Mortality and Morbidity in Cushing's Disease over 50 Years in Stoke-on-Trent, UK: Audit and Meta-Analysis of Literature

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Context: Pituitary ACTH-dependent Cushing's disease (CD) is uncommon, and there are very limited data on long-term mortality.

Objective: The aim was to summarize what is known about mortality in ACTH-dependent CD, to report on our own data, and to provide a meta-analysis of six other reports that addressed mortality of CD.

Design and Methods: Vital status of 60 CD patients was recorded as of December 31, 2009, and the standardized mortality ratio (SMR) was calculated and compared with the general population of England and Wales, United Kingdom. A meta-analysis of SMRs from seven studies (including ours) was performed for overall mortality in CD. Where reported (four studies), a similar meta-analysis was performed for those patients whose hypercortisolism was in remission after treatment compared to those patients from the same center with persistent disease.

Results: 1. From Stoke-on-Trent, 51 of 60 patients were female, median age at diagnosis was in the range of 36–46 yr, and median follow-up was 15 yr. There were 13 deaths, nine due to cardiovascular disease. Overall SMR for the whole cohort was 4.8 (95% confidence interval, 2.8–8.3) ($P < 0001$). SMR for vascular disease was 13.8 (7.2–36.5) ($P < 0001$). For persistent disease (n = 6), SMR was 16 (6.7–38.4) *vs.* remission (n = 54) SMR of 3.3 (1.7–6.7); after adjustment for age and sex, relative risk of death for persistent disease was 10.7 (2.3–48.6) ($P = 0.002$). Hypertension and diabetes mellitus were associated with significantly worse survival. 2. Using a random effects model meta-analysis revealed an overall (remission plus persistent disease) SMR of 2.2 (1.45–3.41) ($P < 0.001$). Pooled SMR was 1.2 (0.45–3.2) (P = not significant) for patients in remission and 5.5 (2.7–11.3) ($P = 0.001$) for patients with persistent disease. Persistence of disease, older age at diagnosis, and presence of hypertension and diabetes are the main determinants of mortality.

Conclusions: Overall mortality in CD is double that of the general population. However, patients with CD in remission fare much better than those with persistence of hypercortisolism, and they appear not to have an increased mortality rate. Hypertension and diabetes mellitus are risk factors for worse outcome. Because diagnosis and treatment of patients are at a young age, much longer follow-up of patients in remission is required before one can be confident that their mortality outcome is no different from that of the general population, especially because cardiovascular risk factors may persist after successful biochemical control of the disease. **(*J Clin Endocrinol Metab* 96: 632–642, 2011)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-1942 Received August 17, 2010. Accepted November 22, 2010.
First Published Online December 30, 2010

Abbreviations: CD, Cushing's disease; CI, confidence interval; CT, computed tomography; NS, not significant; SMR, standardized mortality ratio.

Cushing's syndrome is a rare condition with estimated incidence of two or three per million population per year (1), although it might be higher in selected patient populations such as poorly controlled diabetics, young osteoporotic women and men, and young hypertensives (2). Furthermore, mild (subclinical) Cushing's syndrome may be detected in patients with incidentally discovered adrenal adenomas on abdominal computed tomography (CT) scan performed for other reasons. Untreated Cushing's disease (CD) is associated with a very poor prognosis, estimated 5-yr survival of 50% (3), although this is dramatically improved to 86% after bilateral adrenalectomy (4).

The main causes of the poor outcome in untreated patients are macrovascular disease (strokes, myocardial infarction), uncontrolled diabetes mellitus, and infections. Long-term outcome studies in patients with Cushing's syndrome are very limited. In contrast to patients with acromegaly and nonfunctioning tumors where there is now extensive data on factors that determine mortality, little data are available for Cushing's syndrome. For example, we know that in acromegaly the duration of disease before diagnosis is a predictor for mortality, as is age at diagnosis and the presence of hypertension or cardiac disease at diagnosis (5). It is not known whether similar variables predict mortality in CD, although intuitively this would seem likely. Furthermore, we know that a specific biochemical target with respect to GH and IGF-I is predictive of mortality in acromegaly (6). Is there such a relationship for plasma cortisol in Cushing's syndrome? The question is whether elimination of hypercortisolism, even if present for several years before treatment as is often the case, can restore mortality rates to that of the reference population. The purpose of this report is 2-fold: 1) to determine the long-term outcome for patients with CD referred to and treated in a single UK center between 1958–2010; and 2) to conduct a meta-analysis of literature data on standardized mortality ratios (SMR) and factors predictive of mortality.

Patients and Methods

Local Stoke-on-Trent study

Only those patients with histologically proven ACTH-staining pituitary adenoma or highly likely ACTH-dependent CD (on the basis of biochemical testing and absence of any other source of ACTH) are considered for this analysis because this is the commonest cause of Cushing's syndrome. Retrospective analysis of all available patient records going back to 1958 was performed. We ascertained demographic details, age at and year of diagnosis and treatment, and symptoms and signs at presentation including presence or absence of hypertension and diabetes (defined as being on treatment according to criteria in use at the time). We looked at primary and secondary treatment modalities, remission or persistence of hypercortisolemia, years of follow-up, current age or age at death (as of December 31, 2009), and cause of death (ascertained from hospital records, autopsy, or death certificate). Criteria for biochemical diagnosis of CD varied according to the year of diagnosis. For 1958–1975, criteria included the following: elevated urinary 17-oxogenic steroids, 17-oxosteroids, and 11-hydroxysteroids; absence of plasma cortisol diurnal variation, absence of suppression of plasma cortisol with dexamethasone (2 mg/d for 2 d, followed by 8 mg/d for 2 d, Liddle's test), and responsiveness of urinary steroids as above to exogenous ACTH and metyrapone. After 1975, plasma ACTH measurements and urinary free cortisol became available so they replaced 17-oxogenic,17-oxo,11-hydroxysteroid measurements. All other tests were as before, with the addition of plasma ACTH measurements in the Liddle's test, plus corticotropin-releasing factor testing requiring a greater than 30% rise in plasma cortisol and greater than 50% rise in plasma ACTH. Plasma and urinary free cortisol assays varied over time, and so absolute definitions of abnormality also varied according to the reference ranges supplied by the kit manufacturers.

Radiological assessment included lateral skull x-ray with tomography in the early years, contrast enhanced CT scans of the pituitary, and magnetic resonance imaging scans with gadolinium enhancement and dynamic early phase imaging when available. Patients would also undergo routine chest x-ray (in the early years) and CT of thorax and abdomen when this became available. Initial treatments included transsphenoidal hypophysectomy (n = 34), conventional external beam radiotherapy with or without metyrapone and aminoglutethimide (n = 14), and bilateral adrenalectomy (n = 12). Primary treatment failures were treated by bilateral adrenalectomy after 3 yr in the case of those patients treated with radiotherapy and metyrapone, or sooner after failed hypophysectomy.

Remission of hypercortisolism was defined clinically by resolution of symptoms and clinical signs (although not all hypertensive and diabetic subjects were able to stop medications—they may have been reduced) and biochemically by normalization of relevant urinary steroid excretion, restoration of plasma cortisol suppression by low-dose dexamethasone, and mean normal plasma cortisol day curve for subjects on metyrapone, within 3 yr after treatment. Failure to achieve these targets within 3 yr was defined as persistence of disease despite several treatment modalities. Bilateral adrenalectomy with subsequent cortisone acetate (early years) or hydrocortisone replacement was classified as in remission from the time of adrenalectomy. The reason for using a cutoff period of 3 yr was to ensure that all treatment modalities would have been effective in those patients requiring multiple different treatments sequentially. This differs from several studies in the literature (the surgical series) where remission is defined early after surgery (within the first few months).

The vital status of all patients was ascertained at December 31, 2009, as either alive or dead. SMRs, defined as the ratio of the observed over expected number of deaths, were calculated by multiplying age, sex, and calendar year-specific mortality rates in the general population of England and Wales by the person-years at risk in corresponding age, sex, and calendar year strata in the cohort (7, 8). Cox regression models using attained age as the time metric were employed to derive relative risks. All models were also adjusted for sex. Other comparisons between groups used the Mann-Whitney test. Because this was a retrospective audit study, institutional approval was not required.

Meta-analysis and comparisons

To compare our results with previously published data, we conducted a Medline search for all English language publications using the following terms: Cushing's syndrome, long-term outcomes/results, and mortality. This yielded six reports between 1994 and 2007. We were surprised by the small number of reports, so we also did a Medline search by authors from the centers that have contributed extensively to the literature on CD. We did not retrieve further publications addressing mortality. A meta-analysis for SMR from these and our own study was performed according to Canavan *et al.* (9), using the metan routine in Stata statistical package (StataCorp, College Station, TX). Individual SMRs (overall n = 7), remission, and persistent disease separately (n = 4) were log-transformed and tested for heterogeneity by χ^2 test. The estimates of pooled SMRs and their 95% confidence interval (CI) were obtained by back-transforming the intervals for log SMR. To achieve consistency and direct comparability in reporting our results, this method is used on the data from all studies, rather than taking the 95% CIs reported in the original publications. The 95% CIs reported in our meta-analysis differ slightly from those reported by the individual authors because they are all calculated by the same method herein, whereas in the original publications these are calculated differently. There is no difference in the estimated SMRs between our meta-analysis and the original publications. Results are presented in the form of Forest plots.

Results

Local Stoke-on-Trent data

From our records, 60 patients with CD were identified from 1958–2010. Where pituitary surgery was performed, the resected tissue stained positive for ACTH. Where no surgery was performed (patients treated with radiotherapy, adrenalectomy, or metyrapone), it is highly unlikely that these patients had occult ectopic ACTH secretion because during extended follow-up this has not declared itself. It is likely that these 60 patients represent all those seen by us. Although it is feasible that some patients with Cushing's syndrome may have escaped undiagnosed, we think this is unlikely. Assuming that CD represents 80% of the causes of Cushing's syndrome, there should have been 75 patients diagnosed with the syndrome over the study period; in fact, we have documented 74 when other causes are included. This gives an incidence of 1.5 new cases of Cushing's syndrome per year. Our catchment population for this is approximately 1 million persons, and only those with CD are referred to us for treatment—those with other causes being treated locally. The referring hospitals have remained unchanged throughout the 50-yr period, although the population has increased slightly in line with that of the United Kingdom in general (about 15%). The 1.5 new cases per year is therefore a slight underestimate of the true incidence of Cushing's syndrome, although it is still not far short of that of two to three per million per year reported in the literature. The details of the whole Stoke cohort are shown in Table 1 (demographics as medians). As expected, the majority of patients were females (51 of 60), and the median age at diagnosis of the different subgroups ranged from 36–46 yr (Table 1), which is similar to all other studies.

This study has the longest median follow-up of 15 yr on average for the different groups of patients, many patients being followed for more than 20 yr (Table 1). Nevertheless, because there were small numbers, none of the subgroups (*e.g.* dead *vs.* alive, remission *vs.* persistence, hypertension *vs.* no hypertension) showed any statistically significant differences in demographic details.

At the end of the follow-up period, 13 of 60 (22%) of the cohort had died. The details are shown in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Eight of 13 deaths were defined as being in the remission subgroup after treatment; five of 13 had persistent disease. Six patients had persistent disease, and five of these died (83%) *vs.* eight of 54 in the remission subgroup (15%). Those

TABLE 1. Demographic details of Stoke Cushing's patients

	n	Age at diagnosis (yr)	Age on Dec. 31, 2009 (yr)	Years of follow-up
Alive	47	36 (10-75)	54 (27-75.5)	15 (0.5-41)
Dead	13	46 (20-58)	60 (33-69)	15 (2-29)
Remission	8	38.5 (20-54)	63 (33-69)	17.5 (11-29)
Persistent	5	46 (22-58)	59 (37-62)	13 (2-16)
Remission	54	37 (10-75)	53 (27-75.5)	16.5 (0.5-41)
Persistent	6	46 (22-59)	55 (37-62)	9 (1-16)
Diabetes				
Yes	11	46 (22-66)	60 (37-72)	13 (1-35)
No	49	36 (10-75)	53 (27-75.5)	15 (0.5-41)
Hypertension				
Yes	22	46 (22-75)	60 (37-75.5)	12.5 (0.5-35)
No	38	33 (10-54)	50 (27-74)	16 (3-41)

Values are expressed as median (range). There were no statistical differences between groups for any of the variables by Mann-Whitney test.

TABLE 2. SMRs for Stoke Cushing's patients

	No. of deaths	Expected no. of deaths	SMR (95% CI)	*P* value
Overall	13	2.7	4.8 (2.8-8.3)	<0.0001
Vascular	9	0.65	13.8 (7.2-26.5)	<0.0001
Remission	8	2.4	3.3 (1.7-6.7)	0.0006
Persistent	5	0.3	16.0 (6.7-38.4)	<0.0001
Diagnosis before 1985	10	1.6	6.1 (3.3-11.4)	<0.0001
Diagnosis after 1985	3	1.1	2.8 (0.9-8.6)	0.076

who died in the remission group (n = 8) survived an average of 17.5 yr from diagnosis (range, 11–29 yr) *vs.* 13 (range, 2–16) yr for those with persistent disease (n = 5) who died [*P* = not significant (NS)] (Table 1). Eleven of 13 patients who died survived more than 10 yr after treatment (Supplemental Table 1). SMR data are presented in Table 2. For all subgroups shown in Table 2, the SMR was significantly greater than expected, with the exception of those patients diagnosed and treated after 1985. The patients diagnosed between 1960 and 1985 were the first 25 yr of the cohort before transsphenoidal surgery was routine at our center, and these early patients were treated with radiotherapy, metyrapone, and/or bilateral adrenalectomy. Ten of the 13 deaths occurred in this cohort, with only three deaths after 1985 when transsphenoidal surgery was routine first-line treatment; this latter subgroup did not have an increased SMR (2.8), although this was just short of significance ($P = 0.076$) (Table 2). Although there was no statistical difference in SMR between those patients with persistent disease and those in remission after multivariate Cox's regression analysis correcting for age and sex at diagnosis, the relative risk of death for those with persistent disease was 10-fold compared with those in remission (Table 3). A similar analysis for those diagnosed before *vs.* after 1985 revealed a relative risk for death before 1985 of 2.6 (95% CI, 0.7–10.5), which although not statistically significant ($P = 0.17$) was still increased.

Causes of death are shown in Supplemental Table 1. There was one perioperative death 12 d after hypophysectomy, and autopsy failed to reveal the cause. There were two deaths from cancer unrelated to the pituitary and one from massive gastrointestinal hemorrhage. Nine of 13 deaths could be attributable either directly or indirectly to a vascular cause (cardiovascular in six, cerebrovascular in two, ruptured aortic aneurysm in one). This number of vascular deaths is significantly more than would be expected from the general population (SMR = 13.8; Table 2). Ten of 13 patients were hypertensive on treatment, and five of 13 were diabetic on treatment throughout their follow-up. The two patients who died of cancer were neither hypertensive nor diabetic and were young at diagnosis and death.

TABLE 3. Cox's regression adjusting for age and sex at diagnosis

	Relative risk (95% CI)	*P* value
Persistent *vs.* remission	10.7 (2.3-48.6)	0.002
Diagnosis before 1985 *vs.* after 1985	2.6 (0.7-10.5)	0.17

The influence of hypertension and diabetes mellitus on survival is depicted in the Kaplan-Meir plots shown in Fig. 1. From this it appears that the presence/persistence of hypertension exerts the greater influence; however, the number of deaths was too small to perform a multivariate analysis.

Meta-analysis and literature review

A summary of the studies that describe long-term outcomes in terms of mortality and predictors of this is presented in Table 4 and Supplemental Table 2. Some general comments are pertinent. The period covered from the mid 1970s to late 1990s spans the time when transsphenoidal surgery for pituitary adenomas was well established. The number of patients is small by epidemiological standards, and the number of deaths is even smaller, amounting to less than 10% of the total patient population. Therefore, information on causes of death is limited and cannot be statistically analyzed reliably. The mean age of diagnosis and treatment (late 30s) is similar across all reports, and the median follow-up duration (about 10 yr) is similar, except for the report by Etxabe and Vazquez (11) (shortest) and this study (longest). This means that the age of the patients at the end of the study is less than 60 yr, so unsurprisingly the number of deaths is small given the improvements in the health of the population over this 30- to 40-yr period. Only the first and smallest study by Etxabe and Vazquez (11) reports on the relationship of hypertension and carbohydrate metabolism to mortality (but see our own data in Fig. 1). Some of the other studies reported primarily by pituitary surgeons (10, 13) may be somewhat biased because they will include only those "offered" to them by endocrinologists/physicians and are likely biased in favor of patients thought by the latter to do well from surgery. This may explain the very high

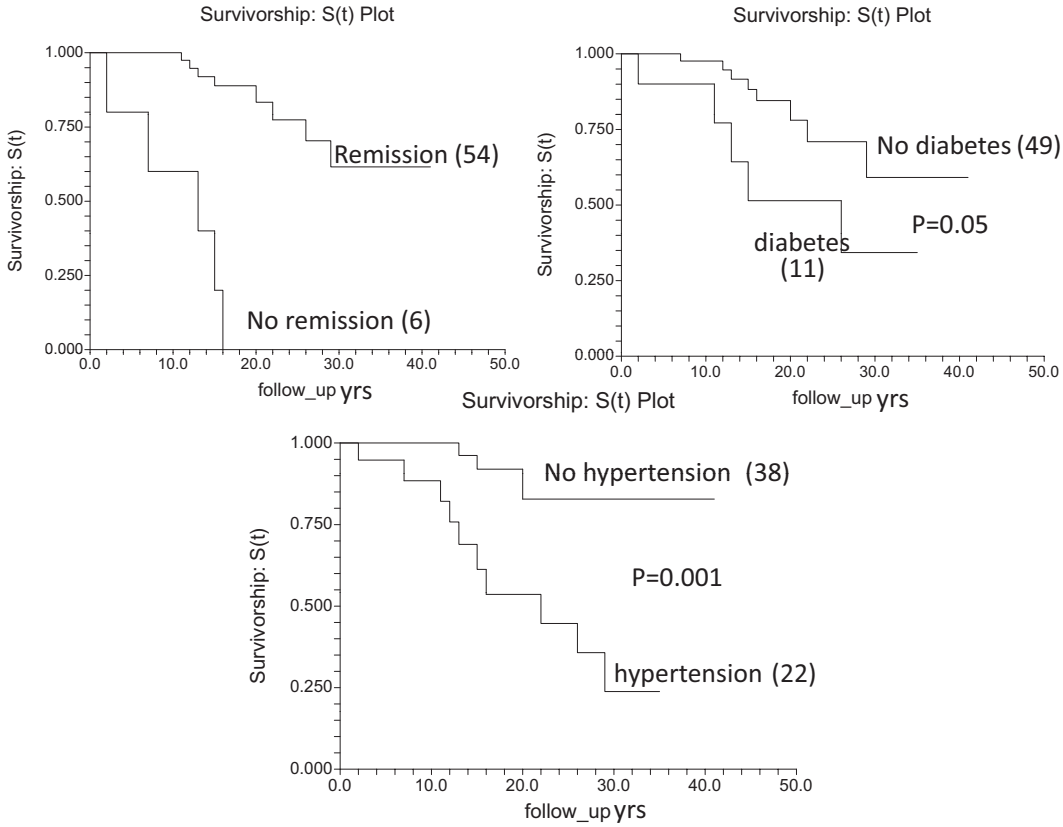


FIG. 1. Kaplan-Meir survival curves for Stoke Cushing's patients, with follow-up duration in years on the x-axis. Number of patients in each subgroup is shown in *parentheses*. *Upper left*, Remission *vs.* persistent disease; *upper right*, diabetes *vs.* no diabetes; *P* value compares the two groups. *Bottom*, Hypertension *vs.* no hypertension.

initial remission rates in the surgical series compared with the others.

A summary of overall SMRs is presented in Fig. 2. The χ^2 test for heterogeneity for the overall mortality data set from the seven studies yielded $\chi^2 = 18.64$ ($P = 0.005$). For the four studies where remission and persistent disease are reported separately, tests for heterogeneity revealed the following: persistent disease data set, $\chi^2 = 9.15$ ($P = 0.03$); and remission data set, $\chi^2 = 16.87$ ($P = 0.001$). Therefore, a random effects model is appropriate in all instances and was used for the meta-analysis.

TABLE 4. Summary of all studies reporting mortality in CD

First author, year (Ref.)	Period covered	No. of patients (mean age at treatment in yr)	Remission of hypercortisolism, no./total (%)	Follow-up duration (months) [median (range)]	No. of deaths	Overall SMR (95% CI)	Significance (*P*)
Etxabe, 1994 (11)	1975-1992	49 (39)	36/41 (87)	56 (6-210)	5/49[a]	3.8 (2.5-17.9)	<0.05
Swearingen, 1999 (10)	1978-1996	161 (38)	137/161 (85)	96 (12-240)	6/159	0.98 (0.44-2.2)	NS
Pikkarainen, 1999 (12)	1981-1994	63 (44)	25/43 (58)	84 (0-180)	6/43	2.67 (0.89-5.25)	NS
Lindholm, 2001 (1)	1985-1995	73 (41)	56/73 (77)	96 (36-168)	7/73	1.7 (0.7-3.5)	NS
					1/45[b]	0.31 (0.01-1.72)	NS
					6/20[c]	5.06 (1.86-11.0)	<0.05
Hammer, 2004 (13)	1975-1998	289 (37)	236/289 (83)	132 (6-288)	25/289[d]	1.42 (0.95-2.I)	NS
					17/236[e]	1.18 (0.7-1.9)	NS
					7/53[f]	2.8 (1.35-5.9)	0.01
Dekkers, 2007 (15)	1977-2005	74 (39)	59/74 (80)	120 (36-204)	12/74	2.39 (1.2-3.9)	<0.05
					7/59[g]	1.8 (0.71-3.37)	NS
					5/15[h]	4.38 (1.38-9.07)	<0.05
Clayton, 2010 (this study)	1960-2009	60 (37)	54/60 (90)	180 (6-492)	13/60	4.8 (2.8-8.3)	<0.001
					8/54[i]	3.3 (1.7-6.7)	<0.001
					5/6[c]	16 (6.7-38.4)	<0.0001

Remission rates are not directly comparable because of varying treatments and varying time to achieve eucortisolemia, so rates should be interpreted with caution.

[a] No information on eight patients; [b] remission after initial surgery; [c] persistent disease; [d] overall; [e] initial remission; [f] initial persistent disease; [g] remission after initial surgery; [h] persistent disease after initial surgery; [i] remission.

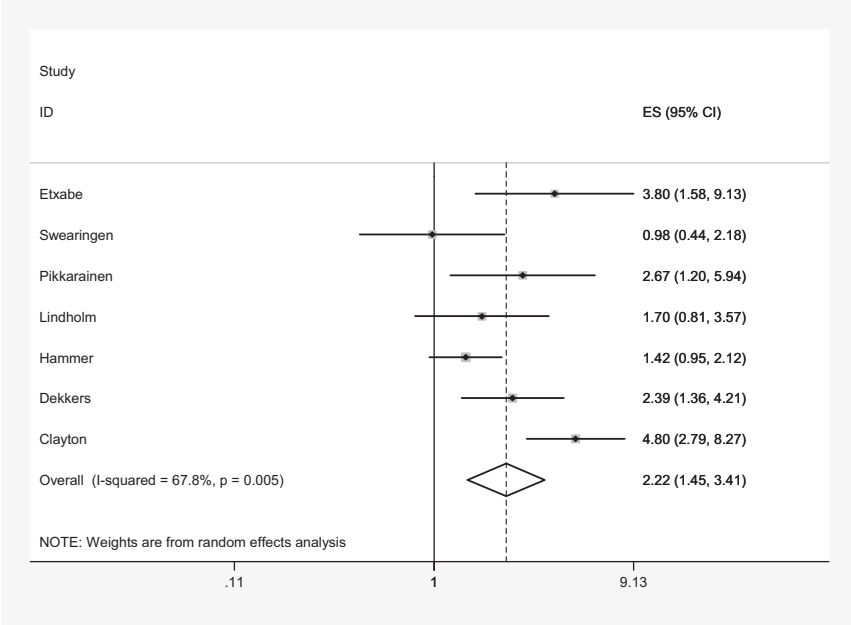


FIG. 2. Forest plot of overall SMRs from seven studies (patients in remission and with persistent disease combined). *Solid black line*, Unity (*i.e.* no difference in SMR from that expected from normal population); *dotted line*, mean pooled SMR through center of diamond (the horizontal points of which show the 95% CIs). ES, Estimated SMR with 95% CIs.

Overall SMR includes all patients, both those in remission and those with persistent disease. Overall SMR of 2.22 (95% CI, 1.45–3.41) was significantly greater than expected ($P < 0.001$). Four reports provided SMRs for those patients in remission and those with persistent disease separately. In all four reports, those with persistent disease fared significantly worse than those in remission. Only our own study showed that those in remission still had a significantly higher SMR (3.3) than expected. Forest plots for the overall SMRs are depicted in Fig. 2, and those for remission and persistent disease are depicted separately in Fig. 3. For the remission groups, pooled SMR of 1.2 (95% CI, 0.45–3.18) was not significantly different from the normal population (Fig. 3A). The respective data for the persistent disease groups pooled are shown in Fig. 3B. Pooled SMR of 5.5 (95% CI, 2.7–11.3) is significantly worse than expected ($P = 0.001$).

Of relevance to interpretation of the pooled data are the criteria used to define remission of hypercortisolism in CD. These are very varied according to each individual group, both qualitatively and quantitatively, as shown in Supplemental Table 3. Not only do the biochemical criteria vary, but also the time after initial treatment that these were assessed ranging from a few days to 3 yr. For example, in our study we chose to define remission or persistent disease only after patients had received their final treatment aimed at "curing" their CD.

Discussion

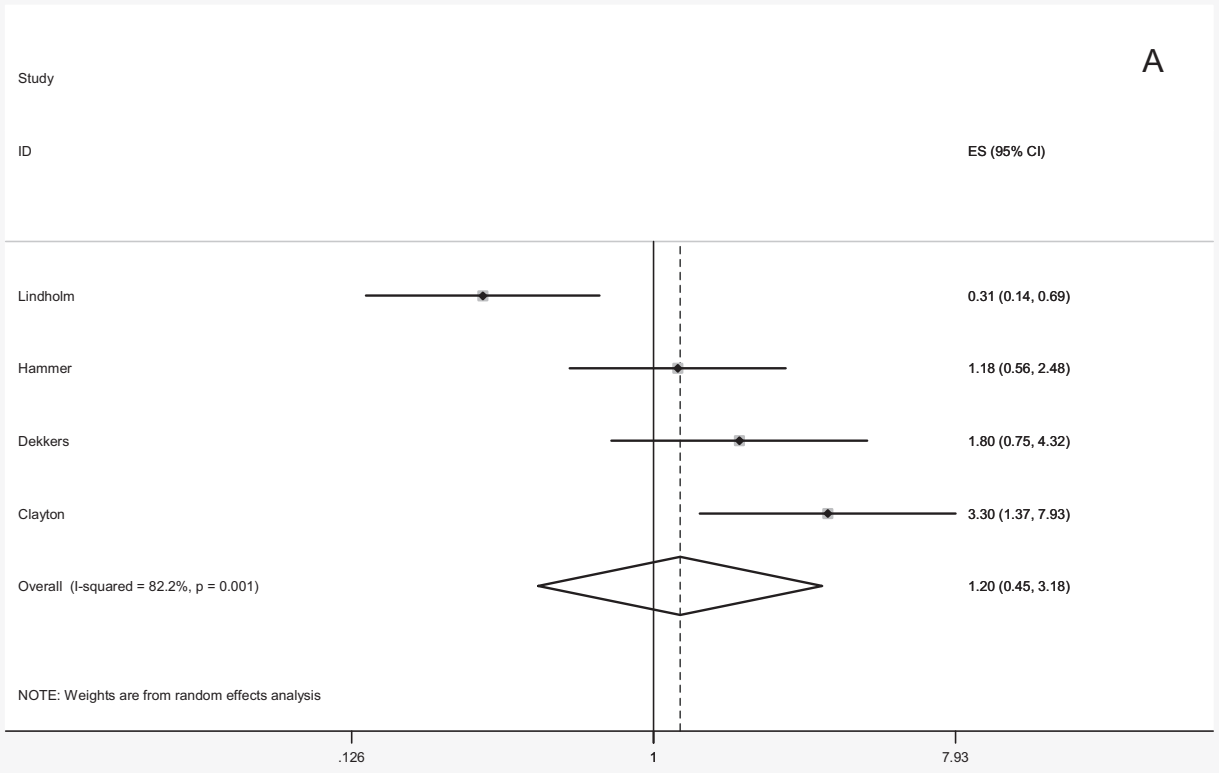
Stoke-on-Trent data

This cohort, although small, was similar in age and sex distribution structure to others in the literature (Table 4). However, it does go back much further to the 1960s, which means that follow-up is on average 5 yr longer than other studies. Although the number of deaths was small, the majority of these occurred in patients treated with radiotherapy and metyrapone, before we routinely used hypophysectomy as first-line treatment. It is possible that pituitary radiotherapy *per se* could be a contributory factor in some deaths because this is known to be a risk factor for mortality in patients with somatotropinomas and nonfunctioning pituitary tumors (14). As with other reports, most deaths were from vascular causes, and both hypertension and diabetes were associated with worse outcomes. In contradistinction to other reports, we still saw an increase in mortality in patients in remission, but this was much smaller than for those patients with persistent disease, relative risk being more than 10 times for persistent hypercortisolism. The explanations for this difference could be severalfold: 1) the longer duration of follow-up of our cohort; 2) not defining remission until patients had been finally "cured," which meant that some remission patients were hypercortisolemic for up to 3 yr after diagnosis, when 90% of the cohort was in remission; and 3) largely treating the early cohort, with the majority of deaths, by radiotherapy and metyrapone; although meeting the biochemical criteria for remission, the patients might have still been mildly hypercortisolemic for several years and not in full remission. An alternative possibility is that patients in the early cohort were by definition older, although the SMRs were adjusted for age and sex, making this a less likely explanation.

Notwithstanding the above differences, patients in remission who had died survived almost twice as long (17.5 yr) as did patients with persistent disease who died (9 yr), so their treatments were beneficial.

Literature review

It is appropriate to comment on the individual studies in turn because each brings out interesting points and has its own caveats to their conclusions.



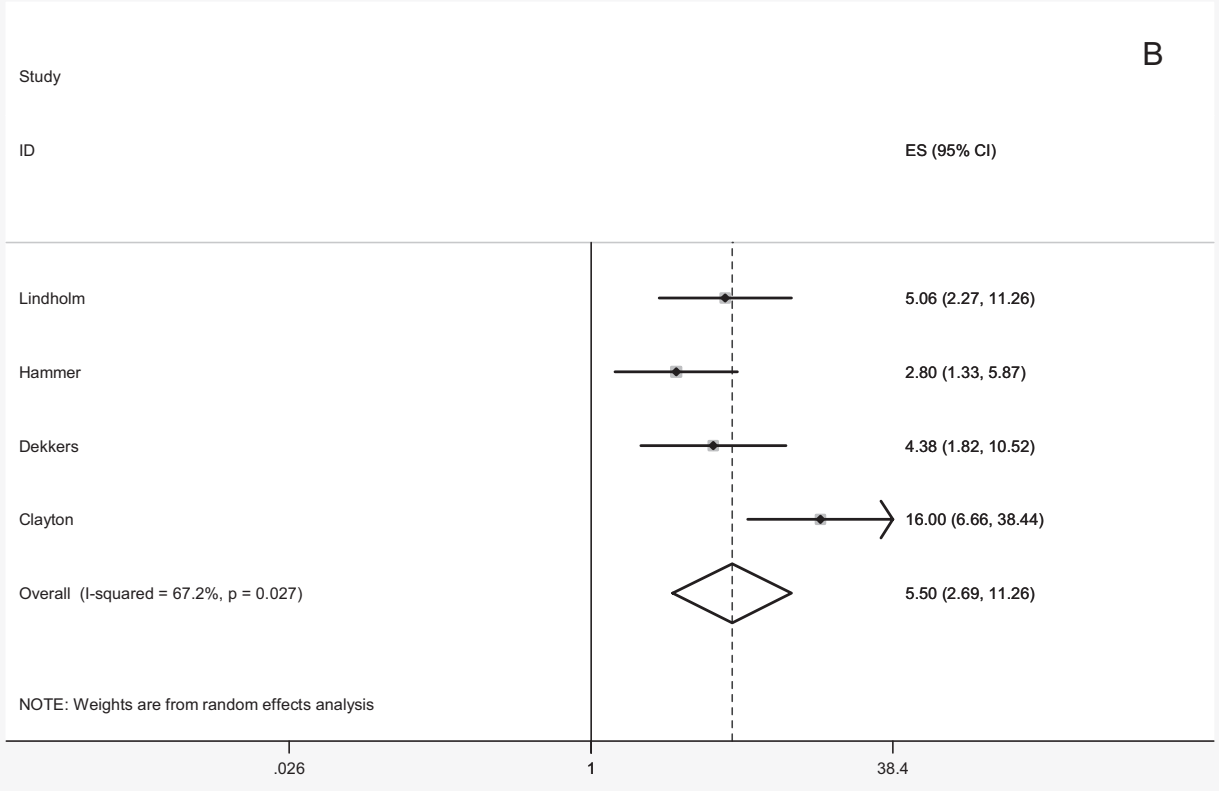


FIG. 3. Forest plot of SMRs from four studies for patients in remission (A) and for patients with persistent disease (B). See Fig. 2 legend for detailed description.

Etxabe and Vazquez (1994) (11)

This is the smallest study by far; no information was provided about eight of 49 patients, reducing the effective total number to 41. Treatments were variable, with 18 patients undergoing bilateral adrenalectomy, inferred as primary treatment, and 16 patients having pituitary radiotherapy. The SMR (3.8) showed significant increase despite 87% of patients achieving remission, but the 95% CI is wide and it is based on only five deaths. It is not clear how long after initial/subsequent treatments patients were defined as being in remission. The authors comment that the SMR for vascular disease of 5 (95% CI, 3.4–48.6) was significant, but this is based on only three deaths so it must be regarded with caution. This was the only report to enter hypertension and disordered carbohydrate metabolism into a multivariate analysis of predictors of mortality. Perhaps unsurprisingly, older age at diagnosis, when the impact of comorbidities with hypercortisolism might be expected to be greater, was a predictor of mortality.

Pikkarainen et al. (1999) (12)

This single center study from Helsinki reports mortality in all cases of Cushing's syndrome, including ACTH-dependent CD (n = 43) and ACTH-independent Cushing's syndrome including adrenal adenomas (n = 20), combined and separately. There is no specification on the biochemical criteria used to make the diagnosis or what criteria define remission after hypophysectomy in CD. It is unclear how many CD patients were in remission after hypophysectomy and at what time after the operation. Mortality data are reported separately for adrenal adenoma and CD, and the 95% CI is wide, reflecting the small number of deaths (n = 6 for CD). The age of death for CD patients ranged from 61–80 and three of six died from cardiovascular causes; this proportion is said to be no different from the general Finnish population, although no statistics were provided. Overall, this study is lacking in detail, and numbers of patients and deaths are small. No predictors of mortality are identified. Notwithstanding this, the conclusion is that adequate treatment of CD seems to confer a normal mortality rate.

Swearingen et al. (1999) (10)

This large series of 161 patients includes only those who had transsphenoidal surgery, and there are no data on those CD patients who were considered unfit for surgery or treated by other modalities. Transsphenoidal hypophysectomy has been the initial treatment of choice for the majority (probably upward of 80%) of patients for the last 30 yr or more, and biochemical and clinical outcomes are excellent in expert hands. However, a minority of patients in this series did require adjunctive treatment with radiotherapy or bilateral adrenalectomy and are included in the remission group although their time to "cure" would have been longer than reported for the transsphenoidal surgery-alone group. Nevertheless, it would have been useful to know how many patients were rejected for surgery or treated by other means because this subgroup, although likely to be small, may skew the mortality statistics. Furthermore, 90% of the patients had microadenomas; only 17 patients had macroadenomas, and therefore the mortality outcomes (only six deaths in total over a median follow-up of 8 yr) reflect that of a highly selected group of patients that would be expected to have the best surgical outcomes with respect to restoring eucortisolemia. Indeed, 10 yr cure rates were 91% for 125 microadenomas *vs.* 55% for 11 macroadenomas. It is unclear why the 11 macroadenomas remained uncured at 10 yr when it is reported that the majority of surgical failures underwent bilateral adrenalectomy. Nevertheless, the outcome for this selected group was excellent, with an SMR of 0.98. There was no analysis of SMR for patients in remission and with persistent disease separately, probably because the total number of deaths was so small as to be meaningless. Cause of death was vascular in four of six instances.

Lindholm et al. (2001) (1)

The power of this study was the ability of the Danish National Patient Register to identify all patients with Cushing's syndrome in Denmark over their recruitment period (1985–1995), so it is a truly unbiased cohort of patients. Furthermore, the numbers and data were such that the authors were able to categorize the patients accurately into those with Cushing's syndrome caused by CD, adrenal tumors, and cancer associated (either malignant or carcinoid). Consequently, it was possible to compare mortality outcomes between the subgroups. Moreover, within the CD cohort, a subgroup was identified as "etiology unproven" in whom a pituitary etiology was inferred but in whom histology was inconclusive or no tissue was available. This subgroup was also 10 yr older at diagnosis. This subgroup had a particularly poor outcome (SMR, 11.5; 95% CI, 5.7–20) in comparison to those in whom a pituitary cause was confirmed histologically (SMR, 1.7; 95% CI, 0.7–3.5). This latter subgroup (the largest) had a good cure rate of hypercortisolemia and a normal long-term mortality rate. Unfortunately, it is not possible to work out the cure rate in the etiology unproven subgroup. The authors subdivided the group into those cured after initial transphenoidal surgery (n = 45) followed for a median of 9 yr and those not cured (n = 20). The cured subgroup had no increase in mortality, whereas for the uncured subgroup mortality was 5-fold higher than

expected. However, the follow-up time was still relatively short (9 yr) given the early age of diagnosis (40 yr). Another interesting observation from this study was that the mortality in patients with unilateral adrenal adenoma (four of 37) was high (SMR, 3.48; 95% CI, 0.95–8.9) but due to small numbers did not achieve significance. The only adverse predictor of mortality identified was persistent hypercortisolism after initial surgery.

Hammer et al. (2004) (13)

This was the largest series by far (n = 289); all patients underwent transsphenoidal hypophysectomy as initial treatment by a single surgeon for presumed CD, and 253 of 289 (87.5%) were confirmed by histology as ACTH adenoma or corticotroph hyperplasia. As with the other surgical series (10), the outcomes apply to a somewhat selected population of patients, and the same caveats apply to the conclusions—the main caveat being that selection for pituitary surgery was presumably made by numerous clinicians by unstated and varying criteria. Initial cure rate was defined in the first week after surgery but was also accepted if the cortisol levels fell to normal within the first 6 months after surgery. Cure rate was high although the criterion of suppression of plasma cortisol to less than 140 nmol/liter would not be considered stringent enough by 2009 criteria. Excluding four patients who died within the first 6 months after surgery, 25 of 285 patients died during follow-up. When compared with the normal population, a greater proportion of patients in the initial persistent disease subgroup ($P < 0.01$) had died compared with the initial remission subgroup (P = NS). Interestingly, their Kaplan-Meir analysis shows that the decreased survival of the initially persistent disease cohort is only apparent after 10 yr. The median age at death of those in the initially persistent disease cohort (n = 7) was 61 yr *vs.* 71.7 yr for the initial remission cohort (n = 17) (no significance tests provided), although the median duration of survival after surgery in those that died was similar (13.7 *vs.* 12.7) for those patients with initially persistent disease (n = 53). Long-term follow-up data were available on just over half (28 of 53) of the patients, and the final status was persistent disease despite further treatments in 10 of 28. If it is assumed that a similar proportion of the 25 for whom no data are available still have persistent disease, then 36% (19 of 53) never had their hypercortisolemia adequately treated. Of the initial remission group (n = 150) for whom long-term data could be obtained, 137 were still in remission, *i.e.* 13 (9%) recurrences at a median interval of 5 yr. If the same recurrence rate is assumed for the remaining 86 patients for whom data are not available, an overall disease-free long-term remission rate is 91% for the initial remission cohort *vs.* only 64% for the initial persistent disease cohort. These data would suggest that long-term persistent hypercortisolemia is the determinant of poorer outcome, and correction of this as soon as possible is paramount.

Dekkers et al. (2007) (15)

Although this is another surgical series from a single center in Leiden, it is of particular interest because it compares mortality outcomes in patients with CD with that of nonfunctioning pituitary tumor patients, thereby inferring that any increase in mortality in CD would be due to hypercortisolemia *per se* rather than hypopituitarism/pituitary tumor in general. The nonfunctioning pituitary tumor cohort (n = 174) did not have an increased SMR (1.24; 95% CI, 0.85–1.74) compared with the normal population, which is somewhat surprising given many reports to the contrary [*e.g.* Tomlinson *et al.* (16)]. The whole CD cohort had an increased mortality despite 93% being in long-term remission. However, the SMR in CD with remission after initial surgery was not significantly different from normal at 1.8 (95% CI, 0.71–3.37) *vs.* SMR of 4.38 (95% CI, 1.38–9.07) for those with persistent disease (seven deaths in the remission group *vs.* five in the persistent group). Despite the fact that many of those with initial persistent or recurrent disease must have been cured of their hypercortisolemia because the long-term cure rate was 93%, these still had a worse outcome.

Conclusions

Despite the fact that the seven series reviewed included a relatively small number of patients by epidemiological standards and an even smaller number of deaths, some common conclusions emerge.

The meta-analysis shows that the overall mortality from CD is about double that of the general population. However, within this analysis are two large surgical series wherein there is no apparent increase in mortality, but this conclusion can only pertain to this selected group of Cushing's patients primarily treated with transsphenoidal surgery. However, this is the majority of patients nowadays. It is impossible to estimate how the inclusion of patients treated primarily by other modalities would have impacted mortality statistics because these numbers are unknown. Where the reports include the entirety of unselected patients, the outcome is not quite so good. That being said, in those limited reports that have analyzed patients in remission and with persistent disease separately, it is clear that in persistent disease mortality is far worse than expected. Also within this limited data set for patients in remission, restoration of eucortisolemia is associated with an SMR that is no longer different from that expected of the general population over a 10- to 20-yr

follow-up period. However, it remains possible that pooled SMRs of 1.2 in this cohort could be significant in longer studies with larger numbers of deaths (as became apparent from the acromegaly papers with more extensive follow-up and larger numbers of deaths). Another caveat is that these patients were on average about 40 yr of age at diagnosis, and many would not have reached 60 yr of age at study end, so the expected number of deaths in the general population is very small. Furthermore, two studies (10, 11) identified older age at diagnosis as an independent predictor of death. So it is important to continue to follow-up these cohorts ultra-long-term (>30 yr) to confirm that cured CD is compatible with normal longevity (as for example appears to be the case with cured acromegaly).

The studies that have related surgical outcome with respect to initial remission of hypercortisolemia to mortality show that if this is achieved, mortality rate is not increased although that of the overall cohort may be increased. All the reports suggest that it is the subgroup of patients with persistent disease that have the worst outcome. Despite the well-recognized fact that hypercortisolemia may have been present for months or years before effective treatment, it is still possible to "normalize" mortality. In none of the studies is any attempt made to relate duration of disease before treatment to worse outcome as has been shown in acromegaly (5). Only two small studies (11) and our own looked at other predictors of mortality and concluded that presence of hypertension and diabetes appeared to be important contributors to the cause of death, which, where reported, was predominantly vascular. Larger studies, which have the power to perform multivariate analyses, are required to answer whether adequate control of these complications improves outcomes.

The above conclusions should be restricted to the largest cohort of patients that have a proven (histologically) ACTH-secreting pituitary adenoma as the cause of their Cushing's syndrome, *i.e.* CD. This is exemplified in the Danish study (1) wherein the subgroup with unproven CD had a much poorer outcome despite apparently having pituitary ACTH-dependent CD.

It follows that it is paramount to correct the hypercortisolemia as quickly as possible to reverse increased mortality. In the majority of cases (70–90%), this can be achieved by transsphenoidal pituitary surgery, but this must be performed by an experienced pituitary surgeon using the most modern techniques. Failure of initial surgery or recurrence must be dealt with promptly and effectively. Notwithstanding the 20–30% risk of developing Nelson's syndrome, the one sure way to do this is by laparoscopic bilateral adrenalectomy. It is of interest that in patients whose Cushing's syndrome is due to unilateral adrenal adenoma, surgical removal to correct the hypercortisolism is associated with a high SMR (1), although not statistically significant. Therefore, it would be especially interesting to know the long-term outcome of a subgroup of failed hypophysectomy plus bilateral adrenalectomy in whom by definition their hypercortisolism will be cured.

Clearly, because the optimum outcomes are in those patients who achieve initial remission, it is critical to examine the criteria used to define remission in these studies. From the summary shown in Supplemental Table 3, it is immediately apparent that these differ considerably both in biochemical terms and in timing after treatment. Moreover, all quote either plasma cortisol or urinary free cortisol values and the normal ranges will have varied over the duration of the studies as will the assays used for measurement. In other words, there is a lack of standardization. What is not clearly apparent from the reports is the clinical cure rate. Admittedly, this is difficult to define, but some indication of resolution of the cardiovascular risk factors would have been useful, *e.g.* what proportion of patients who were hypertensive or diabetic before treatment were able to stop medication afterward. Another issue to be considered is that according to some reports (17, 18), some cardiovascular risk factors, such as hypertension, diabetes, and endothelial dysfunction, persist up to 10 yr after apparent cure of hypercortisolism and might still be expected to impact on mortality in the long term. In this context, our own data of still increased mortality (3-fold) in cured CD support the view that long-term persistence of risk factors is translated into increased mortality from vascular disease. However, the meta-analysis does not support this conclusion, although this is based on only four studies with few deaths and shorter follow-up. Therefore, the conclusion from the meta-analysis that patients in remission do not appear to have worse mortality should be regarded as preliminary.

In short, CD is bad for you physically, emotionally, and for your survival. The good news is that early effective treatment not only cures your symptoms but appears to normalize your survival chances and improve your life expectancy.

Acknowledgments

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Disclosure Summary: None of the authors has anything to declare.

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