	P-value
Gender (male/female)	8/43	8/43	1.00
Age in yrs	53 (13)	54 (13)	0.70
Educational level (n)	Low: 20 Medium: 13 High: 18	Low: 18 Medium: 16 High: 17	0.80
Surgery, n (%)	51 (100%)	NA	NA
Postoperative radiotherapy, n (%)	11 (22%)	NA	NA
Duration of remission in yrs	11 (9)	NA	NA
Duration of follow-up in yrs	14 (10)	NA	NA
Hypopituitarism, n (%)	Any axis: 31 (61%) GH: 20 (39%) LH/FSH: 14 (28%) TSH: 21 (41%) ADH: 10 (20%)	NA	NA
Hydrocortisone substitution, n (%)	27 (53%)	NA	NA

Data are mean ± SD or number and %; NA=not applicable

of 14 or greater, indicative for the presence of clinically significant apathy and irritability, respectively. On the HADS, 26% of the patients with cured Cushing's disease scored greater than 8 on the depression subscale and 20% of the patients scored greater than 8 on the anxiety subscale. This is indicative for the presence of clinically relevant depression or anxiety, respectively. In particular, depression is evident in a substantial amount of the patients. Significantly more patients than controls had clinically relevant scores on these questionnaires (Apathy $P<0.001$; Irritability $P<0.001$; anxiety subscale HADS $P=0.014$; and depression subscale HADS $P=0.002$).

When patients with short-term (<10 yr, 28 patients (six males), aged 54±14yr) and long-term (≥10 yr, 23 patients (two males), aged 52±13yr) remission were compared, several differences were found. After a remission duration of more than 10yr, the patients scored significantly worse on the Apathy Scale ($P=0.002$), the depression subscale of the HADS ($P=0.033$), and the positive affect subscale of the MASQ-30 ($P<0.001$).

Patients treated for NFMA vs. their matched controls

Patients treated for NFMA had a higher total score on the Apathy Scale ($t(108)=3.0$, $P=0.003$) and higher mean scores on the anxiety and depression subscale of the HADS compared with their matched controls ($t(108)=-2.4$, $P=0.017$, and $t(108)=-4.7$, $P<0.001$, respectively), but the scores for the other scales (Irritability Scale and MASQ-30) were not different (Table 5). In patients treated for NFMA, a score of 14 or greater on the Apathy Scale was observed in 40%, a score of 14 or

Table 4 Psychopathology and personality traits in patients cured of Cushing's disease and their matched controls

	Cushing's disease (n=51)	Matched controls (n=51)	P-value
Apathy Scale			
Total score	14.8 (6.5)	9.8 (4.2)	**0.000**
Score ≥14, n (%)	29 (57%)	7 (14%)	**0.000**
Irritability Scale			
Total score	11.5 (7.7)	6.6 (4.2)	**0.000**
Score ≥14, n (%)	16 (31%)	2 (4%)	**0.000**
HADS			
Anxiety	6.2 (4.2)	3.5 (2.5)	**0.000**
Depression	5.6 (4.5)	2.1 (2.5)	**0.000**
Anxiety score >8, n (%)	10 (20%)	2 (4%)	**0.014**
Depression score >8, n (%)	13 (26%)	2 (4%)	**0.002**
MASQ-30			
Negative Affect	18.2 (6.7)	14.2 (4.8)	**0.001**
Positive Affect	25.7 (9.6)	32.1 (7.6)	**0.000**
Somatic Arousal	17.4 (6.6)	13.1 (3.7)	**0.000**
DAPP			
Submissiveness	19.0 (7.7)	15.4 (5.5)	**0.008**
Cognitive distortion	11.5 (5.6)	8.4 (2.6)	**0.001**
Identity problems	13.0 (6.6)	8.7 (3.3)	**0.000**
Affective lability	21.7 (7.8)	13.9 (4.7)	**0.000**
Stimulus seeking	14.6 (4.8)	13.6 (4.3)	0.260
Compulsivity	23.8 (6.6)	20.1 (6.1)	**0.004**
Restricted expression	21.2 (7.3)	18.0 (6.0)	**0.016**
Callousness	16.1 (4.5)	15.3 (4.4)	0.392
Oppositionality	22.9 (8.8)	17.2 (5.5)	**0.000**
Intimacy problems	18.8 (6.4)	20.5 (7.0)	0.188
Rejection	17.2 (5.7)	17.1 (6.0)	0.959
Anxiousness	15.3 (6.2)	11.1 (4.2)	**0.000**
Conduct problems	9.0 (1.8)	9.0 (1.6)	0.953
Suspiciousness	12.6 (5.9)	10.8 (3.0)	0.061
Social avoidance	12.3 (6.3)	9.8 (3.2)	**0.014**
Narcissism	15.0 (5.5)	13.3 (5.0)	0.091
Insecure attachment	13.3 (6.6)	10.7 (4.5)	**0.025**
Self-harm	7.3 (2.9)	6.5 (1.8)	0.110

Data are mean (SD), unless otherwise mentioned

greater on the Irritability Scale in 27%, a score greater than 8 on the HADS anxiety scale in 15%, and a score greater than 8 on the depression scale in 13%. There were significantly more patients than controls with a clinically relevant score on the HADS depression scale (P=0.026). There were no differences between patients with short-term (<10yr) and long-term (≥10yr) duration of follow-up.

Factors associated with psychopathology in patients cured of Cushing's disease
Stepwise linear regression analysis was performed using the absolute test scores of the patients with long-term cure of Cushing's disease as dependent variables and gender, age, education, hypopituitarism, hydrocortisone dependency, additional

Table 5 Psychopathology and personality traits in patients treated for NFMA and their matched controls

	NFMA patients (n=55)	Matched controls (n=55)	P-value
Apathy Scale			
Total score	12.8 (4.7)	10.2 (4.1)	**0.003**
Score ≥14, n (%)	22 (40%)	13 (24%)	0.065
Irritability Scale			
Total score	10.0 (5.8)	8.9 (5.1)	0.289
Score ≥14, n (%)	15 (27%)	10 (18%)	0.255
HADS			
Anxiety	5.0 (3.6)	3.5 (3.0)	**0.017**
Depression	4.6 (3.9)	1.7 (2.1)	**0.000**
Anxiety score >8, n (%)	8 (15%)	3 (6%)	0.105
Depression score >8, n (%)	7 (13%)	1 (2%)	**0.026**
MASQ-30			
Negative Affect	15.6 (5.8)	14.9 (5.8)	0.492
Positive Affect	29.3 (8.3)	30.4 (8.0)	0.491
Somatic Arousal	15.0 (5.7)	13.5 (4.4)	0.137
DAPP			
Submissiveness	16.5 (5.6)	17.1 (6.1)	0.636
Cognitive distortion	9.5 (3.9)	9.8 (4.9)	0.747
Identity problems	10.2 (4.5)	9.6 (4.3)	0.454
Affective lability	18.8 (5.6)	16.1 (5.6)	**0.013**
Stimulus seeking	14.5 (4.4)	14.2 (5.1)	0.748
Compulsivity	22.3 (6.9)	21.9 (6.6)	0.746
Restricted expression	21.9 (4.5)	20.2 (5.2)	0.080
Callousness	16.9 (4.6)	15.9 (4.3)	0.222
Oppositionality	20.3 (6.5)	19.1 (6.7)	0.378
Intimacy problems	20.1 (6.7)	19.3 (6.6)	0.566
Rejection	18.3 (5.8)	17.0 (5.9)	0.260
Anxiousness	12.8 (4.7)	12.9 (4.8)	0.905
Conduct problems	9.7 (2.8)	9.5 (2.4)	0.690
Suspiciousness	11.0 (3.5)	10.9 (4.0)	0.995
Social avoidance	11.3 (3.9)	10.7 (4.0)	0.374
Narcissism	15.6 (4.9)	15.4 (5.9)	0.902
Insecure attachment	13.0 (5.2)	13.1 (5.3)	0.928
Self-harm	6.9 (2.4)	6.4 (1.7)	0.228

Data are mean (SD), unless otherwise mentioned

radiotherapy, and duration of remission as independent variables. The total score on the Apathy Scale was negatively influenced by educational level (β=-0.380, P=0.009), which means that a higher education level predicts a lower score on the Apathy Scale in these patients. The total score on the Irritability Scale was positively associated with additional radiotherapy (β=0.314, P=0.034), which indicates that patients who had additional radiotherapy scored higher on the Irritability Scale. The depression subscale of the HADS was positively influenced by the duration of remission (β=0.358, P=0.015), meaning that a longer duration of remission indicates a higher score on the depression subscale of the HADS. On the MASQ-30, the positive affect subscale was positively influenced by gender (β=0.410, P=0.003), with females scoring higher, and education (β=0.338, P=0.012), with higher educational level predicting higher scores. The positive affect subscale was negatively associated with duration of remission (β=-0.332, P=0.014), with longer duration of remission indicating lower scores on this subscale. The negative affect subscale was negatively associated with gender (β=-0.361, P=0.014), with females scoring lower, and positively influenced by duration of remission (β=0.311, P=0.032), with longer duration of remission indicating higher scores on the negative affect subscale.

Personality

Patients cured of Cushing's disease versus their matched controls

Patients with long-term cure of Cushing's disease scored worse compared with matched controls on the DAPPs personality traits submissiveness (t (90)=2.7, P=0.008), cognitive distortion (t (71)= 3.6, P<0.001), identity problems (t (74)=4.2, P<0.001), affective lability (t (82)=6.1, P<0.001), compulsivity (t (100)=2.9, P=0.004), restricted expression (t (97)=2.5, P=0.016), oppositionality (t (84)=4.0, P<0.001), anxiousness (t (89)=4.0, P<0.001), social avoidance (t (74)=2.5, P=0.014), and insecure attachment (t (88)=2.3, P=0.025), see also Table 4. When using depression and anxiety as covariates, only two traits remained statistically different between patients and controls: affective lability (F (1)=16.3, P<0.001) and anxiousness (F (1)=5.2, P=0.024). This observation increases the likelihood of the presence of these premorbid traits. The traits identity problems (F (1)=3.1, P=0.081), compulsivity (F (1)=2.9, P=0.092), and intimacy problems (F (1)=2.9, P=0.094] showed trend significance. When only co-varying for depression, the traits affective lability (F (1)=15.5, P<0.001) and anxiousness (F (1)=5.7, P=0.019) remained significantly different between patients and controls, whereas the traits identity problems (F (1)=3.5, P=0.064), compulsivity (F (1)=3.3, P=0.071), oppositionality (F (1)=3.0, P=0.087), and intimacy problems (F (1)=3.1, P=0.079) showed trend significance. When patients with short-term (<10yr, 24 patients (17 men), aged 58±11yr) and long-term (≥10yr, 31 patients (13 men), aged 65±7yr) remission were

compared, only minor differences were found. After a remission duration of more than 10yr, the patients scored significantly worse only on the identity problems subscale (P=0.045) and the intimacy subscale (P=0.003) of the DAPPs.

Patients treated for NFMA vs. their matched controls

Patients treated for NFMA scored worse on the trait affective lability (t (108)=2.5, P=0.013) of the DAPPs compared with controls but not on other traits.

When patients with short-term (<10yr) and long-term (≥10yr) duration of follow-up were compared, patients with long-term follow-up scored higher on the intimacy subscale of the DAPPs (P=0.020), see also Table 5.

Factors associated with personality in patients cured of Cushing's disease

On the DAPPs questionnaire, several subscales were associated with the independent variables: the cognitive distortion subscale was negatively associated with education (β=-0.391, P=0.007), with higher education indicating lower scores on the cognitive distortion subscale. The identity problems subscale was positively influenced by additional radiotherapy (β=0.329, P=0.021) and hydrocortisone dependency (β=0.278, P=0.049), with additional radiotherapy and hydrocortisone dependency predicting higher scores. The rejection subscale was positively associated with education (β=0.426, P=0.003), with higher education being associated with higher scores on this subscale. The conduct problems subscale was negatively associated with gender (β=-0.331, P=0.024), with females scoring lower. The suspiciousness subscale was positively associated with hypopituitarism (β=0.302, P=0.042), which indicates that hypopituitarism is associated with higher scores on the suspiciousness subscale. Finally, the self-harm subscale was positively affected by duration of remission (β=0.370, P=0.011), with longer duration of remission being associated with higher scores on the self-harm subscale.

Comparison of Z-scores between patients cured of Cushing's disease and patients treated for NFMA

In comparison with patients treated for NFMA, patients with long-term cure of Cushing's disease had higher scores on the Apathy Scale (P<0.001), the Irritability Scale (P<0.001), and on the anxiety subscale of the HADS (P<0.001). Furthermore, patients with cured Cushing's disease scored higher on the negative affect (P<0.001) and on the somatic arousal (P<0.001) subscales of the MASQ-30, whereas they scored lower on the positive affect subscale (P<0.001). On the DAPPs, patients with cured Cushing's disease scored worse when compared with patients treated for NFMA on submissiveness (P=0.002), cognitive distortion (P<0.001), identity problems (P<0.001), affective lability (P<0.001), compulsivity (P=0.010), oppositionality (P<0.001), anxiousness (P<0.001), conduct problems

Comparison of psychopathology of patients with Cushing's disease and patients with NFMA by Z-scores

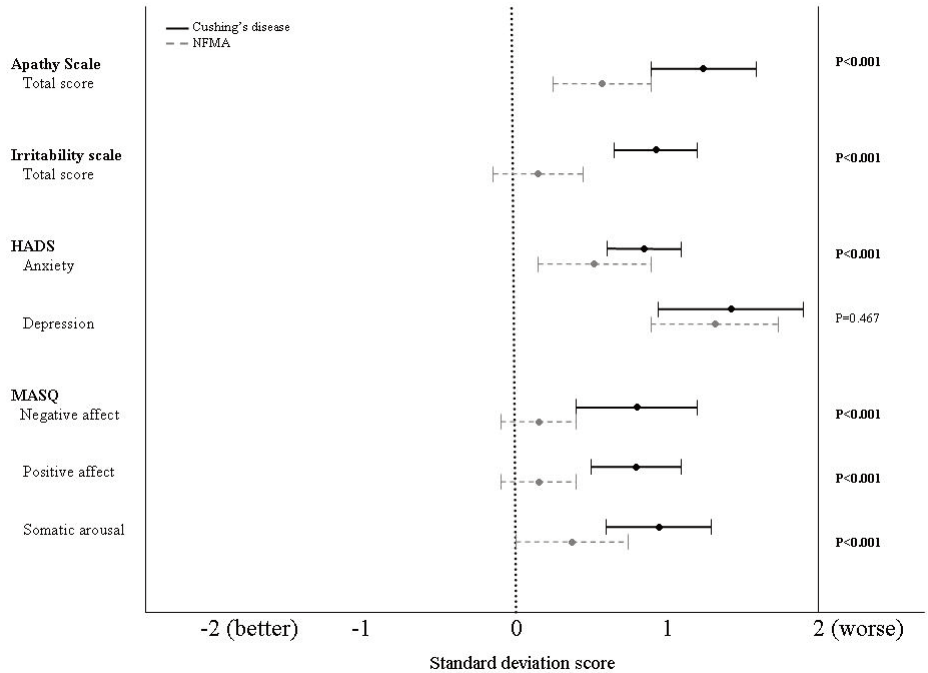

Figure 1: *Figure 1: Z-scores of patients cured from Cushing's disease and of patients treated for NFMA, calculated for each patient group by comparison with their own matched control groups. Z-scores with 95% confidence intervals are shown in this figure. The zero Z-line indicates the scores of the matched controls. On the apathy scale, irritability scale, anxiety subscale of the HADS, and all three subscales of the MASQ-30 patients with long-term cured Cushing's disease scored worse when compared with patients with treated NFMA.*

(P<0.001), suspiciousness (P=0.049), social avoidance (P=0.049), and insecure attachment (P=0.019). This is also shown in Figure 1 and Figure 2.

Discussion

This study demonstrates that patients with long-term cure of Cushing's disease suffer from more psychopathology and maladaptive personality traits compared with matched controls. In addition, patients with long-term cure of Cushing's disease had significantly more psychopathology and maladaptive personality traits than patients previously treated for NFMA, indicating that the presence of psychopathology and maladaptive personality traits was not merely related to pitu-

Comparison of personality traits (DAPPs) of patients with Cushing's disease and patients with NFMA by Z-scores

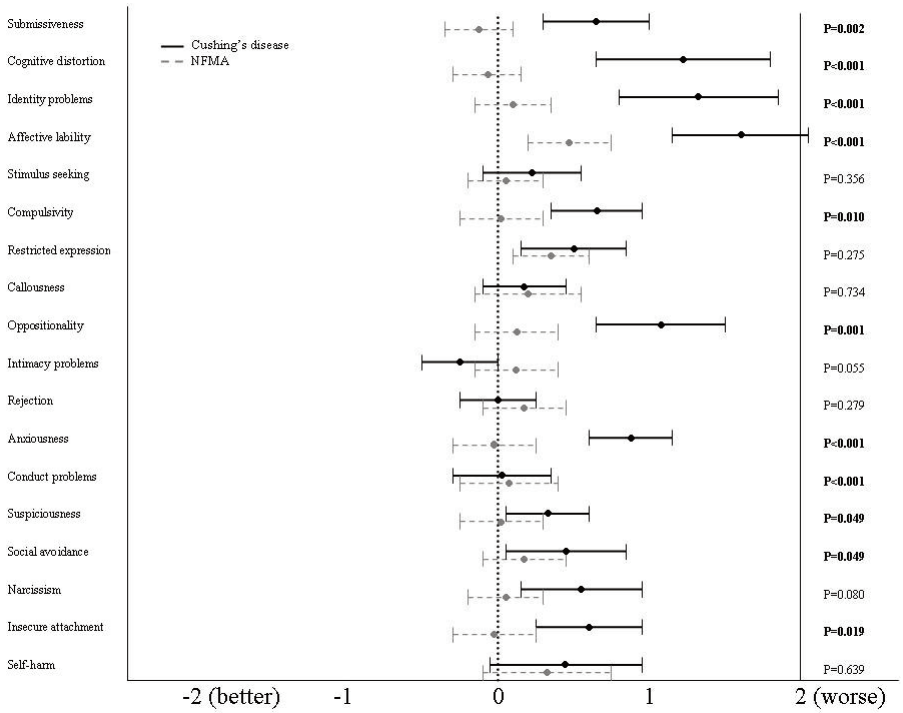

Figure 2*: Z-scores of patients cured from Cushing's disease and of patients treated for NFMA. Patients with long-term cured Cushing's disease scored worse when compared with patients with treated NFMA on the DAPP subscales submissiveness, cognitive distortion, identity problems, affective lability, compulsivity, oppositionality, anxiousness, conduct problems, suspiciousness, social avoidance, and insecure attachment.*

itary tumors and/or their treatment in general. Therefore, the long-term effects of cured Cushing's disease on psychopathology and personality traits are more likely to be the consequence of previous glucocorticoid excess. These observations point to irreversible effects of previous glucocorticoid excess on the central nervous system. Psychopathology is reported to be present in the majority of patients with active Cushing's disease (17). Major depression, atypical depression, or at least one other psychiatric diagnosis, is present in more than 50% of these patients (18–23). Appropriate treatment of hypercortisolism results in improvement of these symptoms in many of these patients (2, 3, 24), and the prevalence of overall psychopathology decreases to 24% of the patients within 1yr after appropriate treatment of active Cushing's disease (21, 22). Therefore, appropriate treatment of Cushing's disease results in improvement of the psychiatric manifestations asso-

ciated with this disease.

Several previous studies evaluated the effects of Cushing's disease and Cushing's syndrome on psychopathology and personality traits. These studies are summarized in Table 1. Several previous studies in patients with active Cushing's disease concluded that patients had a higher tendency for anxiety than controls (6, 19, 25). In contrast, Kelly *et al.* (3) concluded that patients with active Cushing's syndrome and control patients scored equally on personality traits (neuroticism and extraversion). When patients with Cushing's syndrome were reassessed after appropriate treatment, there was a significant decrease in neuroticism score but not extraversion. However, another recent study concluded that were no differences in personality traits between patients with Cushing's syndrome in remission and controls (7). Therefore, maladaptive personality traits are documented after treatment of Cushing's disease in some, but not all, studies. However, these studies included only limited numbers of patients with heterogeneous clinical characteristics. Moreover, the long-term effects of cure of Cushing's disease have not been studied in detail.

A limitation of the present study was the cross-sectional study design instead of a longitudinal design. Consequently, we do not have any information on premorbid functions, the effects of active Cushing's disease, and the extent of reversibility of the disturbed parameters. Nonetheless, these observations do not invalidate our observations that patients with long-term cure show an increased prevalence of psychopathology and maladaptive personality traits compared with matched controls and with patients treated similarly for NFMA. It might be argued that the use of mailed self-rating scales for depression and anxiety is a limitation. However, self-reported scales provide a valuable tool to measure the patients' perception of their illness, which is not possible with observer ratings (26). Furthermore, we intended to screen for symptoms of possible psychopathology, not to establish psychopathology. Another possible limitation is the fact that the most distressed subjects are the ones who are more likely participate. Unselected series (3, 7, 22) reported a prevalence of psychopathology of 24–32% in patients cured from Cushing's disease, which is in accordance with data of the present study.

Patients with long-term cure of Cushing's disease provide a unique human model to study the effects of prolonged, but transient (endogenous), glucocorticoid excess. Furthermore, the results of the current study may be relevant for patients who have previously been treated with prolonged high doses of glucocorticoids (27, 28).

In summary, patients with long term cure of Cushing's disease report a high prevalence of psychopathology, compared with both matched controls and patients previously treated for NFMA. Furthermore, patients with long-term cure of Cush-

ing's disease have a greater degree of maladaptive personality traits. The results suggest that these observations reflect irreversible effects of previous glucocorticoid excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general.

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