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Quality of life (QoL) impairments in patients with a pituitary adenoma: a systematic review of QoL studies

Cornelie D. Andela · Margreet Scharloo · Alberto M. Pereira · Ad A. Kaptein · Nienke R. Biermasz

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Abstract
Purpose Pituitary adenomas give rise to physical and psychological symptoms, which may persist after biochemical cure. Growing attention has been paid to quality of life (QoL) in these patients. We aimed to systematically analyze QoL assessment methods and QoL outcome in these patients.
Methods We conducted a systematic literature search up to January 2014 in PubMed, Web of Knowledge, PsycInfo and EMBASE.
Results 102 papers assessing QoL in patients with a pituitary adenoma were included. In clinical (original) studies in which QoL was the primary outcome parameter (n = 54), 19 studies combined a generic questionnaire with a disease-specific questionnaire. QoL was found to be impaired in patients with active disease relative to controls, and generally improved during biochemical cure. However, no normalization occurred, with patients with remitted Cushing's disease demonstrating the smallest improvement. Somatic factors (e.g., hypopituitarism, sleep characteristics), psychological factors (illness perceptions) and health care environment (rural vs. urban) were identified as influencing factors. Intervention studies (predominantly evaluating medical interventions) have been found to improve QoL.
Conclusions The growing number of studies assessing QoL generally described the negative impact of pituitary adenomas. QoL research in this patient group could be further elaborated by the development of disease-specific questionnaires for prolactinoma and non-functioning adenoma, consequent use of generic and disease-specific questionnaires and using a long-term (longitudinal) follow-up. Surgical and pharmacological interventions improve but not normalize QoL. We postulate that there might be margin for further improvement of QoL, for instance by using psychosocial interventions, in addition to optimal medical treatment.

Keywords Quality of life · Pituitary adenoma · Cushing's disease · Acromegaly · Prolactinoma · Non-functioning pituitary adenoma

Introduction

Pituitary adenomas can result in classical medical conditions, such as Cushing's disease (CD), acromegaly, non-functioning adenoma (NFA) or prolactinoma. Pituitary adenomas can be treated by transsphenoidal surgery, and some patients undergo additional medical treatment or radiotherapy when needed [1]. After successful biochemical treatment many physical, cognitive and psychological symptoms resolve, but may (partly) persist during long-term remission [2].

The research interest for Quality of Life (QoL) in patients with a pituitary adenoma has been emerging in recent years and disease-specific QoL questionnaires have

C. D. Andela · A. M. Pereira · N. R. Biermasz
Division of Endocrinology and Center for Endocrine Tumors Leiden, Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

C. D. Andela (✉)
Department of Endocrinology and Metabolism C7-Q, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands
e-mail: c.d.andela@lumc.nl

M. Scharloo · A. A. Kaptein
Department of Medical Psychology, Leiden University Medical Center, Leiden, The Netherlands

been developed. These disease-specific QoL questionnaires assess QoL aspects relevant to a specific pituitary disease, e.g., ACROQoL for acromegaly [3–5], QoL-AGHDA or the Questions on Life Satisfaction-Hypopituitarism (QLS-H) [6] for growth hormone deficiency (GHD) [7], and the Tuebingen CD-25 and the CushingQoL for CD [8–10]. Numerous other QoL questionnaires can assess general QoL domains (generic questionnaires) or a particular domain of QoL, which usually is relevant for more than one illness (e.g., dyspnea, nausea, pain, fatigue) (domain-specific) [11]. It is usually recommended that a generic questionnaire is combined with a disease-specific questionnaire, in order to assess both specific characteristics and the general perspective of QoL. This also prevents that unexpected impairments in QoL remain undetected [12]. The assessment of QoL is commonly used to evaluate QoL in general or patient populations, to compare treatment in clinical trials, or to support treatment choices in individual patient care [11]. The lack of an unambiguous definition of QoL poses major challenge for the evaluation and interpretation of QoL. QoL can be interpreted differently and authors may mean different topics, from different perspectives [13]. A commonly used definition is that QoL is "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient" [13].

Considering the potential short-term, but also long-term negative impact of pituitary adenomas on QoL, the growing attention for QoL in patients with a pituitary adenoma, and the variety of QoL questionnaires available, we aimed to systematically analyze QoL assessment methods and QoL outcome in patients with a pituitary adenoma. Furthermore, we aim to review identified predictors of QoL and potential interventions to improve QoL.

Methods

Search strategy, eligibility criteria and data extraction

In order to identify papers that examined QoL in patients with pituitary adenomas, we searched Pubmed, Web of Knowledge, PsycInfo and EMBASE up to 16 January 2014. We composed a search strategy focusing on QoL in patients with, or treated for, pituitary adenomas. We used all relevant keyword variations, including free text words. Duplicates were excluded. For the complete search strategy, see Appendix 1. Only original articles were included. Studies were eligible when all of the following criteria were met: (1) addressing patients with pituitary adenomas (CD, prolactinoma, acromegaly, NFA), (2) pituitary disease was not caused by an hereditary component by an hereditary gene mutation (e.g., MEN-I), (3) QoL was assessed and used as a parameter, (4) a clear description of QoL assessment, (5) clear description/presentation of QoL results, (6) groups of pituitary patients $> n = 10$, (7) written in English, and (8) pertaining to adult patients. Reviews, case-reports and letters were excluded. Papers which included patients with pituitary adenomas, but which analyzed data in one group of patients with patients with pituitary adenomas in general (i.e., group consisted of a mixture of patients treated for prolactinoma, craniopharyngioma, non-functioning adenoma, etc.), or combined with patients with other diseases (e.g., other skull based tumors, GHD not related to pituitary adenoma), were not included.

Eligibility and data extraction were assessed by two independent investigators (C.D.A. and A.G.). Inconsistencies were resolved by consensus. The following data were extracted: sample size, gender distribution, disease status (active vs. non-active), design, used QoL scales and outcome.

Results

Identification and selection of literature

The initial search identified 1,364 studies, 1,237 were excluded based on title and abstract. We retrieved 127 studies for detailed assessment. Twenty-five studies were excluded for the following reasons: no clear description of QoL research ($n = 6$), meeting abstracts ($n = 5$), too small number of included patients ($n = 8$), not original article ($n = 3$), article was not available in English ($n = 1$) or article not available ($n = 2$). Consequently, 102 studies were eligible for inclusion (Fig. 1). Based on publication dates of the included articles, it can be seen that over the last decade the number of studies studying QoL assessment in patients with pituitary adenomas has been increasing considerably (Fig. 2).

QoL assessment methods

In the 102 studies a total of 49 different questionnaires have been used (10 generic, nine disease-specific, 30 domain-specific). Sixteen studies assessed QoL with the aim to develop or validate a (disease-specific) questionnaire i.e., the AcroQoL [3–5, 14, 15], the CushingQoL [8, 16–19], the Tuebingen CD-25 [9, 10, 20] and the QoL–AGHDA [21]. Lenderking et al. [22] developed the Impact on lifestyle Questionnaire and validated it in a group of patients with acromegaly. Tiemensma et al. [23] evaluated whether QoL could be assessed with patient's drawings and demonstrated that drawings reflect another dimension.

In the other 86 clinical studies, QoL was the primary outcome in 54 studies (63 %). Nineteen studies combined a generic with a disease-specific questionnaire. Thirty-four

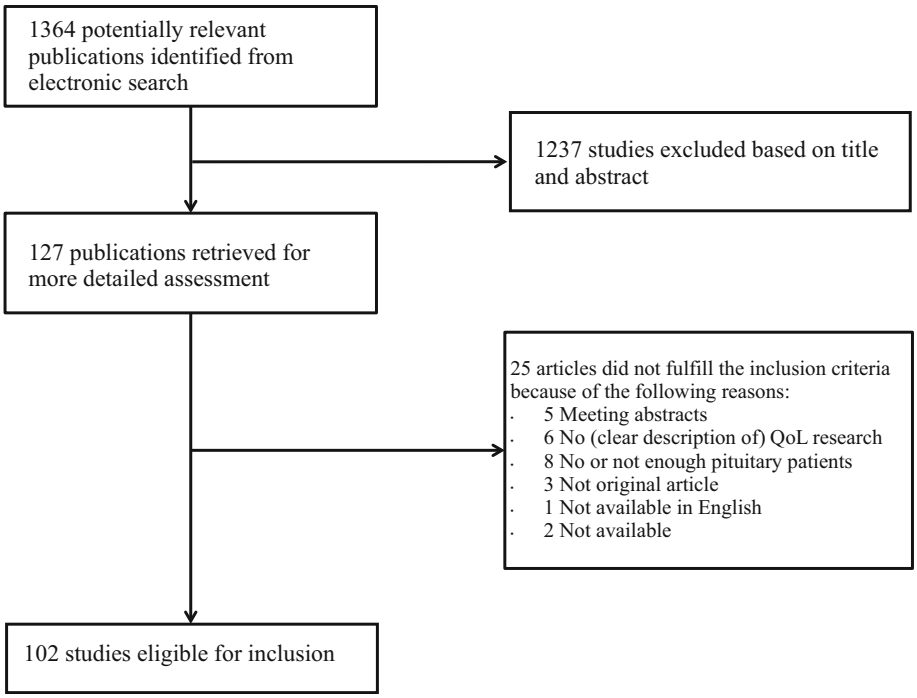


Fig. 1 Flow-diagram of article selection

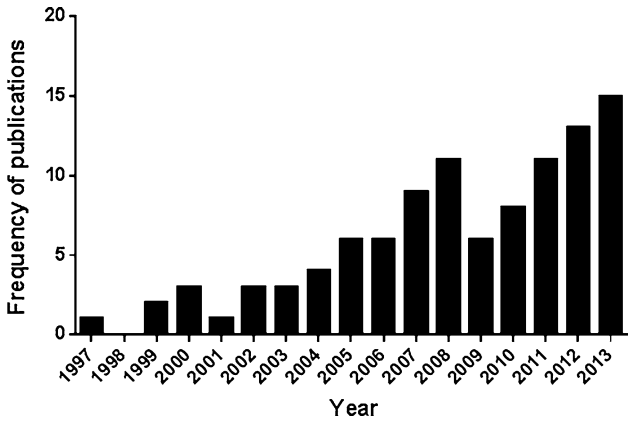


Fig. 2 Frequency of QoL studies in patients with pituitary adenomas over the last few decades

studies (40 %) used a domain-specific questionnaire assessing a particular domain, e.g., anxiety and depressive symptoms, pain, fatigue, cognitive failure, sexual function, or social situation. In three studies (5 %) QoL was assessed by a simple question or a visual analogue scale [24, 25], and in one study the name of the questionnaire was not mentioned [26].

QoL outcome in patients with a pituitary adenoma

Sixty-two studies reported the outcome of QoL in patients with pituitary adenomas i.e., prolactinoma (n = 8), NFA (n = 16), acromegaly (n = 31), and CD (n = 24; Table 1). The majority (n = 58, 94 %) used a cross-sectional design to compare QoL of patients with pituitary disease to QoL of healthy controls (n = 17), reference values (n = 13). A minority used patients with other pituitary adenomas (n = 6), other patient groups (n = 8), or compared patients with the same pituitary disease but with different clinical characters (e.g., male vs. female gender, controlled vs. uncontrolled disease, with or without GHD; n = 16; findings are described in the next paragraph). Most studies included patients with exclusively controlled disease (n = 38, 61 %). Eighteen studies (29 %) included patients with different diseases stages, i.e., active disease and remission, and five studies (8 %) included only patients with active disease. Eight of these studies (13 %) were intervention studies which evaluated QoL at baseline.

In eight studies with a total number of 387 patients with prolactinoma, it was demonstrated that patients treated for a prolactinoma reported impairments in QoL, when compared to healthy controls [27–30] and reference values, with most pronounced impairments in mental measures during active disease [31].

Summarizing fourteen studies on 2,708 patients with NFA (the number of unique patients might be lower, since two studies reported from the KIMS-database) it can be observed that QoL outcome in patients with NFA demonstrated more diversity. Some studies reported a decreased QoL, relative to healthy controls and reference values [32, 33], with most pronounced impairments in physical and mental measures during active disease [31], while others did not find differences in QoL between patients treated for NFA and reference values [30, 34, 35], or other patient groups (i.e., mastoid

Table 1 Observational studies in patients with pituitary adenomas

References	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Prolactinoma								
Baird et al. [65][*1]	22	NA	C	C-S	Other pituitary adenomas	SIP List of symptoms and problems specific to patients with pituitary tumors	G, Dis	Patients reported less impairment on each dimension compared to patients with other pituitary adenomas. However, the relative dysfunction was similar for the two groups
Johnson et al. [31][*]	39	15/24	A	C-S	Acromegaly/CD/NFA) Reference values of the normal population	SF-36	G	QoL was decreased, particularly particular mental health
Heald et al. [63][*]	24	13/11	C	C-S	Acromegaly/CD/NFA Normative data	HADS GHQ-28 WHO-QOL-BREF SAS1-2	G, Dos	QoL was similar to patients treated for acromegaly or NFA, and was better compared to patients with CD
Kars et al. [27]	55	0/55	C	C-S	Age- and gender matched controls	SF-36 NHP MFI-20 HADS	G, Dos	QoL is impaired
Sonino et al. [29][^,*1]	52	NA	C	C-S	Controls matched for socio-demographic variables	DSM-IV interview eliciting psychiatric diagnoses DCPR PSI SF-20	G, Dos	Patients reported more stress and psychological distress and less wellbeing (physical functioning, role functioning, social functioning, mental health, health perceptions and pain)
Cesar de Oliveira Natiato et al. [28]	50	0/50	C	C-S	Controls with similar age, SES and geographic distribution	SF-36	G	QoL is impaired in women with prolactinoma treated with dopamine agonists
Van der Klaauw et al. [64][*]	128	29/99	C	C-S	Acromegaly/CD/NFA Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL compared to controls, but not compared to patients with paragangliomas. QoL was similar to patients treated for NFA or CD, and better compared to patients with acromegaly
Raappana et al. [30][*]	17	11/6	A/C	C-S	Reference values of the general population	15D	G	Patients reported impairments in QoL
NFA								
Page et al. [36]	48	27/21	C	C-S	Control patients who underwent mastoid surgery Normative data	SF-36 GWBS	G	QoL is impaired
Johnson et al. [31][*]	51	25/26	A	C-S	Acromegaly/CD/ prolactinoma Reference values of the normal population	SF-36	G	Patients reported a decreased QoL, reporting impairment in both physical and mental measures

Table 1 continued

References	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Heald et al. [63]*	55	33/22	C	C-S	Acromegaly/CD/ prolactinoma Normative data	HADS GHQ-28 WHO-QOL-BREF SAS1-2 FACT	G, Dos	QoL was similar to QoL of patients treated for acromegaly or prolactinoma, and was better compared to patients with CD
Casanueva et al. [37]Δ	688	438/250	C	C-S	GHD due to TBI	QoL-AGHDA	Dis	QoL of patients with GHD due to NFA were equal to patients with GHD due to TBI or NFA
Verhelst et al. [39]Δ	370	185/185	C	C-S	Patients with GHD due to cranio	QoL-AGHDA	Dis	Male patients with GHD due to a cranio reported worse QoL compared to male patients with GHD due to a NFA, whereas female patients with GHD due to a cranio reported a better QoL than female patients with GHD due to an NFA
Dekkers et al. [32]	99	54/45	C	C-S	Controls with similar age and gender distribution	SF-36 HADS MFI-20 NHP	G, Dos	QoL was reduced after successful treatment
Nielsen et al. [35]	192	116/76	C	O	Age- and sex adjusted normative data.	SF-36 MDI	G, Dos	No differences in QoL. Compared to patients who had undergone transsphenoidal surgery, patients who had undergone craniotomy reported an impaired QoL
Kreitschmann-Andermahr et al. [38]Δ	84	49/35	C	C-S	GHD due to TBI	QoL-AGHDA	Dis	QoL of patients with GHD due to NFA were equal to patients with GHD due to TBI or NFA
Miller et al. [87]*,†	48	27/21	C	C-S	Acromegaly Age-adjusted population norms	SF-36	G	QoL was better in patients with NFA compared to patients with acromegaly
Van der Klaauw et al. [64]*	99	54/45	C	C-S	Acromegaly/CD/ prolactinoma Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL compared to controls, but not compared to patients with paragangliomas. QoL was similar to patients treated for prolactinoma or CD, and better compared to patients with acromegaly
Höybye et al. [60]*,Δ	748	456/292	C	C-S	CD matched for age and gender	QoL-AGHDA	Dis	Patients demonstrated a better QoL compared to patients treated for CD
Pereira-Neto et al. [66]*1	16	NA	C	C-S	CD (n = 5) or acromegaly (n = 4)	*SF-36* HIT-6	G, Dos	There were no differences in QoL according to the hormonal profile of the adenoma
Biermasz et al. [33]	17	9/8	C	C-S	Controls with similar age, gender and BMI distribution	SF-36 HADS MFI-20 NHP	G, Dos	Patients demonstrated more fatigue and impairments in QoL
Capatina et al. [34]	193	NA	C	O	Age-related reference values	SF-36 NHP EQ-5D	G	QoL and subjective health was not compromised in patients

Table 1 continued

References	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Acromegaly								
Feldt-Rasmussen et al. [46]$^{\Delta,*}$	40	14/26	C	C-S	GHD due to several causes	QoL-AGHDA	Dis	Patients with pior acromegaly with current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies
Johnson et al. [31]*	36	30/6	A	C-S	NFA/CD/prolactinoma Reference values of the normal population	SF-36	G	Patients reported a decreased QoL, with patients with acromegaly reporting impairment in measures of physical function
Biermasz et al. [41]	118	61/57	C	C-S	Controls with similar age and gender distribution	SF-36 NHP MFI-20 HADS ACROQoL	G, Dos, Dis	After treatment, patients have a persistently decreased QoL
Heald et al. [63]*	20	7/13	C	C-S	NFA/prolactinoma/CD Normative data	HADS GHQ WHO-QOL-BREF SAS1-2	G, Dos	QoL was similar to QoL of patients treated for prolactinoma or NFA, and was better compared to patients with CD
Kauppinen-Makelin et al. [43]	231	103/128	C	C-S	Sample from the general population with similar age and gender distribution	15-D	G	Patients reported a reduced QoL
Sonino et al. [29]^{*1}	10	NA	C	C-S	Controls matched for socio-demographic variables	DSM-IV interview eliciting psychiatric diagnoses DCPR PSI SF-20	G, Dos	Patients reported more stress, psychological stress, abnormal illness behavior and worse QoL (role functioning, social functioning, mental health, health perceptions)
Mattoo et al. [40]	17	11/6	A/C	C-S	Demographically matched controls	PSLES SSQ CSCL DAQ WHO-QoL-BREF GHQ-12 CPRS	G, Dos	Psychiatric morbidity occurs in a significant percentage of patients. Presence of psychiatric morbidity was associated with dysfunction and poorer QoL
Miller et al. [87]*	58	28/30	C	C-S	NFA Age-adjusted population norms	ACROQoL SF-36 AIMS2	G, Dos, Dis	QoL was lower in patients, in comparison with patients treated for NFA. Patients with musculoskeletal pain had more impairment in QoL
Van der Klaauw et al. [64]*	118	61/57	C	C-S	NFA/CD/prolactinoma Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL, but not compared to patients with paragangliomas. QoL was worse compared to patients with NFA or prolactinoma

Table 1 continued

References	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Leon-Carrion et al. [45]	16	4/12	A		Healthy controls	AcroQoL BDI	Dis, Dos	Compared to healthy controls, acromegalic patients showed higher depression (BDI). ACROQoL scores correlated positively with GH and IGF-I, and negatively with depression measures
Psaras et al. [42]*	37	19/18	A/C	C-S	Age-, gender-, and education matched controls	SF-36 SCL-90-R ACROQoL	G, Dis	Patients reported more QoL impairments independent of disease status. Patients without remission reported poorer mental health compared to those with remission
Raappana et al. [30]	22	12/10	A/C	C-S	Reference values of the general population	15D	G	Patients without suppressive medical treatment had similar QoL compared to the age-standardized general population. Patients needing SA reported QoL impairments
Valassi et al. [47]*1	17	0/17	C	C-S	GHD due to several causes	QoL-AGHDA	Dis	Patients with pior acromegaly with current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies
Caglar et al. [128]	23	13/10	A	C-S	Gender- and age matched healthy controls	BDI ACROQoL	Dos, Dis	BDI scores did not reveal depression or limited QoL
Celik et al. [44]	57	0/57	A/C	C-S	Age-, gender and BMI matched healthy controls	ACROQoL BDI FSFI	Dos, Dis	Sexual dysfunction and depression rates were higher in female patients, compared with female healthy controls. There were no differences in QoL between controlled and uncontrolled patients
Cushing's disease								
Nagesser et al. [26]	44	11/33	C	O	NA	NA	NA	QoL scores were close to optimal, except for mental health and health perception
Lindholm et al. [58]#	68	NA	C	O	Age and gender adjusted normative data	*SF-36*	G	QoL was impaired, independent of disease control or presence of hypopituitarism
Hawn et al. [51]#	18	2/16	C	O	Normative data from the general population	SF-36	G	Patients treated with adrenalectomy demonstrated lower QoL
Feldt-Rasmussen et al. [46]Δ,*	135	30/105	C	C-S	GHD due to several causes	QoL-AGHDA	Dis	Patients with CD current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies
Johnson et al. [31]*	42	9/33	A	C-S	Acromegaly/CD/prolactinoma Reference values of the normal population	SF-36	G	Patients reported a decreased QoL, with patients with patients with patients with CD reporting impairments in all measures
Heald et al. [63]*	15	5/10	C	C-S	Acromegaly/prolactinoma/NFA Normative data	HADS GHQ WHO-QOL-BREF SAS1-2	G, Dos	Patients demonstrated impaired psychological well-being and psychosocial functioning compared with patients with other pituitary tumors (acromegaly, NFA, prolactinoma)
Van Aken et al. [54]	58	10/48	C	C-S	Controls with similar age and gender distribution	SF-36 MFI-20 NHP HADS	G, Dos	Patients with long-term remission experience a decreased QoL, with physical and psychosocial impairments, especially in the presence of hypopituitarism
Lindsay et al. [53]#	23	4/19	A/C	C-S		SF-36	G	Patients demonstrated impaired QoL during active disease, which partly resolves after treatment. However, after long-term follow-up there is still residual impairment

Table 1 continued

References	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Sonino et al. [55]#	24	5/19	C	C-S	Controls matched for age, gender, marital status and social class	SRT	G	Patients displayed higher scores in anxiety, depression, psychotic symptoms, with a generalized compromised QoL
Sonino et al. [29]*1	15	NA	C	C-S	Controls matched for socio-demographic variables	DSM-IV interview eliciting psychiatric diagnoses DCPR PSI SF-20	G, Dos	Patients reported more stress, less well-being and worse QoL (physical functioning, role functioning, social functioning, health perceptions)
Thompson et al. [61]	39	5/34	C	O	NA	SF-12v2 own Cushing-specific questionnaire	G	The majority of the patients treated with bilateral adrenalectomy fell within the top two-thirds of the national average for physical and mental composite score of the SF-12
Van der Klaauw et al. [64]*	58	10/48	C	C-S	NFA/acromegaly/prolactinoma Paragangliomas Controls with similar age and gender distribution	*SF-36* HADS MFI-20 NHP	G, Dos	Patients reported impaired QoL compared to controls, but not compared to patients with paragangliomas. QoL was not significantly different from patients with NFA, prolactinoma of acromegaly
Mattoo et al. [49]	18	4/14	A/C	C-S	Demographically matched controls	PSLES SSQ CSCL DAQ WHO-QoL-BREF GHQ-12 CPRS	G, Dos	Psychological morbidity occurs in a significant percentage of patients. Presence of psychological morbidity is associated with internalizing coping strategies
Smith et al. [56]	40	6/34	C	O	Population norms	SF-36	G	Patients were below population norms on 7 of 8 subscales of the SF-36. There was no evident difference in QoL between patients treated with laparoscopic or open adrenalectomy
Ding et al. [50]	43	14/29	A	O	Normative data from the general population	*SF-36*	G	Patients reported that their health status was good to excellent compared with one year before adrenalectomy. However, they showed lower SF-36 scores compared to the general population
Höybye et al. [60]*,Δ	322	84/238	C	C-S	NFA matched for age and gender	QoL-AGHDA	Dis	Patients with CD demonstrated a poorer QoL compared to patients treated for NFA
Psaras et al. [42]*	24	7/17	A/C	C-S	Age-, gender-, and education matched controls	SF-36 SCL-90-R ACROQoL	G, Dis	Patients with and without remission scored poorer on QoL. Patient with remission scored only higher on the subscale emotional role (SF-36) compared to patients without remission
Valassi et al. [96]#	481	91/390	A/C	C-S	Comparison of subgroups of CS due to pituitary, adrenal, ectopic, other cause	CushingQoL EQ-5D	G, Dis	QoL did not differ between subgroups

Table 1 continued

References	N	Gender (M/F)	Disease status	Design	Control group	Scales	Type of Scale	Outcome
Alcalar et al. [52]	40	31/9	C	C-S	Demographically matched controls	SF-36	G	QoL and body image were lower in patients. Physical functioning, bodily pain and general health were lower in patients without remission, compared to patients with remission and controls
Wagenmakers et al. [57]	123	17/106	C	C-S	Controls with similar age and gender	*SF-36* NHP HADS CushingQoL	G, Dos, Dis	Patients reported a worse QoL
Abraham et al. [59]#	66	14/52	A	C-S	Obese subjects	*SF-36* Locally developed CS symptom questionnaire	G, Dis	QoL was lower in patients, than in obese individuals. After adjusting for symptom count, obese individuals showed worse on mental health scores then the CS population.
Van der Pas et al. [48]	17	4/13	A	C-S	Age-adjusted literature derived reference values	SF-36 NHP HADS MFI-20 CushingQoL	G, Dos, Dis	Patients demonstrated impaired QoL

SF-36: included in spider-plots, *SF-36*: not included in spider plots, because mean scores on a 0–100 scale were not presented

Disease status: *A* active disease, *C* controlled disease

Design: *C-S* cross-sectional, *O* Observational

Types of scales: G = Generic, Dis = Disease specific, Dos = Domain specific

NA not applicable, *GHD* growth hormone deficiency, *GH* growth hormone, *RT* radiotherapy, *CD* Cushing's disease, *Cranio* craniopharyngioma

* Also included groups of patients with other pituitary diseases

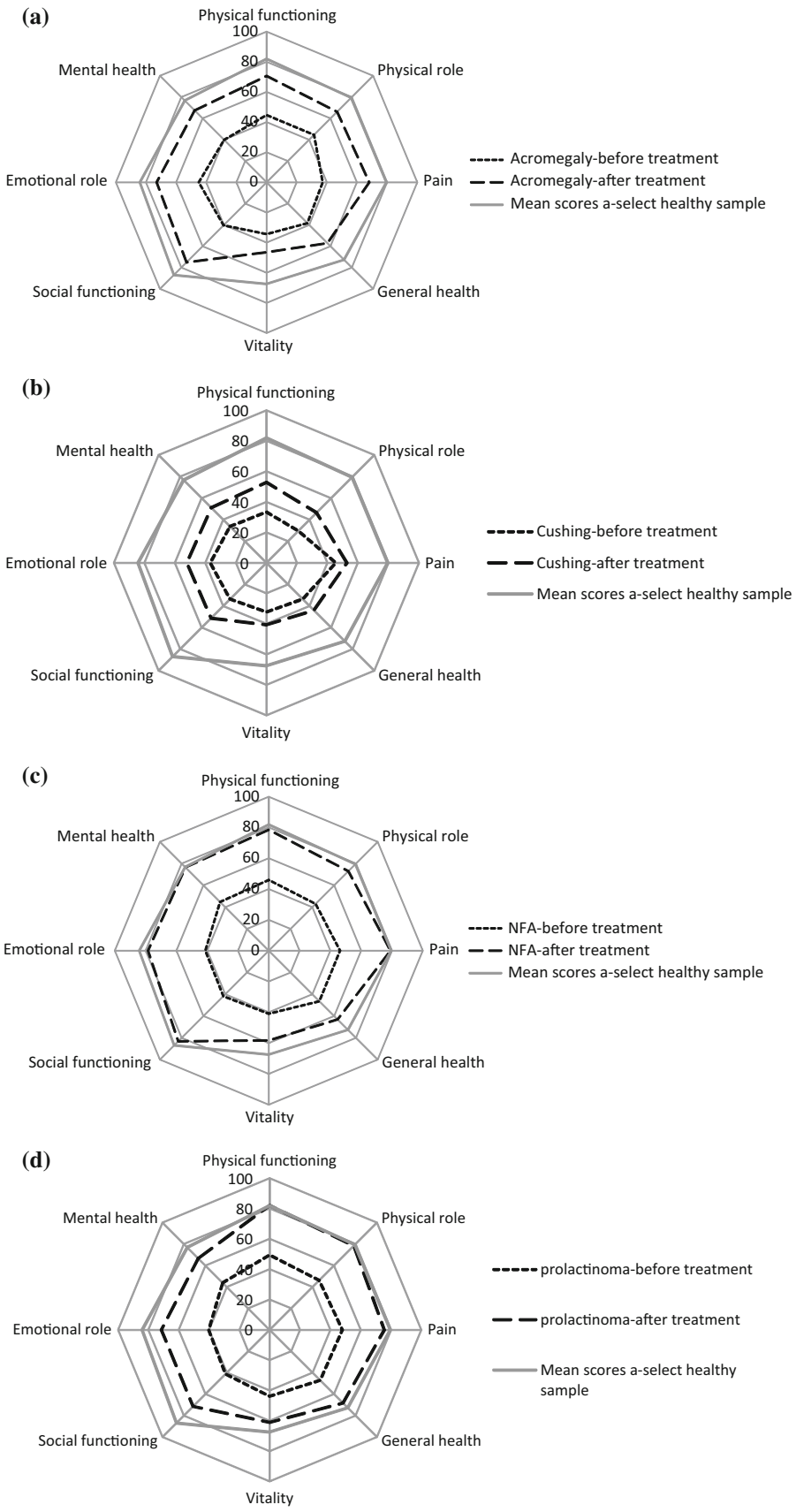
*[1] Also included groups of patients with other pituitary diseases, but other groups were <10 or mixed with other diseases, therefore not mentioned in other tables

Also patients with adrenal Cushing's syndrome included

^ Also patients with idiopathic hyperprolactinaemia included

Δ KIMS-database

For a list of abbreviated questionnaire names, see Table 3


(a)
Physical functioning
Physical role
Pain
General health
Vitality
Social functioning
Emotional role
Mental health
100
80
60
40
20
0
Acromegaly-before treatment
Acromegaly-after treatment
Mean scores a-select healthy sample
(b)
Physical functioning
Physical role
Pain
General health
Vitality
Social functioning
Emotional role
Mental health
Cushing-before treatment
Cushing-after treatment
Mean scores a-select healthy sample
(c)
Physical functioning
Physical role
Pain
General health
Vitality
Social functioning
Emotional role
Mental health
NFA-before treatment
NFA-after treatment
Mean scores a-select healthy sample
(d)
Physical functioning
Physical role
Pain
General health
Vitality
Social functioning
Emotional role
Mental health
prolactinoma-before treatment
prolactinoma-after treatment
Mean scores a-select healthy sample

◀**Fig. 3** **a** SF-36 scores in patients with Acromegaly, **b** SF-36 scores in patients with Cushing's disease, **c** SF-36 scores in patients with NFA, **d** SF-36-scores in patients with Prolactinoma. Acromegaly-before treatment: Johnson et al. [31], Psaras et al. [42], Milian et al. [62]; Acromegaly-after treatment: Biermasz et al. [41], Biermasz et al. [86], Miller et al. [113], Vander der Klaauw et al. [91], Wexler et al. [79], Wassenaar et al. [85], Psaras et al. [42], Valassi et al. [47], Postma et al. [92], Milian et al. [62], Miller et al. [87]; Cushing's disease-before treatment: Johnson et al. [31], Lindsay et al. [53], Psaras et al. [42], Van der Pas et al. [48], Milian et al. [62]; Cushing's disease-after treatment [The study of Alcalar et al. [52] was not included for the spider plots, because SF-36 scores were that low (range), that it can be questioned whether SF-36 was scored adequately]: Van Aken et al. [54], Lindsay et al. [53], Smith et al. [56], Psaras et al. [42], Hawn et al. [51], Tiemensma et al. [23], Milian et al. [62]; NFA-before treatment: Johnson et al. [31]; NFA-after treatment: Page et al. [36], Dekkers et al. [32], Van Beek et al. [75], Nielsen et al. [35], Miller et al. [87], Biermasz et al. [33], Capatina et al. [34]; Prolactinoma-before treatment: Johnson et al. [31]; Prolactinoma-after treatment: Kars et al. [27], Cesar de Oliveira Natiato et al. [28]; mean scores a-select sample: mean scores of an a-select group of individuals in The Netherlands. Scores were published in the Dutch manual of the SF-36 [67]

surgery vs. NFA surgery, NFA with GHD vs. traumatic brain injury with GHD) [36–38]. Compared to patients with GHD due to a craniopharyngioma, male patients with GHD due to a NFA reported a better QoL, whereas female patients with GHD due to an NFA reported worse QoL [39].

Evaluating fifteen studies on acromegaly with a total number of 820 patients, it was demonstrated that patients with active, as well as controlled acromegaly reported more impairments in QoL, relative to healthy controls and reference values, [29–31, 40–43] which encompassed depressive symptoms and sexual dysfunction [44, 45]. Furthermore, patients with prior acromegaly with current untreated GHD reported worse QoL compared to patients with GHD due to other aetiologies [46, 47].

Summarizing twenty-two studies on CD with a total number of 1,713 patients, it can be observed that in patients with active, as well as controlled disease, QoL was impaired compared with healthy controls and reference values [29, 31, 42, 48–58]. Abraham et al. [59] comparing QoL of patients with active CD, with that of obese individuals, demonstrated a reduced QoL in CD. Furthermore, patients with CD with current untreated GHD reported worse QoL than counterparts with GHD due to other aetiologies [46, 60]. Other studies reported a less negative effect on QoL, among which the study of Negasser et al. [26] reporting that after treatment of CD, QoL scores were close to optimal, except for mental health and health perception. Furthermore, Thompson et al. [61] reported that the majority of the patients treated with bilateral adrenalectomy fell within the top two-thirds of the national average for physical and mental composite domains (SF-12).

Studies comparing groups of patients with different pituitary adenomas demonstrated that either patients with CD [31, 60, 62, 63] or patients with acromegaly and patients with CD have worse QoL relative to NFA and prolactinoma patients [64, 65]. A single study did not find differences between patients treated for NFA (n = 16) and small groups of patients treated for CD (n = 5) or acromegaly (n = 4) [66].

Spider plots of studies reporting results of the short-form 36 health survey (SF-36)

The SF-36 was the most frequently used generic questionnaire (n = 44, 43 %), and therefore, we created spider plots to represent the average QoL outcome as assessed with the SF-36 (Fig. 3a–d). Twenty-eight studies (28 %) reported the mean and standard deviation of the SF-36 subscales and we calculated the average score on each subscale, categorized per disease (acromegaly, CD, NFA, prolactinoma) and disease status (non-treated/treated; Appendix 2). Scores of a Dutch sample of healthy controls [67] were also represented in the spider-plots (Dutch data were comparable to normative data of other countries [68–72]).

Examining the four spider plots it can be observed that during active disease patients with CD report most impaired QoL. During remission, patients with CD still report the worst QoL when compared to the other three groups, followed by patients with acromegaly. When comparing QoL in groups of active/non-treated patients, with QoL in groups of controlled/treated patients, it can be seen that QoL generally improves after treatment in patients with a pituitary adenoma. Apparently, the smallest improvement can be seen in patients with CD. When comparing the average QoL of patients after treatment, with QoL of an a-select healthy Dutch sample, it can be seen that QoL does not normalize after treatment. Nevertheless, in patients after treatment for NFA or prolactinoma some subscales were equal to the mean scores of this a-select sample (i.e., NFA: Mental health, Pain; prolactinoma: Physical functioning, Physical role).

Influencing factors

Fifty-six studies (55 %) described influencing factors on QoL in patients with a pituitary adenoma. A great variety of significantly influencing factors has been reported, with same factors being relevant for two or more types of pituitary adenomas, such as current age and gender, while others were only relevant for one specific pituitary adenoma (Fig. 4).

In patients treated for prolactinoma, prolactin levels and free androgen levels were negatively associated with reported QoL [28], whereas others found no correlation with hyperprolactemia [27, 30]. Furthermore, a negative influence was found for problems in reproductive status and higher anxiety and depression levels [27], and present use of dopamine agonists (DA) [30], whereas others found

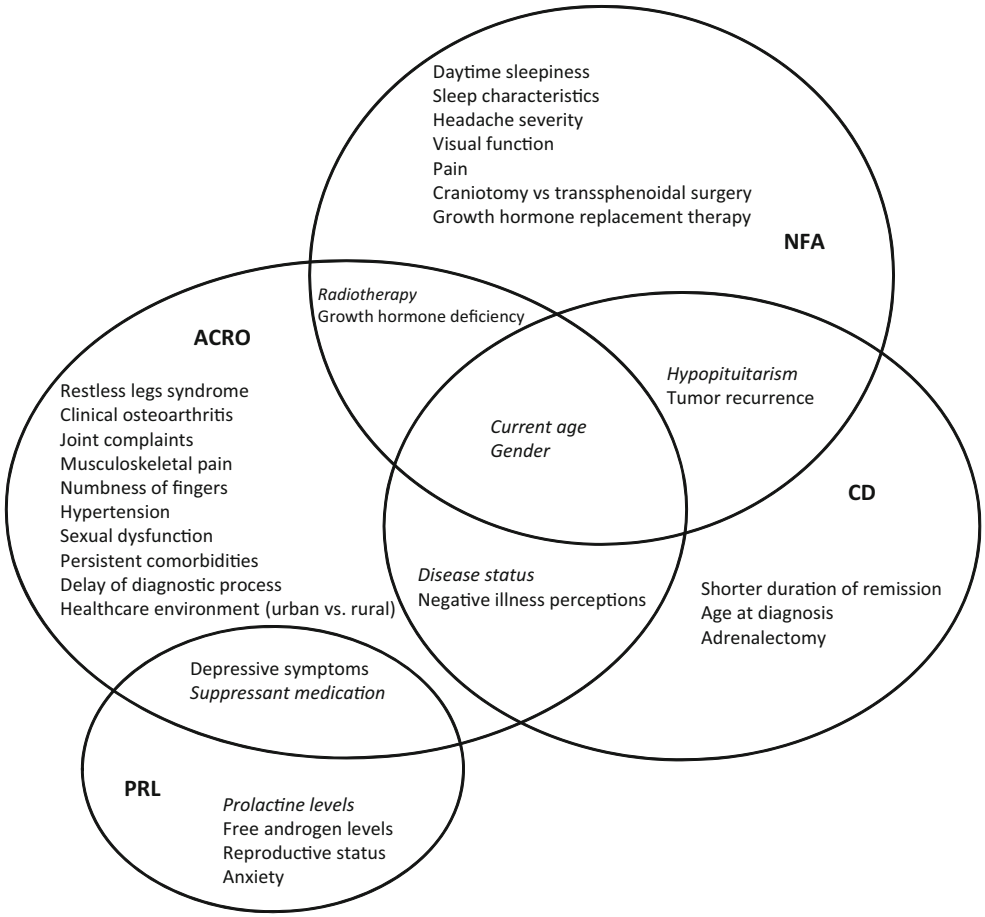


Fig. 4 Influencing factors. Factors which have been found to significantly influence QoL. Normal: consistent between studies. Italian: inconsistent between studies. *ACRO* acromegaly, *NFA* non-functioning pituitary adenoma, *CD* Cushing's disease, *PRL* prolactinoma

no significant effect of DA use [27, 64], nor a significant effect of tumor size (micro/macro) [64].

Factors that negatively influenced QoL in patients with NFA were impairments in visual function, pain [34, 73], sleep disturbances [33], daytime sleepiness [74], older age, female sex, tumor recurrence, hypopituitarism [32, 34, 36, 73, 75], and radiotherapy therapy [36, 73], whereas in other studies no significant influence of pituitary deficiency [30, 36] or radiotherapy was observed [30, 32, 75]. Interestingly, Capatina et al. [34] reported a positive effect of non-replaced GHD on QoL. Patients treated with craniotomy reported more QoL impairments relative to patients who had undergone transsphenoidal surgery [35].

In patients with acromegaly, an uncontrolled disease status or biochemical activity (e.g., high IGF-I levels) were found to negatively influence QoL [43, 45, 76–79], whereas other studies did not find this association [30, 42, 44, 78, 80–83]. Other negatively influencing factors were radiotherapy [30, 42, 44, 78, 80–83, 91], restless leg syndrome [84], clinical osteoarthritis [85], joint complaints [86] musculoskeletal pain [42, 86, 87], numbness of fingers, hypertension [88], sexual dysfunction [44], depressive symptoms [45, 47, 81], GHD [79, 89, 90], and persistent comorbidities [42]. Most studies reported the negative effect of female gender [62, 64, 83, 91, 92], whereas one study reported the negative effect of male gender [30]. As expected, current older age was found to negatively influence QoL [41, 43, 47, 62, 64, 85, 86, 91]. Medical treatment for acromegaly was negatively associated with QoL [30, 78, 82, 92]. Patients only treated with surgery reported a better QoL relative to patients treated with surgery and medical treatment [93], whereas others found no effect of medical treatment versus treatment with surgery and/or radiotherapy [64]. In addition, delay of the diagnostic process (>1 year) and living in an urban health care environment (instead of rural health care environment) were also found to be disadvantageous [94]. In 2011, researchers of our group demonstrated that in patients with long-term remission of acromegaly also psychological factors (i.e., negative illness perceptions) negatively influenced QoL [95].

In patients with remission of CD, shorter duration of remission [53, 57], female gender [54, 57] older age and

Table 2 Intervention studies aiming to improve QoL

References	N	Disease	Disease status	Design	Intervention	Scales	Type of Scales	Positive effect on QoL?
Surgery								
Pikkarainen et al. [25]#	74	CD/CS	C	Ret	Treatment of CS in general	VAS questionnaire dealing with symptoms	Dos	Yes
Lindsay et al. [53]	23	CD	A/C	P	TSS	SF-36	G	Yes
Tanemura et al. [73]	30	NFA	A/C	P	TSS	*SF-36* GHQ-30 NRS-pain	G, Dos	Yes
Milian et al. [62]	94	ACRO/ CD/ PRL/NFA	A/C	C-S F-U	Surgical treatment.	SF-36 SCL-90-R QLS-H ACROQoL	G, Dis	Yes
Pharmaceutical interventions								
Biermasz et al. [107]	14	ACRO	C	P	Increasing dose interval from 4 to 6 weeks within sandostatin LAR treatment	NHP	G	No
Neggers et al. [104]	20	ACRO	C	D-B P-C C-O	Additional weekly Pegvisomant next monthly SSA therapy versus placebo	ACROQoL PASQ	Dis	Yes
Madsen et al. [105]	18	ACRO	C	R C–O	Co-treatment with Pegvisomant versus unchanged SA monotherapy	EQ-5D PASQ	G, Dis	No
Lombardi et al. [99]	51	ACRO	A	F-U	long-acting Lanreotide Autogel	NHP	G	Yes
Schopohl et al. [106]	37	ACRO	C	P	Lanreotide Autogel	ACROQoL	Dis	No
Mangupli et al. [100]	28	ACRO	C	F-U	Octreotide-LAR therapy	ACROQoL	Dis	Yes
Karaca et al. [101]	22	ACRO	A	R	Octreotide LAR versus surgery	ACROQoL	Dis	Yes (both groups)
Trainer et al. [103]	84	ACRO	C	O-L R C	Pegvisomant versus Pegvisomnt + LAR	ACROQoL EQ-5D	G, Dis	Yes
Ghigo et al. [102]	113	ACRO	A	R O-L	Pegvisomant versus octreotide LAR	ACROQoL SSS	Dis	Yes (both groups)
Sonino et al. [98]	10	ACRO	A	P	slow-release lanreotide	KSQ CSKSLPP MSSQ	Dos	Yes
Fleseriu et al. [108]#	50	CD/CS	C	O-L F-U	Mifepristone	*SF-36* BDI	G, Dos	Yes
Katznelson et al. [109]#	46	CD/CS	A	O-L F-U	Mifepristone	*SF-36*	G	Yes
Van der Pas et al. [48]	17	CD	A	P	Stepwise medical therapy	SF-36 NHP HADS MFI-20 CushingQoL	G, Dos, Dis	No

Table 2 Intervention studies aiming to improve QoL

References	N	Disease	Disease status	Design	Intervention	Scales	Type of Scales	Positive effect on QoL?
Growth hormone replacement therapy								
Casanueva et al. [37]$^{\Delta}$	688	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Verhelst et al. [39]$^{\Delta}$	370	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Svensson et al. [111]$^{\Delta}$	380	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Kreitschmann-Andermahr et al. [38]$^{\Delta}$	84	NFA	C	P C-S	GHRT	QoL-AGHDA	Dis	Yes
Van der Klaauw et al. [112]	16	ACRO	C	P	GHRT	HADS MFI-20 NHP QoLAGDHA	G, Dos, Dis	No
Miller et al. [113]	30	ACRO	C	R P-C	GHRT	SF-36 QoL-AGHDA SQ	G, Dos, Dis	Yes
Valassi et al. [47]^{*1}	17	ACRO	C	R P-C C-S	GHRT	SF-36 QoL-AGHDA SQ	G, Dos, Dis	Yes
Giavoli et al. [110]*	22	ACRO/NFA	C	C-S F-U	GHRT	QLS-H	Dis	Yes
Feldt-Rasmussen et al. [46]$^{\Delta,*}$	175	ACRO/CD	C	C-S P	GHRT	QoL-AGHDA	Dis	No
Höybye et al. [60]$^{*,\Delta}$	1,070	CD/NFA	C	C-S P	GHRT	QoL-AGHDA	Dis	Yes
Other interventions								
Hatipoglu et al. [114]	20	ACRO	C	P C	Exercise program	ACROQoL BDI MBSRQ	Dos, Dis	Yes

SF-36: included in spider-plots, *SF-36*: not included in spider plots, because mean scores on a 0–100 scale were not presented

Disease status: *A* active disease, *NA* non-active disease

Design: *C-S* cross-sectional, *P* Prospective; *F-U* Follow-up, *R* randomized, *C* controlled, *P-C* placebo-controlled, *O-L* open-label, *D-B* double-blind, *N-C* non-comparative, *Ret* retrospective, *C-O*: cross-over

GHD growth hormone deficiency, *GH* growth hormone, *GHRT* growth hormone replacement therapy, *RT* radiotherapy, *CD* Cushing's disease

* Also included groups of patients with other pituitary diseases

*[1] Also included groups of patients with other pituitary diseases, but other groups were <10 or mixed with other diseases, therefore not mentioned in other tables

Also adrenal Cushing included

Δ KIMS-database

For a list of abbreviated questionnaire names, see Table 3

older age at diagnosis, and hypopituitarism [54] were found to negatively influence QoL, while Psaras et al. [42] found that younger age and not undergoing reoperation were found to be negatively associated with QoL. Others reported no association with hormonal deficiencies, etiology of CS (pituitary- or adrenal-dependent), treatment strategies [53, 57, 96], and current disease status [42]. On the other hand, Alcalar et al. [52] did demonstrate that the scores for physical functioning, bodily pain, and general health were all lower in patients without

remission, when compared to those in remission. The positive influence of treatment with adrenalectomy was reported [24, 26, 51, 56, 61] without differences in laparoscopic adrenalectomy versus open adrenalectomy [50]. In addition, psychological factors (i.e., negative illness perceptions) were also reported to be negatively related to QoL in patients in remission of CD [97].

Interventions (Table 2)

Twenty-eight intervention studies used QoL as an outcome parameter, including six randomized studies, three placebo controlled studies, and six follow-up studies using more than two measurement time points. In 11 studies QoL was the primary outcome parameter. Apparently, there were no

Table 3 List of abbreviated questionnaire names

Type of Scale	Name
Generic	SF-20/36/SF-6D: Short-Form health survey
	(P)GWBS: (Psychological) General Well-Being Schedule
	NHP: Nottingham Health Profile
	EQ-5D: European Quality of Life Scale
	GHQ-12/28/30: General Health Questionnaire-28/30
	WHO-QOL-BREF: World Health Organization Quality of Life Scale-abbreviated version
	SIP: Sickness Impact Profile
	15D: producing a 15-dimensional profile and a single index score
	SCL-90 (-R): Symptom Checklist 90 (revised)
	SRT: symptom rating test
Disease-specific	ACROQoL: Acromegaly Quality of Life Questionnaire
	SSS: Signs and Symptoms Scale-acromegaly
	PASQ: Patient-assessed-Acromegaly Symptom Questionnaire
	QLS-H: Questionnaire of Life Satisfaction-Hypopituitarism
	CushingQOL: Cushing Quality of Life questionnaire
	Tuebingen CD-25: Tuebingen Cushing's disease quality of life inventory
	QoL-AGHDA: Quality of Life Assessment of Growth Hormone Deficiency in Adults
Domain-specific	HADS: Hospital Anxiety Depression Scale
	MFI-20: Multidimensional Fatigue Inventory
	MDI: Major Depression Inventory
	NRS-pain: Numerical Rating Scale-pain
	CFQ: Cognitive Failure Questionnaire
	FACT: Functional Assessment of Cancer Therapy
	SAS 1-2: Social Adjustment Scale-modified
	FSFI: Female Sexual Function Index
	SSQ: Social Support Questionnaire
	SQ: Symptom Questionnaire (anxiety, depression, somatic symptoms, anger/hostility)
	BDI: Beck Depression Inventory
	MBSRQ: Multidimensional Body-Self Relations Questionnaire
	PSLES: Presumptive Stressful Life Events Scale
	HIT-6: Headache Impact Test scale
	CSCL: Coping Strategies Check List
	AIMS2: Arthritis Impact Measurement Scale 2
	CSKSLPP: Cognitive Scale of Kellner's Screening List for Psychosocial Problems
	CPRS: Comprehensive Psychopathological Rating Scale
	MSSQ: Marks' Social Situation Questionnaire
	KSQ: Kellner's Symptom Questionnaire (psychological distress, well-being)
	DCPR: Diagnostic Criteria for Psychosomatic Research (irritable mood, demoralization, persistent somatization)
	PSI: Psychosocial Index (chronic stress, psychological distress, abnormal illness behavior, psychological well-being)
	DAQ: Dysfunction Analysis Questionnaire (social, vocational, personal, family, cognitive)

intervention studies in patients with prolactinoma using QoL as an outcome parameter.

Surgery (n = 4)

Four studies including 221 patients evaluated the effect of surgery. In patients with NFA, QoL increased after surgery (6 months) [73]. Milian et al. [62] reported that QoL improved within 3 months after surgery in patients with a pituitary adenoma and a trend was found for further amelioration at 12 months after surgery. In patients with CD, surgical treatment (transsphenoidal, as well as adrenalectomy) was found to improve QoL [25, 53].

Pharmaceutical interventions (n = 23)

Twenty-three studies evaluated the effect of pharmaceutical interventions (other than growth hormone replacement therapy), including a total of 464 patients. The majority of the intervention studies evaluated the effect of medical treatment in patients with acromegaly. Treatment with long-acting Lanreotide improved QoL in patients with active acromegaly [98–100]. However, Karaca et al. [101] did not find differences in improvements in QoL after treatment with Octreotide LAR compared to surgery. Furthermore, no differences were found between naïve patients treated with octreotide LAR and naïve patients treated with Pegvisomant [102]. In addition, QoL improvements have been reported after treatment with Pegvisomant, or combination therapy (Pegvisomant/LAR) in patients with controlled acromegaly [103]. Moreover, a placebo controlled study demonstrated the positive effect of combination therapy (somatostatine analog + Pegvismant) vs. monotherapy (somatostatine analog + placebo) [104], whereas others did not find significant improvement of QoL after co-treatment with Pegvisomant in addition to the usual treatment with somatostatine analog [105]. There were no differences found in QoL in patients who previously used Octreotide LAR, who switched to Lanreotide autogel [106]. Biermasz et al. [107] examined whether the interval between sandostatin LAR injections could be increased and demonstrated that there were no differences in QoL during withdrawal after an injection up to 8 weeks.

In patients with CD the relatively new treatment with glucocorticoid receptor antagonist (Mifepristone) was found to positively affect QoL [108, 109]. Recently, Van der Pas et al. [48] evaluated the effect of a stepwise medical treatment (i.e., pasireotide, cabergoline, ketoconazole) on QoL in patients with de novo, residual or recurrent CD and reported no improvement in QoL (except for emotional reaction).

Ten studies investigated the effect of GH replacement therapy, covering a total sample size of 2,852. The number of unique patients might be lower, since two studies reported from the KIMS-database. It was reported that GH replacement therapy positively affects QoL in patients with GHD due to a prior NFA [37–39, 60, 110, 111]. In patients with GHD due to prior acromegaly, some studies reported no effect of GH replacement therapy [46, 112], whereas others did find a positive effect of GH replacement therapy in these patients [47, 110, 113]. Some studies reported that QoL improves after GH replacement therapy in patients with GHD due to prior CD [60], whereas other studies did not report this improvement [46].

Other interventions (n = 1)

Interestingly, a recent study of Hatipoglu et al. evaluated the potential beneficial effects of physical exercise on perceived body-image and QoL in acromegalic patients (n = 20). They demonstrated that an exercise program positively affected self-assessed body-image, but did not affect QoL or depressive symptoms [114].

Discussion

This first systemic review on QoL research in patients with a pituitary adenoma showed that there is considerable variation in used questionnaires and questionnaires combinations. It demonstrated the negative impact of pituitary adenomas on QoL, with patients with acromegaly or Cushing's disease generally demonstrating the most impaired QoL. The cause of this (persistent) impairment in QoL seems to be multifactorial, since a variety of somatic, psychological and environmental factors are found to influence QoL. A relatively small number of studies evaluated interventions aiming to improve QoL. Intervention studies, predominantly evaluating medical interventions, have been demonstrated to improve QoL, but no normalization occurs, with patients biochemically cured for CD demonstrating the smallest improvement in QoL relative to patients with active disease.

Patients with acromegaly or Cushing's disease generally reported the most impairment in QoL relative to patients with prolactinoma or NFA. This observation is in accordance with the findings of Van der Klaauw et al. [64] which demonstrated that patients in remission of acromegaly had the most impaired overall QoL, followed by Cushing's disease, prolactinoma and NFA. We speculate that these differences could be explained by the fact that these patients have not been exposed to elevated hormone secretion and therefore, probably experience less severe consequences. Nevertheless, a disease-specific QoL questionnaire for NFA is lacking, which for instance should assess visual dysfunction, a common symptom which has been found to contribute to QoL in patients with NFA [73]. Therefore, it could be that the impact of NFA is underestimated by the currently available QoL studies. Until a disease-specific questionnaire is available, QoL studies in patients with NFA should take into

consideration the assessment of domain-specific questionnaires, such as the National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) [115, 116].

The majority of the predictors identified in the available literature consist of somatic factors, and surgical and pharmacological interventions targeting these somatic factors have been found to improve QoL. However, the effects of some medical interventions for pituitary disease, such as replacement therapy for hypopituitarism, have not yet been evaluated. As illustrated by the spider-plots (Fig. 3a–d), there might be room for further improvement in QoL for patients with pituitary diseases. Tiemensma et al. demonstrated negative illness perceptions and ineffective coping strategies in patients with pituitary disease [95, 97]. They postulated that these psychological aspects could be a potential target for improving QoL and the authors point toward the potential beneficial effect of psychosocial interventions, adapting illness perceptions and coping strategies, next to medical treatment. Until now, there is only one pilot-study which described the efficacy of a 26-week patient education intervention for patients with neuroendocrine tumors. This program mainly focused on enhancing self-efficacy [117]. The results of this study demonstrated that perceived stress decreased and self-efficacy and physical functioning (SF-36) improved after the intervention [118]. Although the efficacy of psychosocial interventions should be further investigated in a randomized controlled trial in a homogenous group of patients with a pituitary adenoma, this study provided promising data for the efficacy of psychosocial interventions for the improvement of QoL in patients treated for pituitary adenomas.

When examining the selected QoL studies, some interesting facts can be observed. For instance, the number of studies assessing QoL differs considerably between the four patient populations, with the largest number of studies in patients with acromegaly, followed by Cushing's disease and NFA, and the smallest number in patients with prolactinoma. This is in particular interesting, considering the fact, that prolactine hypersecretion is most common in pituitary adenomas [119]. It should be noted that some papers were not selected for the present review, because they did not met inclusion criteria for this review, although they did measure QoL related aspects (e.g., general well-being [120], psychological symptoms [121]). Future research should focus on QoL in this under-evaluated group. Furthermore, studies with patients with other pituitary tumors were also not selected for the present review, although they did measure important QoL-related factors, such as personality traits, psychopathology [122–125] and perceived health [126]. A relatively small number of studies evaluated interventions aiming to improve QoL in patients with pituitary disease, in contrast to the large number of observational studies reporting the impairments in QoL. Furthermore, the number of studies examining QoL in naïve patients is quite small. In addition, only a few studies evaluated QoL in patients during long-term follow-up. More longitudinal studies including naïve patients are needed to provide more information about the time course of QoL in patients with pituitary diseases.

The definition of QoL in the book of Spilker stresses the importance of the patient perspective of QoL [13]. During a recent focus group study of our research group we elucidated the patient perspective of QoL. This study identified QoL aspects which are not (yet) covered by available disease-specific QoL questionnaires [127], such as visual problems, issues with a changed personality, feelings of frustration, and a reduced social network. Therefore, it might be suggested that the available QoL questionnaires can be further elaborated by including the patient perspective. Furthermore, disease-specific QoL questionnaires for NFA, prolactinoma or pituitary diseases in general should be developed, in order to further improve the quality of QoL research is patients with pituitary adenomas.

In conclusion, the growing number of studies using QoL assessment in patients with a pituitary adenoma generally described the negative impact of these medical conditions on QoL of the patients afflicted. QoL research in this patient group could be further elaborated by the development of disease-specific questionnaires, consistent use of generic, as well as disease-specific questionnaires, evaluating naïve patients and using a long-term follow-up. Surgical and pharmacological interventions have been demonstrated to improve QoL. Nevertheless, considering the multi-factorial determination of QoL, we postulate that there is substantial room for further improvement of QoL, by for instance using psychosocial interventions, besides optimal medical treatment.

Acknowledgments We thank research intern Aurelie Girbes for her contribution to this review and Jan W. Schoones for his contribution to the literature search.

Conflict of interest The authors have nothing to disclose.

Appendix 1: Search strategy

PubMed

("Pituitary Neoplasms"[mesh] OR "Pituitary Neoplasms"[all fields] OR "Pituitary Neoplasm"[all fields] OR "Pituitary Tumors"[all fields] OR "Pituitary Tumor"[all fields] OR "Pituitary Adenomas"[all fields] OR "Pituitary Adenomas"[all fields] OR "ACTH-Secreting Pituitary Adenoma"[all fields] OR "ACTH-Secreting Pituitary Adenomas"[all fields] OR "Corticotroph Adenoma"[all fields] OR "Corticotroph Adenomas"[all fields] OR "Cushing syndrome"[mesh] OR "Cushing syndrome"[all fields] OR "Cushing's Syndrome"[all fields] OR "Hypercortisolism"[all fields] OR "Cushing disease"[all fields] OR "Cushing's disease"[all fields] OR "Growth Hormone-Secreting Pituitary

Adenoma"[all fields] OR "Growth Hormone-Secreting Pituitary Adenomas"[all fields] OR "Acromegaly"[all fields] OR "Prolactinoma"[all fields] OR "Prolactinomas"[all fields] OR "Microprolactinoma"[all fields] OR "Microprolactinomas"[all fields] OR "Macroprolactinoma"[all fields] OR "Macroprolactinomas"[all fields] OR "non-functioning adenoma"[all fields] OR "non-functioning adenomas"[all fields] OR "non-functioning pituitary adenoma"[all fields] OR "non-functioning pituitary adenomas"[all fields] OR "non-functioning macroadenoma"[all fields] OR "non-functioning macroadenomas"[all fields] OR "nonfunctioning adenoma"[all fields] OR "nonfunctioning adenomas"[all fields] OR "nonfunctioning pituitary adenoma"[all fields] OR "nonfunctioning pituitary adenomas"[all fields] OR "nonfunctioning pituitary macroadenoma"[all fields] OR "nonfunctioning pituitary macroadenomas"[all fields] OR "nonfunctioning macroadenoma"[all fields] OR "nonfunctioning macroadenomas"[all fields]) AND ("quality of life"[mesh] OR "quality of life"[all fields] OR "life quality"[all fields] OR "qol"[all fields] OR "daily functioning"[all fields] OR "daily routine"[all fields] OR "health related quality of life"[all fields] OR "well-being"[all fields] OR "wellbeing"[all fields]).

PsycINFO

("Pituitary Neoplasms" OR "Pituitary Neoplasms" OR "Pituitary Neoplasm" OR "Pituitary Tumors" OR "Pituitary Tumor" OR "Pituitary Adenomas" OR "Pituitary Adenomas" OR "ACTH-Secreting Pituitary Adenoma" OR "ACTH-Secreting Pituitary Adenomas" OR "Pituitary Corticotropin-Secreting Adenoma" OR "Pituitary Corticotropin-Secreting Adenomas" OR "Corticotroph Adenoma" OR "Corticotroph Adenomas" OR "Growth Hormone-Secreting Pituitary Adenoma" OR "Growth Hormone-Secreting Pituitary Adenomas" OR "Pituitary Growth Hormone Secreting Adenoma" OR "Pituitary Growth Hormone Secreting Adenomas" OR "Prolactinoma" OR "Prolactinomas" OR "Microprolactinoma" OR "Microprolactinomas" OR "Macroprolactinoma" OR "Macroprolactinomas" OR "Acromegaly" OR "non-functioning adenoma" OR "non-functioning adenomas" OR "non-functioning macroadenoma" OR "non-functioning macroadenomas" OR "nonfunctioning adenoma" OR "nonfunctioning adenomas" OR "nonfunctioning pituitary adenoma" OR "nonfunctioning pituitary adenomas" OR "nonfunctioning pituitary macroadenoma" OR "nonfunctioning pituitary macroadenomas" OR "non-functioning macroadenoma" OR "nonfunctioning macroadenomas" OR "Cushing syndrome" OR "Cushing syndrome" OR "Cushing's Syndrome" OR "Hypercortisolism" OR "Cushing disease" OR "Cushing's disease" OR "Cushings Syndrome" OR "Hypothalamic Pituitary Adrenal Axis" OR "Hypopituitarism" OR "Pituitary Disorders" OR "Hypopituitarism") AND ("Quality of Life" OR "Quality of Work Life" OR "Relationship Quality" OR "Family Relations" OR "Life Changes" OR "Life Experiences" OR "Lifestyle" OR "Spirituality" OR "quality of life" OR "quality of life" OR "life quality" OR "qol" OR "daily functioning" OR "daily routine" OR "limitations of functioning" OR "health related quality of life" OR "quality of life" OR "quality of life" OR "life quality" OR "qol" OR "daily functioning" OR "daily routine" OR "limitations of functioning" OR "health related quality of life" OR "well-being" OR "wellbeing").

Web of science

TS = (Pituitary Neoplasms OR Pituitary Neoplasm OR Pituitary Tumors OR Pituitary Tumor OR Pituitary Adenomas OR Pituitary Adenomas OR ACTH-Secreting Pituitary Adenoma OR ACTH-Secreting Pituitary Adenomas OR Corticotroph Adenoma OR Corticotroph Adenomas OR Cushing syndrome OR Cushing syndrome OR Cushing's Syndrome OR Hypercortisolism OR Cushing disease OR Cushing's disease OR Growth Hormone-Secreting Pituitary Adenoma OR Growth Hormone-Secreting Pituitary Adenomas OR Prolactinoma OR Prolactinomas OR Microprolactinoma OR Microprolactinomas OR Macroprolactinoma OR Macroprolactinomas OR Acromegaly OR non-functioning adenoma OR non-functioning adenomas OR non-functioning macroadenoma OR non-functioning macroadenomas OR nonfunctioning adenoma OR nonfunctioning adenomas OR nonfunctioning pituitary adenoma OR nonfunctioning pituitary adenomas OR nonfunctioning pituitary macroadenoma OR nonfunctioning pituitary macroadenomas OR nonfunctioning macroadenoma OR nonfunctioning macroadenomas OR Cushing syndrome OR Cushing syndrome OR Cushing's Syndrome OR Hypercortisolism OR Cushing disease OR Cushing's disease) AND TS = (quality of life OR quality of life OR life quality OR qol OR daily functioning OR daily routine OR health related quality of life OR well-being OR wellbeing).

Embase

(exp hypophysis tumor/OR "Pituitary Neoplasms".mp OR "Pituitary Neoplasm".mp OR "Pituitary Tumors".mp OR "Pituitary Tumor".mp OR "Pituitary Adenomas".mp OR "Pituitary Adenomas".mp OR "ACTH-Secreting Pituitary Adenoma".mp OR "ACTH-Secreting Pituitary Adenomas".mp OR "Corticotroph Adenoma".mp OR "Corticotroph Adenomas".mp OR Cushing syndrome/OR "Cushing syndrome".mp OR "Cushing's Syndrome".mp OR "Hypercortisolism".mp OR "Cushing disease".mp OR

"Cushing's disease".mp OR "Growth Hormone-Secreting Pituitary Adenoma".mp OR "Growth Hormone-Secreting Pituitary Adenomas".mp OR "Acromegaly".mp OR "Prolactinoma".mp OR "Prolactinomas".mp OR "Microprolactinoma".mp OR "Microprolactinomas".mp OR "Macroprolactinoma".mp OR "Macroprolactinomas".mp OR "non-functioning adenoma".mp OR "non-functioning adenomas".mp OR "non-functioning pituitary adenoma".mp OR "non-functioning pituitary adenomas".mp OR "non-functioning macroadenoma".mp OR "non-functioning macroadenomas".mp OR "nonfunctioning adenoma".mp OR "nonfunctioning adenomas".mp OR "nonfunctioning pituitary adenoma".mp OR "nonfunctioning pituitary adenomas".mp OR "nonfunctioning pituitary macroadenoma".mp OR "nonfunctioning pituitary macroadenomas".mp OR "nonfunctioning macroadenoma".mp OR "nonfunctioning macroadenomas".mp) AND (exp "quality of life"/OR "quality of life".mp OR "life quality".mp OR "qol".mp OR "daily functioning".mp OR "daily routine".mp OR "health related quality of life".mp OR "well-being".mp OR "wellbeing".mp).

Appendix 2: Spider plot data

PF: Physical functioning, PR: Physical role, GH: General health, Vit: Vitality, SF: Social functioning, ER: Emotional role, MH: Mental health

Dutch a-select sample (67)

	PF	PR	Pain	GH	Vit	SF	ER	MH
Average score	81.9	79.4	79.5	72.7	67.4	86.9	84.1	76.8

Prolactinoma

Active/naïve patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Johnson et al. [31]	49.3	46.2	47.9	47	43.8	41.3	40.3	43.8
Average score	49.3	46.2	47.9	47	43.8	41.3	40.3	43.8

Controlled/treated patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Cesar de Oliveira et al. [28]	78.6	86	70.1	69	61.1	69.5	67.3	66.6
Kars et al. [27]	85.5	70.9	81.2	67.6		73.4	75.8	
Average score	82.1	78.5	75.7	68.3	61.1	71.5	71.6	66.6

NFA

Active/naïve patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Johnson et al. [31]	45.9	43	46.2	46.4	40.9	41.7	41.2	44.8
Average score	45.9	43	46.2	46.4	40.9	41.7	41.2	44.8

Controlled/treated patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Biermasz et al. [33] (remission)	85.6	76.5	87.8	68.4		89.0	90.2	
Dekkers et al. [32] (remission)	79.0	65	81.3	57.3		79.0	69.1	
Page et al. [36] (treated)	79	73	80	66	57	86	78	75
Nielsen et al. [35] (treated)	84	72.4	82.8	70.1	66.3	90.6	77.5	82.3
Van Beek et al. [75] (RT +)	84	76	84	60	66	85	88	79
Van Beek et al. [75] (RT-)	74	69	81	59	56	77	78	72
Capatina et al. [34] (treated)	71.5	64.5	75.3	62.1	55.0	79.1	75.9	76.6
Miller et al. [87] (after GH therapy)	85.4	98.1	78.1	76.8	61.5	96.2	92.3	85.2
Miller et al. [87] (after placebo)	63.9	62.5	61.1	48.6	46.1	67	57.1	66.3
Average score	78.5	73.0	79.0	63.1	58.3	83.2	78.5	76.6

Acromegaly

Active/naïve patients

	PF	PR	Pain	GH	Vit	SF	ER	MH
Milian et al. [62] (preoperative)	37	45.4	29.7	31.5	25.8	30.8	48.1	34.2
Johnson et al. [31] (active)	46	45	46.5	43.6	43.5	46.7	47.1	47.2
Psaras et al. [42] (no remission)	51	43.2	35.7	39.9	33.8	43.4	39.7	38.2
Average score	44.7	44.5	37.3	38.3	34.4	40.3	45.0	39.9

Controlled/treated patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Miller et al. [113] (after GH therapy)	85.4	98.1	78.1	76.8	61.5	96.2	92.3	85.2
Miller et al. [113] (after placebo)	63.9	62.5	61.1	48.6	46.1	67	57.1	66.3
Wassenaar et al. [85] (spine OA)	72.6	58.9	67.1	54.4		77.2	62	
Wassenaar et al. [85] (no spine OA)	84.7	90	86.9	72.7		93.3	95.5	
Van der Klaauw et al. [91] (follow-up)	72.1	67.4	72.6	59.9		79	75.1	
Wexler et al. [79] (GHD)	72	68	64.9	55.2	38.4	74.5	72	66.7
Wexler et al. [79] (GH sufficient)	94.4	100	84.6	78.3	66.8	95.8	100	78.2
Biermasz et al. [41] (remission)	68.6	57.4	72.2	55.6		79.6	70.3	
Biermasz et al. [86] (no joint problems)	83.9	76.9	92	70.6		88	84	
Biermasz et al. [86] (joint problems)	64	51.7	66.3	51.2		77.1	66.3	
Postma et al. [92] (SSTA +)	65	46	65	49	48	66	78	72
Postma et al. [92] (SSTA-)	79	65	78	63	58	75	75	75
Milian et al. [62] (12 months after surgery)	51.1	54.3	36.5	46.7	52.2	55.8	56.7	60.5
Miller et al. [87] (controlled)	65	65.7	60.7	55.4	51	76.9	76.6	73
Psaras et al. [42] (remission)	34.3	35.9	32.3	33.5	32.5	37.6	38.7	45.2
Valassi et al. [47] (placebo)	63.8	68.8	63.1	38.8	26.9	65.6	62.5	55
Valassi et al. [47] (GH)	80.6	58.3	76.4	61.7	28.9	70.8	77.8	65.3
Average score	70.6	66.2	68.1	57.1	46.4	75.0	72.9	67.5

Cushing's disease

Active/naïve patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Milian et al. [62] (preoperative)	9.6	21.6	24.9	12.1	9.8	12.4	22.1	13
Johnson et al. [31] (active)	36.6	36.1	40.8	36.4	35.4	35	38.8	38.4
Psaras et al. [42] (no remission)	37.6	25	44.6	39.7	47.2	31.6	26	43.8
Lindsay et al. [53] (pre-surgery)	28.3	31.8	41.9	34.4	36.4	29.8	36.6	39.7
Van der Pas et al. [48] (untreated)	54.4	33.6	75.3	45.6		59.4	60.4	
Average score	33.3	29.6	45.5	33.6	32.2	33.6	36.8	33.7

Controlled/treated patient groups

	PF	PR	Pain	GH	Vit	SF	ER	MH
Lindsay et al. [53] (remission)	45.5	45.7	47.4	44.2	46.5	47.2	45.6	47.3
Lindsay et al. [53] (after surgery)	45.9	45.9	48.6	48.1	48.3	46.7	49	51.4
Van Aken et al. [54] (remission)	68	65	73	54		73	67	
Tiemensma et al. [23] (remission)	63.5	51.3	69.6	50.1	48.6	72.1	62.7	61.4
Milian et al. [62] (12 months after surgery)	41.9	39.5	43	37.5	32	40.5	42.9	52.1
Psaras et al. [42] (remission)	43.3	40.1	38.3	31.6	36.9	32.9	58.3	40.7
Hawn et al. [51] (after adrenalectomy)	65	39	52	44	30	53	43	58
Smith et al. [56] (after adrenalectomy)	48.5	45.4	50.1	42.5	41.8	45.1	48.9	46.6
Average score	52.7	46.5	52.8	44.0	40.6	51.3	52.2	51.1

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