Multisystem Morbidity and Mortality in Cushing's Syndrome: A Cohort Study

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Context: Cushing's syndrome (CS) is associated with hypercoagulability, insulin resistance, hypertension, bone loss, and immunosuppression. To date, no adequately large cohort study has been performed to assess the multisystem effects of CS.

Objective: We aimed to examine the risks for mortality, cardiovascular disease, fractures, peptic ulcers, and infections in CS patients before and after treatment.

Design: Population-based cohort study.

Setting: Source population was the entire population of Denmark (1980 to 2010). Data were obtained from the Danish National Registry of Patients and the Danish Civil Registration System.

Patients: Benign CS of adrenal or pituitary origin and a matched population comparison cohort were included.

Outcome measures: We used Cox regression, and computed hazard ratios (HR) with 95% confidence intervals (95% CI). Morbidity was investigated in the 3 years before diagnosis; morbidity and mortality were assessed during complete follow-up after diagnosis and treatment.

Results: Included were 343 CS patients and 34 300 controls. Mortality was twice as high in CS patients (HR 2.3, 95%CI 1.8–2.9) compared with controls. Patients with CS were at increased risk for venous thromboembolism (HR 2.6, 95%CI 1.5–4.7), myocardial infarction (HR 3.7, 95%CI 2.4–5.5), stroke (HR 2.0, 95%CI 1.3–3.2), peptic ulcers (HR 2.0, 95%CI 1.1–3.6), fractures (HR 1.4, 95%CI 1.0–1.9), and infections (HR 4.9, 95%CI 3.7–6.4). This increased multimorbidity risk was present before diagnosis. Mortality and risk of myocardial infarction remained elevated during long-term follow-up. Mortality and risks for acute myocardial infarction, venous thromboembolism, stroke, and infections were similarly increased in adrenal and pituitary CS.

Conclusions: Despite the apparently benign character of the disease, CS is associated with clearly increased mortality and multisystem morbidity, even before diagnosis and treatment. **(*J Clin Endocrinol Metab* 98: 2277–2284, 2013)**

Long-term exposure to cortisol overproduction induces Cushing's syndrome (CS). The annual incidence of the condition is estimated to be about 2 per million persons (1, 2). The most common cause of CS is an ACTH-secreting pituitary adenoma (ie, Cushing's disease), which promotes excess cortisol production from the adrenal glands

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Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CS, Cushing's syndrome; DCRS, Danish Civil Registration System; DNRP, Danish National Registry of Patients; HR, hazard ratio; ICD, International Classification of Diseases; VTE, venous thromboembolism.

(1). About 25% of CS cases are caused by adrenal adenomas or bilateral adrenal hyperplasia. The only curative treatment is surgery, with long-term remission rates of approximately 70% in patients with pituitary CS (3), although positive effects of medical treatment have been shown (4, 5).

Usually, several years elapse between onset of CS and its diagnosis (6), mainly because the manifestations, such as weight gain, hypertension, diabetes, and menstrual cycle irregularities, are nonspecific and common, even in combination. Importantly, if symptoms of CS are treated, the underlying cortisol overproduction remains unaffected. Exposure to supraphysiological cortisol levels exerts ramified harmful effects, such as hypercoagulability, insulin resistance, hypertension, bone loss, and immunosuppression (7–11).

It is assumed that some cortisol-related effects persist after CS is cured, as continued elevation of cardiovascular risk has been observed despite disease remission (12–14). Mortality is increased approximately twofold in patients with CS, with the highest mortality risk occurring in patients with persistent disease (15–17). To date, no adequately large cohort study has been performed to assess the multisystem effects of cortisol by combining data for various clinically relevant endpoints.

The present nationwide cohort study aimed to examine the risks faced by CS patients with respect to mortality, cardiovascular disease, fractures, peptic ulcers, and infections. Moreover, because treatment with high-dose corticosteroids might have similar multisystem effects as CS, the results from our study may have broader implications.

Materials and Methods

Source population

The source population consisted of the entire population of Denmark (7.6 million inhabitants from 1980 to 2010). Data were obtained from the Danish Civil Registration System (DCRS) and the Danish National Registry of Patients (DNRP). The DNRP has recorded all hospital discharge diagnoses and surgical procedures since 1977 and all hospital outpatient specialist clinic and emergency department visits nationwide since 1995 (18). The DCRS has kept electronic records on gender, age, birth date, residence, emigration date, and vital status since 1968 (19). The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to general practitioners and hospitals.

Study population

Cohort of patients with Cushing's syndrome

All patients with an initial diagnosis of CS of pituitary or adrenal origin between 1980 and 2010 were eligible for inclusion. International Classification of Diseases, eighth revision (ICD-8) and 10th revision (ICD-10), codes for the CS diagnosis are provided in Supplemental Appendix, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. Patients who developed CS due to exogenous steroid treatment and patients with adrenal malignancies or ectopic CS were not included. Throughout the article, we use the term CS for the whole cohort (unless otherwise specified), which includes CS from adrenal as well as pituitary CS.

In clinical practice, the CS diagnosis is based on a combination of clinical characteristics and biochemical tests. The diagnosis is challenging and prone to diagnostic misclassification (20). This is partly due to the nonspecific clinical presentation of mild CS and also the potential for false-positive biochemical tests. To minimize misclassification, we added an additional eligibility requirement (ie, surgical intervention [either adrenalectomy or pituitary surgery] within 3 years after the CS diagnosis).

Population comparison cohort

The comparison cohort was sampled from the DCRS. For every CS patient, one hundred CS-free persons of the population were sampled from persons alive on the date of the CS diagnosis (the "index date"), matched for age and sex. Follow-up of persons in the comparison cohort was terminated if they developed CS, in which case they started contributing person-time to the exposed cohort.

Start of follow-up

For the primary analyses, follow-up started on the date of initial CS diagnosis and on the matched index date for the comparison cohort members. Follow-up was censored when an endpoint of interest occurred, on death or emigration, or on 31 December 2010, whichever came first. Risk estimates were calculated for the first year after CS diagnosis, for the long-term follow-up period (>1 to 30 y), and for the entire follow-up period.

It is known that CS patients are exposed to cortisol excess for years before the disease is diagnosed. The prediagnosis period thus represents untreated exposure time (6). For this reason we conducted an additional analysis in which follow-up commenced 3 years before diagnosis for CS patients and 3 years before the index date for matched unexposed cohort members. To permit 3 years of observation before the diagnosis/index date, study inclusion for this analysis started in 1983. By definition, risk estimates were based on nonfatal events during these 3 supplemental years. Moreover, mortality could not be assessed in this time frame.

All study patients with CS underwent surgery, a well-known risk factor for some endpoints examined (ie, venous thromboembolism, infections, and peptic ulcers). We therefore performed a sensitivity analysis for these specific endpoints, in which we compared risk in the year before surgery with risk in the time period including surgery and the 3 months postsurgery. A new population comparison cohort was sampled for this analysis, to preserve matching on calendar time, age, and sex when follow-up time commenced on the date of surgery.

Study endpoints

We estimated and compared mortality rates in CS patients and the comparison cohort. We also studied the first occurrence of venous thromboembolism (VTE), acute myocardial infarction (AMI), stroke, heart failure, peptic ulcer, fracture, and infection

in both cohorts. Registered diagnoses were used to identify these endpoints. Each hospital discharge or outpatient visit is recorded in the DNRP with one primary diagnosis and one or more secondary diagnoses classified according to the ICD-8 until the end of 1993 and ICD-10 thereafter. Relevant ICD codes are provided in the Supplemental Appendix. For each event analyzed (VTE, AMI, stroke, heart failure, peptic ulcer, fracture, and infection), we excluded CS patients and persons from the comparison cohort with a diagnosis of the given condition before the start of follow-up.

Statistical analysis

For the CS patients and persons in the population comparison cohort, we calculated the rate of VTE, AMI, stroke, heart failure, peptic ulcer, fracture, infection, and mortality. Rates were expressed as the number of events per 1000 person-years. We used Kaplan-Meier analysis to construct survival curves and compute risks. Cox regression was used for time-to-event analysis, and hazard ratios (HRs) were computed with accompanying 95% confidence intervals (95% CI). We also performed a Cox regression to adjust for potential baseline imbalances (cancer, diabetes [hospital recorded], hypertension, chronic obstructive pulmonary disease as a proxy for smoking, liver disease, chronic pancreatitis, and alcoholism-related diseases other than those affecting the liver or pancreas).

We performed 3 sensitivity analyses. First, we performed a stratified analysis according to age (age ≤ or >50th percentile). We also assessed mortality and morbidity separately for patients with adrenal Cushing and patients with pituitary Cushing (Morbus Cushing). We considered a patient to have adrenal Cushing in the case of adrenalectomy without accompanying hypophysectomy, cranial radiotherapy, or hypopituitarism. All other patients were considered to have pituitary CS.

Also, we assessed long-term mortality and cardiovascular risk in a subgroup of patients considered cured. We assumed a patient to be cured in one of the following situations: patients with adrenal surgery and patients with pituitary surgery in combination with a diagnosis of hypopituitarism in the first 6 months after operation.

The proportional-hazards assumption was assessed graphically for all outcome variables and found valid. Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics

A total of 343 CS patients and 34 300 age- and gender-matched comparison cohort members were included in the study. The median age of CS patients at time of diagnosis was 43.8 years (interquartile range: 33.0–54.0 y) and 75% were women. Compared with the unexposed cohort, at time of diagnosis, CS patients had a higher prevalence at baseline of CS-related conditions, hospital-registered diabetes (13.1% vs 1.4%), and hypertension (25.4% vs 2.6%). Also, cancer was recorded more often in CS patients (7.6% vs 2.8%). Patient characteristics are shown in Table 1.

Table 1. Baseline Characteristics at Time of Diagnosis of Patients With CS and the Population Comparison Cohort

	Cushing Cohort (n = 343)		Population Comparison Cohort (n = 34 300)	
	N	Percent (%)	N	Percent (%)
Age				
<30 y	68	19.8	6800	19.7
30–49 y	158	46.1	15 800	46.2
≥50 y	117	34.1	11 700	34.1
Gender				
Female	257	74.9	25 700	74.9
Male	86	25.1	8600	25.1
Year of Cushing syndrome diagnosis				
1980–1989	102	29.7	NA	NA
1990–1999	96	28.0	NA	NA
2000–2010	145	42.3	NA	NA
Cancer				
No	317	92.4	33 355	97.2
Yes	26	7.6	945	2.8
Diabetes				
No	298	86.9	33 818	98.6
Yes	45	13.1	482	1.4
Hypertension				
No	256	74.6	33 415	97.4
Yes	87	25.4	885	2.6
Chronic obstructive pulmonary disease				
No	328	95.6	33 466	97.6
Yes	15	4.4	834	2.4
Liver disease or chronic pancreatitis				
No	337	98.3	34 162	99.6
Yes	6	1.7	138	0.4
Other alcoholism-related diseases				
No	337	98.3	33 702	98.3
Yes	6	1.7	598	1.7

Abbreviation: NA, not applicable.

In 26 Cushing patients a total of 40 cancers were found. Most prevalent cancers were breast (n = 6), renal (n = 4), uterus (n = 4), testis (n = 3), colon (n = 2), and prostate (n = 2).

Mortality

During a mean follow-up of 12.1 years (4140 person-years), 74 CS patients died (21.6%). The mortality rate was clearly higher in CS patients (17.9/1000 person-years, 95% CI 14.0–22.2) than in the population comparison cohort (9.5/1000 person-years, 95% CI 9.2–9.7), with a HR of 2.3 (95% CI 1.8–2.9). The HR for mortality was

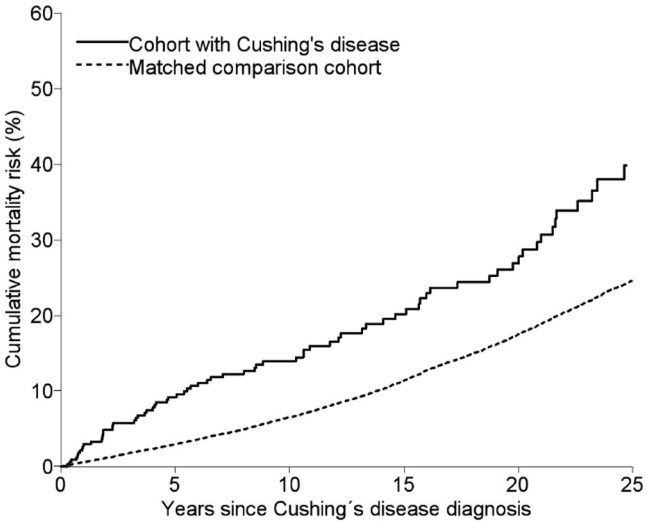

Figure 1. Mortality in patients with Cushing's syndrome from adrenal and pituitary origin and in a population comparison cohort.

higher in the first year after diagnosis (5.2, 95% CI 2.7–9.7) than in subsequent years (2.1, 95% CI 1.7–2.7). After adjustment for differences in baseline characteristics, mortality risk remained increased for CS patients both during the first year following diagnosis (HR 3.5, 95% CI 1.8–6.7) and during long-term follow-up (HR 1.6, 95% CI 1.3–2.1). Mortality is depicted in Figure 1. Relative risk for mortality was slightly higher in younger (≤44 y) patients (HR 3.9, 95% CI 2.6–6.1) than in older (>44 y) patients (HR 2.0, 95% CI 1.5–2.6).

Cardiovascular events: venous thromboembolism, myocardial infarction, stroke, and heart failure

CS patients were at clearly increased risk for VTE (HR 2.6, 95% CI 1.5–4.7), AMI (HR 3.7, 95% CI 2.4–5.5), and stroke (HR 2.0, 95% CI 1.3–3.2). HRs for each endpoint, stratified by follow-up time, are shown in Table 2. Risks of VTE, heart failure, AMI, and stroke were already increased in the 3 years before CS diagnosis. For VTE, stroke, and heart failure, the HRs were highest in the period around the diagnosis and then decreased. VTE risk (HR 1.6, 95% CI 0.8–3.4) and stroke risk (HR 1.8, 95% CI 1.1–3.0) remained elevated during long-term follow-up, unlike the risk of heart failure. For VTE, the risk was markedly increased during the year after diagnosis (HR 20.6, 95% CI 7.8–53.9), suggesting additional risk from surgery. For AMI the risk was elevated in the year after diagnosis (HR 4.5, 95% CI 1.1–18.4), as well as during long-term follow-up (HR 3.6, 95% CI 2.4–5.5).

Relative risk for AMI was higher in younger (≤44 y) patients (HR 5.5, 95% CI 2.4–12.6) than in older (>44 y) patients (HR 3.3, 95% CI 2.1–5.3). Other relative risks for studied conditions were similar for the 2 age categories (Table 3).

Table 2. Rates and Hazard Ratios With 95% Confidence Intervals (95% CI) for the Risk of VTE, AMI, Stroke, Heart Failure, Infections, Ulcers, and Fractures in Patients With CS, Stratified by Follow-up Time

Outcome	Period (y before/after diagnosis)	Rate (95% CI) per 1000 Person-years in CS Cohort	Rate (95% CI) per 1000 Person-years in Control Cohort	Hazard Ratio (95% CI), Age- and Sex-adjusted Model	Hazard Ratio (95% CI), Fully Adjusted Model[a]
VTE	3 y before	4.3 (1.1–9.3)	0.5 (0.4–0.7)	8.4 (3.0–23.4)	6.8 (2.4–19.3)
	1 y after	15.3 (4.9–31.4)	0.9 (0.6–1.2)	20.6 (7.8–53.9)	17.1 (6.4–45.8)
	>1 to 30 y after	1.9 (0.8–3.6)	1.3 (1.2–1.4)	1.6 (0.8–3.4)	1.4 (0.6–2.9)
AMI	3 y before	2.1 (0.2–5.9)	0.9 (0.8–1.2)	2.2 (0.5–8.9)	2.1 (0.5–8.6)
	1 y after	6.1 (0.7–16.9)	1.4 (1.0–1.8)	4.5 (1.1–18.4)	3.5 (0.8–14.7)
	>1 to 30 y after	6.0 (3.8–8.8)	1.9 (1.8–2.1)	3.6 (2.4–5.5)	2.8 (1.8–4.4)
Stroke	3 y before	5.3 (1.7–10.9)	1.1 (0.9–1.3)	5.0 (2.1–12.4)	4.5 (1.8–11.1)
	1 y after	9.1 (1.8–22.0)	1.4 (1.1–1.9)	6.5 (2.0–21.0)	4.3 (1.3–14.2)
	>1 to 30 y after	4.3 (2.5–6.7)	2.7 (2.5–2.8)	1.8 (1.1–3.0)	1.5 (0.9–2.5)
Heart failure	3 y before	4.3 (1.1–9.3)	0.6 (0.5–0.8)	6.8 (2.5–18.6)	6.0 (2.1–17.1)
	1 y after	6.1 (0.7–17.0)	0.9 (0.6–1.3)	6.7 (1.6–28.1)	3.1 (0.7–14.2)
	>1 to 30 y after	1.6 (0.6–3.1)	1.9 (1.8–2.0)	1.0 (0.4–2.2)	0.8 (0.3–1.7)
Fractures	3 y before	14.9 (7.9–24.0)	4.2 (3.8–4.7)	3.4 (2.0–6.0)	3.2 (1.9–5.6)
	1 y after	20.1 (7.4–39.2)	4.6 (3.8–5.4)	4.3 (1.9–9.7)	3.8 (1.7–8.7)
	>1 to 30 y after diagnosis	8.3 (5.5–11.6)	7.2 (6.9–7.4)	1.2 (0.8–1.7)	1.1 (0.8–1.6)
Infections	3 y before	5.5 (1.8–11.3)	2.1 (1.8–2.4)	2.6 (1.1–6.4)	2.4 (1.0–5.9)
	1 y after	51.7 (29.6–80.0)	2.4 (1.9–3.0)	22.3 (12.9–38.5)	17.8 (10.1–31.3)
	>1 to 30 y after	12.7 (9.1–16.9)	3.7 (3.5–3.9)	3.7 (2.7–5.1)	2.9 (2.1–4.1)
Peptic ulcers	3 y before	5.4 (1.7–11.0)	0.8 (0.6–1.0)	6.5 (2.6–16.0)	5.5 (2.2–13.9)
	1 y after	12.3 (3.3–27.0)	1.0 (0.6–1.3)	12.5 (4.4–35.5)	8.9 (3.0–26.3)
	>1 to 30 y after	1.9 (0.8–3.6)	1.6 (1.5–1.7)	1.3 (0.6–2.8)	1.1 (0.5–2.2)

[a] Model adjusted for age, sex, calendar time, cancer, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, and alcoholism-related diseases.

Table 3. HRs with 95% CI for the Risk of VTE, AMI, Stroke, Heart Failure, Infections, Ulcers, and Fractures in Patients with CS 0–30 y After Diagnosis, Stratified by Age Category, and Type of CS

	Hazard Ratio (95% CI), Age- and Sex-adjusted Model			
Outcome	Patients ≤44 y (n = 172)	Patients >44 y (n = 171)	Adrenal Cushing (n = 132)	Pituitary Cushing (n = 211)
Mortality	3.9 (2.6–6.1)	2.0 (1.5–2.6)	2.4 (1.6–3.5)	2.3 (1.7–3.0)
VTE	2.5 (0.9–6.9)	2.7 (1.3–5.4)	2.4 (0.9–6.5)	2.8 (1.4–5.6)
AMI	5.5 (2.4–12.6)	3.3 (2.1–5.3)	3.8 (1.9–7.8)	3.6 (2.2–5.9)
Stroke	2.0 (0.7–5.3)	2.1 (1.2–3.4)	1.9 (0.9–4.3)	2.1 (1.2–3.6)
Heart failure	1.1 (0.2–8.2)	1.3 (0.6–2.7)	1.2 (0.4–3.7)	1.3 (0.5–3.2)
Fractures	1.7 (1.1–2.8)	1.1 (0.7–1.8)	0.8 (0.4–1.8)	1.6 (1.1–2.4)
Infections	5.5 (3.7–8.1)	4.4 (3.1–6.4)	4.9 (3.1–7.7)	4.9 (3.5–6.8)
Peptic ulcers	0.6 (0.1–4.6)	2.5 (1.3–4.6)	2.5 (1.0–6.2)	1.7 (0.7–3.7)

In a sensitivity analysis we assessed long-term mortality and cardiovascular risk in a subgroup of patients considered to be initially cured after operation (n = 186). This subgroup was defined as patients with adrenal surgery and patients with pituitary surgery in combination with a diagnosis of hypopituitarism in the first 6 months after operation. Risk estimates for mortality (HR 2.31, 95% CI 1.62–3.28), VTE (HR 2.03, 95% CI 0.75–5.48), stroke (HR 1.91, 95% CI 0.90–4.05), and AMI (HR 4.38, 95% CI 2.31–8.28) more than 1 year after the operation were also increased in this subgroup. The more extensively adjusted risk estimates were slightly lower, but still increased.

Peptic ulcers, fractures, and infections

In CS patients the risk of peptic ulcers (HR 2.0, 95% CI 1.1–3.6), fractures (HR 1.4, 95% CI 0.9–1.9), and infections (HR 4.9, 95% CI 3.7–6.4) was increased. For fractures (HR 1.2, 95% CI 0.8–1.7) and peptic ulcers (HR 1.3, 95% CI 0.6–2.8) the increased risk became lower with longer follow-up duration, but for infections the risk remained markedly elevated (HR 3.7, 95% CI 2.7–5.1). For peptic ulcers and infections, the highest risk occurred during the year after diagnosis, also suggesting an added risk from surgery. Risks of peptic ulcer, fractures, and infections are presented in Table 2.

Adrenal versus pituitary CS

Of all patients, 132 were considered to have adrenal CS, and 211 considered to have pituitary CS. The incidence of (operated) adrenal CS increased over calendar time, with 50% of all patients being diagnosed in the last 10 years of follow-up (2000–2010). Patients with adrenal CS diagnosed between 1980 and 1999 were younger (mean age 40 y) than patients diagnosed between 2000 and 2010 (mean age 53 y). For pituitary CS the incidence did not increase over time. Mortality risk was the same in adrenal Cushing (HR 2.4, 95% CI 1.6–3.5) and pituitary Cushing (HR 2.3, 95% CI 1.7–3.0). In patients with adrenal CS, effect estimates for mortality (follow-up in this specific analysis was restricted to maximally 10 y) were increased for patients diagnosed between 1980 and 1999 (HR 3.4, 95% CI 1.8–6.3) as well as for patients diagnosed between 2000 and 2010 (HR 2.8, 95% 1.4–5.6). Exclusion of the postoperative period in patients with adrenal CS also showed an increased mortality risk (HR 2.5, 95% CI 1.7–3.7). Detailed assessment of morbidity risk according to type of Cushing is shown in Table 3. Risks for AMI, VTE, stroke, and infections were similarly increased in both groups.

The effect of surgery on the risk of VTE, infections, and peptic ulcers

Risk estimates stratified by time since surgery are shown in Table 4. The risk for VTE (HR 59.9, 95% CI 14.3–250.8) and infections (HR 53.5, 95% CI 24.7–115.9) was remarkably high in the 3-month period commencing with surgery. However, risks in the 1-year period before surgery were also increased (HR for VTE 10.2, 95% CI 3.1–33.5; HR for infections 7.4, 95% CI 3.0–18.5), pointing toward an effect of CS on the risk of VTE and infections independent of surgery. The difference between risk estimates in the pre- and postoperative periods for peptic ulcers was less pronounced. The absolute risks of infection and VTE in the 3 months following surgery were 3.1% (95% CI 1.7–5.7) and 0.9% (95% CI 0.3–2.7), respectively.

Discussion

Our study showed that patients with CS are at increased risk of mortality, cardiovascular events, peptic ulcers, fractures, and infections despite the apparently benign character of the disease. This multisystem risk is already elevated during the 3 years before diagnosis, indicating that it is caused by cortisol overproduction rather than treatment for CS. Mortality, risk of AMI, and risk of in-

Table 4. Preoperative vs Postoperative Risk for VTE, Infections, and Peptic Ulcers

Outcome	Period	Hazard Ratio (95% CI), Age- and Sex-adjusted Model	Hazard Ratio (95% CI), Fully Adjusted Model[a]
VTE	1 y before operation	10.2 (3.1–33.5)	8.6 (2.5–29.3)
	Operation to 3 mo postoperatively	59.9 (14.3–250.8)	58.8 (13.9–248.7)
	>3 to 12 mo pos to peratively	5.8 (0.8–43.6)	3.6 (0.4–28.6)
Infections	1 y before operation	7.4 (3.0–18.5)	5.7 (2.2–14.4)
	Operation to 3 mo postoperatively	53.5 (24.7–115.9)	38.2 (16.9–86.1)
	>3 to 12 mo pos to peratively	14.1 (6.0–33.1)	8.3 (3.3–20.4)
Peptic ulcers	1 y before operation	7.5 (1.8–31.7)	7.1 (1.6–31.3)
	Operation to 3 mo postoperatively	13.9 (3.2–61.2)	9.9 (2.1–47.4)
	>3 to 12 mo pos to peratively	8.9 (2.1–37.8)	6.1 (1.4–27.6)

[a] Model adjusted for age, sex, calendar time, cancer, diabetes, hypertension, chronic obstructive pulmonary disease, liver disease, and alcoholism-related diseases.

fections remained elevated even during long-term follow-up. Risks of VTE and infection were high specifically during the first 3 months following surgery. Mortality and morbidity risk seems not restricted to patients with persistent disease after initial operation. Mortality and risks for AMI, VTE, stroke, and infections were similarly increased in adrenal and pituitary CS.

Increased cortisol levels are known to affect the coagulation system, glucose-homeostasis, arterial-wall stiffness, bone formation, heart function, and the immune system (7–11, 21). It is therefore not surprising that the multisystem effects of cortisol excess translate into increased risk for several comorbidities in CS patients. It is intriguing that in our study the increased risk of some conditions (VTE, fractures, heart failure, and peptic ulcers) was largely transient, whereas for others (infections and AMI) the risk remained elevated over a long period. The long-term cardiovascular risk points to the need for adequate risk factor management in patients with CS (22). The risk for VTE in the postoperative period (about 1%) highlights the need for adequate perioperative prophylaxis (23).

The more than twofold increased mortality risk among CS patients is consistent with previous reports (15). In our study, mortality risk decreased the first year after diagnosis, but remained higher than mortality in the general population. In a subgroup of patients considered to be cured after initial surgical therapy, mortality risk, and risk for VTE, AMI and stroke were also elevated during long-term follow-up, with risk estimates comparable to the whole cohort. This is in line with the fact that cardiovascular risk factors remain elevated even when CS is cured and underlines that successful surgery does not normalize cardiovascular and mortality risk (13, 14, 16). Whether other factors like pituitary insufficiencies also contribute to mortality risk could not be determined from our data. Our study showed that mortality risk was similarly increased in patients with adrenal and in patients with pituitary CS. Although the increased mortality risk for pituitary CS is known, there is debate whether this applies equally for adrenal CS. In a meta-analysis on patients with adrenal CS, the relative risk for mortality was 1.9 (15). In contrast to our study, a study from New Zealand showed no increased mortality risk after the postoperative period (24). Larger studies on adrenal adenomas are needed to assess the effect on mortality with more precision.

Our data were obtained from population-based registries, covering the entire Danish population. The main advantage of these databases is the large number of patients they provide and the ability to select a very large and carefully matched comparison cohort. This ensured precise risk estimates. Moreover, because the databases cover the complete population, selection bias is not an issue. The positive predictive values of diagnoses in the DNRP have previously been validated and found to exceed 90% for most of the outcomes diagnosis (25). At the same time, however, detailed information on biochemical results, (co)medication, cure rate after surgery, and potential pituitary deficiencies after surgery are lacking. Because hypertension and diabetes are hospital recorded diagnoses, they will underestimate the true prevalence. Moreover, without access to individual records the distinction cured/noncured cannot be made with certainty. By relying on a registered "hypopituitarism" diagnosis postoperatively, we have identified a subset of cured patients. It is unlikely that all other patients are truly uncured. For this reason we have not formalized a comparison between cured and uncured patients. Similarly, a distinction between adrenal and pituitary CS based on individual medical records was not possible. It might therefore be that some patients with pituitary CS are misclassified as adrenal CS if they have been treated with adrenalectomy without concomitant pituitary surgery or have been operated in calendar years where radiotherapy was not recorded in the databases (ICD8). Compared to an article based on clinical data of Danish CS patients by Lindholm et al (1), in our cohort the proportion of patients with adrenal CS was higher. In addition to a small risk of misclassification, there are 2 rea-

sons for this apparent difference. First, our cohort is based on operated patients only, and more importantly, our data show a marked increased incidence in adrenal CS in the period 2000–2010, whereas in the period 1980–1999 the proportion of adrenal CS was clearly lower (~30%) and similar to the proportion in the article by Lindholm et al (27%). Whether the increased incidence in adrenal CS reflects a true increased incidence, a change in treatment policy, or a change in screening strategy cannot be answered with certainty from our data. However, the fact that patients diagnosed with adrenal CS between 2000 and 2010 were on average more than 10 years older suggests an increased incidence due to more frequent use of imaging techniques with incidental findings of adrenal cortisol-producing adenomas. It is important to consider that that even in the case of an incidentally discovered adrenal CS-negative effects on glucose and lipid metabolism, blood pressure and bone mineral density are shown, suggesting that even mild hypercortisolism exerts multisystem effects (26).

The recurrence rate of pituitary CS after surgery in patients initially cured is about 15% for Danish CS patients (1), which is consistent with data from other countries (27, 28). This finding indicates that CS patients included in this study are likely to be representative. Still, it should be kept in mind that our cohort was limited to patients with a CS diagnosis who underwent pituitary or adrenal surgery within a few years after diagnosis. The study did therefore not include CS patients with a more subtle clinical form of CS for which surgery was deemed unnecessary. For this reason our risk estimates are not generalizable to patients with mild CS (29).

Two aspects of the analysis deserve attention. First, we included follow-up time before the diagnosis was made, which, in principle, introduces immortal time bias (30). Because both CS patients and comparison cohort members were "immortal" in the 3 years before study inclusion, immortal time bias is not a major limitation, although all comorbidity detected before CS diagnosis/index date had to be nonfatal by definition and mortality could not be studied. Second, we compared CS patients to the general population. We present risk estimates that were adjusted only for age, sex, and calendar time, as well as risk estimates that were adjusted for baseline imbalances. The more extensively adjusted risk estimates are slightly lower (Table 2). Patients with CS had a higher prevalence of diabetes and hypertension than the comparison cohort. This may be considered to reflect the clinical manifestations of CS. Patients with CS had a higher prevalence of diabetes and hypertension than the comparison cohort. This may be considered to reflect the clinical manifestations of CS. It might be that the higher cancer prevalence at baseline is an effect of CS-induced obesity and insulin resistance (31), although this topic certainly will need further elucidation. If one holds the view that in principle CS patients may not have been different from the general population before their cortisol hypersecretion developed, and the baseline differences are a result of the disease, then the estimates that are only adjusted for age, sex, and calendar time give the true impact of CS. A population-based control group is, for this reason, a valid comparator.

In the general population, by far the most common cause of exposure to glucocorticoid excess is iatrogenic. Owing to their anti-inflammatory and immunosuppressive properties, glucocorticoids are one of the most widely prescribed therapeutic agents, used by approximately 1% of the adult population (32). Patients using glucocorticoids are already at increased morbidity and mortality risk due to their underlying condition. The period before CS diagnosis in patients with endogenous glucocorticoid excess is characterized by untreated hypercortisolism and can thus be considered a model for the use of exogenous glucocorticoids. Our study showed that the increased risk for cardiovascular events, fractures, peptic ulcers, and infections was already present before CS diagnosis. Possibly this reflects the situation during use of high exogenous steroids. This an important consideration given that studies assessing the risk of long-term glucocorticoid use often suffer from confounding by indication (observational studies) or limited follow-up (clinical trials).

In conclusion, our study showed a clearly increased risk for mortality, cardiovascular events, peptic ulcers, infections, and fractures in patients with CS, starting already before diagnosis. The long-term increased risk for AMI, in particular, underscores the need for adequate monitoring and risk factor management in patients with CS. It should not be taken for granted that the mere (surgical) treatment of the hypersecretion will in itself be sufficient to attenuate the metabolic consequences. Furthermore, our study points toward the multisystem risks potentially associated with long-term use of glucocorticoids, because the cortisol overproduction characterizing CS may be considered a model for the effects of glucocorticoid use in patients with inflammatory and malignant conditions.

Acknowledgments

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