Reduced sleep quality and depression associate with decreased quality of life in patients with pituitary adenomas

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Abstract

Objectives: Several studies reported decreased quality of life (QoL) and sleep as well as increased rates of depression for patients with pituitary adenomas. Our aim was to explore to what extent differences in depression and sleep quality contribute to differences in QoL between patients with pituitary adenomas and controls.

Design: A cross-sectional case–control study.

Setting: Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry, Munich, Department of Internal Medicine, Ludwig-Maximilians-University, Munich, and the Institute of Clinical Psychology and Psychotherapy, Technical University, Dresden.

Participants: Patients with pituitary adenomas ($n=247$) and controls (from the DETECT cohort, a large epidemiological study in primary care patients) matched individually by age and gender ($n=757$).

Measurements: Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) and QoL was measured by the generic EQ-5D and calculated by the time trade-off- and VAS-method. Depression was categorized as ‘no depression’, ‘subclinical depression’, and ‘clinical depression’ according to the Beck Depressions Inventory for patients and the Depression Screening Questionnaire for control subjects.

Statistical analyses: General linear and generalized, logistic mixed models as well as proportional odds mixed models were calculated for analyzing differences in baseline characteristics and in different subgroups.

Results: Patients with pituitary adenomas showed decreased QoL (VAS index: $0.73 \pm 0.19$) and sleep (PSQI score: $6.75 \pm 4.17$) as well as increased rates of depression (subclinical or clinical depression: $41.4\%$) compared with their matched control subjects (VAS index: $0.79 \pm 0.18$, PSQI score: $5.66 \pm 4.31$, subclinical or clinical depression: $25.9\%$). We have shown that a substantial proportion of the reduced QoL (48\% respectively 65\%) was due to the incidence of depression and reduced sleep quality.

Conclusions: These findings emphasize the importance of diagnosing depressive symptoms and sleep disturbances in patients with pituitary disease, with the ultimate goal to improve QoL in patients with pituitary adenomas.
Introduction

Several studies have reported decreased quality of life (QoL) for patients with pituitary adenomas such as acromegaly, Cushing’s disease, prolactinomas, and nonfunctioning pituitary adenomas (NFPAs). Van der Klaauw et al. (1) compared QoL in patients with different pituitary adenomas and showed disease-specific impairments in QoL for patients with acromegaly, Cushing’s disease, prolactinomas, and NFPAs. Perceived QoL was especially decreased in treated patients with acromegaly compared with treated patients with NFPAs or prolactinomas. Biermasz et al. (2) showed that patients with acromegaly have persistently reduced QoL despite long-term biochemical cure of growth hormone (GH) excess. Furthermore, Webb (3) concluded that not only biochemical and radiological parameters should be evaluated in acromegaly since QoL was affected even in patients with controlled disease. Even though, as has been shown by Johnson et al. (4) or Paisley et al. (5), both insulin-like growth factor 1 (IGF1) levels and QoL scores improve with treatment, QoL levels remain reduced compared with age- and gender-matched controls. For Cushing’s disease, previous studies demonstrated similar results with decreased QoL, even when patients are doing well from a biochemical point of view (e.g. (6, 7)). Kars et al. (8) showed that the QoL is impaired in female patients treated for microprolactinomas, especially due to increased anxiety and depression. Finally, Naliato et al. (9) confirmed the results, further reporting that the impaired QoL was inversely associated with prolactin (PRL) levels.

Besides the widely documented decreased QoL in patients with pituitary adenomas, also a decreased quality of sleep has been reported. Copinschi et al. (10) reported decreased sleep quality for patients with untreated acromegaly as well as decreased QoL, and assumed that disturbed sleep is likely to be partly responsible for increased tiredness. Even in patients with long-term biochemical remission of acromegaly, increased daytime sleepiness was observed. Patient’s sleep duration and timing of sleep did not differ from healthy controls (11). Frieboes et al. (12) showed increased slow-wave sleep for patients with prolactinomas compared with a control group. Nevertheless, data on subjective sleep quality in these patients are still missing as is the case for patients with Cushing’s disease. In addition, Van der Klaauw et al. (13) concluded that patients cured from craniopharyngiomas or nonfunctioning macroadenomas suffered from increased daytime somnolence despite normal sleep patterns (onset, sleep timing, duration, and rise time) compared with healthy controls. Furthermore, Biermasz et al. (14) observed reduced sleep efficiency, less rapid eye movement sleep, more N1 sleep, and more awakenings in the absence of excessive apnea or periodic limb movements in patients previously treated for nonfunctioning pituitary macroadenomas compared with age-, gender-, and BMI-matched controls. Actigraphy revealed a longer sleep duration and profound disturbances in diurnal movement patterns, with more awakenings at night and less activity during the day. Patients scored higher on fatigue and reported impaired QoL than healthy controls.

Regarding depressive symptoms in pituitary patients, the data seems to be relatively clear. Sievers et al. (15) and Tiemensma et al. (16) showed that acromegaly is associated with an increased prevalence and a specific pattern of affective disorders. Also for Cushing’s disease, many studies have stressed that depression and anxiety-related personality disorders are common comorbidities in these patients (17, 18, 19, 20, 21). Patients with prolactinomas seem to experience increased neuroticism, high fear of uncertainty, and also increased fatigability and asthenia (22), but further studies are lacking. For patients with NFPAs, such data are still missing. Weitzner et al. (23) assumed that emotional problems (e.g., depression, anxiety) of patients with pituitary adenoma could be a result of long-term effects that the pituitary tumor itself, treatment, and/or hormonal changes have on the hypothalamic–pituitary–end organ axis; however, they presented four cases in which treatment for depression showed only little response, but treatment for apathy syndrome improved patients’ conditions.

In summary, while impaired QoL has been a consistent finding in patients with pituitary adenomas, treatment of the underlying disorders has only partial effects on QoL in these patients. Possible determinants of QoL are depressive mood and reduced sleep quality, with the former already demonstrated in some but not all patient groups with pituitary adenomas, and the latter rather neglected so far. The aim of this study was, therefore, to explore QoL, depression, and sleep quality in all pituitary patient groups and to explore the association of sleep quality and depression with QoL in patients with pituitary adenomas.

Subjects and methods

Subjects

This study was a case–control study. Patients diagnosed with acromegaly (n = 62), Cushing’s disease (n = 58),
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Clinical Study

Diagnosis of pituitary adenomas, assessment of comorbidities, and biochemical variables and pituitary patient group

The clinical characteristics of the patients with pituitary adenomas were assessed via clinical interviews, physical examination, and laboratory analyses. Tumour characteristics were determined by magnetic resonance imaging including a specific sellar protocol including contrast medium. Visual field defects at the time of diagnosis were reported. In addition, history of treatment (surgery, radiotherapy, and medication), history of comorbidities including cardiovascular features, metabolic features, respiratory features, bone and joint features, malignancies and endocrine consequences such as thyroid goiter and pituitary deficiencies, past medical history, and actual symptoms were reported.

Somatic comorbidities were diagnosed according to standard diagnostic procedures. Therapies used followed the consensus treatment guidelines for the respective pituitary disease.

For acromegaly, the current biochemical disease control was evaluated based on the consensus criteria with i) GH below 1 µg/l during a glucose tolerance test over 2 h (if available) and ii) IGF1 within two s.d. of an age- and gender-adjusted normative range (25, 26). Serum concentrations of GH were measured using the automated advantage chemiluminescent assay system (Nichols Diagnostics Institute, Bad Vilbel, Germany), and IGF1 was measured by automated chemiluminescent assays (IMMULITE 2000) (27, 28).

Biochemical disease control of hypercortisolism in Cushing’s disease was i) urinary free cortisol values greater than the normal range for the assay and ii) serum cortisol >1.8 g/dl (50 nmol/l) after 1 mg dexamethasone (1 mg DST), according to the Endocrine Society Clinical Practice Guideline 2008 (29).

Biochemical disease control in the prolactinoma patients was defined as PRL under the upper normal range of 25 ng/ml for women and 20 ng/ml for men with the commonly used assays for men (1 ng/ml is equivalent to 21.2 mIU/l WHO Standard Reference Number 84/500).

Evaluation of pituitary function comprised basal fasting measurements of IGF1, thyrotropin, free thyroxine, total triiodothyronine, luteinizing hormone, follicle-stimulating hormone, PRL, and testosterone (in men) or estradiol (in women) in all patients, as well as stimulation tests such as a short adrenocorticotropic test, the GH-releasing hormone/arginine test or insulin–hypoglycemia test in the case of suspected pituitary deficiencies in the corticotroph or somatotroph axis.

All patients with secondary hypoadrenalism, hypothyroidism, hypogonadism, and hyposomatotropism were studied while on optimized replacement therapy (including hydrocortisone, thyroid hormone, transdermal gonadal steroids or i.m. testosterone, and GH therapy where appropriate).

Assessment of depression

Depression was categorized as ‘no depression’, ‘subclinical depression’, and ‘clinical depression’ according to the Beck Depressions Inventory (BDI) for patients (BDI: 0–9, 10–18, > 18), and the Depression Screening Questionnaire (DSQ) for control subjects (DSQ: 0–4, 5–7, > 7) (30, 31). The psychometric properties of the DSQ are considered as satisfying (32, 33, 34).

prolactinomas (n=74), and NFPAs (n=53) were recruited from the Endocrine Outpatient Unit of the Max Planck Institute of Psychiatry and the Department of Internal Medicine, Ludwig-Maximilians-University, in Munich between 2007 and 2010 (response rate 56%, for further informations see e.g., Sievers et al. (15)). Reasons for nonparticipation were relocation and distance to study centers or unwillingness to spend time and effort on examinations. Exclusion criteria were the inability or unwillingness to perform the psychopathological assessments (i.e., insufficient language skills or diagnosed dementia).

The control subjects were selected from the 2007 follow-up assessment of the Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment study (DETECT) study (24). DETECT is a large multistage prospective-longitudinal study. The baseline study consisted of a nationwide representative sample of doctors with primary care functions (medical practitioners, general practitioners, and general internists), and included a total of 55 518 unselected consecutive patients in 3188 primary care offices in Germany. In the DETECT study, a representative sample of 7519 subjects was randomly chosen out of the baseline sample for additional laboratory tests and evaluated for a 5-year time period. For our control population, we matched one:max four controls selected from the follow-up assessment by age and gender to our patients and obtained hereby a group of 757 individually matched controls.

All subjects gave their written informed consent. The study was approved by the local ethic committee.
Assessment of QoL

QoL was measured by the generic preference-based EQ-5D (35) which quantifies health-related QoL in five different dimensions (mobility, self-care, usual activities, pain and discomfort, anxiety and depression). Patients and controls rated their health state with the use of the EQ-5D descriptive system. Each dimension has three levels (level 1: no health problems, level 2: moderate health problems, and level 3: extreme health problems). A unique health state is assigned for each subject ranging from ‘11 111’ (perfect health) and ‘33 333’ (worst possible state), resulting in a total of 243 health states. German reference values were used for calculating the QoL index by the time trade-off (TTO) and VAS method (31). In general, in the TTO health state valuation method, subjects are asked how much of their life expectancy they would be willing to trade for a shorter life in full health (36, 37, 38).

Assessment of sleep quality

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) (39), an established international measure of sleep quality. The PSQI consists of 19 items, relates to the last 1-month time interval, and generates an overall score and seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. In this study, we considered subjective sleep latency, sleep duration, sleep efficiency, and the global score. The global score has a range of 0–21 points with a higher number of points indicating poorer sleep quality. The controls answered a shorter version of the PSQI where three items had been omitted. To accommodate for this, we explored the relationship between the full and the abbreviated scale in a large independent sample of psychiatric–neurological patients (n = 82), healthy subjects (n = 160), and persons with sleeping disorders (n = 144). Consistent across groups, the abbreviated score was systematically related by a factor of 1.134 to the full score and we therefore weighted the control subjects’ PSQI global score by this factor.

Statistical analyses

All descriptive statistics are given as simple statistics for the patient groups and as weighted statistics for the control group with weighting factor being 1/m and m being the number of matched control subjects per single patient.

To compare BMI, frequency of comorbidities, depression, QoL, and sleep between all patient and controls and within each subgroup of patients and controls, general linear and generalized, logistic mixed models were used with a random intercept for each individual patient–control group.

In addition, we tested whether differences between patients and controls in depression, QoL, and sleep parameters were different for: i) patient groups (acromegaly, Cushing’s disease, prolactinomas, NFPAs); ii) age groups (up to 45, 46–55, 56–65, >66 years); iii) men vs women; and iv) patients that are considered as biochemically controlled vs those that were not (only in three groups: acromegaly, Cushing’s disease, prolactinomas). These were tested with a group (patients vs controls)× subgroup interaction effect in linear (sleep, QoL) and proportional odds (depression categories) mixed models, which tests the hypothesis that patient–control differences are larger or smaller in specific patient groups, age groups, or in men and women. All analyses were controlled for between group differences in BMI and comorbidities.

To explore the role of depression and sleep quality with regard to between-group differences in QoL, we compared a model with only group differences (model 1) with one where we controlled additionally for differences in sleep quality (model 2), depression (model 3), or both (model 4). The best linear unbiased predictions and approximate standard errors were derived from these mixed effects models for comparison.

All data analysis was undertaken with R 2.15.1 (40) and the nlme (41), the lme4 (42) and ordinal (43) packages in R.

Results

The characteristics of patient and control groups are given in Tables 1 and 2. Patients were aged 53.25 ± 12.16 years, and had a mean BMI of 27.11 ± 6.08 kg/m². The prevalence of cardiovascular disease for patients was 20%, of arterial hypertension 44%, of diabetes mellitus 15%, and of pulmonary disease 9%.

Patients differed from their matched control subjects in the following characteristics: BMI, hypertension, diabetes mellitus, and cardiovascular disease. Therefore, all effects were estimated controlling for between group differences in these variables.

Quality of life

Overall, patients with pituitary adenomas reported lower QoL as evaluated with the VAS and TTO index.
## Table 1

### Description of patients and controls.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Subgroups</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 247)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td></td>
<td></td>
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<tr>
<td>Cushing's disease</td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>Nonfunctioning pituitary adenomas</td>
<td></td>
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<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 757)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male/female, n (%))</td>
<td>91/156 (37/63)</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean ± S.D.)</td>
<td>53.25 ± 12.16</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m², mean ± S.D.)</td>
<td>27.11 ± 6.08</td>
<td></td>
</tr>
<tr>
<td>Duration of disease (years, mean ± S.D.)</td>
<td>12.27 ± 8.66</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgery (%) 66.7</td>
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</tr>
<tr>
<td>Comorbidities</td>
<td>Cardiovascular disease (%)</td>
<td>20</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>44b</td>
<td>44b</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>44b</td>
<td>44b</td>
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<tr>
<td>Pulmonary disease (%)</td>
<td>15b</td>
<td>15b</td>
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</table>

### Table 2

### Description of comorbidities.

<table>
<thead>
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<th>Effects</th>
</tr>
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<tbody>
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<td><strong>Controls</strong></td>
<td></td>
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<tr>
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<td>15b</td>
<td>15b</td>
</tr>
</tbody>
</table>

*Frequencies, proportions, means, and S.D. are weighted summaries, accounting for differences in the number of matched controls per patient.*

**Note:**
- Differences from respective control group with *P < 0.05.
- According to laboratory values.

**Source:** European Journal of Endocrinology.
Table 3 Differences in depression, quality of life, and sleep between patients and controls.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Patients (n = 247)</th>
<th>Controls (n = 757)</th>
<th>Effects</th>
<th>Test statistic, P</th>
<th>Test statistic, P</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No depression (%)</td>
<td>58.70</td>
<td>74.07</td>
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<td>$\chi^2 = 16.261$</td>
<td>$P &lt; 0.0001$</td>
</tr>
<tr>
<td>Subclinical (%)</td>
<td>25.51</td>
<td>13.70</td>
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<td>$&lt; 0.0001$</td>
<td>$P = 0.0104$</td>
</tr>
<tr>
<td>Clinical (%)</td>
<td>15.79</td>
<td>12.22</td>
<td></td>
<td></td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS $^\text{a}$</td>
<td>0.73 ± 0.19$^\text{a}$</td>
<td>0.79 ± 0.18$^\text{b}$</td>
<td>$F = 26.109$</td>
<td>$F = 3.777$</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>TTO $^\text{b}$</td>
<td>0.83 ± 0.22$^\text{a}$</td>
<td>0.88 ± 0.18$^\text{b}$</td>
<td>$&lt; 0.0001$</td>
<td>$P = 0.0012$</td>
<td>$P = 0.0001$</td>
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<tr>
<td>Sleep parameters</td>
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</tr>
<tr>
<td>Sleep latency (min, mean)$^\text{a}$</td>
<td>24.41</td>
<td>20.09</td>
<td>$F = 2.311$</td>
<td>$F = 1.721$</td>
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<tr>
<td>Sleep duration (decimal hours, mean ± s.d.)</td>
<td>6.71 ± 1.25</td>
<td>6.61 ± 1.19$^\text{c}$</td>
<td>$P = 0.1288$</td>
<td>$P = 0.1613$</td>
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<tr>
<td>Sleep efficiency (%, mean ± s.d.)</td>
<td>84.29 ± 14.11</td>
<td>83.74 ± 14.20$^\text{d}$</td>
<td>$F = 1.486$</td>
<td>$F = 0.379$</td>
<td></td>
</tr>
<tr>
<td>PSQI-score $^\text{e}$ (mean ± s.d.)</td>
<td>6.75 ± 4.17$^\text{a}$</td>
<td>5.66 ± 4.31$^\text{a}$</td>
<td>$P = 0.9156$</td>
<td>$P = 0.6131$</td>
<td></td>
</tr>
</tbody>
</table>

VAS, quantified using the VAS method; TTO, quantified using the time trade-off (TTO) method; PSQI, Pittsburgh Sleep Quality Index. $^\text{a}$lower values equal better quality of life, $^\text{b}$higher values equal better sleep quality. $^\text{c}Differs from respective control group with $P < 0.05$. $^\text{d}$Frequencies, proportions, means, and s.d. are weighted summaries, accounting for differences in the number of matched controls per patient. $^\text{e}$Was log transformed for all analyses.

We also observed a significant group × subgroup interaction effect, with a larger reduction in QoL – measured by the VAS – in patients with Cushing’s disease compared with all other groups (Table 3). Gender, age, or the biochemical disease control of the patients had no influence on patient–control differences in QoL.

### Sleep quality

For this study, we compared subjective sleep duration, sleep onset latency, sleep efficiency, and the PSQI global score between patients and controls (Table 3). There was no difference between patient and controls in sleep duration, sleep onset latency, or subjective sleep efficiency and neither age, gender, nor treatment status had an influence on patient–control differences in these variables.

In contrast, the PSQI score was significantly increased in patients with pituitary adenomas. This patient–control difference did not depend on the specific patient group, age, gender, or the biochemical disease control.

### Depression

Overall, patients with pituitary adenoma had average BDI scores of 9.87 ± 9.16. There was a significant difference between patient groups ($F = 3.589, P = 0.014$). BDI scores were significantly higher for patients with Cushing’s disease (13.21 ± 9.94) than for all other patient groups (acromegaly 8.76 ± 8.40, prolactinomas 9.32 ± 9.80, NFPAs 8.30 ± 7.34). This difference, however, was no longer statistically significant when controlling for differences in age and gender between patient groups ($F = 2.128, P = 0.097$).

For both patients and controls, depression scores had been classified as no depression, subclinical depression, and depression (see ‘Materials and methods’ section). Proportional odds mixed models showed that the incidence of both subclinical and clinical depression was higher in patients with pituitary adenomas (Table 3). This difference was not dependent on the specific patient group, the age, or the biochemical disease control of the patient. Gender, however, had a significant influence on the patient–control differences in depression ($\chi^2 = 16.746, P < 0.001$). Although in both patient and control groups, more females showed depressive symptoms, the difference between patient and controls was even higher for females (Fig. 1).

### The role of depression for QoL and sleep quality

As patients differed from controls in QoL, sleep quality, and depression, we sought to determine to what extent...
depression and sleep quality accounted for the differences in QoL. To that end, we compared predictions for patient–control differences derived from a model with only the group effect (model 1), with predictions when controlling for differences in sleep (PSQI global score, model 2), depression (model 3), or both (model 4). The results are illustrated in Fig. 2. The significant difference between patients and controls in the QoL (VAS scores: $F=26.109$, $P<0.001$) remained significant when controlling for sleep quality ($F=13.829$, $P<0.001$), depression ($F=13.448$, $P<0.001$), or both ($F=10.284$, $P=0.001$). The magnitude of the expected difference between patient and controls, however, was considerably decreased by 34% (sleep quality), 39% (depression), and 48% (sleep quality and depression).

This effect was even more pronounced when considering the TTO. While in the basic model, there were significant differences between patients and controls ($F=10.616$, $P=0.001$), there was only a trend when controlling for sleep quality ($F=3.577$, $P=0.059$) or depression ($F=2.970$, $P=0.085$). When controlling for both sleep and depression, a difference between patients and controls was no longer observable ($F=1.690$, $P=0.194$). Controlling for differences in sleep quality reduced the observed patient–control differences by 46%, control for depression reduced the difference by 53%, and accounting for both variables decreased the effect by 65% (Fig. 2, right panel).

**Discussion**

This large case–control study including 247 patients and 757 controls aimed at investigating the role of depression and sleep on QoL in patients with acromegaly, Cushing’s disease, prolactinomas, and NFPAs. This study provides the first and most comprehensive results comparing patients with different pituitary adenomas.

The main findings of our study are as follows: patients with pituitary adenomas reported decreased QoL as well as decreased subjective sleep quality compared with healthy controls; there was a larger reduction in QoL in patients with Cushing’s disease compared with all other patient groups; the incidence of both subclinical and clinical depression was higher in patients with pituitary adenomas; and a substantial proportion of the reduced QoL (48% respectively 65%) in patients with pituitary adenomas is due to the incidence of depression and reduced sleep quality.

Patients with pituitary adenomas reported decreased QoL and sleep compared with their matched controls. These findings are in accordance with previous results about QoL in patients with pituitary adenomas (1) as well as with results about the subjective sleep quality of individual patient groups, e.g. of acromegaly (10), NFPAs (14), or craniopharyngeomas (44).
In addition, patients with Cushing’s disease showed a larger reduction in QoL compared with all other patient groups. Moreover, we could not find any significant differences in QoL between patients and controls in subgroups based on different sex and age, as well as in the subgroups of biochemically cured patients and those who were not cured. The result of decreased QoL despite long-term biochemical cure is in accordance with previous findings (1, 2, 6, 7, 45, 46).

Furthermore, the results of our study suggest that patients with pituitary adenomas differ from control subjects in depression: while only 25% of primary care–control subjects, nearly 41% of patients showed subclinical respectively clinically relevant depression. Patients with Cushing’s disease showed also the highest rates of depression compared with other patient groups. So far, psychiatric aspects of Cushing’s disease have been the best described in the recent literature (17, 18, 19, 20). However, the higher incidence of depression for patients with Cushing’s disease in our study is partly explained by the fact that there are predominantly females in this group. This may explain why a previous study (1) had found no disease-specific differences in the subscales of the Hospital Anxiety and Depression Scale comparing patients with acromegaly, Cushing’s disease, prolactinomas, and NFPA's. Gender had a significant influence on the patient–control differences in depression. Although in both patient and control groups, more females showed depressive symptoms, the difference between patient and controls was even higher for females. Taken into account that higher rates of affective disorders are more frequent in females in general, these results are not surprising. Nevertheless, it suggests that women may be especially vulnerable to the consequences of their disease.

Finally, we could show that a substantial proportion of the reduced QoL is due to the incidence of depression and reduced sleep quality. Up to now, there has been only evidence for Cushing’s disease that depression leads to a reduced QoL (47). Because both depression and sleep quality can be treated, this offers complementary approaches for the improvement of patients’ conditions in contrast to previous recommendations (23). Whether this will improve QoL in these patients has to be investigated in further studies.

**Limitations**

This study has several limitations which we have to take into account when interpreting the results. The control group consisted of primary care patients and not healthy controls (for further information (48)). Therefore we cannot exclude that control subjects showed decreased QoL and impaired sleep quality or increased rates of depression for other reasons, too. Hence, we might have underestimated the

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**Figure 2**

Effect of controlling for differences in sleep quality and depression on patient (P)-control (C) differences in quality of life measures. Left panel, VAS; right panel, TTO. AS and TTO are methods to calculate QoL assessed with the EQ-5D whereas the higher the score the better the QoL. All models are controlled for differences in BMI, hypertension, cardiovascular disease, and diabetes between patients and controls. Interval for approximate standard errors: VAS = (0.143–0.175) and TTO = (0.162–0.188). NS, no significant differences between patients and controls; *patients differ from control group with \( P < 0.05 \).
differences between patients and controls in depression, QoL, and sleep, which might be even larger compared with healthy subjects. Furthermore, we did not control for differences in drug use/intake, especially in antidepressants and sleep-inducing drugs, respectively, and differences due to receiving other treatments for depression, e.g. psychotherapy. On the other hand, if there had been differences, misclassification of patients would have resulted in lower rates of depression and respectively better sleep quality. Moreover, we have to consider that pituitary patients and primary care controls had different backgrounds: controls were recruited from a nationwide primary care population, while pituitary patients were recruited from a referral area for endocrine patients. However, as our main outcomes are depression/sleep/QoL and both groups are patients with somatic diseases, there should not be a preferential selection of patients with psychiatric symptoms in one or the other cohort. Only patients with acromegaly were evaluated for obstructive sleep apnea by asking them for previous screenings. Since that information could not be classified as objective and reliable data, we did not include them in the analyses. Furthermore, we cannot exclude that reduced QoL, impaired sleep quality, and depression in patients are partly due to disease-related problems. But since duration of disease averages about 12 years, we did not measure only the acute reaction after the diagnosis. However, the reasons for impaired sleep quality, depression, and as consequence for a reduced QoL should play a certain role in designing disease-specific interventions for these patients. More importantly, the use of two different measures of depression (BDI for patients and DSQ for controls) is not ideal. However, as we felt that a pituitary-independent comparison group would be helpful to study the burden of symptoms in relationship with other primary care patients, we decided to design the study as presented with the compromise that we could only use the categorized variable ‘depression’. As we did not compare raw values of different instruments, but frequencies of depression categorized as ‘no depression’, ‘subclinical depression’, and ‘clinical depression’, we believe that comparability should be high. Finally, this study is a cross-sectional case-control study but not a longitudinal survey. No causal conclusions can be drawn from the data, but we contribute to the important question which factors due to a reduced QoL in patients with pituitary adenomas.

**Conclusion**

In conclusion, our findings of reduced QoL and sleep as well as increased rates of depression in patients with pituitary adenomas may have implications for the long-term management of these patients. The knowledge that a substantial proportion of the reduced QoL is due to the incidence of depression and reduced sleep quality emphasizes the need for a diagnostic work-up including these entities with the ultimate goal to improve QoL in these patients.

**Declaration of interest**

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