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Mortality in Patients Treated for Cushing's Disease Is Increased, Compared with Patients Treated for Nonfunctioning Pituitary Macroadenoma

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Context: Increased mortality in patients with pituitary tumors after surgical treatment has been reported. However, it is unknown to what extent excess mortality is caused by pituitary tumors and their treatment in general and to what extent by previous exposure to hormonal overproduction.

Objective: The aim of the study was to compare mortality between patients treated for Cushing's disease and nonfunctioning pituitary macroadenomas (NFMAs).

Design: This was a follow-up study.

Patients: We included 248 consecutive patients with pituitary adenomas treated by transsphenoidal surgery in our hospital for NFMAs (n = 174) and ACTH-producing adenomas (n = 74). The mean duration of follow-up after surgery was 10.1 ± 7.2 yr for the whole cohort.

Outcome Measures: The standardized mortality ratio (SMR) was calculated for the whole cohort and also for the two diseases separately. Cox regression analysis was used to compare mortality in patients with Cushing's disease with NFMA patients.

Results: Patients with Cushing's disease (39.1 ± 16.1 yr) were significantly younger at time of operation than NFMA patients (55.3 ± 13.4 yr). The SMR for the whole cohort was 1.41 [95% confidence interval (CI), 1.05–1.86]. The SMR in NFMA patients was 1.24 (95% CI, 0.85–1.74) *vs.* 2.39 (95% CI, 1.22–3.9) in patients with Cushing's disease. In patients with Cushing's disease, compared with NFMAs, the age-adjusted mortality was significantly increased: hazard ratio 2.35 (95% CI, 1.13–4.09, $P = 0.008$).

Conclusions: Mortality in patients previously treated for Cushing's disease is increased, compared with patients treated for NFMAs. This implies that previous, transient overexposure to cortisol is associated with increased mortality. **(*J Clin Endocrinol Metab* 92: 976–981, 2007)**

PITUITARY ADENOMAS ARE benign neoplasms associated with considerable morbidity due to mass effects, hormonal overproduction, and pituitary insufficiency. In nonfunctioning pituitary macroadenomas (NFMAs), morbidity is caused by mass effects of the tumor leading to visual field defects, decreased visual acuity, and pituitary insufficiency in the majority of patients (1). In functioning pituitary adenomas, morbidity is caused by hormonal overproduction, in addition to tumor mass effects in cases of macroadenomas. In Cushing's disease, cortisol excess causes central obesity, insulin resistance, hypertension, hyperlipidemia, and osteoporosis (2, 3). Moreover, cortisol overproduction is associated with increased cardiovascular risk, continuing even after remission of the disease (4, 5).

In addition to increased morbidity, a number of studies have reported increased mortality in patients with pituitary tumors (6–10) and associated conditions such as hypopituitarism (11–13). In the majority of these studies the general population was used as a control group to assess mortality risk in patients with pituitary adenomas. However, this approach is not able to make a distinction between the effects of hormone overproduction *per se vs.* the general aspects of the pituitary tumor and their treatment, on mortality.

We performed a single-center study to assess mortality rates during long-term follow-up after transsphenoidal surgery in patients with nonfunctioning pituitary macroadenomas and Cushing's disease. Mortality in pituitary adenomas is associated with general aspects of pituitary tumors and their treatment but also with disease-specific morbidity due to overproduction of pituitary hormones. To answer the question to which extent previous exposure to hormonal overproduction *per se* is associated with increased mortality, we compared mortality in patients operated for Cushing's disease to mortality in patients operated for NFMAs because patients treated for NFMAs lack cortisol excess specific for Cushing's disease.

Patients and Methods

Patients

All 248 consecutive patients treated at the Leiden University Medical Center between 1977 and 2005 by primary transsphenoidal surgery for NFMAs (n = 174) and Cushing's disease (n = 83) were eligible for inclusion in the study. Because the Leiden University Medical Center is a tertiary referral center for both NFMAs and Cushing's disease, patients were referred in the same way. It is unlikely that there were differences

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Abbreviations: CI, Confidence interval; FT4, free T_4; ITT, insulin tolerance test; MRI, magnetic resonance imaging; NFMA, nonfunctioning pituitary macroadenoma; SMR, standardized mortality ratio.

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in referral between both diseases. The majority of these patients were described in previous studies (1, 14). For mortality analysis, information on emigration, death, or survival was available for all patients. Nine of the patients with Cushing's disease were excluded from the analysis because the initial treatment, before transsphenoidal surgery, consisted of unilateral adrenalectomy followed by pituitary irradiation. Therefore, we included 74 patients with Cushing's disease in the analysis.

Clinical, endocrinological, visual, and radiological preoperative assessment was available for all patients. Clinical, endocrinological, and visual characteristics were assessed within the first 2 months after surgery and, subsequently, every 6–12 months during prolonged follow-up.

The follow-up of the patients was part of regular medical care. The approaches described in this paper did not involve any randomization or any experimental intervention. According to Dutch law, each patient has to be fully informed on the pros and contras of each treatment strategy, and each patient can be treated only after giving oral informed consent for each treatment.

Diagnostic criteria and criteria for cure/recurrence

NFMA was diagnosed if there was a pituitary macroadenoma without clinical or biochemical evidence of hormonal overproduction. The diagnosis of Cushing's disease was made on clinical grounds together with biochemical confirmation, based on the following tests: increased 24-h urinary excretion of free cortisol (criterion > 220 nmol per 24 h), failure of serum cortisol to suppress after low-dose dexamethasone (1 mg), suppression of serum cortisol during a 7-h iv dexamethasone suppression test (15), and a normal or exaggerated response of serum ACTH and cortisol to iv CRH stimulation (16). In patients with Cushing's disease, in whom a pituitary adenoma was not visualized by magnetic resonance imaging (MRI), selective inferior petrosal sinus sampling was performed. A central to peripheral ACTH gradient of greater than 2 (basal) or 3.5 (after CRH) was considered confirmative for an ACTH-producing adenoma.

Tumor recurrence in patients with NFMA was defined as an increase in tumor volume on sequential radiological imaging. Biochemical cure in Cushing's disease was defined as a normal suppression of serum cortisol levels to 1 mg oral dexamethasone (cortisol < 100 nmol/liter the following morning) and normal 24 urine free cortisol excretion in two consecutive samples. Persistent Cushing's disease was defined as a failure to fulfill biochemical criteria for remission 3–6 months after the first operation (14). Relapse of Cushing's disease was defined as recurrence of hypercortisolism, using the above-mentioned criteria for Cushing's disease.

Assays

Until 1986 cortisol was measured by in-house RIA with an interassay coefficient of variation of 10%. Between 1986 and 1994, a fluorescence energy-transfer immunoassay Syva Advance (Syva Co., Palo Alto, CA) was used, with an interassay variation coefficient of 3.6–6.1%. From 1994 cortisol was measured by fluorescence polarization assay on a TDx (Abbott, Abbott Park, IL). The interassay variation coefficient is 5–6% above 0.5 μmol/liter and amounts to 12% less than 0.20 μmol/liter.

Hormonal evaluation and treatment

GH deficiency was defined by an IGF-I level below the reference range for age and sex (17) and an insufficient rise in GH levels (absolute value < 3 μg/liter) after stimulation during an insulin tolerance test (ITT). An ITT was performed in all patients except in patients with a contraindication such as cardiac arrhythmias and epilepsy. In those patients a combined arginine-GHRH test was performed (reference values GH in healthy adults > 8 μg/liter) (18).

ACTH deficiency was defined by a basal cortisol level at 0800 h of less than 0.12 μmol/liter and/or an insufficient increase in cortisol levels (absolute value < 0.55 μmol/liter) after an ITT (nadir glucose < 2.2 nmol/liter). When secondary amenorrhea was present for more than 1 yr, premenopausal women were defined as LH/FSH deficient. Postmenopausal women were defined as LH/FSH deficient when gonadotrophin levels were below the normal postmenopausal range (LH < 10 U/liter, FSH < 30 U/liter). In men, LH/FSH deficiency was defined as a low testosterone level (<8.0 nmol/liter) with an inappropriate low LH/FSH. TSH deficiency was defined as low free T_4 (FT4) with an inappropriately low serum TSH. We always measured TSH and FT4 together. However, we consider FT4 levels as the marker for the pituitary thyroid axis in patients with pituitary diseases. The reason to use this hormone is that TSH levels are not a reliable marker of the status of the pituitary thyroid axis in secondary hypothyroidism. TSH levels can be low, normal, or even slightly elevated in the case of secondary hypothyroidism (19). Likewise, we used testosterone levels in men as the marker for pituitary-gonadal function. In postmenopausal women we used LH and FSH levels as a marker for pituitary gonadal axis.

In case of ACTH deficiency, patients were treated with hydrocortisone (standard treatment regimen: 20 mg daily), and TSH deficiency was treated with levothyroxine. In case of LH/FSH deficiency, treatment in men was substituted with testosterone and women younger than 50 yr with estrogen/progesterone replacement. From 1994 onward, patients with documented GH deficiency were treated with recombinant human GH.

Tumor size classification and radiological follow-up

Radiological imaging was performed by computed tomography (until 1985) and subsequently by MRI. Tumor size was classified according to Hardy (20). For the present study, the classification was simplified to microadenoma (Hardy I^{0}), noninvasive macroadenoma (Hardy $II^{0,A,B,C}$), and invasive macroadenomas (with suprasellar or parasellar invasive growth; *i.e.* Hardy $II^{D,E}$, Hardy $III^{0\text{-}E}$, and Hardy $IV^{0\text{-}E}$). Radiological imaging was performed according to protocol. In patients with NFMA, imaging was performed within 1 yr after the initial surgical treatment, and subsequently computed tomography or MRI scanning was performed every second year. In patients with Cushing's disease, repeat radiological imaging was performed in case of persistent or recurrent disease or according to the judgment of the treating physician.

Treatment

All 248 patients were operated by transsphenoidal approach. Postoperative, conventional radiotherapy was applied in 50 cases to prevent recurrence in NFMA or to treat persistent active Cushing's disease. Recurrent disease in NFMA was treated by radiotherapy, repeat surgery, or both. Persistent or recurrent disease in Cushing's disease was treated by bilateral adrenalectomy, radiotherapy, repeat surgery, or a combination of these treatment modalities.

Statistics and mortality analysis

We used two different methods to assess mortality in patients with pituitary adenomas. First, we calculated the standardized mortality ratio (SMR) for the whole cohort as well as for the two different pituitary diseases included in the study, *i.e.* NFMA and Cushing's disease. The SMR enables the comparison between mortality in the general population and the diseased population. Normal mortality rates for the Dutch population were obtained from the Dutch Central Bureau of Statistics (The Netherlands) using mortality rates per sex, age groups of 5 yr, and calendar periods of 5 yr (1975, 1980, 1985, 1990, 1995, and 2000). Expected mortality rates were determined based on the person-year follow-up for each sex and age group and each calendar period and compared with the observed mortality rate. Second, for a direct comparison between the groups, we used Cox-regression analysis to assess the effect of different pituitary adenomas on mortality. The model adjusted for sex and age at the time of operation. We did not correct for tumor volume and hypopituitarism because, although these factors might be associated with mortality, they are closely associated with the underlying diagnosis. Data are expressed as mean ± SD, unless otherwise mentioned. The χ^2 test was used for categorical data.

Results

Patient characteristics (Table 1)

We included 248 consecutive patients in this study, who were transsphenoidally operated for NFMA (n = 174) and Cushing's disease (n = 74). The mean duration of follow-up for the total cohort was 10.1 ± 7.2 yr, comprising a total of 2497 person-years. The mean age at time of operation was

TABLE 1. Patient characteristics

	Nonfunctioning macroadenoma	Cushing's disease
No. of patients	174	74
Age at operation (yr)	55.3 ± 13.4	39.1 ± 16.1
Male/female	98/76	18/56
Mean follow-up (yr)	9.1 ± 6.6	12.8 ± 7.3
Radiological characteristics		
Microadenoma (%)		85
Noninvasive macroadenoma (%)	70	11
Invasive macroadenoma (%)	30	4
Pituitary function		
Preoperative pituitary insufficiency (%)	85	3
Preoperative GH deficiency (%)	79	3
Preoperative LH/FSH deficiency (%)	71	3
Preoperative TSH deficiency (%)	47	1
Preoperative ACTH deficiency (%)	51	
Postoperative pituitary insufficiency (%)	91	18
Postoperative GH deficiency (%)	83	15
Postoperative LH/FSH deficiency (%)	84	15
Postoperative TSH deficiency (%)	57	10
Postoperative ACTH deficiency (%)	55	
Pituitary insufficiency longest follow-up (%)	93	44
GH insufficiency longest follow-up (%)	85	32
LH/FSH insufficiency longest follow-up (%)	86	30
TSH insufficiency longest follow-up (%)	65	32
ACTH insufficiency longest follow-up (%)	64	41

significant younger in patients with Cushing's disease (39.1 ± 16.1 yr), compared with patients with NFMA (55.3 ± 13.4 yr, $P < 0.001$). Female gender was more prevalent in Cushing's disease (77%) than in NFMA (44%, $P < 0.001$). All NFMA patients had a macroadenoma, whereas patients with Cushing's disease had a high prevalence of microadenomas (85%). Preoperative pituitary insufficiency was significantly more prevalent in NFMA patients (85%), compared with patients with Cushing's disease (3%) ($P < 0.001$).

In patients with Cushing's disease 16% had diabetes mellitus, and 79% had hypertension at initial presentation. In patients with NFMA, 4% had diabetes mellitus, and 49% had hypertension, at presentation.

Treatment and treatment outcome (Table 2)

Long-term tumor control, *i.e.* the absence of radiological evidence of tumor recurrence, was achieved in 84% of all NFMA patients. Tumor recurrence in NFMA was treated by radiotherapy (n = 14), surgery (n = 4), or combined surgery and radiotherapy (n = 5). In three other patients, a wait-and-see approach was undertaken after recurrence of the adenoma because of high age and serious comorbidity.

Eighty percent of the patients operated for Cushing's disease achieved initial remission. Eight patients relapsed after initial remission. Persistent disease (n = 15) or recurrent (n = 8) disease was treated by repeat surgery (n = 4), radiotherapy (n = 8), or a combination of these treatment modalities with or without adrenalectomy (n = 9). In patients in whom radiotherapy was offered, treatment with ketoconazole also was started to minimize ongoing effects of hypercortisolism. In two patients a wait-and-see approach was undertaken because of high age (n = 1) and because the patient refused additional treatment (n = 1). These two patients were alive at the time of the final evaluation. Long-term remission of Cushing's disease was achieved in 93% of all patients.

At longest follow-up, 93% of patients with NFMA and 44% of patients with Cushing's disease had pituitary insufficiency in at least one axis. All patients with ACTH deficiency and/or TSH deficiency were substituted with hydrocortisone (20 mg/d) and/or levothyroxine. Male patients with LH/FSH deficiency were treated with testosterone, premenopausal female patients with combined estrogen and progesterone substitution. Of all patients with GH deficiency, 39% (NFMA) and 46% (Cushing's disease) were treated with recombinant human GH.

Mortality

During a mean follow-up period of 10 yr, 47 patients with a mean age 71.1 ± 12.0 yr died (NFMA, n = 35; Cushing's disease, n = 12). The all-cause mortality was 20% in NFMA patients and 16% in Cushing's disease. However, the mean age at death was younger in patients with Cushing's disease (62.4 ± 11.5 yr), compared with patients with NFMA (74.1 ± 10.7 yr, $P < 0.05$). Causes of death were cardiovascular dis-

TABLE 2. Treatment characteristics

NFMA (n = 174)	
Transsphenoidal surgery	174
Repeat surgery for recurrence	9 (in 5 cases combined with radiotherapy)
Postoperative radiotherapy	63
Prophylactic	42
For recurrence	19
Cushing's disease (n = 74)	
Transsphenodal surgery	74
Bilateral adrenalectomy	6
Repeat surgery	10
For persistent disease	4
For recurrence	6
Radiotherapy	14
Prophylactic	1
For persistent disease	7
For recurrent disease	6

TABLE 3. SMRs and causes of mortality after transsphenoidal surgery for pituitary adenomas

	Total cohort (n = 248)	Nonfunctioning macroadenoma (n = 174)	Cushing's disease (n = 74)
No. of deaths	47	35	12
Age of dying (yr)	70.5 ± 10.7	74.1 ± 10.7	62.4 ± 11.5
SMR	1.41, 95% CI 1.05–1.86	1.24, 95% CI 0.85–1.74	2.39, 95% CI 1.22–3.9
Causes of death			
Cardiovascular	11	7	4
Malignancies	9	8	1
Infectious	8	7	1
Cerebrovascular	6	5	1
Persistent disease despite multimodality treatment	1		1
Unknown	5	3	2
Other	7	5	2

ease in 23.4%, cerebrovascular disease in 12.8%, malignancy in 19.1%, and infectious diseases in 17% of all patients. The cause-specific mortality for NFMA and Cushing's disease is provided in Table 3. One patient with Cushing's disease died because of persistent severe Cushing's disease, despite multimodality treatment.

SMRs (Table 3)

A total of 2497 person-years was available for comparison with normative data of the Dutch population. The SMR for the whole cohort, derived from the observed to expected ratio (47:33.2), was 1.41 [95% confidence interval (CI) 1.05–1.86].

The SMR in NFMA patients was 1.24 (95% CI, 0.85–1.74), whereas in patients with Cushing's disease, the SMR was 2.39 (95% CI, 1.22–3.9). The SMR in patients with Cushing's disease with remission after transsphenoidal surgery was 1.80 (95% CI, 0.71–3.37), whereas the SMR in patients with persistent disease was 4.38 (95% CI, 1.38–9.07).

Mortality in Cushing's disease, compared with nonfunctioning adenomas (Fig. 1)

We performed Cox regression analysis to assess the effect of two different diseases, NFMA and Cushing's disease, on mortality. In the regression analysis, we adjusted for age at initial operation and sex because age and sex distribution were significantly different between the two study groups. We used the NFMA patients as reference group to assess the difference in mortality rate compared with Cushing's disease.

In patients with Cushing's disease, compared with NFMA, mortality was significantly increased: hazard ratio 2.35 (95% CI, 1.13–4.09, $P = 0.008$). By regression analysis, in a model adjusted for age and gender, radiotherapy and hypopituitarism were not associated with increased mortality risk.

Discussion

In the present single-center study, we assessed mortality rates during long-term follow-up of patients with NFMA and Cushing's disease after treatment by transsphenoidal surgery. The mortality of these patients was increased by 41%, compared with the expected rate of the general population, despite adequate treatment. Mortality in Cushing's disease was increased, compared with mortality in NFMA. More-

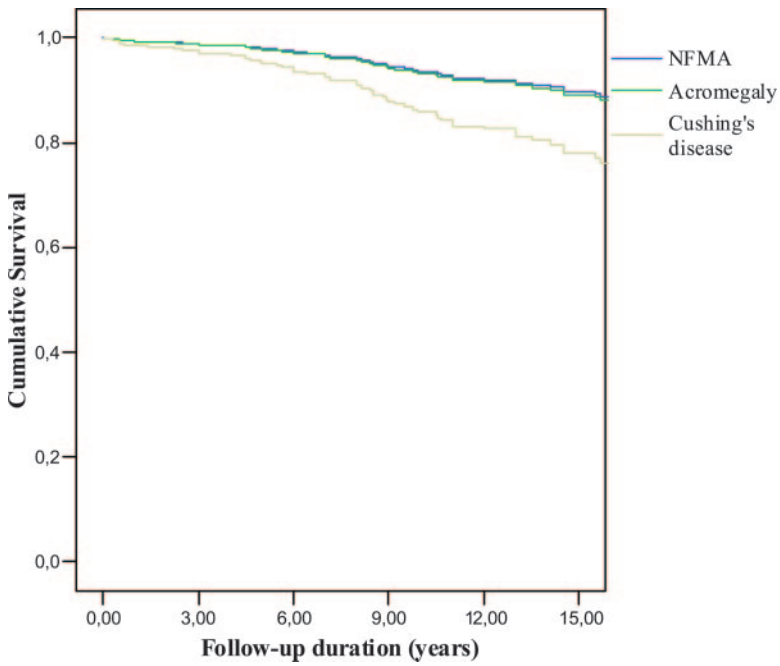

FIG. 1. Mortality in patients treated for nonfunctioning macroadenoma, acromegaly, and Cushing's disease (Cox model, corrected for age and gender).

over, the mortality risk was increased in patients with persistent Cushing's disease after operation, compared with cured patients. This implies that transient overexposure to cortisol is associated with an increased mortality, and that mortality risk seems to be correlated with the duration of overexposure to cortisol.

Mortality in pituitary adenomas is associated with general aspects of pituitary tumors and their treatment but also with disease-specific morbidity due to overproduction of pituitary hormones. We compared patients with Cushing's disease with patients treated for NFMA to assess the possible role of hormonal excess in increased mortality because patients treated for NFMA lack cortisol excess specific for Cushing's disease. The patients presented in this single-center study are comparable in several aspects. First, the time of inclusion was comparable between NFMA and Cushing's disease. Second, all patients underwent transsphenoidal surgery as primary treatment. Third, patients were operated by the same team of neurosurgeons. This is important because treatment outcomes after transsphenoidal surgery have shown to be different among different centers and are dependent on the experience of the surgeon (21). Fourth, all patients underwent the same follow-up and treatment regimen, especially with respect to hormonal substitution. Despite these similarities, patients treated for NFMA still differ from Cushing's disease for relevant factors, in addition to the lack of overproduction to cortisol: size of the adenomas, pituitary insufficiency, age, and sex ratio. In patients with NFMA, by definition, macroadenomas are more prevalent than in patients with Cushing's disease. Therefore, in most patients the mass effects of the adenomas are greater in NFMA patients, resulting in higher rates of pituitary insufficiency in NFMA than Cushing's disease. However, this would adversely affect prognosis in NFMA rather than that in Cushing's disease. Therefore, even if adenoma size and pituitary insufficiency would have affected mortality in NFMA patients, this would have decreased, rather than increased, the difference between both patient groups. Finally, Cushing's disease is associated with a much younger age of the patients, compared with NFMA, and a higher preponderance of female patients. These discrepancies are inherent to the clinical phenotypes of both pituitary diseases. We addressed the confounding affects of differences in age and sex ratios between both patient groups on mortality risk by comparing the mortality rates of both groups separately with the mortality rates per sex and age groups of 5 yr of the Dutch population. In a Cox regression analysis, we were able to make a direct comparison between the mortality in NFMA and Cushing's disease despite differences in age and sex ratio. The age-adjusted comparison revealed an increased mortality in Cushing's disease, compared with NFMA.

Contributors to the increased mortality risk in pituitary tumors in general are factors related to treatment and to hypopituitarism. Transsphenoidal surgery is associated with a perioperative mortality of only approximately 0.9% (21, 22). The preoperative mortality in our study was 0.8% (n = 2). Results of the effects of radiotherapy on long-term mortality are conflicting (7, 12, 23, 24). In our study, the application of radiotherapy was not associated with excess mortality. However, this issue requires further investigation because the comparison between irradiated and nonirradiated patients is not straightforward. Potential bias is introduced because the indication for radiotherapy has changed over time, and a longer period after radiotherapy is required before remission established. Hypopituitarism, present in the majority of patients treated for pituitary macroadenomas, is associated with increased mortality (11, 12). Although the exact mechanisms by which hypopituitarism might cause an increase in mortality is unclear, it is suggested that hypopituitarism is associated with premature vascular disease (13, 25–27). Several authors point toward the role of untreated GH-deficiency in this respect (13, 28).

In this study 174 patients with NFMA were included. After a mean follow-up period of 9 yr, in only 16% of them tumor recurrence was observed. It is, however, likely that a prolonged follow-up period would reveal a higher recurrence rate (29). In our study we found an 1.24-fold increased mortality in NFMA patients, compared with the general population, although this difference was not significant. Mortality was 1.7-fold increased in a larger series with more than 500 NFMA patients (12). In that study, a substantial part of the patients was operated by transcranial approach. This might, at least in part, account for the difference in estimated SMRs with our study because transcranial surgery was associated with an increased mortality, compared with transsphenoidal surgery (12). Moreover, in a recent study, Lindholm *et al.* (30) reported a SMR of 1.18 in transsphenoidal operated patients with NFMA, in accordance with the results of our study.

Cushing's syndrome is a fatal condition in the absence of adequate treatment (31). Recent studies have reported SMR in treated patients with Cushing's disease ranging from 1.0 to 3.8 (9, 10, 32, 33). However, confidence intervals in these studies were broad. It is noteworthy that the SMR seems to be directly related to the initial cure rate in Cushing's disease (32). The highest SMR (3.8) is reported in a study with the lowest cure rate (32%) (9), whereas the lowest SMR (1.0) was reported in the study with the highest cure rate (85%) (33). In the present study, mortality in patients treated for Cushing's disease was 2.4-fold increased, compared with the general population. Moreover, mortality risk after transsphenoidal surgery for Cushing's disease was also increased, compared with NFMA patients, who were treated identically. This points toward effects of previous exposure to cortisol excess on mortality risk in patients with Cushing's disease. The importance of cortisol in mortality excess is further underscored by the fact that mortality is increased in patients with persistent Cushing's disease after treatment, compared with cured patients (32, 34). This indicates that the duration of exposure to overproduction of cortisol is a major contributor to the increased mortality risk observed in Cushing's disease. Cortisol excess induces central obesity, diabetes mellitus, hyperlipidemia, and hypertension (2). There is evidence that the increased cardiovascular risk in Cushing's disease continues, even after remission of the disease (3, 4). Therefore, the effects of transient cortisol overproduction may not be reversible with respect to certain biological properties that influence mortality.

To further evaluate our conclusion that cortisol excess is responsible for the increased mortality in Cushing's disease, we also compared mortality in Cushing's disease with mor-

tality in patients after transsphenoidal surgery for acromegaly. These mortality data from our center in patients with acromegaly after transsphenoidal surgery have been published previously, and patient and treatment characteristics have been described in detail (24). We performed a Cox regression to assess mortality in Cushing's disease, compared with acromegaly. Also compared with acromegaly, the mortality, adjusted for sex and age, in patients with Cushing's disease was increased: hazard ratio 2.4 (95% CI, 1.13–4.91) (Fig. 1). This suggests that the increased mortality in patients with Cushing's disease is not due to hormonal overproduction in general but to intrinsic properties of the exposure to cortisol excess.

In conclusion, this study demonstrates that mortality in patients during long-term follow-up after transsphenoidal surgery for Cushing's disease is increased. Moreover, the mortality is increased in patients with Cushing's disease, compared with both NFMA and acromegaly. This implicates that transient exposure to cortisol excess is a major contributor of the increased mortality, even after cure of Cushing's disease. This observation may also be of relevance for patients treated with exogenous glucocorticoids for nonendocrine diseases.

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