Clinical consequences of endogenous and exogenous glucocorticoid excess

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Chapter 9

Improvement but no normalization of quality of life and cognitive functioning after treatment for Cushing's syndrome: a systematic review and meta-analysis

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Abstract

Background
Cushing's syndrome is characterized by glucocorticoid excess, which induces physical and mental symptoms, and impairments in quality of life. Biochemical cure improves symptoms, but quality of life and cognitive function may remain impaired.

Objective
To perform a systematic review and meta-analysis evaluating changes in health-related quality of life and cognitive functioning in patients with Cushing's syndrome after treatment.

Methods
Eight electronic databases were searched in March 2017, and PubMed again in May 2018, to identify potentially relevant articles. Eligible studies were (randomized controlled) trials, cohort studies, and cross-sectional studies assessing quality of life or cognitive functioning in patients treated for Cushing's syndrome. Quality of life measures were standardized; differences were expressed as standardized mean difference, and reported with 95% confidence intervals. We compared patients before and after treatment (improvement), and patients after treatment and healthy controls (normalization).

Results
We included 47 articles with in total 2,643 patients. Most patients had Cushing's disease and were in remission after treatment. Both quality of life and cognitive functioning improved after treatment in all studied domains. Compared to a healthy control population, quality of life did not normalize. Cognitive functioning normalized in part, but not all, of the studied domains.

Conclusions
Treatment of Cushing's syndrome improves quality of life and cognitive functioning. As normalization was not achieved in quality of life and in some aspects of cognitive functioning, special and continuous attention should be given to these aspects for patients after treatment. Effective interventions for further improvement and possibly normalization are urgently needed.

Introduction

Cushing's syndrome due to endogenous glucocorticoid excess is a rare condition and is either adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent, both with a variety of underlying causes (1). Glucocorticoid excess causes osteoporosis, central obesity, insulin resistance, dyslipidemia, proximal muscle weakness, hypertension, hypercoagulability, and neuropsychiatric disorders. Patients report fatigue, a variety of mental and physical symptoms, and impairment in quality of life (2-3). Mortality and morbidity are increased even after long-term correction of glucocorticoid excess, including cognitive functioning, indicating irreversible adverse effects of previous hypercortisolism (4-6).

Cushing's disease resulting from an ACTH-secreting pituitary adenoma accounts for approximately 70% of cases of endogenous Cushing's syndrome, and has a reported incidence of 1.2-1.7 patients per million each year (7). The other causes for endogenous Cushing's syndrome are ectopic Cushing's syndrome resulting from a non-pituitary ACTH-producing source (approximately 5% of cases), and ACTH-independent Cushing's syndrome that is caused by a cortisol-producing adrenal adenoma or carcinoma (approximately 25% of cases) (1, 8). First-choice treatment for Cushing's disease is transsphenoidal pituitary surgery, selectively removing the corticotroph adenoma (9). Cushing's syndrome is generally approached by removing the ACTH-producing tumor in ectopic Cushing's syndrome and by adrenalectomy in ACTH-independent Cushing's syndrome (10). If necessary to establish cure, repeat surgeries, radiotherapy, and pharmaceutical therapies are considered. After surgical treatment, many patients face a period of transient or permanent adrenal insufficiency and sometimes other hormone deficits (11). A particular issue after surgery, but sometimes also during medical therapy, is the steroid withdrawal syndrome with its severe musculoskeletal pains, fatigue, and emotional lability (12).

In 2012, a literature review summarized the effects of Cushing's disease on clinical symptoms, including health-related quality of life and cognitive functioning, stating that current treatment options may not completely reverse the effects of chronic hypercortisolism (13). In 2015, another systematic review summarized quality of life in patients with a pituitary adenoma, concluding that patients with Cushing's disease, along with patients with acromegaly, demonstrated the greatest impairment in quality of life, and the smallest improvement (14). For Cushing's disease, two disease-specific quality of life questionnaires have been developed: the Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25), and the Cushing Quality of Life questionnaire (CushingQoL) (15-17). Also, a pituitary patient-specific questionnaire, the Leiden Bother and Needs Questionnaire, was developed for use in Cushing's disease (18). It is now generally accepted that disease-specific

questionnaires should be combined with a generic questionnaire to assess health-related quality of life. In addition, structural and functional brain abnormalities were shown to be persistent after biochemical cure of Cushing's syndrome, which was related to both quality of life and cognitive functioning impairments in patients with Cushing's syndrome (5). Until now, no meta-analysis has been performed to evaluate health-related quality of life or cognitive functioning in patients with Cushing's syndrome before and after treatment.

Study aims

The aim of the present study is to evaluate improvement in, and normalization of, health-related quality of life and cognitive functioning in patients with Cushing's syndrome. Improvement in health-related quality of life and cognitive functioning will be evaluated by comparing patients before treatment to patients after treatment of Cushing's syndrome. Whether health-related quality of life and cognitive functioning can normalize will be evaluated by comparing patients with Cushing's syndrome after (multimodality) treatment to a healthy control population.

Methods

Eligibility criteria

(Randomized controlled) trials, cohort studies (measuring at different time points) and cross-sectional studies (measuring at one point in time), assessing quality of life or cognitive functioning in patients with Cushing's syndrome were eligible for inclusion. Comparative studies (before-after treatment comparisons, or patients with Cushing's syndrome compared to healthy controls) and non-comparative studies were considered for inclusion. Eligible quality of life questionnaires were validated generic, disease-specific (for Cushing's syndrome), and domain-specific questionnaires. Articles were excluded if no separate results for patients with Cushing's syndrome were described, if the study included children only, or if no quantitative data of quality of life questionnaires or cognitive functioning tests were presented (e.g. only figure without numbers). There were no restrictions regarding treatment for Cushing's syndrome. If multiple studies with (partially) overlapping populations described the same questionnaire or test, only the data from the largest cohort were included per analysis. To minimize risk of selection bias, at least ten patients had to be included per study group. Articles irretrievable online were requested by contacting the authors. Only articles written in English were considered.

Search strategy

PubMed, Embase, Web of Science, COCHRANE Library, CENTRAL, Emcare, LWW, and ScienceDirect were systematically searched in March 2017 in cooperation with a specialized librarian to identify potentially relevant articles (see Supplemental Data 1 for the complete search strategy). In May 2018, the search was repeated in PubMed. References of included articles were searched for relevant eligible articles.

Data extraction

The identified articles were all entered in EndNote 8 (Thomson Reuters, Philadelphia, PA, USA). First, the studies were screened by title and abstract. Two independent reviewers reviewed potentially relevant articles in detail. For reporting, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were used (19).

The following data were extracted from all included articles: study period, study center, study design, etiology of Cushing's syndrome, number of patients, treatment of Cushing's syndrome, age, sex, duration of follow-up, type and number of control subjects, quality of life questionnaires and cognitive functioning tests used, and outcomes of these tests. If available, separate outcomes were extracted for patients in remission and patients not in remission after treatment.

If data were only presented according to categories (e.g., remission status or sex), the data were combined into one outcome score using a fixed effects meta-analysis for the main analyses. Combination scores were calculated from the subscale scores for the following questionnaires: CushingQoL (15), Symptom Rating Test (SRT) (20), Multidimensional Fatigue Inventory-20 (MFI-20) (21), Nottingham Health Profile (NHP) (22), and the Hospital Anxiety and Depression Scale (HADS) (22). For one article, the scores after treatment were calculated using the scores before treatment and the difference between before and after treatment, imputing the standard deviation (SD) from before treatment as the best estimate of the SD after treatment (23). If estimate and 95% confidence interval (CI), but not SD, were given for a single group, the following formula was used to calculate SD: ((CI)/2)/TINV(0.05;n-1)*SQRT(n), with n=number of patients. If data for two groups were combined as described above, SD was calculated using the following formula: SQRT((((n1-1)*SD1^2)+((n2-1)*SD2^2))/((n1+n2)-2)), with n1=number of patients in group 1, SD1=SD in group 1, n2=number of patients in group 2, and SD2=SD in group 2. From one article two questionnaires were excluded (Short Form health survey-36 [SF-36] and Beck Depression Inventory [BDI]) (24), and from another article one questionnaire was excluded (State Trait Anxiety Inventory [STAI]) (25), due to highly improbable or impossible outcomes (e.g. STAI score <20 points).

Risk of bias assessment

A component approach was used to assess risk of bias for all included studies. Components that could potentially bias a reported association between treatment for Cushing's syndrome and quality of life or cognitive functioning were included as follows:

1. Loss to follow-up <5% was considered low risk of bias for follow-up studies; similarly, missing quality of life or cognitive functioning data in <5% of patients was considered low risk of bias for cross-sectional studies.
2. Inclusion of patients: consecutive inclusion of all eligible patients or a random sample was considered low risk of bias.
3. Criteria for diagnosis of Cushing's syndrome: at least one of the following biochemical parameters had to be increased for low risk of bias: 24-h urinary free cortisol or midnight salivary cortisol.
4. Criteria for remission of Cushing's syndrome: at least normalization of biochemical hypercortisolism had to be measured for low risk of bias.
5. Test quality: number of cognitive domains assessed, validation of used questionnaires and tests, reporting of test instructions for cognitive tests, and reporting of sequence of cognitive tests were described for each study. Low risk of bias is considered use of only validated questionnaires and tests and reporting both test instructions and sequence of cognitive tests.

Risk of bias assessment was used to explore potential heterogeneity. Confounding was assessed by comparing baseline characteristics (age, sex, duration of follow-up, and treatment methods) for all included studies, as well as by comparing study group characteristics per study with a direct comparison before versus after treatment, or between patients after treatment and healthy controls. These assessments were made based on study level data.

Study endpoints

Quality of life scores were pooled for generic, disease-specific, and domain-specific (per domain) questionnaires separately. Analysed domains were anxiety, depression, and fatigue, as these were the only domains with enough data for analysis. Cognitive functioning was analysed in the following categories: intelligence (including concept formation), executive functioning (i.e. visuomotor tracking, inhibition, and mental flexibility), attention (i.e. divided, sustained), and memory (i.e. auditory, visual). In the category intelligence, the following tests were analysed: 1. Wechsler Adult Intelligence Scale – Revised (WAIS-R), 2. Similarities, and 3. Raven's Progressive Matrices (RPM). In the category executive functioning, the following tests were analysed: 1. Trail Making Test (TMT, trail A-D), and 2. Fluency tests (Verbal fluency, Word fluency, and the FAS test). In the category attention, the following tests were

analysed: 1. Substitution tests (Digit Symbol [Substitution] Test [D(S)ST], Digit symbol coding, and Letter-Digit Substitution Test [LDST]), and 2. Digit span. For the category memory, no analyses could be performed due to the large variety in used memory tests.

Per analysis, all quality of life questionnaires and cognitive functioning tests were included, with notifications for studies with (partially) overlapping populations using different questionnaires or tests. Separate analyses were performed per questionnaire or test (including subscales if provided) reported by at least two articles. Stratified analyses were performed for longitudinal and cross-sectional studies. Main analyses were performed in all included studies. Subgroup analyses were performed for patients with Cushing's disease only, and for patients in remission and patients not in remission after treatment.

Data were displayed separately for quality of life and cognitive functioning scores of patients before treatment for Cushing's syndrome, after treatment for Cushing's syndrome, and for a healthy control population. Notifications were added stating for which questionnaires and tests a higher score represents a lower quality of life or worse cognitive functioning.

Statistical analysis

Primary study outcomes were the standardized mean differences (SMD) before versus after treatment, as well as treated patients versus healthy controls, within studies. As a rule of thumb for the interpretation of the SMD, an effect size of 0.2 represents a small effect, 0.5 represents a moderate effect, and 0.8 represents a large effect (26). A random-effects model was used, as no fixed effect could be assumed due to the heterogeneity in questionnaires or tests; a fixed-effect model was used for analyses per questionnaire or test including <5 articles as in this case the between-study variance cannot be estimated reliably. All SMD scores were accompanied by 95% CI. No overall scores were presented per analysis with various tests/questionnaires, because a different number of (sub)scales per included article resulted in unintentional inequality in assigned weights per study, leading to incorrect effect estimates and confidence intervals. For meta-analyses only, questionnaires and tests in which a higher score represents a lower quality of life or worse cognitive functioning were reversed by multiplying the outcome with -1, ensuring that all outcomes were in the same direction. For three articles, '±' was interpreted as SD in the analyses, as this remained unclear after reading the articles (24, 27-28). The D(S)ST and LDST were included in the analyses in items/second, the TMT in seconds, and fluency tests in number/minute. All analyses were performed in Stata 14.2 (Stata Corp., College Station, TX, USA).

Results

Study selection

The initial search yielded 717 potentially relevant articles. After searching through references of included articles and repeating the search in PubMed in May 2018, another nine articles were added, providing 726 articles. After screening the articles by title and abstract, 603 articles were excluded, leaving 123 articles for detailed review. In total, 47 articles were included in this review, of which 32 reported on quality of life only, ten on cognitive functioning only, and five reported on both quality of life and cognitive functioning. Reasons for excluding articles are summarized in Figure 1.

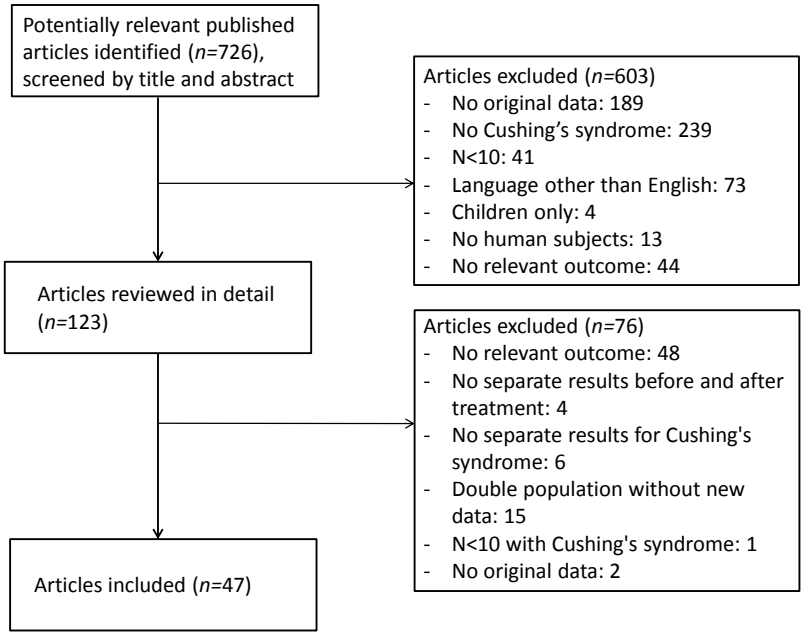

Figure 1: Flow-chart of inclusion of articles in this systematic review.

Study characteristics (Supplemental Data 2)

We included 27 cross-sectional studies (6, 22, 24-25, 27, 29-50), sixteen cohort studies (28, 51-65), one article that included both a cross-sectional study part and a cohort study part (66), one single-arm trial (67), and two articles about the same randomized controlled trial (pasireotide 600 µg versus pasireotide 900 µg) (23, 68). Studies were published between 1985 and 2017. Of the included studies, 28 reported on Cushing's disease only, one on adrenal Cushing's syndrome only, seventeen described a mixed population, and one study included a cohort of patients with

Cushing's disease only, as well as a mixed population cross-sectional study part. In total, the included studies described 2,643 patients, partially from overlapping populations.

Seventeen articles included a healthy control group (n=2,335, also partially from overlapping populations), of which fifteen studies matched controls on at least age and sex, and nine articles used normative data from the general population or literature reference values. Studies comparing patients before and after treatment by design included the same population for both measurement times, reducing risk of confounding, although bias remains possible through loss to follow-up, as described below.

Baseline characteristics varied between all included studies. As data were insufficient to estimate risk of confounding, and inclusion of articles for meta-analysis differed per analysis and per domain, baseline characteristics data were summarized for all articles. Average age was between 33.6 and 57.0 years. Percentage female patients varied between 40% and 100%. Average duration of follow-up for cohort studies was 6 to 54 months. Four studies, which were not included in any meta-analysis, did not present data after treatment. Of the remaining 43 studies, 23 used multimodality treatment, fifteen used surgical procedures only, three only used pharmaceutical treatment, and two did not describe the nature of the treatment.

Risk of bias assessment (Supplemental Data 2)
Loss to follow-up was reported by fourteen out of twenty cohort studies and trials, with a range of 0-74% loss to follow-up. Only four studies reported a loss to follow-up <5%. Of the 27 cross-sectional studies, 6 (22%) reported missing data for quality of life or cognitive functioning ≥5%. Fourteen articles (30%) explicitly stated including consecutive patients. Criteria for diagnosis of Cushing's syndrome were reported adequately by 21 studies (45%). Criteria for remission of Cushing's syndrome were reported adequately by 26 studies out of 43 with postoperative measurements (61%).

Study outcomes
Quality of life was reported in 37 articles, using eleven different generic questionnaires, two disease-specific questionnaires (i.e., CushingQoL and Tuebingen CD-25), and 21 domain-specific questionnaires (including amongst others five anxiety, six depression, and five fatigue questionnaires). Twelve studies reported quality of life both before and after treatment. Quality of life data were reported for patients with Cushing's syndrome before treatment by fifteen studies, for patients with Cushing's syndrome after treatment by 34 studies, and for a healthy control population by seventeen studies.

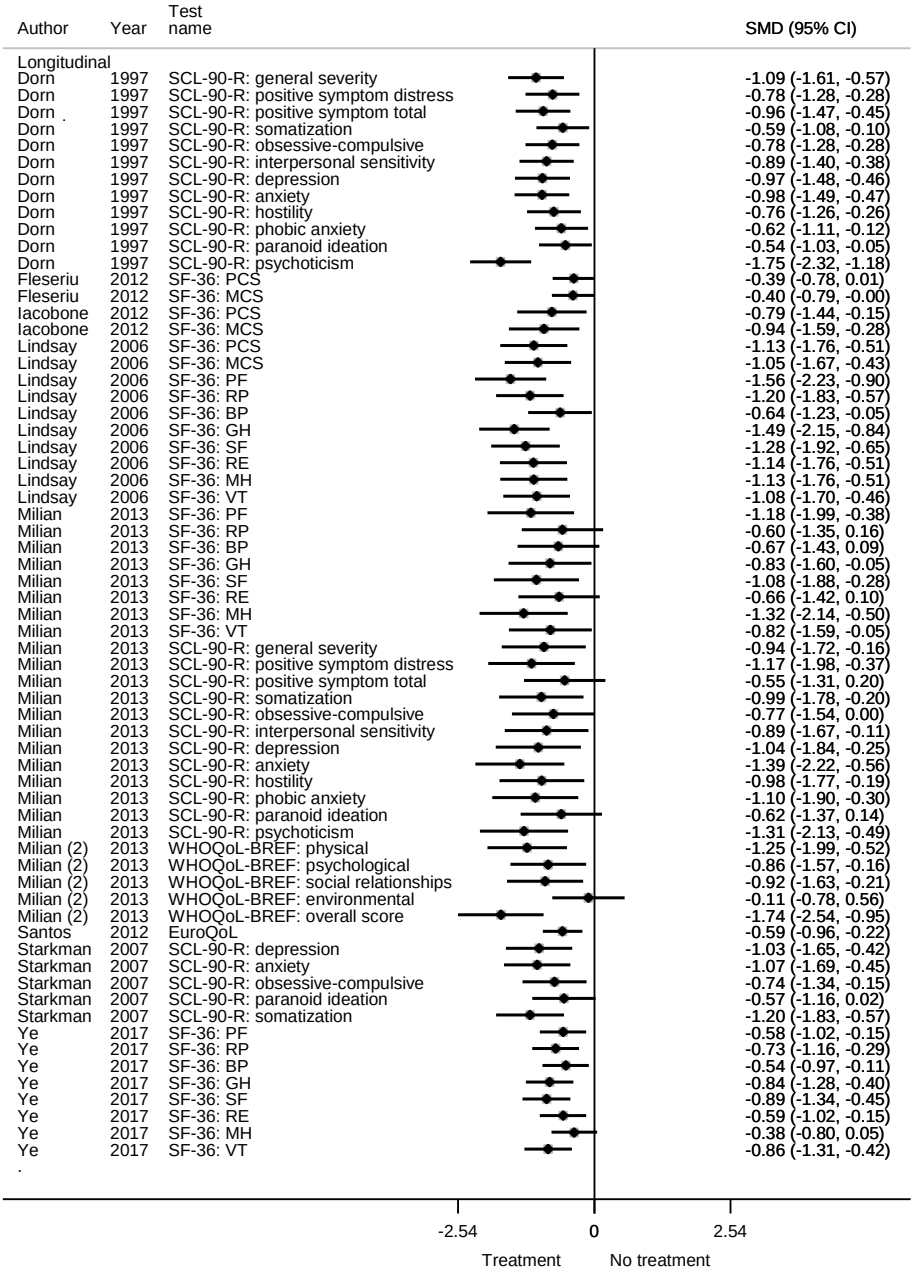

Figure 2: Generic quality of life before versus after treatment for Cushing's syndrome.

Cognitive functioning was reported in fifteen articles, using 35 different tests (including four tests on intelligence and concept formation, six on executive functioning, ten on attention, and fourteen on memory). Only six studies reported

cognitive functioning both before and after treatment. Cognitive functioning scores were reported for patients with Cushing's syndrome before treatment by eight studies, for patients with Cushing's syndrome after treatment by thirteen studies, and for a healthy control population by twelve studies. Detailed study outcomes and an overview of all included questionnaires and tests with abbreviations can be found in Supplemental Data 2.

Meta-analyses of improvement of quality of life and cognitive functioning

Quality of life and cognitive functioning improved after treatment in all studied categories (generic, disease-specific, domain-specific: anxiety, and domain-specific: depression quality of life, and the cognitive functions intelligence, executive functioning and attention). Generic quality of life improved by a SMD of 0.11 to 1.75 in all included studies (see Figure 2). Disease-specific quality of life improved by a SMD of 0.16 to 1.57 in all included studies (see Figure 3). For domain-specific quality of life and cognitive functioning, studies showed SMDs of 0.08 to 0.86, indicating improvement in all aspects of quality of life and cognitive functioning.

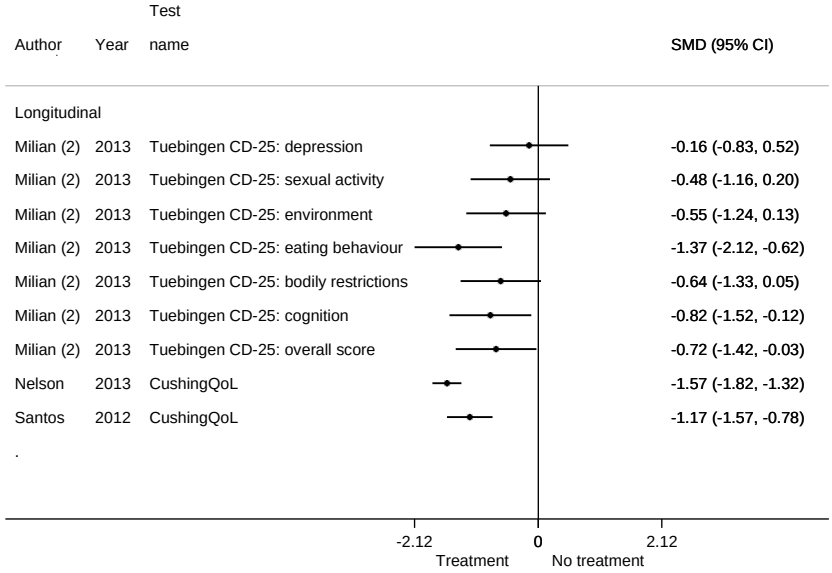

Figure 3: Disease-specific quality of life before versus after treatment for Cushing's syndrome.

Table 1 shows a summary of all meta-analyses regarding improvement in quality of life and cognitive functioning, including subgroup analyses for patients with Cushing's disease only, and analyses stratified by remission status after treatment. Supplemental Data 3-6 show the raw figures for the main analyses, analyses for patients with Cushing's disease only, analyses according to remission status, and analyses according to remission status for patients with Cushing's disease only, respectively.

Table 1: Summary of results of improvement in and normalization of quality of life and cognitive functioning in Cushing's syndrome.

	Main analysis (all etiologies included)	Cushing's disease only	Stratified by remission status: remission	Stratified by remission status: no remission	Cushing's disease only and stratified by remission status: remission	Cushing's disease only and stratified by remission status: no remission
Generic quality of life						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=9, t=65): SMD 0.11 (a) to 1.75 (a)	Yes (l, s=5, t=48): SMD 0.11 (a) to 1.74 (a)	Yes (l, s=5, t=25): SMD 0.11 (a) to 1.75 (a)	Insufficient data for meta-analysis	Yes (l, s=2, t=10): SMD 0.11 (a) to 1.74 (a)	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	No (c, s=7, t=59): SMD 0.05 (a) to 1.61 (h)	No (c, s=6, t=58): SMD 0.05 (a) to 1.61 (h)	No (c, s=5, t=53): SMD 0.05 (a) to 1.61 (h)	No (c, s=2, t=28): SMD 0.40 (a) to 2.25 (h)	No (c, s=4, t=52): SMD 0.05 (a) to 1.61 (h)	No (c, s=2, t=28): SMD 0.40 (a) to 2.25 (h)
Disease-specific quality of life						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=3, t=9): SMD 0.16 (a) to 1.57 (a)	Yes (l, s=2, t=8): SMD 0.16 (a) to 1.57 (a)	Yes (l, s=3, t=9): SMD 0.16 (a) to 1.37 (a)	Yes (l, s=2, t=2): SMD 0.63 (a) to 1.60 (a)	Yes (l, s=2, t=8): SMD 0.16 (a) to 1.37 (a)	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
Quality of life, domain: anxiety						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=2, t=3): SMD 0.25 (a) to 0.59 (a)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	No (c, s=3, t=4): SMD: 0.50 (h) to 0.96 (h)	No (c, s=3, t=4): SMD: 0.50 (h) to 0.96 (h)	No (c, s=3, t=4): SMD: 0.50 (h) to 0.96 (h)	Insufficient data for meta-analysis	No (c, s=3, t=4): SMD: 0.50 (h) to 0.96 (h)	Insufficient data for meta-analysis

Table 1: Summary of results of improvement in and normalization of quality of life and cognitive functioning in Cushing's syndrome (continued).

	Main analysis (all etiologies included)	Cushing's disease only	Stratified by remission status: remission	Stratified by remission status: no remission	Cushing's disease only and stratified by remission status: remission	Cushing's disease only and stratified by remission status: no remission
Quality of life, domain: depression						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=2, t=2): SMD 0.35 (a) to 0.51 (a)	Insufficient data for meta-analysis	Yes (l, s=2, t=2): SMD 0.35 (a) to 0.41 (a)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	No (c, s=4, t=5): SMD 0.33 (h) to 1.20 (h)	No (c, s=4, t=5): SMD 0.33 (h) to 1.20 (h)	No (c, s=4, t=5): SMD 0.33 (h) to 1.20 (h)	Insufficient data for meta-analysis	No (c, s=4, t=5): SMD 0.33 (h) to 1.20 (h)	Insufficient data for meta-analysis
Quality of life, domain: fatigue						
1. Improvement? (Do patients after treatment score better than before treatment?)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	No (c, s=2, t=7): SMD 0.20 (h) to 1.08 (h)	Insufficient data for meta-analysis	No (c, s=2, t=7): SMD 0.20 (h) to 1.08 (h)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
Cognitive function: intelligence						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=3, t=6): SMD 0.08 (a) to 0.77 (a)	Insufficient data for meta-analysis	Yes (l, s=3, t=6): SMD 0.08 (a) to 0.77 (a)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	Partially (l, s=3, t=6): SMD 0.55 (a) to 0.78 (h)	Insufficient data for meta-analysis	Partially (l, s=3, t=6): SMD 0.55 (a) to 0.78 (h)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis

Table 1: Summary of results of improvement in and normalization of quality of life and cognitive functioning in Cushing's syndrome (continued).

	Main analysis (all etiologies included)	Cushing's disease only	Stratified by remission status: remission	Stratified by remission status: no remission	Cushing's disease only and stratified by remission status: remission	Cushing's disease only and stratified by remission status: no remission
Cognitive function: executive functioning						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=3, t=6): SMD 0.19 (a) to 0.86 (a)	Yes (l, s=2, t=2): SMD 0.19 (a) to 0.78 (a)	Yes (l, s=3, t=6): SMD 0.19 (a) to 0.86 (a)	Insufficient data for meta-analysis	Yes (l, s=2, t=2): SMD 0.19 (a) to 0.78 (a)	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	Yes (l, s=2, t=4): SMD: 0.48 (a) to 0.31 (h) Unclear (c, s=4, t=9): SMD 0.00 to 0.31 (h)	Unclear (c, s=2, t=3): SMD 0.00 to 0.11 (h)	Yes (l, s=2, t=4): SMD: 0.48 (a) to 0.31 (h) Unclear (c, s=3, t=7): SMD 0.00 to 0.33 (h)	Insufficient data for meta-analysis	Unclear (c, s=2, t=3): SMD 0.00 to 0.33 (h)	Insufficient data for meta-analysis
Cognitive function: attention						
1. Improvement? (Do patients after treatment score better than before treatment?)	Yes (l, s=2, t=4): SMD 0.53 (a) to 0.71 (a)	Insufficient data for meta-analysis	Yes (l, s=2, t=4): SMD 0.53 (a) to 0.71 (a)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	Yes (l, s=2, t=4): SMD 0.25 (a) to 0.14 (h) No (c, s=3, t=5): SMD 0.16 (h) to 0.31 (h)	No (c, s=2, t=2): SMD 0.21 (h) to 0.31 (h)	Yes (l, s=2, t=4): SMD 0.25 (a) to 0.14 (h) Unclear (c, s=2, t=2): SMD 0.11 (a) to 0.31 (h)	Insufficient data for meta-analysis	Unclear (c, s=2, t=2): SMD 0.11 (a) to 0.31 (h)	Insufficient data for meta-analysis
Cognitive function: memory						
1. Improvement? (Do patients after treatment score better than before treatment?)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis
2. Normalization? (Do patients after treatment score as well as or better than healthy controls?)	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis	Insufficient data for meta-analysis

a=indicates that patients after treatment performed better than before treatment, b=indicates that patients before treatment performed better than patients after treatment, c=cross-sectional, h=indicates that healthy controls performed better than patients after treatment, l=longitudinal, s=number of studies included, SMD=standardized mean difference, t=number of (sub)tests or (sub)questionnaires included

Meta-analyses of normalization of quality of life and cognitive functioning

Quality of life did not normalize after treatment for Cushing's syndrome. For generic quality of life SMDs varied across included studies from 0.05 in favor of patients after treatment to 1.61 in favor of healthy controls (see Figure 4). For domain-specific quality of life, SMDs varied from 0.20 to 1.20, indicating that healthy controls consistently have higher quality of life than patients after treatment for Cushing's syndrome.

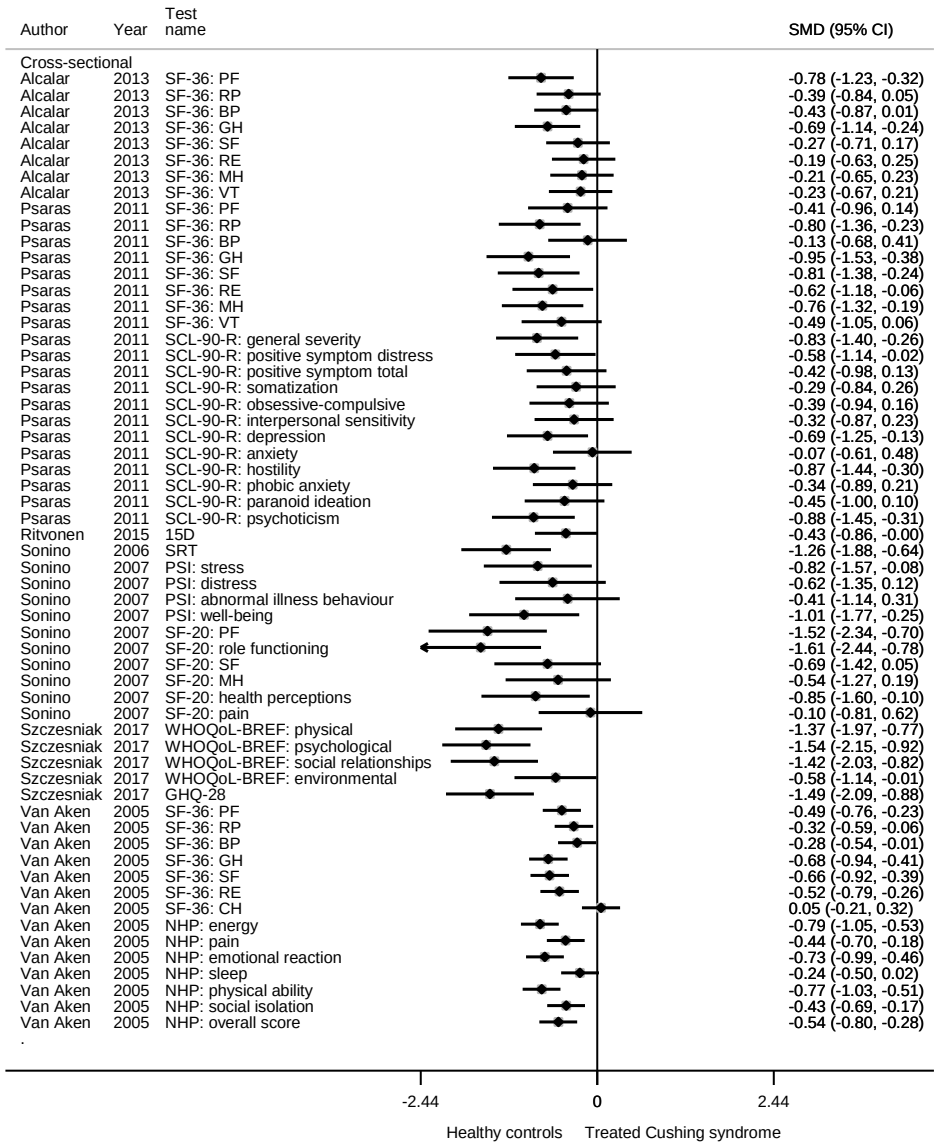

Figure 4: Generic quality of life after treatment for Cushing's syndrome versus healthy controls.

Cognitive functioning partially normalized after treatment for Cushing's syndrome. SMDs for intelligence varied across studies from 0.55 in favor of patients after treatment to 0.78 in favor of healthy controls. Executive functioning and attention were tested in both longitudinal as well as cross-sectional studies, which showed conflicting results. The longitudinal studies showed normalization of both domains of cognitive functioning, with SMDs varying between 0.48 in favor of patients after treatment and 0.31 in favor of healthy controls. The cross-sectional studies showed SMDs of 0.00 to 0.31 in favor of healthy controls, suggesting that no normalization of cognitive functioning had occurred. More detailed results regarding normalization of quality of life and cognitive functioning can be found in Table 1 and Supplemental Data 3-6, including subgroup analyses.

Discussion

The present systematic review and meta-analysis shows that quality of life and cognitive functioning improve after treatment for Cushing's syndrome. However, quality of life does not normalize, and only partial normalization occurs in cognitive functioning. These results demonstrate that biomedical treatment of Cushing's syndrome is the first step towards improvement in quality of life and cognitive functioning, but that room for further improvement remains in aiming to establish normalization of quality of life and cognitive functioning.

The present observations are in line with the results of a previous literature review by Feelders *et al.*, which described that health-related quality of life improved in patients with Cushing's disease during biochemical remission, but that it remained impaired compared to healthy controls. The same study also found that cognitive functioning did not improve short-term, and suggested that there may be a delay between correction of hypercortisolism and recovery of impairments in cognitive functioning (13). This is in contrast with our findings, since we found improvement and partial normalization of cognitive functioning. However, no truly short-term studies with only patients up to one year follow-up were included in this review, preventing extensive analyses according to follow-up time for both cognitive functioning as well as quality of life. This might explain the different findings regarding cognitive functioning improvement, and it would also support the suggestion of a delay between correction of hypercortisolism and recovery of impairments in cognitive functioning. Our findings are in accordance with another systematic review, which described quality of life in patients with a pituitary adenoma in general, and found that patients with Cushing's disease showed the smallest improvement and no normalization after treatment. They also reported room for further improvement in quality of life, potentially by psychosocial

interventions as well as optimal medical treatment (14). Two articles were published after our last search in May 2018. Our results were in accordance with the first one by Valassi *et al.*, which demonstrated that quality of life, as assessed with the EQ-5D and CushingQoL, improved after treatment for Cushing's syndrome (69). The second article by Osswald *et al.* compared quality of life, as assessed with the SF-36, CushingQoL, and Tuebingen CD-25, between patients in remission of ectopic Cushing's syndrome and patients with remitted Cushing's disease, and observed that female patients with ectopic Cushing's syndrome reported a better quality of life compared to female patients with Cushing's disease. This difference was not observed in male patients. Comparing the quality of life scores of these patients to the quality of life scores reported in our included studies, it can be observed that the patients in the study of Osswald *et al.* scored better on all three questionnaires. As this study included a small population (n=69), their results would have meant a small change towards better quality of life in the average that we found for analyses including these questionnaires after treatment for Cushing's syndrome only (70).

Although quality of life and cognitive functioning have been addressed before separately in systematic reviews, this is the first study investigating both quality of life as well as cognitive functioning. Furthermore, not only patients with Cushing's disease were included, but all patients with Cushing's syndrome. The following study limitations need to be taken into account when interpreting the results. Included studies showed heterogeneity regarding etiology of Cushing's syndrome, treatment strategy, and remission status after treatment. Results were consistent across the subgroup analyses for Cushing's disease only and the subgroup analyses stratified by remission status. Due to lack of sufficient data per category, no separate analyses stratified by treatment strategy could be performed. As longitudinal studies were expected to differ less in treatment strategy and follow-up time between individual patients than cross-sectional studies, analyses were performed separately for longitudinal versus cross-sectional studies. Only two cognitive functioning domains were tested by enough longitudinal and cross-sectional studies to perform and compare both analyses, hindering extensive comparison between the two study designs. Studies directly comparing different treatment strategies should be performed to determine the effect of treatment strategy on quality of life and cognitive functioning improvement and normalization.

As there were already few articles included per category, no sensitivity analysis with only low risk of bias studies could be performed. Only two of the included articles had low risk of bias on all components. Most of the included articles were not low risk of bias because they had too high loss to follow-up or because they selected patients based on remission status. High loss to follow-up could have caused bias in longitudinal studies. As it is most likely that patients who perform worse find it

important to participate in quality of life research, our results may be too pessimistic, meaning that the improvement after treatment is actually larger than we observed. Publication bias was minimized by searching for otherwise unpublished meeting abstracts in Embase, Web of Science, and COCHRANE Library. This did not lead to additional data.

As glucocorticoid excess is known to cause not only physical symptoms, but also reduced quality of life and cognitive symptoms (2-3), improvement in quality of life and cognitive functioning after treatment of Cushing's syndrome could be explained by the normalization of cortisol concentrations with accompanying reduction in physical symptoms of Cushing's syndrome. Lack of normalization of quality of life and cognitive functioning after treatment might be explained by the structural and functional brain abnormalities observed in patients with active Cushing's syndrome, that even persist after long-term remission of Cushing's syndrome (5). The partial normalization in cognitive functioning found in this study has not been described previously. Only the results from two small cohort studies showed clear normalization in cognitive functioning (54, 59). Larger cohort or cross-sectional studies, or (randomized controlled) trials comparing different treatment methods, are necessary to confirm the normalization in cognitive functioning observed in these two small cohort studies. Theoretically, partial normalization in cognitive functioning might be explained by the involvement of different brain regions in cognitive functioning tasks that showed normalization, than the brain regions affected by structural and functional abnormalities as described above.

In conclusion, treatment of Cushing's syndrome is the first effective step in improving quality of life and cognitive functioning. However, the most effective treatment regimen for Cushing's syndrome regarding improvement in quality of life and cognitive functioning is still unknown, and probably consists of a multidisciplinary approach of at least endocrinology, surgery, and psychology, as well as early diagnosis to minimize permanent structural and functional brain abnormalities. As no normalization could be achieved in quality of life and part of the cognitive functioning domains, patients require special attention from the clinician for quality of life as well as for cognitive functioning after effective treatment for Cushing's syndrome. Interventions for further improvement and possibly normalization of quality of life and cognitive functioning should be investigated with priority.

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