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Clinical Research Article

The Socioeconomic Consequences of Cushing's Syndrome: A Nationwide Cohort Study

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Abstract

Context: The long-term somatic and psychiatric consequences of Cushing's syndrome are well-described, but the socioeconomic consequences are largely unknown.

Objective: We studied employment status, educational level, risk of depression, and other socioeconomic outcomes of Cushing's syndrome in the years before diagnosis and after surgery.

Design: Nationwide register-based cohort study.

Methods: We used a validated algorithm to identify 424 patients operated for adrenal (n = 199) or pituitary Cushing's syndrome (n = 225) in Denmark from January 1, 1986 to December 31, 2017. We obtained socioeconomic registry data from 10 years before diagnosis (year −10) to 10 years after surgery (year +10) and included a sex- and age-matched reference population. We identified prognostic factors for returning to work using modified Poisson regression.

Results: Compared to the reference population, the patients' employment was permanently reduced from year −6 [relative risk (RR) 0.92, 95% CI 0.84-0.99] to year +10 (RR 0.66, 95% CI 0.57-0.76). Sick leave (RR 2.15, 95% CI 1.40-3.32) and disability pension (RR 2.60, 95% CI 2.06-3.27) were still elevated in year +10. Annual income, education, parenthood, relationship status, and risk of depression were also negatively impacted, but parenthood and relationship status normalized after surgery. Among patients, negative predictors of full-time employment after surgery included female sex, low education, comorbidity, and depression.

Conclusion: Cushing's syndrome negatively affects a wide spectrum of socioeconomic variables many years before diagnosis of which only some normalize after treatment. The data underpin the importance of early diagnosis and continuous follow-up of Cushing's syndrome and, not least, the pervasive health threats of glucocorticoid excess.

Key Words: Cushing's disease, cortisol-producing adrenocortical adenoma, epidemiological, socioeconomic outcomes, employment, disability pension

Endogenous Cushing's syndrome (CS) is a rare endocrine disorder caused by prolonged exposure to high levels of circulating glucocorticoids. Most cases are caused by benign corticotropin-producing pituitary adenomas (pitCS) or cortisol-producing adrenocortical adenomas (adrCS) (1, 2).

It is well-described that pitCS and adrCS cause excess mortality (1-4) as well as a plethora of somatic (5) and psychiatric complications (6, 7), impaired cognition (7), and decreased quality of life (8), neither of which fully reverse after disease control. Conversely, data on the socioeconomic consequences of CS are sparse and restricted to uncontrolled cross-sectional surveys (9-11). Nonetheless, socioeconomic data are of vital importance not only for the patient but also for healthcare providers and the society as a whole (12, 13).

We therefore conducted a nationwide longitudinal study of the socioeconomic consequences of CS before diagnosis and after surgery as compared to a large reference population matched for age and sex.

Methods

Source Population

The source population included the entire Danish population from January 1, 1986 to December 31, 2017 (average annual population 5.4 million with 171.8 million years of follow-up). Data were obtained from the Danish Civil Registration System, the Danish National Patient Registry, and socioeconomic registries from Statistics Denmark. The Civil Registration System has kept records on sex, age, birth date, residence, emigration date, and vital status of all individuals residing in Denmark since January 1, 1968. The Danish National Patient Registry has recorded diagnosis codes and

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surgical procedures for all somatic hospital admissions since January 1, 1977 and on all outpatient and psychiatric contacts since January 1, 1995. Denmark provides universal, tax-paid healthcare, guaranteeing free access to general practitioners and hospitals (14).

Study Design

We used the patient registry to identify all patients diagnosed with and operated for pitCS and adrCS. Each patient was age- and sex-matched with 10 random CS-free individuals (the reference population), and we compared their socioeconomic outcomes from 10 years before diagnosis to 10 years after surgery as described in more details in the following sections. We followed the RECORD guideline for the reporting of observational studies that use routinely collected health data (15).

Identification of CS Patients

We developed and validated an algorithm for identifying patients operated for pitCS and adrCS. The algorithm, which was based on previous studies (5), is described in details in Supplementary Section 1 (16). In brief, we extracted all patients with a first CS diagnosis code in the Danish National Patient Registry from January 1, 1986 to December 31, 2017. We restricted inclusion to patients with an additional surgical code for adrenal or craniobasal surgery. We excluded patients for whom the first CS diagnosis was registered >3 years before or >1 year after surgery. Finally, we excluded patients with ectopic CS, adrenocortical carcinoma, iatrogenic CS, adrenal metastases, etc [details in Supplementary Section 1 (16)].

To further validate our algorithm, we applied it on all patients at our own department registered with a CS diagnosis code (n = 234) from May 16, 2011 to December 17, 2020. We reviewed each patient's records and compared it with the algorithm's results. Thirty-seven of the 40 individuals identified by the algorithm as CS patients had true pitCS or adrCS [positive predictive value: 92.5% (95% CI 79.6-98.4)] and the algorithm missed 2 of the 39 patients with pitCS or adrCS [completeness: 94.9% (95% CI 82.7-99.4)]. The validation study is described in details in the Supplementary Section 2 (16).

We defined the date of the first recorded diagnosis as date of diagnosis and the date of first surgical procedure as date of surgery, respectively, and whichever of the 2 dates came last was the patient's index date. For most patients, index date was the date of surgery, and we therefore use the 2 terms synonymously.

We considered patients to have adrCS if they had undergone unilateral adrenalectomy, and pitCS if they had undergone pituitary surgery or bilateral adrenalectomy [codes in Supplementary Section 1 (16)].

Reference Population

Each was matched on sex and year of birth (ie, age) with 10 CS-free individuals from the Danish population who were alive at the index date (ie, the reference population).

Socioeconomic Outcomes

The outcomes included employment status, educational level, income, relationship status, parenthood, and depression. We obtained outcome data from national registries through Statistics Denmark. Each outcome is outlined in the following discussion with additional details in Supplementary Section 3 (16).

We obtained weekly employment status from the Danish National Labor Market Authority's DREAM database on public transfer payments (available from August 5, 1991 to June 30, 2019). The DREAM database provides validated information on all individuals in Denmark, who have received any form of unemployment benefit, compensation for sickness, or other social or health-related benefits for at least 1 day in a given week (17). We divided employment status into (1) employed (including self-employed, under education, and self-supporting individuals), (2) unemployed, (3) sick leave (including health-related benefits for individuals in part-time employment due to reduced working capacity), and (4) disability pension (including individuals on early retirement; ie, before the age 65).

Data on the highest level of education and its date of achievement were obtained from the Danish Educational Attainment Registry (available from January 1, 1970 to September 30, 2018).

We obtained annual earned income from the Personal Income Registry, which is based on data from the Danish Tax Agency (available from January 1, 1980 to December 31, 2017).

We obtained relationship status at January 1 each year from Statistics Denmark's Population Registry (available from January 1, 1986 to January 1, 2019). We considered individuals who were married or cohabitating with a partner to be in a relationship.

We obtained number of children in each individual's family at January 1 each year from the Family Registry (available from January 1, 1986 to January 1, 2019). The Family Registry does not distinguish between an individual's biological children, adopted children, and stepchildren (18). We therefore defined parenthood as living in a family with a small child (age 0-2 years), which we considered more likely to reflect biological parenthood.

We obtained prescriptions for antidepressants from the Danish National Prescription Registry (available from January 1, 1995 to December 31, 2018) and depression-related hospital contacts from the Danish National Hospital Registry in the same time period [codes in Supplementary Section 3 (16)]. In accordance with previous studies (6, 19), we defined individuals as being depressed in a given year if they redeemed at least 1 prescription for antidepressants or had a depression-related hospital contact.

Statistical Methods

For employment status and income, we followed the patients and the reference population from 10 years before diagnosis, age 18, or inception date of the relevant registry (whichever came last) until 10 years after surgery, age 65, death, emigration, or last available year in registry data (whichever came first). The same procedure was used for relationship status and depression, except we did not stop the follow-up at age 65. Parenthood and educational level were followed from age 18 to 49.

We used relative risk (RR) assessment to compare the risk of being in each category of employment status (by week), relationship status, parenthood, educational level, and depression (by year). To compare education, we calculated the

annual RR of each CS patient being below the median educational level of their 10 matched CS-free individuals. For income, we calculated each patient's relative annual income in percent of the median income among the patient's 10 matched CS-free individuals. Since we censored individuals who died, we conducted a sensitivity analysis to ensure that we did not miss a negative socioeconomic impact due to healthy survivor bias. In this sensitivity analysis, we included all individuals who died in the worst socioeconomic outcome categories (disability pension, low educational level, no income, not in a relationship, no children, and depressed), but this had a negligible impact on the results, and the data are not presented.

We evaluated potential prognostic factors for CS patients being in full-time employment 2 years after surgery. In this analysis, we only included CS patients aged 18 to 62 years at time of surgery (to allow at least 2 years before ordinary retirement at age 65) and excluded individuals who were already on permanent disability pension before diagnosis (20). We defined full-time employment as being employed at least 75% of the time from week 53 to 104 after surgery. We examined the following potential prognostic factors: (1) sex, (2) age, (3) education, (4) Charlson Comorbidity Index at diagnosis, (5) history of depression, and (6) employment in the year before diagnosis. We used Poisson regression with robust error variance (21) to calculate crude and adjusted RR of returning to work. We adjusted RR for potential confounders (sex, age, index year, and education) but not comorbidity, depression, or recent employment, which we considered to be indicators of CS severity.

Finally, we also calculated incidence-rates of CS in Denmark during the study period (assuming new cases followed a Poisson distribution) and patients' hazard ratio (HR) for death compared to the reference population (Cox regression).

Data analysis was conducted in SAS, version 9.4 (SAS Institute, Cary, NC, USA) and in Stata Statistical Software, release 16.1 (StataCorp LLC, College Station, TX, USA).

Ethical Considerations

The project was approved by Statistics Denmark (reference 707623) and the Danish Health Data Authority (reference 00004458). As per Danish laws, informed consent from study participants is not required for a registry-based study. The Danish Health Authorities approved the review of in-house medical records without patient consent for the validation study (reference 3-3013-1021/2).

Results

Study Cohort

We identified 541 individuals registered with a CS diagnosis and pertinent surgery from January 1, 1986 to December 31, 2017 [patient flow chart in Supplementary Figure 1 (16)]. Of these, 54 were excluded as the CS diagnosis was registered more than 3 years before surgery (n = 16) or registered more than 1 year after surgery (n = 38). Sixty-three patients were excluded on the suspicion of adrenocortical carcinoma (n = 29), adrenal metastasis (n = 8), ectopic CS (n = 7), or other indications for adrenalectomy (n = 19). In total, the study cohort consisted of 424 patients with CS (225 pitCS and 199 adrCS).

The incidence of CS increased during the study period from 2.2 cases (95% CI 1.7-2.7) per million person-years between 1986 and 1993 to 3.4 cases (95% CI 2.9-4.0) per million person-years between 2010 and 2017 (Fig. 1). During the study period, the incidence of adrCS increased (0.6-2.0 per million person-years), while the incidence of pitCS showed a modest decline (1.6-1.4 per million person-years). The corresponding pitCS to adrCS ratio reversed from 2.7 to 1 in the first quarter of the study period to 0.7 to 1 in the last quarter (Fig. 1).

Patient Characteristics

Of 424 patients, 326 (76.9%) were women (Table 1). The median age at diagnosis was 45.9 years [interquartile range (IQR) 35.3-56.9]. Seventeen patients (4.0%) were <18 years of age at diagnosis and 42 (9.9%) were ≥65 years. The majority of patients underwent a single surgical procedure (n = 346, 81.6%), whereas 78 patients (18.4%) underwent multiple surgeries (up to 4 surgical procedures) (Table 1). Compared to patients with pitCS, patients with adrCS were older and more were women, had comorbidities, and a history of depression, but fewer underwent multiple surgical procedures [Supplementary Table 1 (16)].

Comorbidities and Mortality

Compared to the reference population, CS patients were more often diagnosed with some comorbidity [25.0% (106/424) vs 9.8% (416/4240)] or severe comorbidity [6.6% (28/424) vs 1.7% (72/4240)] before the date of diagnosis (Table 1). Similarly, a history of depression before diagnosis was more common among CS patients [29.2% (89/305) vs 17.0% (518/3048)]. The HR for death was increased in the patients [HR 1.79 (95% CI 1.43-2.25)]. The HR was slightly higher for patients with pitCS [HR 1.94 (95% CI 1.45-2.58)]

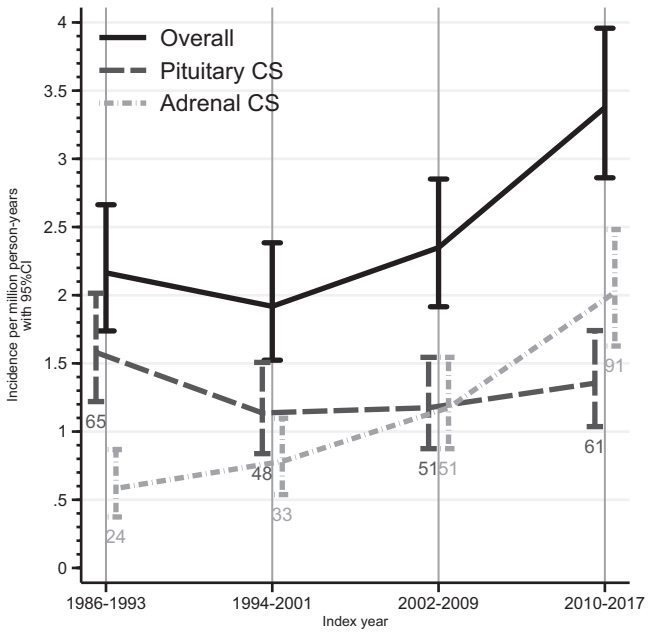

Figure 1. Incidence of Cushing's syndrome during the study period. Incidence rate of new cases per million person-years assuming a Poisson distribution. Incidence rates are summarized by index year in four 7-year time periods. The number of patients are provided in the figure. Ratio of corticotropin-producing pituitary adenoma to cortisol-producing adrenocortical adenoma patients was 2.7 to 1 in 1986-1993, 1.5 to 1 in 1994-2001, 1.0 to 1 in 2002-2009, and 0.7 to 1 in 2010-2017. Abbreviations: CS, Cushing's syndrome.

Table 1. Patients and reference population characteristics

	Patients with CS	Reference population
Total, n	424	4240
Age at diagnosis, n (%)		
<18 years	17 (4.0)	170 (4.0)
18-39 years	135 (31.8)	1351 (31.9)
40-64 years	230 (54.2)	2315 (54.6)
≥65 years	42 (9.9)	404 (9.5)
Median years (IQR)	45.9 (35.3-56.9)	46.0 (35.3-57.0)
Sex, n (%)		
Men	98 (23.1)	980 (23.1)
Women	326 (76.9)	3260 (76.9)
Index year, n (%)		
1986-1993	89 (21.0)	890 (21.0)
1994-2001	81 (19.1)	810 (19.1)
2002-2009	102 (24.1)	1020 (24.1)
2010-2017	152 (35.8)	1520 (35.8)
Comorbidity at diagnosis, n (%)		
None (CCI 0)	290 (68.4)	3752 (88.5)
Some (CCI 1-2)	106 (25.0)	416 (9.8)
Severe (CCI 3 or above)	28 (6.6)	72 (1.7)
Surgical procedures, n (%)		
1	346 (81.6)	-
Multiple	78 (18.4)	-
Education, n (%)		
Low	137 (34.1)	1249 (31.1)
Medium	164 (40.8)	1630 (40.6)
High	101 (25.1)	1137 (28.3)
Parenthood, n (%)		
No children	236 (60.8)	2260 (58.0)
At least 1 child	152 (39.2)	1637 (42.0)
History of depression, n (%)		
No	216 (70.8)	2530 (83.0)
Yes	89 (29.2)	518 (17.0)

Comorbidity was based on diagnosis codes registered before CS diagnosis. Number of surgical procedures included both index surgery and any later surgeries during follow-up. Educational level at time of diagnosis was available for 402 (94.8%) of 424 patients and 4016 (94.7%) of 4240 individuals in the reference population. Patient characteristics by CS etiology are available in Supplementary Table 1 (16).
Abbreviations: CCI, Charlson Comorbidity Index; CS, Cushing syndrome; IQR, interquartile range (25th-75th percentile).

than patients with adrCS [HR 1.61 (95% CI 1.12-2.32)] [Supplementary Figure 2 (16)].

Employment Status

In the period from 10 to 7 years before diagnosis, employment status were similar for patients and the reference population (Fig. 2). Six years before diagnosis, however, the patients' employment rate started to decrease [year –6: 70.1% vs 76.6%, RR 0.92 (95% CI 0.84-0.99)] and remained low until diagnosis [year –1: 59.3% vs 73.9%, RR 0.80 (95% CI 0.73-0.89)]. Three years before diagnosis, the patients' risk of being on sick leave or other health-related benefits started to increase [year –3: 7.6% vs 4.4%, RR 1.77 (95% CI 1.15-2.73)] and continued to do so until the time of diagnosis [year –1: 10.0% vs 4.6%, RR 2.22 [(95% CI 1.51-3.26)]. The risk of disability pension or early retirement showed a similar trend with a moderate increase, which started 4 years before diagnosis (Fig. 2).

After surgery, the patients' employment rate remained decreased (Fig. 2). Sick leave seemed to be the major contributor to the decreased employment in the first year after surgery [year 1: 21.6% sick leave vs 4.5%, RR 5.03 (95% CI 3.85-6.58)]. The patient's risk of being on sick leave remained elevated up to 10 years after surgery [year 10: 12.2% vs 5.5%, RR 2.15 (95% CI 1.40-3.32)]. From the second year after surgery, disability pension became the most prevalent reason for the decreased employment, and 10 years after surgery a third of the patients were on disability pension [year 10: 33.9% vs 13.1%, RR 2.60 (95% CI 2.06-3.27)].

Education

The educational level of the patients was lower compared to the reference population (Fig. 3A). This difference emerged before diagnosis [year –1: 29.3% below median educational level vs 24.1%, RR 1.21 (95% CI 0.98-1.50)], peaked 4 years after surgery [year 4: 32.1% vs 24.3%, RR 1.32 (95% CI 1.04-1.68)], and subsided 6 years after surgery [year 6: 27.3% vs 23.8%, RR 1.14 ([95% CI 0.86-1.52)].

Income

The patients' annual income was similar to the reference population from 10 to 6 years before diagnosis (Fig. 3B). In the fifth year before diagnosis, the patients' relative income started to decrease [year –5: median 96.0% (IQR 26.7-135.8) of the reference population's annual income] and continued to do so until diagnosis [year –1: median 83.6% (IQR 0.1-129.5)]. The patients' relative income remained significantly reduced from the first year after surgery [year 1: median 54.2% (IQR 0.0-116.8)] until the end of follow-up [year 10: median 58.2% (IQR 0.0-115.8)].

Relationship Status and Parenthood

The patients were slightly less likely to be in a relationship from 5 years before diagnosis [year –5: 68.5% vs 73.8%, RR 0.93 (95% CI 0.86-1.00)] to 5 years after surgery [year 5: 65.8% vs 72.2%, RR 0.91 (95% CI 0.84-0.99)] (Fig. 3C). The patients were also less likely to live in a family with small children aged 0 to 2 years after surgery [year 1: 7.6% vs 16.1%, RR 0.47 (95% CI 0.29-0.76)] (Fig. 3D). This difference was not present before diagnosis and waned as a function of time after surgery. A sensitivity analysis only including female patients showed similar results (data not shown).

Depression

The patients had a higher risk of depression from the fifth year before diagnosis [year –5: 14.1% vs 7.9%, RR 1.79 (95% CI 1.29-2.49)] until diagnosis [year –1: 19.1% vs 8.6%, RR 2.22 (95% CI 1.71-2.87)] (Fig. 4). This risk peaked in the first year after surgery [year 1: 20.7% vs 8.9%, RR 2.34 (95% CI 1.83-2.98)] and remained elevated up until 10 years after surgery [year 10: 16.7% vs 9.3%, RR 1.80 (95% CI 1.30-2.49)] (Fig. 4).

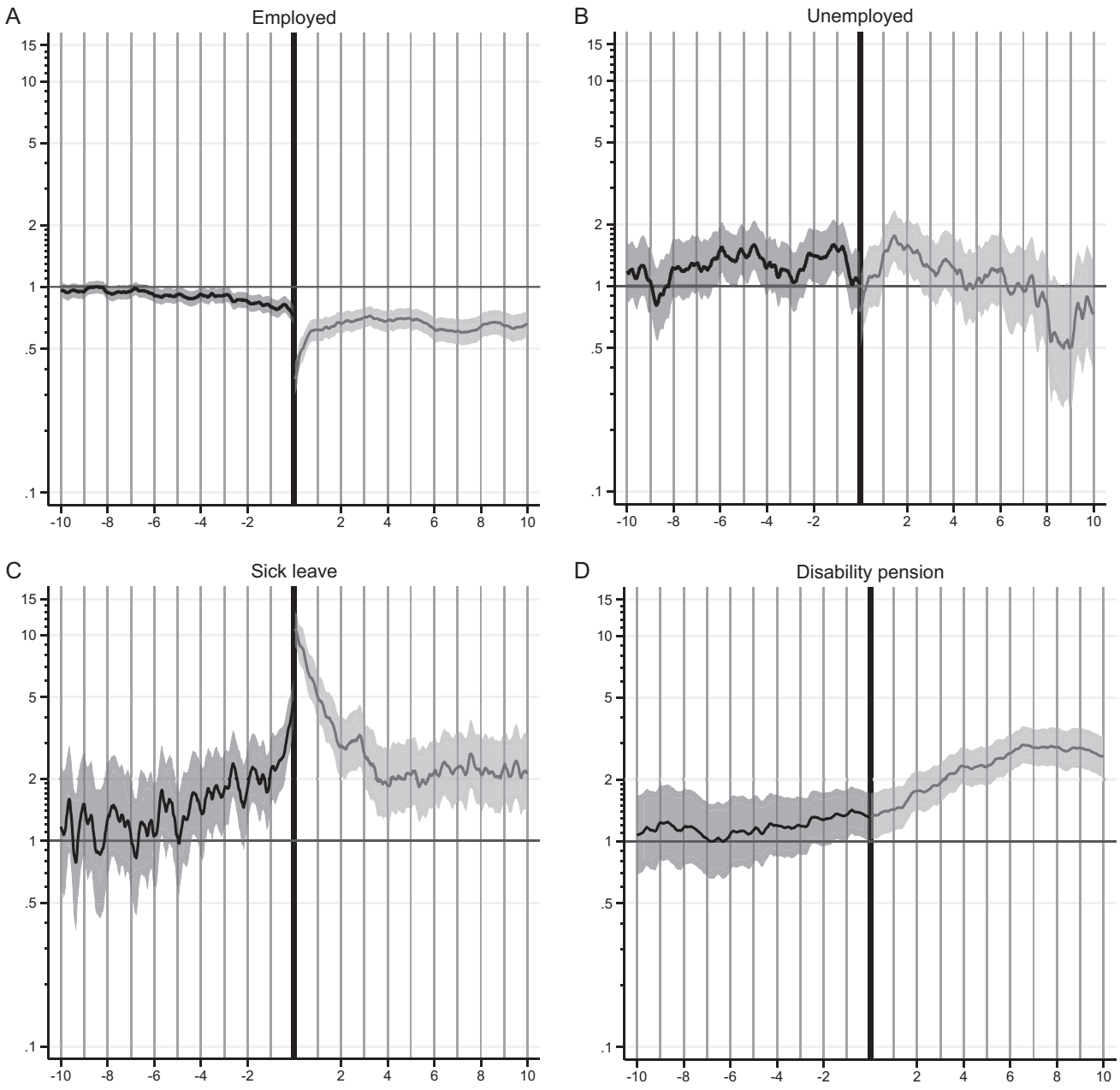

Figure 2. Employment status. Weekly employment status for patients aged 18 to 65 years compared to the reference population. Results are shown on a logarithmic y-axis and as 9-week smoothed averages. Each figure shows the relative risk (RR) of being in that specific category vs the 3 other categories, which is why RR of employment and unemployment are not complementary. Data on employment status were available for 399 patients, with a median of 13.6 (interquartile range 9.8-17.7) years of available data per patient [details in Supplementary Tables 2 and 3 (16)].

Prognostic Factors for Employment After Surgery

Patient factors predicting a lower likelihood of being in full-time employment 2 years after surgery included female sex, index year, low education, whether a patient had been employed in the year before diagnosis, index year, existing comorbidity, and a history of depression (Table 2). Age and CS etiology were not important prognostic factors. Compared with the reference population, even patients with the most favorable prognostic factors (high education, full-time employment before diagnosis, no comorbidity, and no history of depression) had lower chance of being in full-time work 2 years after surgery than their respective sex- and age-matched CS-free individuals [Supplementary Table 4 (16)].

Sensitivity Analysis

In a sensitivity analysis, all socioeconomic analyses were repeated for pitCS and adrCS separately. Overall, patients with pitCS and adrCS had similar socioeconomic outcomes, although adrCS was associated with an earlier and more gradual decline in employment status before diagnosis, pitCS was associated with a slightly higher risk of sick leave and disability pension after surgery, and patients with adrCS were less likely to be in a relationship [Supplementary Figure 3 (16)].

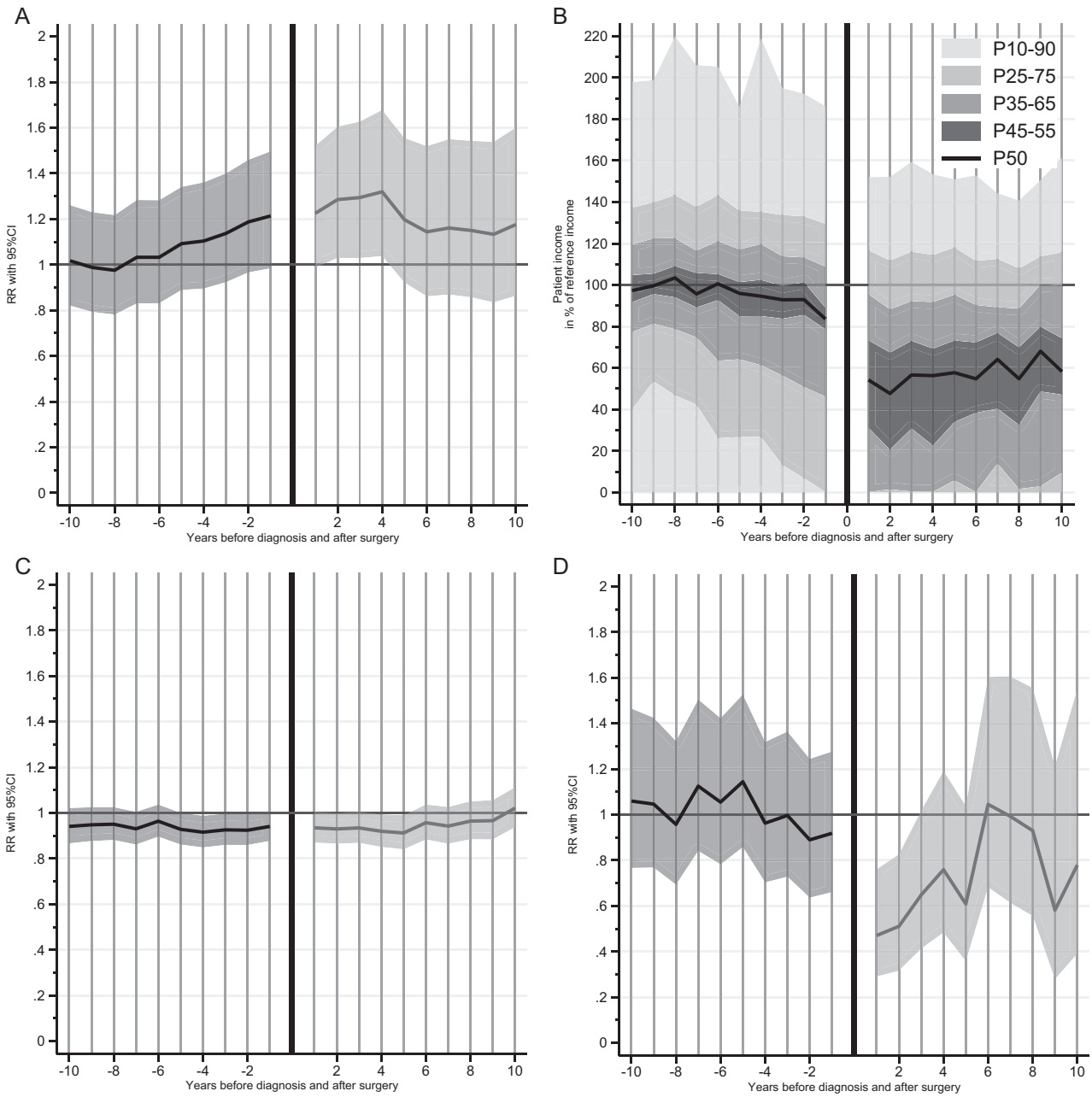

Figure 3. Other socioeconomic outcomes. (A) Annual relative risk (RR) of patients aged 18 to 49 years being below the median educational level of their respective sex- and age-matched comparisons in the reference population. (B) Annual earned income for patients aged 18 to 65 years relative to the median income among their ten respective sex- and age-matched Cushing's syndrome–free individuals. The solid black line represents median relative income and the grey shades indicate percentiles. (C) Annual RR of being in a relationship for patients aged ≥18 years compared to the reference population. Relationship included marriage or cohabitation at January 1 in a given year. (D) Annual RR of being a parent for patients aged 18 to 49 years compared to the reference population. Individuals were considered to be parents if living in a family with children aged 0 to 2 years at January 1 in a given year. The data do not distinguish between biological, adopted, or step-children. Data availability: registry data were available on education for 330 patients (median 12 [interquartile range (IQR) 8-17] years of available data per patient), on income for 412 patients [median 15 (IQR 11-20) years], on relationship status for 420 patients [median 16 (IQR 12-20) years], and on parenthood for 324 patients [median 11 (IQR 7-16) years] [details in Supplementary Tables 2 and 3 (16)].

Discussion

In this nationwide longitudinal study, we found CS to be complicated by an array of negative socioeconomic effects, which were detectable 6 years before the diagnosis and persisted up to 10 years after surgery.

Our data strongly suggest an diagnostic delay of at least 6 years, which is more than twice as long as previously estimated (22). This is to our knowledge the first study to provide population-based longitudinal socioeconomic data, but questionnaire-based cross-sectional surveys have reported decreased employment rates in CS patients (4, 9-11). It is not surprising that educational level, comorbidity, history of depression, and employment in the years prior to the diagnosis were strong predictors for returning to work. It is, on the other hand, reassuring that two thirds of the patients who

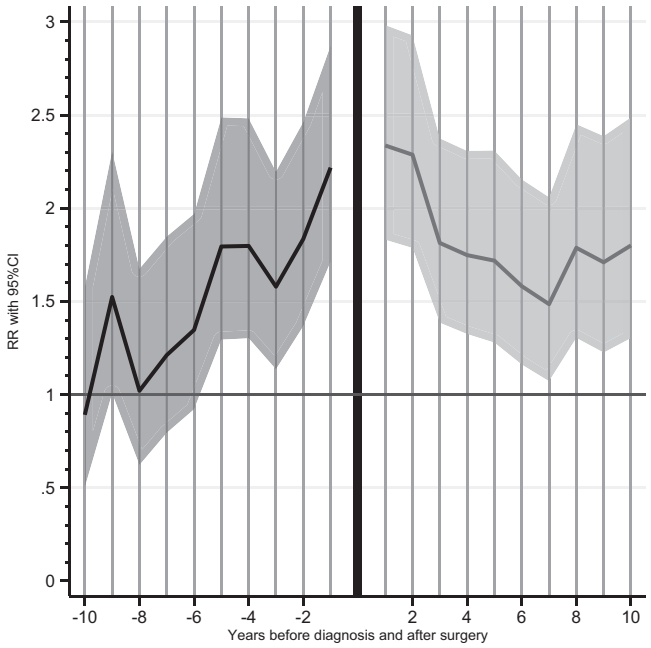

Figure 4. Depression. Annual risk of depression for patients aged ≥18 years compared to the reference population. Individuals were considered depressed if they redeemed a prescription for antidepressants or had a depression-related hospital contact within a given year. Data on prescriptions and hospital contacts were available for 409 patients, with a median of 13 (interquartile range 10-17) years of available data per patient [details in Supplementary Tables 2 and 3 (16)]. Abbreviation: RR, relative risk.

were employed before diagnosis returned to full-time employment after surgery. Our observation that women were more severely affected is in accordance with questionnaire-based data (11), but it was unexpected that pitCS and adrCS had a comparable prognosis inasmuch as hypopituitarism is seen in 29.6% of pitCS patients after surgery (23) and is an important negative determinant of socioeconomic outcome in other patient groups (10, 24).

In our study, educational achievements, being in relationships, and parenthood were less severely and more transiently affected. This contrasts somewhat with previous observations of impaired cognition associated with CS (7), decreased educational level despite long-term remission (11), and cross-sectional surveys suggesting that CS negatively impacts family life (9) and female fertility (25). We cannot say whether the normalization of educational level and family life after surgery was due to improved cognition, reversal of morbidities, or the result of social interventions.

The patients were at an increased risk of being diagnosed with depression and 1 in 5 patients received anti depressive treatment at the time of diagnosis and surgery. A higher prevalence of major depression has previously been reported (7), and we may have missed milder cases of depression managed without antidepressants (19). Regardless of the exact magnitude of this comorbidity, it is concerning when considering that a diagnosis of pitCS (26) is associated with an increased suicide rate.

Interestingly, we observed that the expected 2-to-1 ratio between pitCS and adrCS (1) reversed during the study period due to an increasing incidence of adrCS. The changing etiology of CS is in line with 2 recent studies reporting a 1-to-1 ratio between pitCS and other types of endogenous CS (27) and 1.2-to-1 ratio between pitCS and adrCS (28). The same pattern was indeed also detectable in a previous survey (2) from Denmark. This change is undoubtedly driven by increased adrenal imaging and awareness of incidentally found adrenal tumors (28, 29). It remains to be further studied whether the biochemical disease activity and clinical phenotype of adrCS at diagnosis also change with time.

In our study, we excluded patients with adrenocortical carcinoma and patients with ectopic corticotropin-producing tumors since these conditions carry a distinctly worse prognosis in terms of both morbidity and mortality (2). By definition, we also excluded patients not receiving surgical treatment, who are also likely to have a worse prognosis (23). This approach has obvious limitations when it comes to providing epidemiological data on the full spectrum of patients with endogenous CS, but the observations made in our study population are, on the other hand, more likely to reflect the effects of hypercortisolism per se. It is uncertain whether our results can be generalized to the 3% of the population who are prescribed systemic glucocorticoids each year. We speculate that this could be the case inasmuch as somatic and psychiatric complications of glucocorticoid treatment are highly prevalent (30, 31), but it remains to be further studied.

Due to the longitudinal registry-based design, this study has several strengths and some limitations. The main strength is the use of nationwide registries with virtually complete follow-up, which allowed us to identify all patients operated for CS in Denmark and compare their socioeconomic outcomes to a matched reference population. This longitudinal matched study design negated the risk of recall bias and selection bias, which often challenge questionnaire-based studies conducted at specialized centers. The most important limitation is the lack of access to clinical data from medical records. While our validation efforts make us confident that our cohort consisted of true cases of pitCS and adrCS, clinical data on CS severity, surgical complications, medical treatment, and recurrence would have allowed for more detailed analyses of prognostic factors. Since our study was conducted in an affluent country with an extensive welfare system and a relatively homogenous population, it may not be globally representative of CS patients.

Conclusion

In conclusion, we have found that CS negatively impacts several socioeconomic factors many years before diagnosis and after treatment, which emphasize the long diagnostic delay, the importance of long-term follow-up, and the pervasive health threats of glucocorticoid excess. Awareness of nonsomatic complications is important and demands a partnership between healthcare providers and patient organizations to identify and provide the necessary supportive measures.

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Table 2. Prognostics factors for patients being in full-time work 2 years after surgery

	Returned to work, % (n full-time/total)	Crude RR (95% CI)	Adjusted RR (95% CI)
CS type			
AdrCS	50.9 (58/114)	1	1
PitCS	48.1 (62/129)	0.94 (0.73-1.22)	0.84 (0.66-1.09)
Age at index (in quartiles)			
Q1 (18-34)	51.7 (30/58)	1	1
Q2 (34-41)	52.5 (31/59)	1.02 (0.72-1.44)	0.91 (0.65-1.28)
Q3 (41-49)	47.5 (28/59)	0.92 (0.64-1.32)	0.92 (0.63-1.33)
Q4 (49-62)	46.3 (31/67)	0.89 (0.62-1.28)	0.81 (0.56-1.17)
Sex			
Men	57.1 (24/42)	1	1
Women	47.8 (96/201)	0.84 (0.62-1.13)	0.69 (0.51-0.93)
Index year			
1986-1993	65.4 (17/26)	1	1
1994-2001	45.8 (27/59)	0.70 (0.47-1.04)	0.70 (0.47-1.04)
2002-2009	52.2 (36/69)	0.80 (0.56-1.14)	0.74 (0.50-1.09)
2010-2017	44.9 (40/89)	0.69 (0.48-0.99)	0.67 (0.46-0.98)
Educational level			
Low	31.8 (21/66)	0.52 (0.35-0.78)	0.47 (0.32-0.70)
Medium	53.5 (53/99)	0.88 (0.68-1.14)	0.87 (0.67-1.13)
High	60.8 (45/74)	1	1
Employment in the year before diagnosis			
None (0%)	7.5 (3/40)	0.12 (0.04-0.35)	0.14 (0.05-0.41)
Part-time (1-74%)	35.4 (17/48)	0.55 (0.36-0.82)	0.57 (0.38-0.86)
Full-time (75-100%)	65.0 (89/137)	1	1
Charlson Comorbidity Index at diagnosis			
None (CCI 0)	56.0 (98/175)	1	1
Some (CCI 1-2)	32.1 (18/56)	0.57 (0.38-0.86)	0.59 (0.40-0.89)
Severe (CCI 3 or above)	33.3 (4/12)	0.60 (0.26-1.34)	0.54 (0.25-1.19)
History of depression			
No	52.6 (82/156)	1	1
Yes	28.3 (13/46)	0.54 (0.33-0.87)	0.59 (0.36-0.95)

The analysis included 243 patients, as 84 were <18 or >62 years of age at time of surgery: 36 were already on permanent disability pension, and 61 did not have 2 years of follow-up after surgery. Full-time work is defined as patients working at least 75% of the time from week 53 to 104 after surgery. RR is adjusted for sex, education, age, and index year with the latter 2 as continuous variables.
Abbreviations: adrCS, adrenal Cushing's syndrome; CCI, Charlson Comorbidity Index; pitCS, pituitary Cushing's syndrome; RR, relative risk.

Author Contributions

J.O.L.J. conceptualized the study. A.E., P.J., and K.S. contributed to the study design. A.E. collected the data under supervision of E.S., P.L.P., and J.O.L.J. M.M., H.L.M.S., and A.E. conducted the analysis. A.E. drafted the article. All authors contributed to critical revision and final approval of the article.

Disclosures

The authors have nothing to disclose.

Data Availability

Danish law on data protection restricts the availability and sharing of patient data. Upon reasonable request, the corresponding author will provide additional details on these restrictions and under which conditions access to some of the data and statistical code may be provided.

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