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Lessons from rare diseases: pathophysiology of stress-related diseases and organization and evaluation of care for patients with Cushing's syndrome

Haalen, F.M. van

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PART

ORGANIZATION, OUTCOME EVALUATION
AND QUALITY OF CARE FOR
CUSHING'S SYNDROME



CHAPTER

6

MORTALITY REMAINS INCREASED IN CUSHING'S DISEASE DESPITE BIOCHEMICAL REMISSION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Femke M van Haalen, Leonie HA Broersen, Jens O Jorgensen,
Alberto M Pereira, and Olaf M Dekkers

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ABSTRACT

The aim of this systematic review and meta-analysis was to investigate whether mortality is increased in patients biochemically cured after initial treatment for Cushing's disease. This is a systematic review and meta-analysis of follow-up studies in patients cured from Cushing's disease after initial treatment was performed. Eight electronic databases were searched from 1975 to March 2014 to identify potentially relevant articles. Original articles reporting the standardized mortality ratio (SMR) for patients cured of Cushing's disease were eligible for inclusion. SMRs were pooled in a random effects model. I^2 statistics was used for quantification of heterogeneity. Eight cohort studies with a total of 766 patients were included. Out of eight studies, seven showed an SMR above 1.0 for cured patients. The pooled SMR was 2.5 (95% CI 1.4–4.2). The I^2 statistics showed evidence for statistical heterogeneity (78%, Q-statistics $P < 0.001$), which was largely explained by two outliers. This meta-analysis reveals that mortality remains increased in patients with Cushing's disease even after initial biochemical cure remission, suggesting that cure does not directly reverse the metabolic consequences of long-term overexposure to cortisol. Other conditions such as hypopituitarism, including persistent adrenocortical insufficiency after surgery, may also contribute to the increased mortality risk.

INTRODUCTION

Cushing's disease is characterized by endogenous glucocorticoid excess resulting from an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma. The incidence of Cushing's disease is estimated to be 1.2–2.4/million per year ¹, although it is higher in selected patient populations such as poorly controlled diabetics and in young patients with osteoporosis or hypertension ². Glucocorticoid excess induces changes in body composition (sarcopenia, osteoporosis, and central obesity), an adverse metabolic profile (dyslipidemia, hypercoagulability, insulin resistance, and diabetes mellitus), and hypertension ³. Moreover, the association between Cushing's disease and neuropsychiatric disorders is well established ⁴. Untreated Cushing's disease has a poor prognosis as the 5-year survival is estimated to be only 50% ⁵. The increased mortality in Cushing's disease is mainly caused by macrovascular disease (myocardial infarction and stroke), but poorly controlled diabetes mellitus and infections may also play a role ⁶. Selective removal of the corticotrope adenoma by transsphenoidal surgery remains the standard treatment for Cushing's disease. In patients diagnosed with Cushing's disease, mortality is increased compared with the general population ^{6,7}. However, whether mortality is also increased in patients cured after initial therapy is yet to be elucidated. In addition, data on the factors predictive of mortality in this population are rare.

The question whether mortality remains increased after initial cure is important for risk stratification in order to devise strategies for follow-up and treatment of co-morbidities. For proper patient management, it is also important to provide adequate information to the patients. The primary aim of this systematic review and meta-analysis was to answer the question whether mortality is increased or not after initial biochemical cure for Cushing's disease.

METHODS

Search strategy

To review currently available studies on mortality rates in Cushing's disease cured by transsphenoidal surgery, we conducted a search for all publications in English, French, German, Spanish, Dutch, and Danish languages on the topic (all languages spoken by the authors). The following databases were searched from 1975 to March 2014: PubMed, Cochrane Library, Web of Science, EMBASE, CINAHL, Central, Academic Search Premier, and Science Direct. We constructed a search string focusing on Cushing's disease, transsphenoidal surgery, mortality, and standardized mortality ratio (SMR), with the cooperation of a trained librarian. These keywords were database-specifically translated. We restricted the search to articles published after 1975, as transsphenoidal surgery for Cushing's disease was introduced since then. Original studies were eligible for inclusion if they met the following criteria:

1. A cohort study including minimally ten patients with Cushing's disease cured after initial therapy.
2. A mean follow-up period of at least 1 year.
3. Mortality risk expressed as SMR.

Studies were excluded when restricted to children. In the event of (partial) duplication of cohorts, the study with the longest follow-up period was included.

Data review and analysis

All identified articles were entered in EndNote version 7 (Thomson Reuters, Philadelphia, PA, USA). The initial selection of studies by title and abstract was performed by one reviewer (F M van Haalen) and the remaining studies were retrieved for closer examination by three reviewers (F M van Haalen, L H A Broersen, and O M Dekkers) and disagreement was solved by consensus. Retrieved articles were screened using a gauge for judgment meeting our inclusion and exclusion criteria. From included studies, we extracted the recruitment period, the duration of follow-up, inclusion and exclusion criteria, the number of patients included, the number of patients cured, SMR, the number of patients lost to follow-up, the methods used for diagnosis, the criteria for cure, surgical, radiological, and histological details, and other therapies used besides transsphenoidal surgery. Finally, we searched whether predictors for mortality in cured patients were reported.

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Definition of cure

For definition of cure, we used the definition as provided in the individual articles. In all articles included, patients were considered cured in case of biochemical remission (i.e. eucortisolism or hypocortisolism). Minimal requirements were suppressed post-surgical cortisol with the need for replacement therapy, or, if no replacement therapy was used, normal 24-h urinary free cortisol (UFC) and/or the normal overnight 1mg dexamethasone suppression test (DST).

Risk of bias assessment

For all included studies, the risk of bias was assessed using the following components, as they could potentially bias an association between the exposure (cure of Cushing's disease by transsphenoidal surgery) and outcome (SMR).

1. Loss to follow-up <5% was considered a low risk of bias.
2. No exclusion of patients with late recurrences was considered a low risk of bias, as exclusion of these patients may underestimate the mortality risk.
3. Adequate definition of cure of Cushing's disease represents a low risk of bias.
4. Ascertainment of exposure to Cushing's disease by histological assessment of the adenoma was considered a low risk of bias.

Statistical analysis

The pooled SMR after successful treatment of Cushing's disease was the primary outcome measure of this analysis. For all studies, the SMR was extracted with its accompanying CI. Meta-analysis for SMR was performed using the metan command in Stata 12.1 (Stata Corp., College Station, TX, USA) in a random effects model. For one article⁸, the SMR was calculated from the observed and expected mortalities mentioned in the article, and the CI was calculated using the method by Vandenbroucke⁹. I² statistics and Cochran's Q-test were used to quantify statistical heterogeneity.

Meta-analysis of SMR for patients not cured of Cushing's disease was performed to compare the results with the pooled SMR for patients cured of Cushing's disease. A meta-regression was performed to compare the mortality risk in cured patients vs uncured patients using the metareg command in Stata.

RESULTS

The initial search resulted in a total of 1089 publications, of which 1058 were excluded based on the title and abstract. Of the remaining 31 articles, eight cohort studies were included^{1, 7, 8, 10, 11, 12, 13, 14}; see Figure 1 for the flow chart. In one study, results were stratified by the size of the adenoma (microadenoma vs macroadenoma). Included studies were published between 2001 and 2013.

Study characteristics

A summary of characteristics of included studies reporting SMR in cured Cushing's disease is presented in Table 1. Eight studies included a total number of 766 cured patients who were diagnosed with Cushing's disease, the majority (79%) of whom were females.

Reported mean age at diagnosis was similar in all studies, ranging from 36 to 45 years. In all studies, the proportion of patients initially treated by transsphenoidal surgery was >50%, with 100% in three studies. A similar definition of cure was used by six studies (resolution of symptoms and clinical signs, adrenal insufficiency requiring cortisol replacement therapy, or no replacement, and normal UFC and/or a normal overnight 1mg DST). In two studies, only post-operative morning cortisol measurements below 1.8g/dl (50nmol/l) were used as a definition for cure^{12, 13}. Furthermore, only limited data were provided on surgical, radiological, and histological details stratified by cure status.

Risk of bias assessment

Loss to follow-up was not mentioned in any of the included studies. Only one article¹² excluded eight patients (11% of total) with late recurrence of the disease. Therefore, the risk of underestimation of the SMR due to exclusion of late recurrences is considered to be low. The percentage of adenomas histologically proven to be ACTH secreting was only reported in three of the included studies, varying from 71.1 to 100%. The mean duration of follow-up was 8.9 years. Definition of cure was adequate in all articles.

Meta-analysis of mortality risk in patients cured of Cushing's disease

Reported SMRs ranged between 0.3 and 10.0, with seven out of eight studies reporting an SMR with a point estimate >1.0 (Figure 2). We estimated a pooled SMR of 2.5 (95% CI 1.4–4.2) in a random effects model, with evidence of statistical heterogeneity: $I^2=78\%$ (Cochran's Q statistic $P<0.001$). Two reported SMRs were clear outliers (0.3 and 10.0)^{1, 13}. A sensitivity analysis without these two datasets showed a similar pooled SMR of 2.1 (95% CI 1.5–3.0), but with lower heterogeneity ($I^2=40\%$, Cochran's Q statistic $P=0.125$). In addition, we searched for possible predictors of mortality in cured Cushing's disease, such as age at diagnosis, sex, tumor size and invasiveness, time to cure, persistent

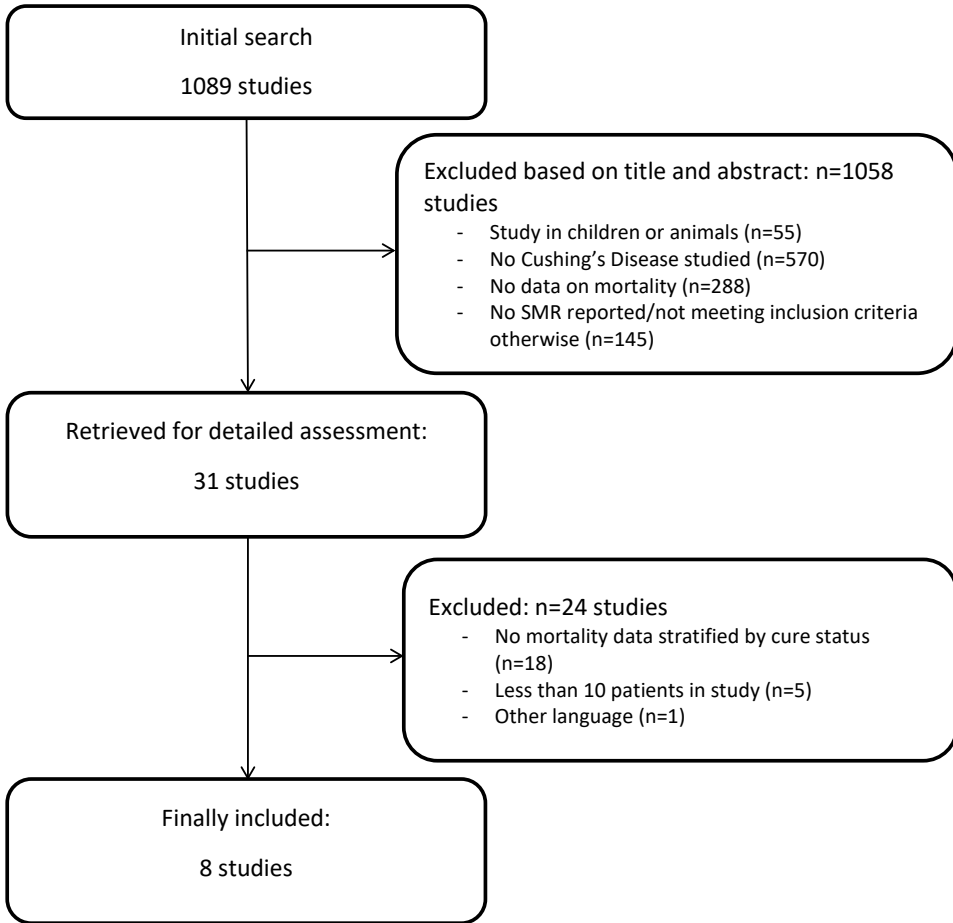


Figure 1. Flow-chart of study inclusion.

adrenal insufficiency, hormonal axis deficiency after surgery, and pre-operative disease severity. Unfortunately, we could not extract sufficient data from the original articles for additional analyses.

Meta-analysis of SMRs for patients not cured of Cushing's disease

For seven articles, the SMR for patients without initial cure by transsphenoidal surgery was also reported (Figure 3). Reported SMRs ranged between 2.4 and 16.0. We found a pooled SMR of 4.6 (95% CI 2.9–7.3). The seven included studies showed some evidence of statistical heterogeneity ($I^2=40\%$, Cochran's Q statistic $P=0.113$).

A meta-regression was performed to address the question whether mortality risk in uncured Cushing's disease (SMR 4.6) was significantly higher compared with cured Cushing's disease (SMR 2.5). This analysis showed an increased risk for uncured patients with Cushing's disease compared with cured patients with Cushing's disease: 1.8 (95% CI 0.9–3.7).

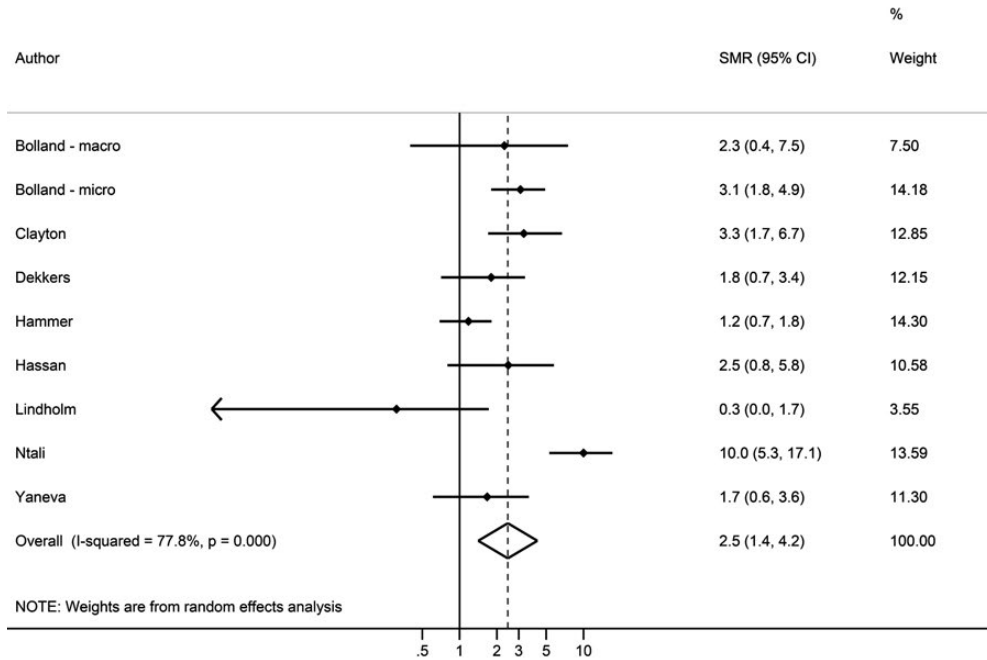


Figure 2. Meta-analysis of mortality risk in cured Cushing's disease.

DISCUSSION

This systematic review and meta-analysis shows that mortality risk is increased despite biochemical cure in Cushing's disease. The pooled SMR was 2.5 (95% CI 1.4–4.2), and remained increased in a sensitivity analysis excluding two outliers. The persistently increased mortality risk despite remission of hypercortisolism suggests irreversible effects of long-term glucocorticoid excess exposure.

To date, results of two previous meta-analyses on mortality in patients successfully treated for Cushing's disease have been published. The first study by Clayton et al.¹⁰ included four studies, all of which were also included in the present meta-analysis. This study found a pooled SMR of 1.2 (95% CI 0.5–3.2) for cured patients, and a pooled SMR of 5.5 (95% CI 2.7–11.3) for patients with persistent disease. The second meta-analysis by Graversen et al.¹⁵ included three studies, all of which were also included in the meta-analysis by Clayton et al. and in the present meta-analysis. They also found a pooled SMR of 1.2 (95% CI 0.5–3.0) in cured patients and 3.7 (95% CI 2.3–6.0) in patients with persistent disease. We additionally included four recently published studies, thereby increasing the power of the meta-analysis, which resulted in the finding that mortality is increased despite cure. Two studies included in our meta-analysis were clear outliers. The study by Lindholm et al.¹ showed an SMR of 0.3 (95% CI 0.0–1.7), and the study by Ntali et al.¹³ with an SMR of 10 (95% CI 5.3–17.1). Both SMRs had large CIs, pointing toward the uncertainty that accompany the effect estimates. However, exclusion of these two studies in a sensitivity analysis did not significantly change the results and interpretation of our conclusion.

Table 1. Summary of included studies reporting mortality in Cushing's disease.

| First author (year) | Lindholm (2001) | Hammer (2004) | Dekkers (2007) | Bolland - macroadenoma (2011) |
|--|---|---|---|--|
| Period covered | 1985-1995 | 1975-1998 | 1977-2005 | 1960-2005 |
| Gender (M/F) | 23/50 | 50/239 | 18/56 | 8/22 |
| Mean age at diagnosis (yrs) | 41 ^a | 36 ^b | 39 ^b | 45 |
| Number of cured patients | 45 | 236 ^c | 59 | 19 |
| Mean follow-up (yrs) | 8.1 ^a | 11.1 ^a | 12.8 | 6.9 |
| Definition of cure | Subnormal plasma cortisol after ACTH test and/or normal UFC / or panhypopituitarism | Normal basal cortisol or DST and/or UFC, symptoms resolution, and no additional therapy | Normal DST and UFC in 2 consecutive samples | Adrenal insufficiency requiring replacement therapy; or no glucocorticoid therapy and normal UFC; or normal DST at last FU |
| Initial transsphenoidal surgery (%) ^f | 53.6 | 100 | 100 | NR |
| Recurrent disease during follow-up (%) | 4 (2/45) | 9 (13/150) | 14 (8/59) | 26 (5/19) |
| Post-surgical hormone deficiencies | 27% (12/45) panhypopituitarism | 27 (=11%) total postoperative hormonal replacement | 18% pituitary insufficiency (44% at least one axis) | NR |

NR, not reported; ACTH, adrenocorticotropic hormone; UFC, 24-h urinary free cortisol; DST, dexamethasone suppression test; FU, follow-up.

^aMedian. ^bAge at operation instead of diagnosis. ^cOf which 150 had a FU >6 months. ^dOut of 159 with initial transsphenoidal surgery. ^eOut of 154 with initial transsphenoidal surgery. ^fCharacteristics based on total cohort and not on cured patients only. ^g100% in patients diagnosed after 1985.

A limitation of the present systematic review is that included studies mainly provided patient characteristics for the whole cohort rather than stratified by cure status. This limited the possibility to assess potential causes of increased mortality in more detail by meta-regression techniques. Similarly, the percentage of post-treatment hypopituitarism could not be abstracted from all included studies and the percentages reported varied widely from 8.7 to 71%^{8,12}. It is also important to consider that patients included were not necessarily cured by transsphenoidal surgery, but were also treated by transcranial surgery, radiotherapy, or adrenalectomy. However, as shown in Table 1, the vast majority of patients were treated by initial transsphenoidal surgery. The three studies in which 100% of patients were initially treated by transsphenoidal surgery^{8,11,12} also point toward an increased mortality risk after biochemical cure (SMR 1.2, 1.8, and 2.5 respectively).

From a pathophysiological as well as epidemiological point of view, it is sensible to assume that mortality in cured Cushing's disease is increased when compared with the general population. There is increasing evidence that glucocorticoid excess-related morbidity decreases after successful treatment of Cushing's disease, but does not normalize. It has been shown that patients cured from Cushing's disease still have a high prevalence of atherosclerosis and maintain an increased cardiovascular risk, probably due to residual abdominal obesity and/or insulin resistance

| Bolland - microadenoma (2011) | Clayton (2011) | Hassan (2012) | Ntali (2013) | Yaneva (2013) |
|--|---|---|---|--|
| 1960-2005 | 1958-2010 | 1988-2009 | 1967-2009 | 1965-2010 |
| 36/122 | 9/51 | 15/57 | 45/137 | 43/197 |
| 36 | NR | 40 | 40 ^a | 38 |
| 117 | 54 | 52 | 99 ^d | 85 ^e |
| 7.5 | 1.3 ^a | 4.6 ^a | 12 ^a | 7.1 ^a |
| Adrenal insufficiency requiring replacement therapy; or no glucocorticoid therapy and normal UFC; or normal DST at last FU | Symptoms resolution; normal UFC and DST (and normal plasma cortisol day curve for those on metyrapone), < 3 yrs after treatment | Normal morning postsurgical cortisol and continued biochemical cure during FU | Undetectable postsurgical cortisol and continued biochemical cure during FU | Absence of clinical hypercortisolism; normal/low UFC or 17-OH and ketosteroids (earlier cases) and normal DST at last clinical visit |
| NR | 58.3 ^g | 100 | 87.4 | 66 |
| 15 (18/117) | NR | 13 (8/60) | 9 (9/99) | NR |
| NR | NR | 71% (51/72) deficiency of at least one hormone | 22-54% for various hormones | NR |

syndrome¹⁶. In addition, MRI studies showed favorable changes in body fat distribution and a decrease in some cardiovascular risk factors (for example, insulin resistance, leptin, and total cholesterol), but other markers such as adiponectin and C-reactive protein did not change after remission¹⁷. In line with this, it was shown in a large cohort study that the risk for myocardial infarction and stroke remained increased during a long-term follow-up⁶. Subtle cognitive impairments and an increased prevalence of psychopathology after long-term cure of Cushing's disease are also documented^{18,19}. To address the question whether mortality is increased after biochemical cure, it is important not to adjust for baseline imbalances in cardiovascular risk, as the higher prevalence of risk factor in patients with Cushing's disease is a direct consequence of the disease. The SMR is a ratio measure that provides such unadjusted estimates.

Besides direct cortisol-excess related effects, hypopituitarism including secondary adrenocortical failure after surgical cure of Cushing's disease may contribute to the observed increased mortality, because hypopituitarism per se is associated with an increased mortality^{20,21}. Current glucocorticoid replacement therapy does not mimic physiological cortisol secretion, resulting in over- or under-replacement, and improved replacement modalities improve adverse cardiovascular risk profile and the quality of life²². Unfortunately, included articles did not provide detailed clinical data to address

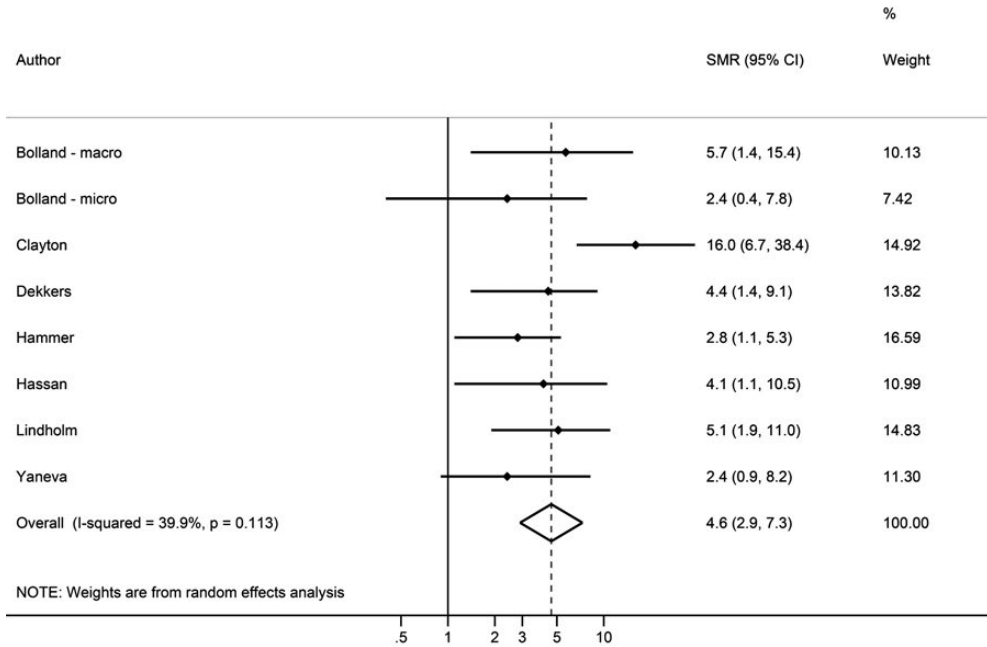


Figure 3. Meta-analysis of mortality risk in uncured Cushing’s disease.

the effect on mortality of the factors mentioned above. Accordingly, we were not able to assess whether the increased mortality risk despite cure was mainly due to patients with a late recurrence, as late recurrences appear to be increasingly recognized²³ and might contribute to mortality. By not excluding late recurrences, the analyses were performed based on characteristics known at the time of prediction without the risk of selection bias.

In conclusion, this meta-analysis shows that mortality in Cushing’s disease remains elevated after biochemical cure. This finding suggests that biochemical cure does not fully reverse the metabolic consequences of long-term overexposure to cortisol, which is supported by evidence showing persistent multisystem morbidity after biochemical cure. Other conditions, such as hypopituitarism (including adrenocortical insufficiency) after surgery, may also contribute to the increased mortality risk. Future research should aim to disentangle risk factors contributing to mortality in cured patients.

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