

## Epidemiology and mortality of Cushing's syndrome

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# **Epidemiology and Mortality of Cushing's Syndrome**

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## **Abstract**

Endogenous Cushing's syndrome (CS) is a rare endocrine disorder characterised by excess cortisol secretion due to either ACTH-dependent conditions [commonly an ACTH-producing pituitary adenoma (Cushing's disease)] or ACTH-independent causes (with most common aetiology being a benign adrenal adenoma). Overall, the annual incidence of CS ranges between 1.8-3.2 cases per million population. Mortality in active CS is elevated compared to the general population, and a number of studies support the view that survival is also compromised even after apparent successful treatment. The main cause of death is cardiovascular disease highlighting the negative impact of cortisol excess on cardiovascular risk factors. Early diagnosis and prompt treatment of the cortisol excess, as well as vigilant monitoring and stringent control of cardiovascular risk factors are key elements for the long-term prognosis of these patients.

## **Keywords:**

Cushing's syndrome, Cushing's disease, mild autonomous cortisol secretion, epidemiology, incidence, prevalence, mortality, standardised mortality ratio (SMR)

## **Introduction**

Endogenous Cushing's syndrome (CS) is a rare but potentially life-threatening endocrine disorder defined as exposure to excess cortisol secretion. Its most common cause is an ACTH-producing pituitary tumour [Cushing's disease (CD)] forming 70% of the CS cases, followed by adrenal aetiologies (benign adrenal adenomas being the most common) and ectopic CRH/ACTH-producing tumours. CS is associated with multiple co-morbidities (including obesity, insulin resistance, diabetes mellitus, dyslipidaemia, hypertension, atherosclerosis, osteoporosis, hypercoagulability, immune suppression, and neuropsychiatric disturbances) and high mortality, even after apparent successful treatment of the hypercortisolaemia (1–7). Furthermore, cases of mild autonomous cortisol secretion (formerly known as “subclinical Cushing's syndrome”) are increasingly discovered while investigating adrenal incidentalomas, which are also frequently recognized due to the increasing use of advanced imaging modalities (2,8,9). The term “autonomous cortisol secretion” has been endorsed by the 2016 European Society of Endocrinology Clinical Practice Guideline and is defined as serum cortisol values of  $>1.8 \mu\text{g/dL}$  ( $50 \text{ nmol/L}$ ) on the 1mg overnight dexamethasone suppression test (1mg-ONDST) in the absence of specific clinical features of CS (2,10). Nonetheless, it has been associated with an increased risk of diabetes mellitus (11), hypertension (11), cardiovascular (CV) events (12), metabolic bone disease (11,13), and a potentially higher risk of mortality (2). This review will address the main literature on the epidemiology and mortality of CS due to CD and benign adrenal pathologies, including mild autonomous cortisol secretion.

## **Epidemiology of Cushing's Syndrome**

Population studies looking at the epidemiology of CS are limited, and most of them focus on CD. One of the earliest epidemiological studies on the field conducted in Spain and published in 1994 suggested that the annual incidence of CD was around 2.4 per million, while the prevalence was 39.1 per million population (14). Another study from Iceland found an incidence for CD of 0.3-0.5 per 100,000 per year, while the prevalence reached 6.21/100,000, with a significant female predominance and a

median age at diagnosis of 42 years (15). Fernandez *et al.* in a community-based cross-sectional study in Oxfordshire, UK, found a prevalence of 1.2/100,000 people for CD (16), and Daly *et al.* in a community-based population sample from the Province of Liège, Belgium in 2006, reported 94 clinically relevant pituitary adenomas per 100,000 people, with 5.6% being CD (17).

Over the last two decades, three studies [Table 1] involving patients with CS were conducted with a careful review of their medical records to ratify the diagnosis and the underlying cause of CS (4,18,19). The first one was from Denmark, where Lindholm *et al.* (4) reviewed 166 patients with endogenous CS between 1985 and 1995. The annual incidence was 2.3-2.7/million for all aetiologies of endogenous CS; 1.2-1.7/million for CD (additional 0.5/million was when cases with possible CD were included), 0.6/million for adrenal adenoma, 0.3/million for ectopic CS, and 0.2/million for adrenocortical carcinoma (ACC). At the first presentation, the median age was 41.4 years with a female preponderance (4). The second study was conducted by Bolland *et al.* (18) in New Zealand, identifying 253 patients with CS between 1960 and 2005. After excluding cases with malignant ectopic CS and ACC from the analyses, the annual incidence of CS was 1.8/million; 1.3/million for CD, 0.3/million for adrenal adenoma, and 0.1/million for non-malignant ectopic CS. The prevalence of CS was 79 cases per million, and the mean age at diagnosis was 39 years, with a 74% female preponderance (18). The most recent epidemiological study was performed in Sweden by Wengander *et al.* (19) and reviewed the medical records of 236 patients from Västra Götaland County in Sweden with a given diagnostic code of CS between 2002 and 2017. After ratifying the diagnosis and including only confirmed cases of endogenous CS and those living in the defined geographical area by the end of the study, 82 patients were analysed for incidence and prevalence. The annual incidence of CS found 3.2/million; 1.5/million for CD, 0.5/million for adrenal adenoma, 0.8/million for ectopic CS, and 0.2/million for ACC. Prevalence was reported as 57 cases per million. The mean age at diagnosis was 50 years, and 70% of CS cases were females (19).

[Note: for the publisher: Insert Table 1 here, please]

Recently, Ragnarsson *et al.* (20) carried out a nationwide study in Sweden, assessing the incidence of CD in 390 patients with a confirmed diagnosis between 1987 and 2013. The mean annual incidence was 1.6 cases per million. The mean age at diagnosis was 43 years, and 77% were women. Notably, the incidence was increasing during the study period, which might reflect either an actual increment or rather an increased awareness and earlier diagnosis (20). Furthermore, Ahn *et al.* (21) reported on the incidence of adrenal CS in a Korean nationwide study, identifying 1199 patients between 2002 and 2017. The age-standardized annual incidence of adrenal CS was significantly higher than previously reported, 1.27 cases per million, with a prevalence of 23.4 per million. The mean age was around 45 years, and the female to male ratio was 3.2:1. Noteworthy, this study included 72 (6%) patients with malignant adrenal CS (21).

Lastly, most epidemiological data on autonomous cortisol secretion or subclinical CS come from studies investigating adrenal incidentalomas, with a prevalence varying between 5 and 20% (9,22) and reaching up to 30% of the adrenal incidentalomas in some reports (12). It tends to be slightly more common in women and patients older than 50 years (9,22). Notably, adrenal incidentalomas can be found in 4.5% of computed tomography scans and up to 10% of patients >70 years (8,23). Autonomous cortisol secretion has also been recognized in subset patients with type 2 diabetes mellitus, with prevalence ranging between 2 and 9% (24–26). More recently, Ebbehøj *et al.* (27) identified 1287 patients with adrenal tumours between 1995 and 2017 in a retrospective population-based study conducted in Olmsted County, Minnesota, USA. Notably, 81.6% of these adrenal tumours were discovered incidentally, with higher prevalence in older patients and slight female preponderance, confirming the data from previous reports. However, only 244 patients had available ONDST results, and 89 of them were found to have mild autonomous cortisol secretion, comprising 6.9% of the study cohort. (27).

**Table 1.** Summary of the population-based epidemiological studies that included both Cushing’s disease and adrenal Cushing’s syndrome.

<b>Study</b>	<b>Number of patients</b>	<b>Gender F/M</b>	<b>Age Median (range) Mean (SD) years</b>	<b>Incidence (Cases/million/year)</b>	<b>Prevalence</b>
Lindholm <i>et al.</i> (4) (Denmark) 1985 – 1995	73 CD 37 AA	50/23 CD 33/4 AA	41.1 (7.6–69.7) CD 38.3 (3.6–77.7) AA	All CS: 2.3-2.7 CD: 1.2-1.7 AA: 0.6	---
Bolland <i>et al.</i> (18) (New Zealand) 1960 – 2005	158 CD (micro) 30 CD (macro) 46 AA	122/36 CD (micro) 22/8 CD (macro) 40/6 AA	36 (15) CD (micro) 45 (14) CD (macro) 41 (13) AA	All CS: 1.8 CD: 1.3 AA: 0.3	79 cases / million (for all CS cases)
Wengander <i>et al.</i> (19) (Sweden) 2002 – 2017	39 CD 14 AA	27/12 CD 12/1 AA	48 (17) CD 46 (15) AA	All CS: 3.2 CD: 1.5 AA: 0.5	57 cases / million (for all CS cases)

Abbreviations: F: females, M: males, SD: standard deviation, CD: Cushing’s disease, AA: adrenal adenoma, CS: Cushing’s syndrome, micro: microadenoma, macro: macroadenoma

## Mortality of Cushing's Syndrome

### Mortality in CD

Several studies have reported on mortality in patients with CD (active or in remission). This section summarises studies that reported the standardised mortality rate (SMR) in CD, [Table 2]. One of the earliest mortality studies on CD was conducted by Etxabe *et al.* (14), where they reviewed data of 49 patients with CD between 1975 and 1992. Median follow-up was 56 months, and the criteria for remission were normal 24-hour urinary free cortisol (UFC) and suppressed serum cortisol in response to dexamethasone, which was achieved in 87.5% of the patients. There was no recurrence during the mean follow-up period of 27.1 months following trans-sphenoidal adenohipophysectomy (TSA). Mortality was reported to be around four times higher than the general population (SMR 3.8, 95% CI: 2.5-17.9), and it was even higher in women (SMR 4.5, 95% CI: 2.94-21). The most common cause of death was CV disease; nevertheless, persistent hypertension and abnormal glucose metabolism were independent factors (14).

In a neurosurgical series by Swearingen *et al.* (28), 161 patients with CD were identified between 1978-1996. They were followed-up for a median duration of 8 years, and remission was confirmed based on morning serum cortisol of <138 nmol/L and UFC <55 nmol/24h within ten days after TSA (achieved in 85% of the cases). Recurrence occurred in 7% of patients during the monitoring period, although data on remission at the last follow-up were not reported. Compared to an age- and sex-matched sample of the general USA population, mortality was not significantly elevated (SMR 0.98, 95% CI: 0.44-2.2). Of note, most cases were due to microadenoma (89%), and a potential limitation to this study is that it may represent well-selected patients who had optimal surgical outcomes (28).

Pikkarainen *et al.* (29) studied 43 patients with confirmed CD between 1981 and 1994 (37 with microadenoma and 6 with macroadenoma). Mean follow-up was 7.4 years, and remission was determined by normal UFC, disappearance of symptoms and absence of relapses. 15 (42%) patients



had a relapse (7 treated with surgery alone, 6 with surgery followed by radiotherapy, and two with radiotherapy alone). There were 6 deaths (3 due to CV causes, one from aspiration pneumonia following hip surgery, one due to pancreatitis and one because of Morbus Parkinson). Nevertheless, overall mortality did not differ from that of the general population (SMR of 2.67, 95% CI 0.89-5.25) (29,30).

In a nationwide population study, Lindholm *et al.* (4) retrieved data for 73 patients with a proven diagnosis of CD in the period of 1985-1995. Median follow-up was 8.1 years, and remission was defined by 1) suboptimal serum cortisol response to short Synacthen stimulation at 30 minutes ( $<18$  ug/dL; 500 nmol/L) and/or UFC  $<18$  ug/24h (50 nmol) measured 12–180 days after the operation; or 2) in case of ambiguous postoperative results, development of hypopituitarism or UFC values  $<90$  ug/24 h at 5 years after the first operation. Among the 68 patients who underwent pituitary surgery, 3 died within 90 days of the first operation, and 45 achieved initial remission (39 maintained long-term remission). However, one died of a ruptured aortic aneurysm, resulting in a mortality rate similar to the background population (SMR of 0.31, 95% CI 0.01-1.72). The remaining 20 patients did not attain initial remission (11 achieved long-term remission after additional surgery), and 6 of them died; the mortality in this group was elevated compared to the general population (SMR of 5.06, 95% CI 1.86-11.0) (4).

Dekkers *et al.* (31) 74 patients with CD who underwent TSA between 1977 and 2005. Median follow-up was 10 years, and initial remission was confirmed in 80% of the patients using the criteria of serum cortisol  $<100$  nmol/L on overnight dexamethasone suppression test (ONDST) and two samples of normal 24-h UFC. Long-term remission was achieved in 93% in this series, but mortality was increased (SMR 2.39, 95% CI: 1.22-3.9). Moreover, mortality was higher in those with persistent disease (SMR was 4.38, 95% CI: 1.38-9.07). Notably, 85% of the cases were due to microadenoma (31).

Clayton *et al.* (32) reviewed 60 patients with the diagnosis of CD between 1958 and 2009. Median of follow-up was 15 years, and remission was defined by serum cortisol <100 nmol/L on ONDST or by average serum cortisol <350 nmol/L on a cortisol day curve for those on metyrapone or by having bilateral adrenalectomy within three years from first treatment. Persistent disease was defined as failure to meet remission criteria within three years despite receiving various treatment modalities. Long-term remission was achieved in 90% of all patients by the end of follow-up. Mortality was high in all groups (SMR 4.8, 95% CI: 2.8-8.3 for all patients, 3.3, 95% CI: 1.7-6.7 for those in remission, 16.0, 95% CI: 6.7-38.4 for patients with persistent disease). While vascular diseases were the most common cause of death (SMR 13.8, 95% CI: 7.2-26.5), diabetes mellitus and hypertension had negatively affected survival (32).

Bolland *et al.* (18) assessed 188 patients with CD during the period 1960-2005. Median follow-up was 7.8 years for those with macroadenoma (158 patients) and 7.6 years for microadenoma (30 patients). Remission was determined by the presence of adrenal insufficiency and requirement of glucocorticoid replacement, by normal UFC if not on glucocorticoid replacement, or by normal serum cortisol response on ONDST. 93% of the macroadenoma and 91% of the microadenoma cases achieved remission by the end of the monitoring period. Increased mortality was observed in both macroadenoma (SMR 3.5, 95% CI: 1.3-7.8) and microadenoma (SMR 3.2, 95% CI: 2.0-4.8) cases. Mortality was also high in patients with microadenoma who achieved remission after surgery (SMR 3.1, 95% CI: 1.8-4.9). Noteworthy, there was no difference in mortality between those diagnosed before or after 1980 (18).

Hassan-Smith *et al.* (33) analysed the mortality in 72 patients with CD who had TSA between 1988 and 2009. Median follow-up duration for mortality was 10.9 years. Initial remission was confirmed by morning cortisol of  $\leq 1.8$  ug/dl measured between day 4 and week 6 post-operatively (achieved in 83% of the cases), while long-term remission was defined as absence of hypercortisolism at last follow-up (achieved in 72% of the cases). Mortality was elevated in all groups (SMR 3.17, 95% CI: 1.7-5.43 for

all patients, 2.47, 95% CI: 0.8-5.77 for those who were in remission, and 4.12, 95% CI: 1.12-10.54 for patients with persistent or recurrent disease). The most frequent cause of death was CV cause (33).

Yaneva *et al.* (34) evaluated the mortality over a median follow-up of 8.8 years in 240 patients with CD treated with various modalities between 1965 and 2010. Remission was verified by normal or low UFC or 17-OH and ketosteroids in earlier cases and adequate serum cortisol suppression on ONDST during the last clinical assessment. Long-term remission was maintained in 79% of the cases following either TSA alone or in combination with other therapies. In this study, mortality was similar to that of the general population (SMR 1.88, 95% CI: 0.69-4.08) (34).

Ntali *et al.* (35) reviewed 182 patients with CD diagnosed between 1967 and 2009 with a median follow-up of 12 years. Remission was defined as undetectable 9.00 am serum cortisol following surgery and normal UFC or mean serum cortisol of 150-300 nmol/L on a 5-point cortisol day curve or development of adrenal insufficiency following pituitary radiotherapy. Long-term remission was attained in 85% of patients after various treatment modalities. Mortality was high in this series for all patients (SMR 9.3, 95% CI: 6.2-13.4) and for all types of pituitary adenoma (SMR 7.6, 95% CI: 4.7-11.7 for microadenoma and 15.6, 95% CI: 5.7-34.6 for macroadenoma). Moreover, mortality was elevated in a subgroup of patients who maintained long-term remission following their initial surgery (SMR 10.8, 95% CI: 6.0-18). The main causes of death were CV causes and infections (35).

Ragnarsson *et al.* (36) assessed the mortality in 502 patients with CD between 1987-2013 over a median follow-up of 13 years. Remission was determined by resolution of clinical features of Cushing's, normal UFC, normal midnight salivary or serum cortisol, suppressed serum cortisol on ONDST, development of adrenal insufficiency, and/or undergoing bilateral adrenalectomy. 83% of the patients achieved remission. However, mortality was increased in all groups (SMR 2.5, 95% CI: 2.1-2.9 for all patients, 1.9, 95% CI: 1.5-2.3 for those in remission, and 6.9, 95% CI: 4.3-10.4 for those who were not in remission by the end of the study). SMR due to CV diseases was notably elevated in both remission and non-remission groups (36).

Clayton *et al.* (37) conducted a multinational, multicentre, retrospective cohort study reviewing records of 320 patients from specialist centres in the UK, Denmark, the Netherlands, and New Zealand. Median follow-up was 11.8 years from study entry, and mortality was assessed in those who were in remission for at least 10 years at the time of entering the study and had no relapse until the database was frozen or until death. Increased all-cause mortality was noted in this study population (SMR 1.61, 95% CI: 1.23-2.12), and the SMR for circulatory disease was 2.72, 95% CI: 1.88-3.95. This study ratifies the long-lasting impact of hypercortisolism on survival which seems to persist even after successful treatment of CD. Notably, higher mortality was observed in patients treated with multiple therapeutic approaches (SMR 2.53, 95% CI: 1.82-3.53), whereas those who achieved remission by surgery alone had normal survival probability (SMR 0.95, 95% CI: 0.58-1.55) (37).

Roldán-Sarmiento *et al.* (38) evaluated the mortality rate of 172 patients diagnosed with CD between 1979 and 2018 who completed a median follow-up of 7.5 years. 79% (136 patients) had microadenoma, and pituitary surgery was the primary therapeutic intervention in 80% of cases (77% TSA and 3% transcranial). Remission was achieved in 71% of the patients, and it was confirmed by postoperative serum cortisol of  $<2$  ug/dL ( $<55.2$  nmol/L) and requirement of corticosteroid replacement, and eventually achieving normal 24-h UFC [ $<140$  ug/day ( $<386$  nmol/day)] following corticosteroid cessation. At last follow-up, 100 cases (58%) remained in remission, and 54 (31%) required bilateral adrenalectomy [of these, 34 patients (63%) developed Nelson's syndrome]. The SMR of all-cause mortality was elevated (3.1, 95% CI: 1.9–4.8), and was higher for CV disease (4.2, 95% CI: 1.5–9.3), which was the leading cause of death (38).

Overall, mortality is undeniably elevated in patients with persistent disease. In contrast, there is a discrepancy in the data for those in remission. Variability in the criteria defining remission, the duration of exposure to hypercortisolaemia, the recurrence rates, the follow-up periods, and the therapeutic approaches are amongst the main contributing factors to this inconsistency. Furthermore, diagnosis and management of CD have significantly evolved throughout the periods covered in

published studies. Possible selection bias in the surgical series from large specialist centres and the impact of hypopituitarism and its management need to be also considered. Finally, CV disease remains the main cause of death; given that chronic hypercortisolaemia is a major risk factor for visceral obesity, insulin resistance, impaired glucose tolerance, dyslipidaemia, systemic hypertension, atherosclerosis, and hypercoagulability, which seem to persist even after remission of CD, regular screening and strict control of these CV risk factors is mandatory.

### **Predictors of elevated mortality in CD**

Data on the effect of age at diagnosis on mortality in CD are inconsistent; however, in the large multicentre study by Clayton *et al.* (37), remission was achieved 8 years later in those who died than in those who survived by the end of the study (aged 42 vs 34 years, respectively,  $p < 0.001$ ), implying a possible detrimental effect of hypercortisolism in older ages. Similarly, data on the association between gender and mortality are discordant. While some studies reported mortality to be higher in females (14,33), others found higher mortality in males (34). At the same time, a number of studies showed no gender differences in mortality (31,36). Interestingly, higher mortality has been noted in patients treated with bilateral adrenalectomy for CD (18,36). This can be explained by the fact that this therapeutic option is usually reserved for patients with primary or recurrent CD that did not respond to other treatments. Moreover, adrenal crises or glucocorticoid over-replacement might contribute to lower survival rates. Pituitary radiotherapy has been associated with increased mortality in one (18) but not in other studies (31,36). Finally, Roldán-Sarmiento *et al.* (38) found that diabetes mellitus and persistently high serum cortisol levels in the late afternoon (16.00 hours) at the time of diagnosis were associated with higher mortality, not only in patients with active CD but also in those who were in remission at last follow-up.

[Note: for the publisher: Insert Table 2 here, please]

**Table 2.** Studies reporting on standardised mortality rates in Cushing's disease.

<b>Study</b>	<b>Number of patients</b>	<b>Follow-up</b> Mean ( $\pm$ SD) Median (range) years	<b>SMR (95% CI)</b>
Etxabe <i>et al.</i> (14) (Spain) 1975 – 1992	49	6.3 ( $\pm$ 0.8) 4.6 (0.5 – 17.5)	3.8 (2.5 – 17.9)
Sweaningen <i>et al.</i> (28) (USA) 1978 – 1996	159*	8 (1 – 20)**	0.98 (0.44 – 2.2)
Pikkarainen <i>et al.</i> (29) (Finland) 1981 – 1994	43	Mean 7.4 Range (0 – 15)	2.67 (0.89 – 5.25)
Lindholm <i>et al.</i> (4) (Denmark) 1985 – 1995	73	8.1 (3.1 – 14.0)	0.31 (0.01 – 1.72) immediate remission 5.06 (1.86 – 11.0) required additional treatment
Dekkers <i>et al.</i> (31) (Netherlands) 1977 – 2005	74	12.8 ( $\pm$ 7.3)	2.39 (1.22 – 3.9) total group 1.8 (0.71 – 3.37) remission group 4.38 (1.38 – 9.07) persistent disease
Clayton <i>et al.</i> (32) (UK) 1958 – 2010	60	15 (0.5 – 41)	4.8 (2.8 – 8.3) total group 3.3 (1.7 – 6.7) remission group 16.0 (6.7 – 38.4) persistent disease
Bolland <i>et al.</i> (18) (New Zealand) 1960 – 2005	188	6.9 (0 – 30) macro 7.5 (0 – 46) micro	3.5 (1.3 – 7.8) macroadenoma 3.2 (2.0 – 4.8) microadenoma
Hassan-Smith <i>et al.</i> (33) (UK) 1988 – 2009	72	10.9 (4.9 – 15.6)	3.17 (1.7 – 5.43) total group 2.47 (0.80 – 5.77) remission group 4.12 (1.12 – 10.54) persistent group

Yaneva <i>et al.</i> (34) (Bulgaria) 1965 – 2010	240	8.8 (0 – 41.2)	1.88 (0.69 – 4.08)
Ntali <i>et al.</i> (35) (UK) 1967 – 2009	182	12 (0.1 – 46)	9.3 (6.2 – 13.4) total group 10.8 (6.0 – 18) immediate remission 10.0 (5.3 – 17.1) remission at last review 9.9 (3.6 – 21.9) not in remission at last review
Ragnarsson <i>et al.</i> (36) (Sweden) 1987 – 2014	502	13 (6 – 23)	2.5 (2.1 – 2.9) total group 1.9 (1.5 – 2.3) remission group 6.9 (4.3 – 10.4) not in remission
Clayton <i>et al.</i> (37) (UK, Denmark, Netherlands, New Zealand) 1958 – 2014	320	11.8 (17 – 26)***	1.61 (1.23 – 2.12) total group 2.72 (1.88 – 3.95) circulatory causes 0.94 (0.57 – 1.53) TSA as 1 <sup>st</sup> and only treatment
Roldán-Sarmiento <i>et al.</i> (38) (Mexico) 1979 – 2018	172	7.5 (2.4 – 15)	3.1 (1.9 – 4.8) all-cause mortality 4.2 (1.5 – 9.3) CV mortality
Abbreviations: SMR: standardized mortality ratio, CI: confidence interval, SD: standard deviation, TSA: transsphenoidal adenohypophysectomy, CV: cardiovascular, CD: Cushing's disease. *number of patients with survival data; **for those with survival data; ***since study entry			

## **Mortality in Adrenal Cushing's**

Mortality in CS of adrenal origin has been assessed in a number of studies [Table 3]. Pikkariainen *et al.* (29) evaluated mortality in a series of 20 patients diagnosed with CS due to adrenal adenoma between 1981 and 1994 over a follow-up period of 7.4 years. All patients underwent adrenalectomy. Two patients had died: one at age 64 years due to microcellular lung cancer (six years after CS diagnosis) and one at age 62 years due to intracerebral haemorrhage (one year after CS diagnosis). Mortality was similar to that of the general population (SMR 1.35, 95% CI: 0.16-4.89) (29).

Lindholm *et al.* (4) estimated mortality in a group of 25 patients who underwent unilateral adrenalectomy for CS due to adrenal adenoma. The median follow-up was 7.1 years; however, remission rate or criteria were not specified in this study. Three patients died: one due to myocardial infarction, one due to mesothelioma, and one because of breast cancer (0.7, 5.5, and 4.2 years after the first admission, respectively). Even though mortality was elevated during the first year after initial admission (SMR 3.48, 95% CI: 0.95-8.9), the long-term mortality was not increased in comparison to the general population (SMR 3.95, 95% CI: 0.81-11.5) (4).

In a nationwide study by Bolland *et al.* (18), mortality was assessed in 37 patients with CS due to adrenal adenoma over a period of 3.1 years and in 9 patients due to bilateral adrenal hyperplasia over 5.7 years. Remission was achieved in 95% in those with adrenal adenoma and in 56% in bilateral adrenal hyperplasia using the same criteria to define remission in CD (mentioned previously). Mortality was increased in both groups, with an SMR of 7.5, 95% CI: 1.9-20 and 14, 95% CI: 3.7-40, respectively (18).

Yaneva *et al.* (34) reviewed 84 patients with adrenal adenoma (median follow-up of 4.2 years) and 11 with bilateral adrenal hyperplasia (median follow-up of 5.5 years) causing CS. Remission was confirmed applying the same criteria used for CD cohort (mentioned previously). Mortality was



similar to that of the general population in both groups (SMR 1.67, 95% CI: 0.20-6.02 for adrenal adenoma, and 1.14, 95% CI: 0.21-6.34 for bilateral adrenal hyperplasia) (34).

Ntali *et al.* (35) analysed mortality in 16 patients with Cushing's syndrome due to either unilateral adrenal adenoma or bilateral adrenal hyperplasia over a median follow-up period of 5 years. 92% of the patients were in remission at the last assessment. Only one patient died in this subgroup, and it was attributed to a CV event. Mortality was not elevated (SMR 5.3, 95% CI: 0.3-26). Nonetheless, the number of events was small (which explains the wide CI) (35).

In a nationwide study by Ahn *et al.* (21), 1127 patients with benign adrenal CS were identified between 2002 and 2017. Median follow-up was 9.7 years. Mortality was high with an SMR of 3.0, 95% CI 2.4-3.7 for benign adrenal CS. However, using diagnostic coding to retrieve data has led to several limitations in this series, including lack of information on biochemical, imaging, and pathological results, and of data on the underlying aetiology of benign adrenal CS, as well as the cause of death (21).

In summary, the published data on mortality in patients with CS due to benign adrenal pathology are not consistent, and the inclusion of patients with or without remission in the analyses may have contributed to the discrepant results.

[Note: for the publisher: Insert Table 3 here, please]

**Table 3.** Studies reporting on standardised mortality rates in Cushing's syndrome of adrenal origin

<b>Study</b>	<b>Number of patients</b>	<b>Follow-up</b> Mean ( $\pm$ SD) Median (range) years	<b>SMR (95% CI)</b>
Pikkarainen <i>et al.</i> (29) (Finland) 1981 – 1994	20	Mean 7.4 Range (0 – 15)	1.35 (0.16 – 4.89)
Lindholm <i>et al.</i> (4) (Denmark) 1985 – 1995	37	7.1 (3.1 – 13.8)	3.95 (0.81 – 11.5)
Bolland <i>et al.</i> (18) (New Zealand) 1960 – 2005	37 (AA) 9 (BH)	3.1 (0 – 18) 5.7 (1.5 – 39)	7.5 (1.9 – 20) unilateral adenoma 14 (3.7 – 40) bilateral hyperplasia
Yaneva <i>et al.</i> (34) (Bulgaria) 1965 – 2010	84 (AA) 11 (BH)	4.2 (0 – 31) 5.5 (0 – 15)	1.67 (0.20 – 6.02) unilateral adenoma 1.14 (0.21 – 6.34) bilateral hyperplasia
Ntali <i>et al.</i> (35) (UK) 1967 – 2009	16	5 (0.1 – 14.5)	5.3 (0.3 – 26)
Ahn <i>et al.</i> (21) (South Korea) 2002 – 2017	1127	9.7 (4.7-12.5)	3.0 (2.4 – 3.7)

Abbreviations: SMR: standardized mortality ratio, CI: confidence interval, SD: standard deviation

## **Mortality in Mild Autonomous Cortisol Secretion**

Even though there is no study reporting SMR in this group of patients, it is worth addressing the available published series evaluating mortality. Di Dalmazi *et al.* (12) assessed mortality in 198 patients with adrenal incidentaloma diagnosed between 1995 and 2010 for a mean follow-up period of 7.5 years. Baseline 1mg-ONDST was used to categorize patients into three groups: 129 with non-secreting adenomas (<50 nmol/L) with a mean age of 61.3 years, 59 with intermediate phenotype (50-138 nmol/L) with a mean age of 65.4 years, and 10 with subclinical Cushing's syndrome (>138 nmol/L) with a mean age of 70.4 years. Follow-up 1mg-ONDST resulted in reclassification of 15 out of 129 patients with non-secreting lesions into either intermediate phenotype (14 patients) or subclinical CS (one patient), and eight of 59 patients with intermediate phenotype into subclinical CS. By the end of the study, 21 patients died: 10 (48%) due to CV disease, 9 (43%) due to cancer, and two (10%) due to complications following a fractured hip. The unadjusted survival for all-cause mortality was lower in the cohorts of stable intermediate phenotype and subclinical CS compared to the stable non-secreting adenoma cases (57% vs 91.2%,  $p=0.005$ ). Moreover, the unadjusted survival for CV-specific mortality was lower in the cohorts of stable intermediate phenotype and subclinical CS in comparison to those with stable non-secreting adrenal incidentalomas (78.4% vs 97.5%,  $p=0.02$ ), and in those 23 patients who had worsening secretion patterns upon follow-up (60.0% vs 97.5%,  $p=0.01$ ). The main predictive factors for mortality were age (HR 1.06, 95% CI 1.01-1.12) and mean serum cortisol levels post 1mg-ONDST (HR 1.1, 95% CI 1.01-1.19) (12).

Debono *et al.* (23) assessed mortality in 206 patients diagnosed with benign adrenal incidentaloma between 2005 and 2013 over a median follow-up of 4.2 years. 111 patients (median age of 69 years) were found to have abnormal 1mg-ONDST (>1.8 ug/dL/50 nmol/L), whilst 95 patients (median age of 63 years) had normal response. The total number of deaths observed was 18 (with only one in the non-secreting incidentaloma), and the median age at death was 73 years. In the survival analysis and based on the results of the ONDST, the patients were classified into two groups: group 1 with serum cortisol of 1.8–5 µg/dL (50–137 nmol/L) comprised of 92 patients where 12 died (13%), and group 2 with

serum cortisol of  $>5 \mu\text{g/dL}$  ( $>138 \text{ nmol/L}$ ) included 19 patients where five died (26%). The survival rate was significantly lower and got worse with the increasing post-ONDST cortisol cut-offs (HR of 12.0 [1.6–92.6] for group 1, and 22.0 [2.6–188.3] for group 2) in comparison to the non-secreting incidentaloma group. Circulatory events were the most frequent causes of death, followed by respiratory and infectious causes, 50% and 33%, respectively. Of note, the post-ONDST cortisol values were the main predictive factors. Age, gender, and comorbidities did not play a significant role in mortality in this series (23).

Lastly, Patrova *et al.* (39) analysed the data of 365 patients with adrenal incidentaloma diagnosed between 2003 and 2010 over a mean follow-up period of 5.2 years. The cohort was divided into three groups according to the cortisol results on baseline 1mg-ONDST: 204 normal cortisol response ( $\leq 50 \text{ nmol/L}$ ), 128 possible (51-138 nmol/L), and 33 autonomous cortisol secretion ( $>138 \text{ nmol/L}$ ). 37 patients died in this series: 16 (7.8%) in the non-secreting group, 15 (11.7%) in the possible autonomous cortisol secretion group, and 6 (18.2%) in the autonomous cortisol secretion group. Interestingly, non-adrenal malignancy was the most frequent leading cause of death (59% for the whole cohort, 45% for non-secreting, 50% for possible, and 100% for autonomous cortisol secretion). Mortality correlated with size of the adenoma (HR 1.04, 95% CI 1.02–1.05), age of the patient (HR 1.06, 95% CI 1.00–1.11), and with cortisol levels post-ONDST only if used as a continuous variable (HR 1.006, 95% CI 1.002–1.010) (39).

In summary, despite their limitations and the lack of SMR reporting, the available studies suggest increased mortality in patients with autonomous cortisol secretion causing mild CS. . The degree of autonomous cortisol secretion and, to some extent, age and size of the adenoma seem to predict mortality; however, more studies with a larger number of events are required to confirm these findings. The main cause of death remains to be CV events.

## **Conclusions**

CS syndrome remains a rare entity with an annual incidence ranging between 1.8-3.2 cases per million population. CD is still the most common and prevalent aetiology of CS. Mortality in active CS is elevated, whereas the data of studies evaluating survival in patients in remission are not consistent, mainly due to methodological differences and variability in the diagnostic and treatment approaches used. Nonetheless, there is substantial evidence supporting increased mortality even after apparent biochemical remission, with long-lasting metabolic and vascular effects of hypercortisolism being the main contributing factors leading to CV events. This necessitates early and rapid diagnosis and effective treatment of the CS, as well as screening and appropriate management of its associated metabolic abnormalities.

### **Practice points**

- CS is associated with significantly compromised survival necessitating early diagnosis and rapid therapeutic intervention to achieve remission and minimise exposure to hypercortisolaemia.
- CV disease is the main cause of death in patients with CS.
- Given that chronic hypercortisolaemia is associated with visceral obesity, insulin resistance, impaired glucose tolerance, dyslipidaemia and systemic hypertension, regular screening and strict control of these CV risk factors are mandatory even after apparent biochemical remission.

### **Research agenda**

- Identification of predictive factors of mortality in patients with CS is needed. These include the impact of duration of exposure to cortisol excess, hypopituitarism, and various therapeutic modalities, including pharmacotherapy.
- Mortality in patients CS attributed to benign adrenal pathology remains to be clarified with methodologically robust studies.
- Studies assessing SMR in cases of mild autonomous cortisol secretion from adrenal incidentalomas are required.

## References:

1. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet Lond Engl.* 2006;367(9522):1605-1617. doi: 10.1016/S0140-6736(06)68699-6
2. Javanmard P, Duan D, Geer EB. Mortality in Patients with Endogenous Cushing's Syndrome. *Endocrinol Metab Clin North Am.* 2018;47(2):313-333. doi: 10.1016/j.ecl.2018.02.005
3. Barbot M, Zilio M, Scaroni C. Cushing's syndrome: Overview of clinical presentation, diagnostic tools and complications. *Best Pract Res Clin Endocrinol Metab.* 2020;34(2):101380. doi: 10.1016/j.beem.2020.101380
- \*4. Lindholm J, Juul S, Jørgensen JO, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin Endocrinol Metab.* 2001;86(1):117-123. doi: 10.1210/jcem.86.1.7093
5. Ntali G, Hakami O, Wategama M, et al. Mortality of Patients with Cushing's Disease. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc.* Published online July 9, 2020. doi: 10.1055/a-1197-6380
6. Dekkers OM, Horváth-Puhó E, Jørgensen JOL, et al. Multisystem Morbidity and Mortality in Cushing's Syndrome: A Cohort Study. *J Clin Endocrinol Metab.* 2013;98(6):2277-2284. doi: 10.1210/jc.2012-3582
7. Ntali G, Grossman A, Karavitaki N. Clinical and biochemical manifestations of Cushing's. *Pituitary.* 2015;18(2):181-187. doi: 10.1007/s11102-014-0631-4
8. Bovio S, Cataldi A, Reimondo G, et al. Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *J Endocrinol Invest.* 2006;29(4):298-302. doi: 10.1007/BF03344099
9. Araujo-Castro M, Sampedro Núñez MA, Marazuela M. Autonomous cortisol secretion in adrenal incidentalomas. *Endocrine.* 2019;64(1):1-13. doi: 10.1007/s12020-019-01888-y

10. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol.* 2016;175(2):G1-G34. doi: 10.1530/EJE-16-0467
11. Di Dalmazi D, Vicennati V, Rinaldi E, et al. Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large cross-sectional study. *Eur J Endocrinol.* 2012;166(4):669-677. doi: 10.1530/EJE-11-1039
- \*12. Di Dalmazi G, Vicennati V, Garelli S, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. *Lancet Diabetes Endocrinol.* 2014;2(5):396-405. doi: 10.1016/S2213-8587(13)70211-0
13. Morelli V, Eller-Vainicher C, Salcuni AS, et al. Risk of new vertebral fractures in patients with adrenal incidentaloma with and without subclinical hypercortisolism: a multicenter longitudinal study. *J Bone Miner Res Off J Am Soc Bone Miner Res.* 2011;26(8):1816-1821. doi: 10.1002/jbmr.398
14. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clin Endocrinol (Oxf).* 1994;40(4):479-484. doi: <https://doi.org/10.1111/j.1365-2265.1994.tb02486.x>
15. Agustsson TT, Baldvinsdottir T, Jonasson JG, et al. The epidemiology of pituitary adenomas in Iceland, 1955-2012: a nationwide population-based study. *Eur J Endocrinol.* 2015;173(5):655-664. doi: 10.1530/EJE-15-0189
16. Fernandez A, Karavitaki N, Wass JAH. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf).* 2010;72(3):377-382. doi: 10.1111/j.1365-2265.2009.03667.x

17. Daly AF, Rixhon M, Adam C, et al. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab.* 2006;91(12):4769-4775. doi: 10.1210/jc.2006-1668
- \*18. Bolland MJ, Holdaway IM, Berkeley JE, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. *Clin Endocrinol (Oxf).* 2011;75(4):436-442. doi: <https://doi.org/10.1111/j.1365-2265.2011.04124.x>
- \*19. Wengander S, Trimpou P, Papakokkinou E, Ragnarsson O. The incidence of endogenous Cushing's syndrome in the modern era. *Clin Endocrinol (Oxf).* 2019;91(2):263-270. doi: 10.1111/cen.14014
20. Ragnarsson O, Olsson DS, Chantzichristos D, et al. The incidence of Cushing's disease: a nationwide Swedish study. *Pituitary.* 2019;22(2):179-186. doi: 10.1007/s11102-019-00951-1
21. Ahn CH, Kim JH, Park MY, Kim SW. Epidemiology and Comorbidity of Adrenal Cushing Syndrome: A Nationwide Cohort Study. *J Clin Endocrinol Metab.* doi: 10.1210/clinem/dgaa752
22. Terzolo M, Pia A, Reimondo G. Subclinical Cushing's syndrome: definition and management. *Clin Endocrinol (Oxf).* 2012;76(1):12-18. doi: <https://doi.org/10.1111/j.1365-2265.2011.04253.x>
- \*23. Debono M, Bradburn M, Bull M, et al. Cortisol as a Marker for Increased Mortality in Patients with Incidental Adrenocortical Adenomas. *J Clin Endocrinol Metab.* 2014;99(12):4462-4470. doi: 10.1210/jc.2014-3007
24. Steffensen C, Dekkers OM, Lyhne J, et al. Hypercortisolism in Newly Diagnosed Type 2 Diabetes: A Prospective Study of 384 Newly Diagnosed Patients. *Horm Metab Res Horm Stoffwechselforschung Horm Metab.* 2019;51(1):62-68. doi: 10.1055/a-0809-3647
25. Reimondo G, Pia A, Allasino B, et al. Screening of Cushing's syndrome in adult patients with newly diagnosed diabetes mellitus. *Clin Endocrinol (Oxf).* 2007;67(2):225-229. doi: 10.1111/j.1365-2265.2007.02865.x



26. Chiodini I, Torlontano M, Scillitani A, et al. Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. *Eur J Endocrinol.* 2005;153(6):837-844. doi: 10.1530/eje.1.02045
27. Ebbelohj A, Li D, Kaur RJ, et al. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. *Lancet Diabetes Endocrinol.* 2020;8(11):894-902. doi: 10.1016/S2213-8587(20)30314-4
28. Swearingen B, Biller BM, Barker FG, et al. Long-term mortality after transsphenoidal surgery for Cushing disease. *Ann Intern Med.* 1999;130(10):821-824. doi: 10.7326/0003-4819-130-10-199905180-00015
29. Pikkarainen L, Sane T, Reunanen A. The survival and well-being of patients treated for Cushing's syndrome. *J Intern Med.* 1999;245(5):463-468. doi: <https://doi.org/10.1046/j.1365-2796.1999.00483.x>
30. Graversen D, Vestergaard P, Stochholm K, et al. Mortality in Cushing's syndrome: A systematic review and meta-analysis. *Eur J Intern Med.* 2012;23(3):278-282. doi: 10.1016/j.ejim.2011.10.013
31. Dekkers OM, Biermasz NR, Pereira AM, et al. Mortality in Patients Treated for Cushing's Disease Is Increased, Compared with Patients Treated for Nonfunctioning Pituitary Macroadenoma. *J Clin Endocrinol Metab.* 2007;92(3):976-981. doi: 10.1210/jc.2006-2112
- \*32. Clayton RN, Raskauskiene D, Reulen RC, Jones PW. Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metab.* 2011;96(3):632-642. doi: 10.1210/jc.2010-1942
33. Hassan-Smith ZK, Sherlock M, Reulen RC, et al. Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. *J Clin Endocrinol Metab.* 2012;97(4):1194-1201. doi: 10.1210/jc.2011-2957

34. Yaneva M, Kalinov K, Zacharieva S. Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center. *Eur J Endocrinol.* 2013;169(5):621-627. doi: 10.1530/EJE-13-0320
- \*35. Ntali G, Asimakopoulou A, Siamatras T, et al. Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. *Eur J Endocrinol.* 2013;169(5):715-723. doi: 10.1530/EJE-13-0569
- \*36. Ragnarsson O, Olsson DS, Papakokkinou E, et al. Overall and Disease-Specific Mortality in Patients with Cushing Disease: A Swedish Nationwide Study. *J Clin Endocrinol Metab.* 2019;104(6):2375-2384. doi: 10.1210/jc.2018-02524
- \*37. Clayton RN, Jones PW, Reulen RC, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. *Lancet Diabetes Endocrinol.* 2016;4(7):569-576. doi: 10.1016/S2213-8587(16)30005-5
38. Roldán-Sarmiento P, Lam-Chung CE, Hinojosa-Amaya JM, et al. Diabetes, Active Disease, and Afternoon Serum Cortisol Levels Predict Cushing's Disease Mortality: A Cohort Study. *J Clin Endocrinol Metab.* 2021;106(1):e103-e111. doi: 10.1210/clinem/dgaa774
- \*39. Patrova J, Kjellman M, Wahrenberg H, Falhammar H. Increased mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: a 13-year retrospective study from one center. *Endocrine.* 2017;58(2):267-275. doi: 10.1007/s12020-017-1400-8