Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-025-02670-w

ORIGINAL ARTICLE

# Hypertension and kidney dysfunction despite long-term remission of Cushing's syndrome

**Katrin Ritzel[1] · Vanessa Fedtke[1] · Cornelia Then[1] · Elisabeth Nowak[1] · Frederick Vogel[1] · Leah Braun[1] · Stephanie Zopp[1] · Petra Zimmermann[2] · Annette Peters[3,4,5,6] · Margit Heier[3,11] · Birgit Linkohr[3,4] · Michael Roden[6,7,8] · Martin Bidlingmaier[1] · Felix Beuschlein[1,9,10] · Martin Reincke[1] · German Rubinstein[1]**

Received: 12 June 2025 / Accepted: 22 July 2025


## Abstract

**Purpose** Hypertension is the most frequent co-morbidity in active Cushing's syndrome (CS) and regarded as a major cardiovascular risk factor. It is unknown whether blood pressure and related parameters, such as kidney function, recover in the long-term following remission of CS.

**METHODS** Blood pressure and related co-morbidities were analyzed in a cohort of 81 patients with CS (Cushing's disease: 52, ectopic CS: 8, adrenal CS: 21) from a single tertiary care center. Patients were longitudinally evaluated at baseline, at 7.1 years (6.3–7.4) and at 14 years (13.5–14.4) after biochemical remission. Data were compared to a control group matched for BMI, age and sex ($n=243$) from the "Cooperative Health Research in the Region of Augsburg" study (KORA) in a 1:3 fashion.

**RESULTS** Patients with CS showed a higher median blood pressure and lower median glomerular filtration rate (GFR) compared to the matched controls, at baseline, 7 and 14 years after biochemical remission. Although the prevalence of hypertension and chronic kidney disease increased over time in the KORA cohort, patients treated for CS had a significantly higher prevalence of both comorbidities. Notably, the number of patients on antihypertensive medication declined in the Cushing's cohort, resulting in significantly higher rates of uncontrolled hypertension at follow-up.

**CONCLUSION** The prevalence of hypertension and impaired kidney function remained elevated in patients with CS years after biochemical remission, potentially contributing to an unfavorable long-term clinical outcome. This highlights the critical need for increased monitoring and treatment of co-morbidities in patients with CS following surgical remission.

**Keywords** Cushing's syndrome · Co-morbidities · Remission · Hypertension · Blood pressure · Kidney function

✉ Katrin Ritzel
Katrin.Ritzel@med.uni-muenchen.de

1 Department of Medicine IV, Ludwig-Maximilians-Universität München, LMU University Hospital, LMU Munich, Ziemssenstrasse 5, 80336 Munich, Germany

2 Department of General, Visceral and Transplantation Surgery, LMU University Hospital, LMU Munich, Munich, Germany

3 Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Munich, Germany

4 German Centre for Cardiovascular Research (DZHK e.V.), Munich Heart Alliance, München, Germany

5 Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, Ludwig-Maximilians-Universität München, Munich, Germany

6 German Center for Diabetes Research (DZD), München-Neuherberg, Germany

7 Department of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University and University Hospital Düsseldorf, Düsseldorf, Germany

8 Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

9 Department of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Zürich (USZ), University of Zurich (UZH), Zurich, Switzerland

10 The LOOP Zurich - Medical Research Center, Zurich, Switzerland

11 KORA Study Centre, University Hospital Augsburg, Augsburg, Germany

Published online: 29 July 2025

**Abbreviations**

| | |
|---|---|
| ACS | Adrenal Cushing's syndrome |
| ACTH | Adrenocorticotropic hormone |
| ADX | Adrenalectomy |
| BADX | bilateral adrenalectomy |
| BP | Blood pressure |
| BMAD | Bilateral macronodular adrenocortical disease |
| BMI | Body mass index |
| CD | Cushing's disease |
| CS | Cushing's syndrome |
| CUSH | Cushing's cohort |
| DST | Dexamethasone suppression test |
| DDD | Defined daily doses |
| ECS | Ectopic Cushing's syndrome |
| GFR | Glomerular filtration rate |
| IQR | Interquartile range |
| KORA | KORA cohort |
| LNSC | Late-night salivary cortisol |
| PDD | Prescribed daily doses |
| RFM | Relative fat mass |
| TSS | Transsphenoidal surgery |
| UAE | Urinary albumin excretion |
| UFC | Urinary free cortisol |

## Introduction

Endogenous Cushing's syndrome (CS) is a group of endocrine diseases with high morbidity and mortality [1, 2]. A recent meta-analysis including 20 cohorts representing over 3500 patients demonstrated a threefold higher risk of death across all subtypes. Most patients in the analysis died from cardiovascular disease [3].

In overt CS, hypertension is one of the most frequent comorbidities affecting 80–95% of all patients [1, 2, 4]. In the general population, hypertension is a major cardio-vascular risk factor and the leading cause for mortality worldwide [5]. In patients with CS, previous studies indicated a high rate of hypertension even years after biochemical cure of hypercortisolism [4, 6, 7]. On the other hand, blood pressure gradually increases with age, causing hypertension to progressively occur over time, independent of underlying hormonal diseases. To our knowledge, it has not been investigated in a large cohort, whether blood pressure remains elevated long after biochemical remission in patients with CS compared to an aging control group.

Hypertension and chronic kidney disease display a mutual relationship: Similar to blood pressure, the glomerular filtration rate (GFR) as a surrogate of kidney function, changes with age. Although some data have indicated impaired kidney function in overt CS [8, 9], there is a lack of data on the long-term development of kidney function after remission of hypercortisolism.

To address these open questions, we compared the long-term development of blood pressure and associated parameters including kidney function in a large, single center cohort of patients after remission of CS with a control group with a similar ethnic and environmental background in a population-based longitudinal study.

## Methods

### Study design

We conducted a retrospective cohort study, using data from the German Cushing's registry CUSTODES. Patients were diagnosed and treated for CS at the Endocrine Department of the University Hospital LMU Munich, Germany and gave written consent to being included in the German Cushing's registry (Ethical approval: Ethics Committee LMU University Munich, No. 152−10). Diagnosis and differential diagnosis of CS as well as biochemical control and remission following surgery were established according to the Endocrine Society Clinical Practice Guidelines [10] and a recent Pituitary Society consensus [11], based on the presence of relevant clinical features and biochemical confirmation as described in detail in a previous study [12]. Patients were selected from the registry after successful treatment of CS when follow-up of at least 7 years after remission of hypercortisolism was available. Patients with mild autonomous cortisol secretion, CS caused by aggressive malignant tumors and patients with recurrence of hypercortisolism were excluded. Out of 107 patients, who met the selection criteria, 26 patients with a BMI over 35 kg/m² were excluded due to a lack of matching controls.

Data from patients with CS were compared to controls from the KORA (Cooperative Health Research in the Region of Augsburg) study. Patients were matched 1:3 based on BMI and age at baseline and on sex.

KORA is a prospective adult cohort study in the Region of Augsburg, Germany for population-based health research with randomly selected participants from population registries. Participants were recruited (KORA S4, $N=4{,}261$ participants aged 25 to 74 years) in 1999–2001 and followed up after 7 years in 2006–2008 (F4, $N=3{,}080$) and after 14 years in 2013–2014 (FF4, $N=2{,}279$), (Ethical approval: Ethics Committee of the Bavarian Chamber of Physicians (S4: EC No. 99186, F4 and FF4: EC No. 06068). Recruitment and eligibility criteria for the KORA studies have been described elsewhere [13, 14].

**Table 1** Clinical characteristics at baseline of the cohort of patients with cushing's syndrome (CUSH) and controls (KORA) in percentage or as median and IQR

| Characteristics at baseline | CUSH | KORA | *P* value |
|---|---|---|---|
| N | 81 | 243 | n/a |
| Age at baseline (years) | 44 (36–53) | 44 (34–53) | 0.9583 |
| Sex (female) | 75.3% | 76.1% | 0.8807 |
| BMI (kg/m$^2$) | 26,2 (23,1–29,4) | 25,8 (22,9–29,2) | 0.6955 |
| HbA1c (%) | 5.8 (5.5–6.7) | 5.5 (5.3–5.7) | <0.0001 |
| Triglycerides (mg/dl) | 117.5 (74.6-181.5) | 109.5 (83.0-150.0) | 0.7842 |
| Cholesterol (mg/dl) | 203.0 (174.0-244.0) | 218.2 (196.2-247.5) | 0.6299 |
| LDL cholesterol (mg/dl) | 123.0 (97.8-148.5) | 126.1 (104.2-156.3) | 0.0810 |
| HDL cholesterol (mg/dl) | 59.0 (48.5–63.0) | 59.8 (49.2–74.3) | 0.3628 |
| Smoking | 17.3% | 19.5% | 0.7424 |
| Hypertension | 84.9% | 23.9% | <0.0001 |
| Diabetes mellitus | 32.6% | 1.3% | <0.0001 |
| Hypercholesterolemia | 16.6% | 18.6% | 0.7589 |
| Antihypertensive drugs | 60.8% | 10.7% | <0.0001 |
| Antidiabetic drugs | 19.1% | 1.0% | <0.0001 |
| Lipid lowering drugs | 17.7% | 9.1% | 0.0779 |

Abbreviations: IQR: interquartile range, BMI: body mass index

**Table 2** Parameter of cortisol metabolism and hormone substitution at baseline, 7 years and 14 years after biochemical remission in patients with cushing's syndrome (CS, CUSH) in percentage or as median and IQR

| CUSH | At baseline | After 7 years | After 14 years |
|---|---|---|---|
| N (CD/ACS/ECS) | 81 (52/21/8) | 81 (52/21/8) | 42 (27/10/5) |
| Basal cortisol in ug/dl | 23.02 (16.4–30.9) | 6.0 (1.5–10.3) | 5.3 (3.6–10.0) |
| 24-hour UFC index | 4.1 (2.2–6.1) | 0.5 (0.2-1.0) | 0.9 (0.3–1.3) |
| LNCS in ng/ml | 7.6 (4.4–15.0) | 1.1 (0.8–1.9) | 1.35 (0.9–2.7) |
| 1 mg DST, Cortisol in ug/dl | 15.0 (8.4–24.0) | 1.0 (0.7-2.0) | 1.25 (0.7–1.9) |
| Cortisol lowering drugs | 3.2% | n/a | n/a |
| Adrenal insufficiency | n/a | 44.4% | 47.6% |
| Hormone substitution | 9.8% | 23.2% | 17.3% |
| Thyroid axis | 1.2% | 3.7% | 6.2% |
| Somatotropic axis | 8.6% | 22.2% | 13.6% |
| Gonadotropic axis | | | |

Abbreviations: IQR: interquartile range, LNSC: late-night salivary cortisol, DST: Dexamethasone suppression test, UFC index: 24 h-urinary free cortisol value divided by assay specific upper limit of normal. In patients with adrenal insufficiency ($n=36$ at year 7 and $n=20$ at year 14), only basal cortisol levels were assessed

## Description of the cohorts

In total, 81 patients with CS were analyzed (Cushing's cohort, CUSH) and compared to 243 matched controls from the KORA study (KORA cohort, KORA). Characteristics of the two cohorts at baseline are reported in Table 1.

The cohort of patients with CS comprised 52 patients with Cushing's disease (CD), 8 patients with ectopic CS (ECS) and 21 patients with adrenal CS (ACS, 17 with unilateral adenoma, 4 macronodular bilateral hyperplasia). Detailed information about treatment modalities and duration of hypercortisolism are provided as supplemental material (Supplemental Text 1). All patients achieved long-term remission of Cushing's syndrome. A subset of patients developed permanent primary adrenal insufficiency after bilateral adrenalectomy (19% at 7 years, 26% at 14 years) or secondary adrenal insufficiency after successful treatment of hypercortisolism (26% at 7 years, 21% at 14 years). All Patients with adrenal insufficiency were treated with hydrocortisone (20 mg; 15–25 mg corresponding 0.26 mg/kg; 0.19–0.31 mg/kg at 7 years, and 20 mg; 20–25 mg corresponding 0.29 mg/kg; 0.16–0.33 mg/kg at 14 years) and those with primary adrenal insufficiency also received fludrocortisone (0.1 mg; 0.05–0.1 mg at both 7 and 14 years), following standard healthcare guidelines. Parameters of cortisol metabolism and hormone substitution at baseline, 7 years and 14 years after biochemical remission are reported in Table 2.

## Data collection

Data from patients with CS were evaluated before treatment of CS (baseline) and after median of 7.1 years (6.3–7.4) and 14 (13.5–14.4) years after biochemical remission, respectively, and then compared to matched controls from the KORA cohort. The data included weight (kg), height (cm), body mass index (BMI; kg/m2), waist circumference (m), blood pressure (average between the second/third office blood pressure measurement, mmHg), glycated hemoglobin (HbA1c, %), fasting triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol (mg/dl for all lipid parameters), creatinine (mg/dl), estimated glomerular filtration rate (GFR, MDRD formula in ml/min/1.73m2), current co-morbidities, and medication status. The ratio between the prescribed daily doses (PDD) and defined daily doses (DDD) was calculated as an estimate of therapeutic intensity (PDD/DDD). Relative fat mass (RFM) was calculated as RFM = 64 - (20 × height/waist circumference in meters) + (12 × sex (0 for male, 1 for female)) [15].

Blood pressure was measured on the day of consultation after sitting in an upright position, using an automatic digital sphygmomanometer and recorded as systolic over diastolic. Patients were categorized as hypertensive based on outpatient systolic blood pressure (SBP) measurements ≥140

mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, or if they reported taking antihypertensive medication [5]. Uncontrolled hypertension was defined as SBP≥140 and/or a DBP≥90 mmHg. Patients were instructed to take their medication on the morning of their visit. Patients were categorized as diabetic according to the use of antihyperglycemic drugs or a HbA1c ≥6.5%. Hypercholesterolemia was diagnosed in patients taking lipid lowering drugs or having an LDL-cholesterol ≥130 mg/dl (3.4 mmol/l).

In patients with CS, serum cortisol was measured by chemiluminescence immuno-assay (Liaison, DiaSorin Cat# 313261, RRID: AB_2893155), 24-h urinary free cortisol (UFC) measured by the same chemiluminescence immunoassay after extraction with dichloromethane, late-night salivary cortisol measured by chemiluminescence immunoassay (Immunodiagnostic Systems Cat# IS-4900, RRID: AB_3095089), ACTH measured by chemiluminescence immuno-assay (Liaison, DiaSorin Cat# 313221, RRID: AB_3095090).

### Statistical analysis

A propensity score matching method was applied to balance the groups based on relevant covariates (age, sex, and BMI) to establish comparability between patients and controls. Propensity scores were estimated using a logistic regression model, where group membership (patients vs. controls) served as the dependent variable. Matching was performed using the nearest-neighbor method at a ratio of 1:3. A caliper of 0.1 standard deviations of the propensity score was specified as a tolerance threshold to ensure high-quality matching and to minimize systematic differences between groups. Observations without suitable matches within the defined caliper were excluded from the analysis.

Data for descriptive statistics are presented as median and interquartile range (IQR). Normal distribution was assessed by Shapiro Wilk normality test. Statistical differences of the variables were assessed using student's t test and mixed-effects analysis for parametric, or Mann-Whitney test and Kruskal-Wallis test for nonparametric variables. Fisher's Exact test was used for categorical variables. Spearman correlation was used to estimate association between variables. Odds ratios (ORs) and 95% confidence interval were calculated from a logistic regression model. All statistical tests were two-sided; a P value of $<0.05$ was considered to indicate statistically significant differences. Statistical analysis was performed using standard statistical software (Prism 10.3.0, GraphPad Software, Boston, MA, USA).

## Results

### Longitudinal data of the Cushing's cohort

Patients with CS experienced a significant reduction in elevated systolic and diastolic blood pressure after 7 and 14 years (both $p<0.0001$). Initially, hypertension affected 84.9% of patients, but this ratio significantly ($p<0.0001$) decreased to 52.8% after 7 years, and to 48.7% after 14 years. The proportion of patients using antihypertensive medication also dropped from 60.8% at baseline to 40.6% after 7 years and to 29.0% after 14 years ($p=0.0065$). Correspondingly, the median number of antihypertensive drug classes reduced from 3 (range: 1–4) at baseline to 2 (range: 1–3) at 7 years and to 1 (range: 1–2) after 14 years ($p=0.0114$). The median PDD/DDD was 1.04 at baseline (0.94–2.00), went down to at 0.88 (0.59–1.27) after 7 years, and was 0.46 (0.31–1.06) after 14 years ($p=0.0458$). Glomerular filtration rate (GFR) declined in patients after remission of CS from 86.09 ml/min/1.73m$^2$ (73.26-100.05) at baseline to 81.45 ml/min/1.73m$^2$ (68.31-91.00) after 7, and 74.91 ml/min/1.73m$^2$ (66.49–85.51) after 14 years ($p=0.0006$). Urinary albumin excretion (UAE) was higher before treatment of hypercortisolism (7.5 mg/g Crea, 0.58–32.78) and decreased to 3.5 mg/g Crea (0.5–6.23) after 7 and 3.8 mg/g Crea (0.5–13.6) after 14 years ($p=0.0020$).

In a subgroup analysis, patients with adrenal insufficiency receiving standard replacement therapy were compared to those with normal adrenal function. No statistically significant differences were observed between the two groups in terms of blood pressure, BMI, or the prevalence of arterial hypertension (see Supplemental Fig. 1). Additional subgroup analyses comparing the different etiologies of Cushing's syndrome showed no significant differences in blood pressure, GFR, or BMI development after 7 and 14 years among the groups (see Supplemental Fig. 2).

### Analyses of blood pressure and related co-morbidities of the Cushing's cohort vs. the KORA cohort

In both groups, BMI was similar at baseline. While BMI declined in patients with CS, it increased in the KORA cohort over time (Fig. 1A). Patients with CS had higher baseline blood pressure and heart rate than matched controls from the KORA cohort. Despite reduction in blood pressure following treatment for CS, levels remained significantly elevated compared to the control group (KORA cohort) at 7 and 14 years (Fig. 1B and C; Supplemental Tables 2–4).

Correspondingly, although the prevalence of hypertension declined after CS treatment, it remained significantly higher than in the KORA group, which experienced an

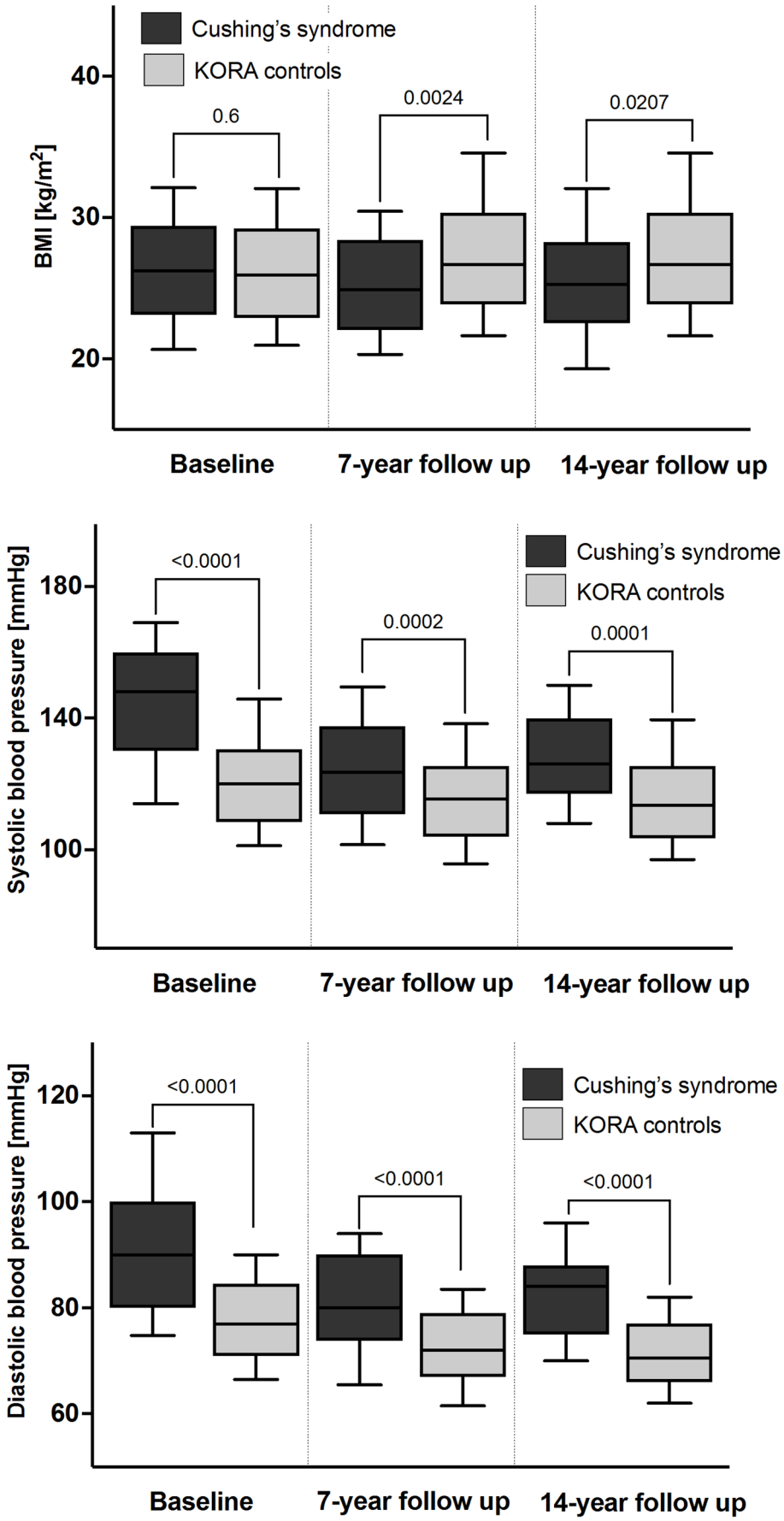



**Fig. 1** BMI (**A**), systolic (**B**) and diastolic (**C**) blood pressure in the Cushing's cohort (CUSH) and controls from the KORA study (KORA) at baseline, 7 years and after 14 years after biochemical remission of CS. Box plots are displaying the 90/10 percentile at the whiskers, the 75/25 percentiles at the boxes, and the median in the center line

increase in hypertension cases over time (Fig. 2A; Supplemental Tables 2–4).

In the CS cohort, the percentage of patients on antihypertensive medication declined after treatment of hypercortisolism, whereas it increased with age in the KORA cohort. At the start, CS patients used antihypertensive medications at a rate five times higher than KORA patients. This gap decreased to twice as high after seven years, and by 14 years, the difference was no longer statistically significant (Fig. 2B; Supplemental Tables 2–4). Despite similar antihypertensive treatment at 14 years, uncontrolled hypertension remained significantly more prevalent among CS patients across all time points, with nearly one-third still affected at follow-up compared to consistently lower levels in the KORA cohort.

Kidney function measured by GFR was significantly lower in patients with CS at baseline and decreased in both cohorts with time. It remained lower in patients with CS at 7 years and at 14 years (Fig. 3A; Supplemental Tables 2–4). The prevalence of chronic kidney disease was significantly higher in the Cushing's cohort at baseline and after 7 years (Fig. 3B; Supplemental Tables 2–4).

### Parameters associated with hypertension and renal impairment in the Cushing's cohort

To identify parameters associated with hypertension in the Cushing's cohort we used Spearman's rank-order correlation. There was no significant relationship between systolic blood pressure at 7 and 14 years of follow-up with morning serum cortisol concentrations, cortisol after dexamethasone suppression, and late-night salivary cortisol at any time point and duration of untreated cortisol excess. Likewise, BMI, RFM, GFR, heart rate, glucose, HbA1c, insulin, total cholesterol, HDL-cholesterol, triglycerides, AST and UAE were not associated with systolic blood pressure (data not shown).

A moderate association was found between systolic blood pressure at 7 years and both age at baseline ($r=0.303$, $p=0.0087$) and baseline LDL-cholesterol levels ($r=0.387$, $p=0.0422$). GGT levels at 7 years were positively associated with systolic blood pressure at 14 years ($r=0.459$, $p=0.0366$). GGT at 14 years also showed a significant positive correlation with systolic ($r=0.375$, $p=0.0045$) and diastolic blood pressure ($r=0.433$, $p=0.019$) at the same time point. Additionally, AST levels after 14 years were correlated with both systolic ($r=0.475$, $p=0.0091$) and diastolic blood pressure ($r=0.575$, $p=0.0011$), suggesting a co-occurrence of elevated blood pressure and metabolic dysfunction-associated steatotic liver disease in the post-remission phase of CS.

Logistic regression showed significant association between hypertension at 7 years and age at baseline (OR 1.123; 1.085–1.201; $p<0.0001$), RFM at 7 years (OR 1.175; 1.068–1.321; $p=0.0025$), and BMI at 7 years (OR 1.138; 1.017–1.293; $p=0.038$). Simple logistic regression also indicated a significant association between the prevalence of hypertension at 7 years and the presence of dyslipidemia (OR = 2.853; 95% CI: 1.050–8.090; $p=0.0430$).

Notably, reducing blood pressure medication after remission of CS was associated with an almost five-fold increased risk of uncontrolled hypertension after seven years (OR 4.571; 1.454–15.42; $p=0.0108$) and an approximately seven-fold increase in risk at 14 years (OR 6.667; 1.091. −47.64; $p=0.0435$).

There was no significant relationship between GFR at 7 and 14 years of follow-up with laboratory markers of cortisol metabolism, blood pressure, glucose, insulin, total cholesterol, HDL-cholesterol, triglycerides, GGT, ALT, AST or urinary albumin excretion (UAE) in Spearman's rank-order correlation.

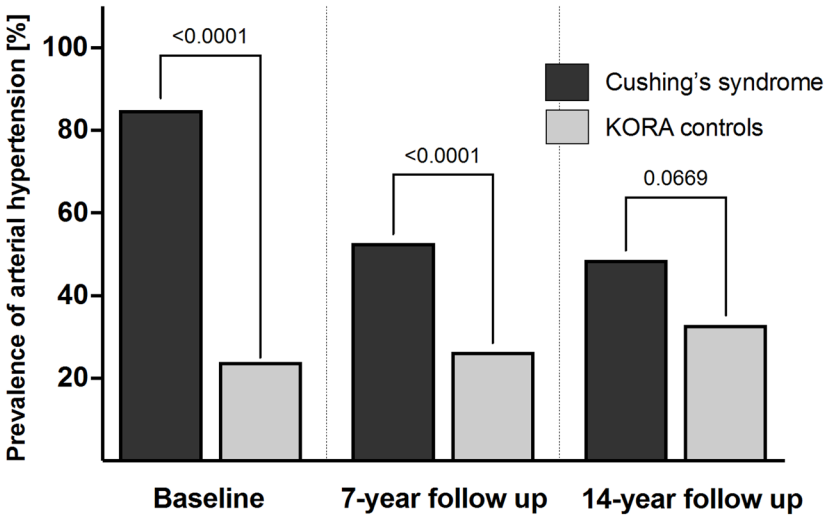
A moderate negative correlation was observed between LDL-cholesterol levels at both 7 and 14 years and GFR at 14 years ($r=-0.424$, $p=0.0494$ and $r=-0.373$, $p=0.0356$, respectively). Additionally, HbA1c at 7 years showed an inverse correlation with GFR at the same time point ($r=-0.415$, $p=0.0007$).

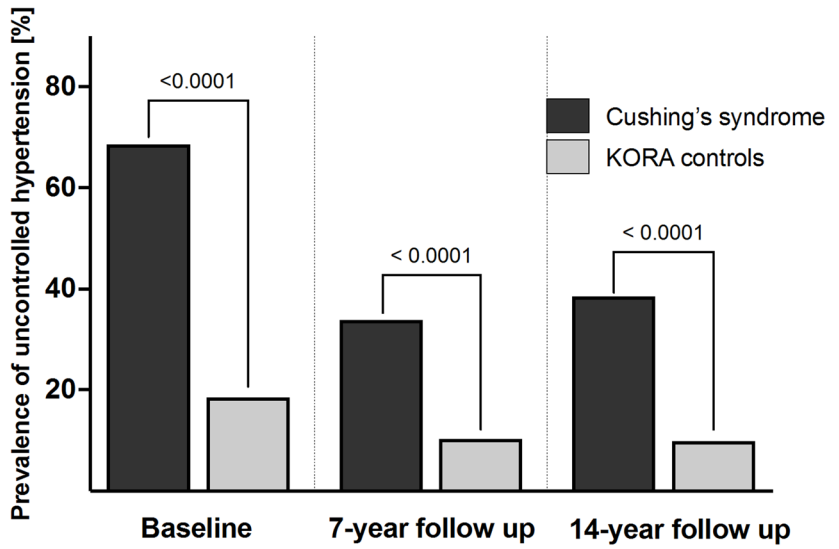
In simple logistic regression, the probability for chronic kidney disease after 7 years was associated with RFM after 7 years (OR 1.117; 1.010–1.263; $p<0.0476$). There was also a strong association between the prevalence of chronic kidney disease and the prevalence of diabetes mellitus after 7 years (OR 10.95; 2.221–64.21; $p=0.0042$).

## Discussion

This is the first study to investigate blood pressure and kidney function in a cohort of patients with CS for up to 14 years post-treatment in comparison to an BMI-, age- and sex-matched control group with a similar ethnic and environmental background. We identified two main findings:

Firstly, blood pressure remained notably higher in patients treated for CS than in an appropriate population-based control group, with a greater prevalence of both hypertension and uncontrolled hypertension after 7 and 14 years. Although hypertension rates increased in the control group, blood pressure remained stable through increased antihypertensive treatments. In contrast, fewer patients with CS continued blood pressure medication post-surgery, resulting in higher rates of uncontrolled blood pressure over time. Secondly, kidney function, assessed by GFR, remained



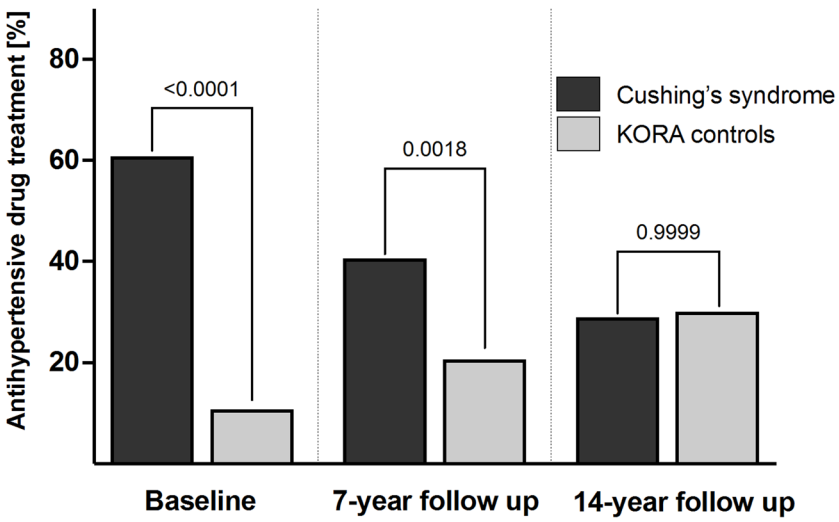




**Fig. 2** Prevalence of arterial hypertension (**A**), prevalence of uncontrolled hypertension (**B**) and rate of antihypertensive drug treatment (**C**) in the Cushing's cohort (CUSH) and controls from the KORA study (KORA) at baseline, 7 years and after 14 years after biochemical remission of CS

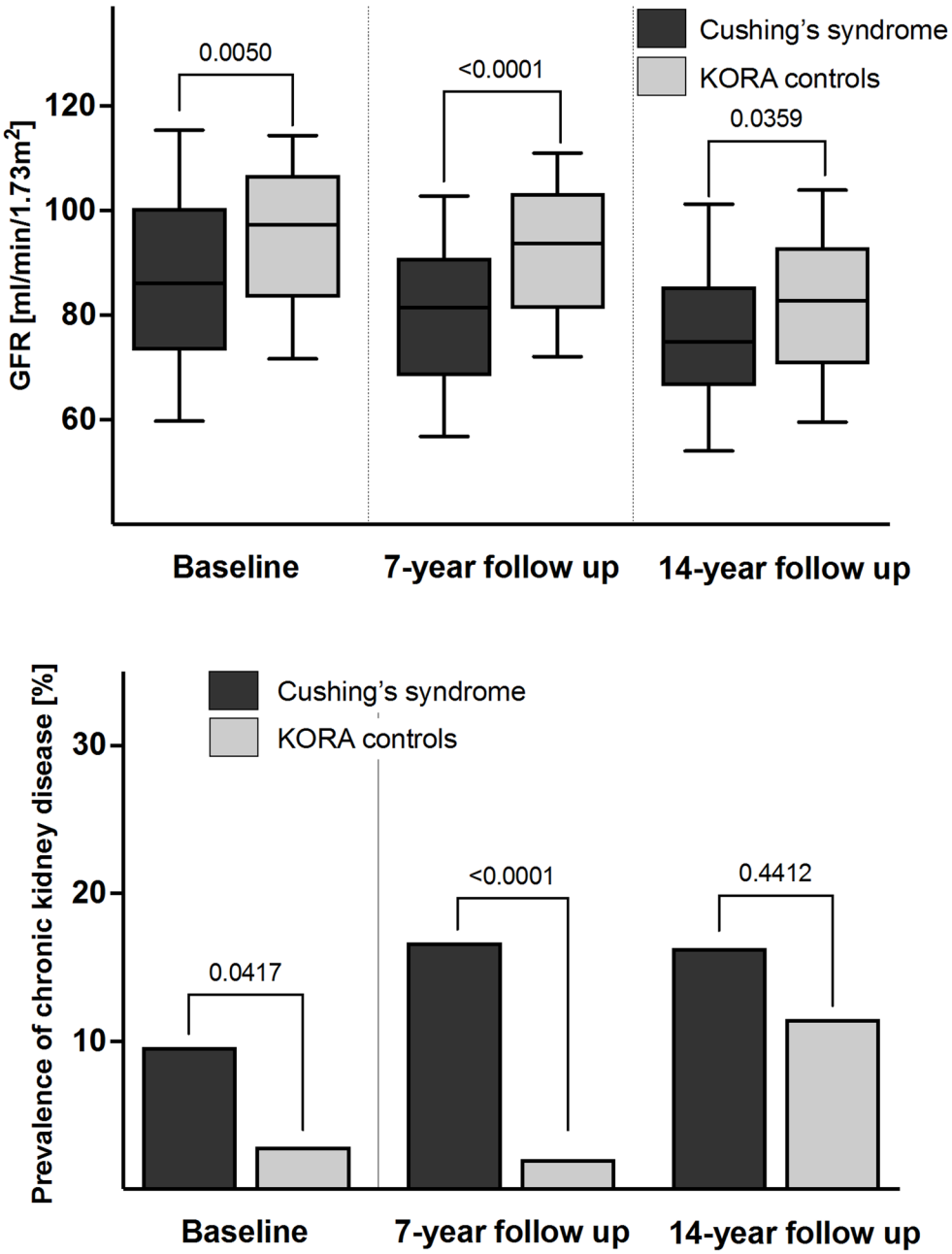



**Fig. 3** Glomerular filtration rate (GFR, A) and prevalence of possible chronic kidney disease (defined as GFR < 60 ml/min/1.73m$^2$) (B) in the Cushing's cohort (CUSH) and controls from the KORA study (KORA) at baseline, 7 years and after 14 years after biochemical remission of CS. Box plots are displaying the 90/10 percentile at the whiskers, the 75/25 percentiles at the boxes, and the median in the center line Data availability The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research data cannot be shared KORA data and bio samples can be requested by scientists for research projects by means of a project agreement via the KORA. PASST use and access hub (https://helmholtz-muenchen.managed-otrs.com/external). The KORA Board is responsible for review and approval of the requests. The rights of study participants, adherence to Good Scientific Practice and the goals of the KORA study guide the decision. The European General Data Protection Regulation (GDPR) applies to all applicants

lower in the CS group, with CKD impacting approximately one in six patients after 7 and 14 years.

The persistence of co-morbidities and cardiovascular risk factors following remission of CS has serious health implications and has been the focus of recent research [1, 2]. Hypertension after CS remission has been examined in five prior studies [4, 6, 7, 16, 17] with a median follow-up time ranging from one to elven years. Prevalence of hypertension at last follow-up varied from 22% [17] to over 60% [4]. Only one study from Terzolo et al. compared the rate of hypertension to a control group who had surgery for non-functioning adenomas/NFA. They found that only 22% of patients with CS in remission remained hypertensive, matching the NFA control group, and concluded that successful surgery may reduce cardiovascular risks and mortality [17]. Conversely, our analysis showed a significantly higher rate of post-surgery hypertension compared to the control group. This discrepancy may be due to Terzolo's study involving younger patients (median age of 36), an older control group (median age of 49) and a shorter follow-up period (4.7 years) than ours. Overall, our findings align with previous studies, indicating that the vascular impact of hypercortisolism cannot be fully reversed when cortisol levels are normalized [4, 7, 18].

This raises the question of why hypertension persists despite biochemical remission. Although our study did not aim to answer this directly, some findings may provide directions for future research.

In our regression analysis, arterial hypertension was associated to measures of body composition (BMI and RFM) in patients with CS. RFM, which uses waist circumference for a more precise estimate of body fat [15] showed that each one-unit increase correlated with an 18% higher hypertension risk. Given the strong link between visceral obesity and hypertension [19], weight reduction and reversal of Cushing-associated sarcopenia may help reduce persistent high blood pressure in patients after cure of hypercortisolism. Arterial stiffness and atherosclerotic vascular damage could be additional reasons why some patients continue to have high blood pressure after remission of CS [20, 21]. The associations between blood pressure, baseline age, and LDL-cholesterol suggest that dyslipidemia- and age-related vascular changes may also play a role in persistent hypertension after CS remission aligning with previous reports [4, 18]. It would be valuable for future research to examine measures of arterial damage such as pulse wave velocity and plaque load in patients after recovery from Cushing's syndrome in comparison to an adequate control group.

Furthermore, positive correlations between GGT, AST, and blood pressure suggest a link between hepatic steatosis and vascular risk. Together, these findings expose a broader metabolic phenotype after remission of CS and highlight the need for continued multidisciplinary management.

Approximately half of the patients in our cohort suffered from primary or secondary adrenal insufficiency after successful treatment of hypercortisolism with the need of adrenal hormone replacement therapy. Previous studies have indicated that excessive hydrocortisone replacement may lead to elevated blood pressure and changes in BMI in patients with adrenal insufficiency [22, 23]. However, in our subgroup analysis, we observed no significant differences in blood pressure or BMI between patients receiving adrenal replacement therapy and those who were not. This may be explained by the cautious dosing of hydrocortisone, reducing the risk of over-replacement.

A key finding of our study is the reduction in the number of patients receiving blood pressure medication following surgical remission (Fig. 2B), which has resulted in an increase in uncontrolled hypertension cases. The probability for uncontrolled hypertension was about five- to seven-times higher in patients with a reduction of antihypertensive medication after 7 and 14 years. De-escalation of antihypertensive drugs is likely triggered by the initial drop in blood pressure observed after biochemical control of hypercortisolism, potentially leading to the misconception that co-morbidities like hypertension fully resolve with normalized cortisol levels. Our data uncover an increase in cases of uncontrolled hypertension, exposing a gap in adequate treatment for patients with CS. Reduced frequency of healthcare visits post-treatment may further contribute to this undertreatment. Given insights from our study and other recent research highlighting cardiovascular morbidity and higher mortality rates in CS after biochemical remission [2, 24], patients with CS should be considered as high-risk cardiovascular patients. Continuous monitoring and comprehensive management of cardiovascular co-morbidities and risk factors should be prioritized in the long-term care of patients with CS post-surgical cure.

Blood pressure and kidney function are closely interconnected, yet there are limited data on kidney health in patients with CS, and CKD is not typically seen as a co-morbidity of CS. Our findings indicate that patients with CS have lower GFR compared to the control group, both initially and after 7 and 14 years. The further decline in GFR over time resulted in a significantly higher prevalence of CKD (defined as GFR $< 60$ ml/min/1.73 m²) 7 years post-surgical remission. We also observed inverse correlations of GFR with LDL-cholesterol and HbA1c which might point to early atherogenic and glycemic effects on renal function in patients with CS, consistent with patterns seen in initial diabetic nephropathy [25]. To date, only two studies have specifically addressed renal function in CS. In 2005, Haentjens et al. found that patients with active or recently treated Cushing's disease had reduced GFR levels compared to healthy controls [8]. A second study looked at GFR after adrenalectomy in patients with unilateral adrenal Cushing's syndrome and found a similar drop in kidney function to what is seen in primary hyperaldosteronism [9]. The underlying mechanisms for renal dysfunction in CS remain largely unclear. While previous studies identified the duration of uncontrolled hypercortisolism and pre-treatment systolic blood pressure as predictors of kidney dysfunction, our analysis did not find significant associations with the duration of hypercortisolism, blood pressure, or urinary albumin excretion, a marker of glomerular damage.

The ongoing decline in kidney function can worsen the already elevated cardiovascular risk in people with CS. This link between hypercortisolism and kidney health highlights the need for more research into how CS affects kidney function.

## Conclusion

This cohort study addresses a critical gap in understanding the long-term outcomes following surgical remission of Cushing's syndrome. We found that hypertension and impaired kidney function remain highly prevalent in a

significant number of patients even long after surgical treatment in comparison to a population-based control group. Nonetheless, in a prominent fraction of patients, blood pressure medication was decreased after surgical remission of CS, leading to a notable rise in uncontrolled hypertension cases over time.

Our findings provide further evidence that cardiovascular effects of hypercortisolism are not entirely reversible with the normalization of cortisol levels and enhance our understanding of the deteriorative long-term cardiovascular consequences of chronic hypercortisolism. Thus, monitoring and effectively managing persistent co-morbidities should be prioritized in both clinical practice and research efforts.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40618-025-02670-w.

**Acknowledgements** This work is part of the German Cushing's Registry CUSTODES and has been supported by a grant from the Else Kröner-Fresenius Stiftung to MRe. (2012_A103 and 2015_A228). FB and MRe are supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project number: 314061271-TRR 205). FV is supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, project number: 413635475 (FV) and the Munich Clinician Scientist Program (MCSP) of the LMU München. LB and EN are supported by the Clinician Scientist Program RISE (Rare Important Syndromes in Endocrinology), supported by the Else-Kröner-Fresenius Stiftung and Eva Luise und Horst Köhler Stiftung. We thank the COST Action CA20122 Harmonisation for supportive networking. The KORA study was initiated and financed by the Helmholtz Zentrum München– German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. Additionally, for MC Health financed staff or senior staff linked to MC Health: Furthermore, KORA research was supported within the Munich Center of Health Sciences (MC Health), Ludwig-Maximilians-Universität, as part of LMUinnovativ. Additionally, for publications with data from KORA-Age: The KORA-Age project was financed by the German Federal Ministry of Education and Research (BMBF FKZ 01ET0713 and 01ET1003A) as part of the 'Health in old age' program. Cardiovascular Research in KORA 2018–2024 is funded by the Bavarian State Ministry of Health and Care through the research project DigiMed Bayern (www.digimed-bayern.de). German Centre for Cardiovascular Research (DZHK): Supported by the DZHK (German Centre for Cardiovascular Research) and by the BMBF (German Ministry of Education and Research).

**Author contributions** All authors were involved in the conception and design of the study. Katrin Ritzel, Vanessa Fedtke and German Rubinstein carried out the material preparation, data collection, and analysis. The initial draft of the manuscript was written by Katrin Ritzel. All authors commented on previous versions of the manuscript. All authors reviewed and approved the final manuscript.

## Declarations

**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

## References

1. Braun LT, Vogel F, Reincke M (2022) Long-term morbidity and mortality in patients with cushing's syndrome. J Neuroendocrinol 34(8):e13113
2. Puglisi S, Perini AME, Botto C, Oliva F, Terzolo M (2024) Long-Term consequences of Cushing syndrome: A systematic literature review. J Clin Endocrinol Metab 109(3):e901–e919
3. Limumpornpetch P, Morgan AW, Tiganescu A, Baxter PD, Nyawira Nyaga V, Pujades-Rodriguez M, Stewart PM (2022) The effect of endogenous Cushing syndrome on All-cause and Cause-specific mortality. J Clin Endocrinol Metab 107(8):2377–2388
4. Schernthaner-Reiter MH, Siess C, Gessl A, Scheuba C, Wolfsberger S, Riss P, Knosp E, Luger A, Vila G (2019) Factors predicting long-term comorbidities in patients with cushing's syndrome in remission. Endocrine 64(1):157–168
5. Brouwers S, Sudano I, Kokubo Y, Sulaica EM (2021) Arterial hypertension. Lancet 398(10296):249–261
6. Gomez RM, Albiger NM, Diaz AG, Moncet D, Pitoia FA, Bruno OD (2007) Effect of hypercortisolism control on high blood pressure in cushing's syndrome. Med (B Aires) 67(5):439–444
7. Jha S, Sinaii N, McGlotten RN, Nieman LK (2020) Remission of hypertension after surgical cure of cushing's syndrome. Clin Endocrinol (Oxf) 92(2):124–130
8. Haentjens P, De Meirleir L, Abs R, Verhelst J, Poppe K, Velkeniers B (2005) Glomerular filtration rate in patients with cushing's disease: a matched case-control study. Eur J Endocrinol 153(6):819–829
9. Nakamura Y, Yokoyama M, Yoshida S, Tanaka H, Kijima T, Ishioka J, Matsuoka Y, Saito K, Minami I, Yoshimoto T et al (2020) Postoperative renal impairment and longitudinal change in renal function after adrenalectomy in patients with cushing's syndrome. Int J Urol 27(5):395–400
10. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM (2008) The diagnosis of cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 93(5):1526–1540
11. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD et al (2021) Consensus on diagnosis and management of cushing's disease: a guideline update. Lancet Diabetes Endocrinol 9(12):847–875
12. Ritzel K, Fazel J, August L, Fedtke V, Nowak E, Vogel F, Braun L, Zopp S, Then C, Kunzel H et al (2024) Biochemical Control in Cushing's syndrome: Outcomes of the treatment in a large single center cohort. J Clin Endocrinol Metab
13. Rathmann W, Strassburger K, Heier M, Holle R, Thorand B, Giani G, Meisinger C (2009) Incidence of type 2 diabetes in the elderly German population and the effect of clinical and lifestyle risk factors: KORA S4/F4 cohort study. Diabet Med 26(12):1212–1219
14. Atasoy S, Johar H, Peters A, Ladwig KH (2019) Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/KORA study. Eur Heart J 40(9):732–738
15. Woolcott OO, Bergman RN (2018) Relative fat mass (RFM) as a new estimator of whole-body fat percentage horizontal line A cross-sectional study in American adult individuals. Sci Rep 8(1):10980
16. Iacobone M, Mantero F, Basso SM, Lumachi F, Favia G (2005) Results and long-term follow-up after unilateral adrenalectomy for ACTH-independent hypercortisolism in a series of Fifty patients. J Endocrinol Invest 28(4):327–332

17. Terzolo M, Allasino B, Pia A, Peraga G, Daffara F, Laino F, Ardito A, Termine A, Paccotti P, Berchialla P et al (2014) Surgical remission of cushing's syndrome reduces cardiovascular risk. Eur J Endocrinol 171(1):127–136
18. Barahona MJ, Resmini E, Vilades D, Pons-Llado G, Leta R, Puig T, Webb SM (2013) Coronary artery disease detected by multislice computed tomography in patients after long-term cure of cushing's syndrome. J Clin Endocrinol Metab 98(3):1093–1099
19. Bogaert YE, Linas S (2009) The role of obesity in the pathogenesis of hypertension. Nat Clin Pract Nephrol 5(2):101–111
20. Faggiano A, Pivonello R, Spiezia S, De Martino MC, Filippella M, Di Somma C, Lombardi G, Colao A (2003) Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 88(6):2527–2533
21. Ikeda A, Steptoe A, Shipley M, Abell J, Kumari M, Tanigawa T, Iso H, Wilkinson IB, McEniery CM, Singh-Manoux A et al (2021) Diurnal pattern of salivary cortisol and progression of aortic stiffness: longitudinal study. Psychoneuroendocrinology 133:105372
22. Werumeus Buning J, van Faassen M, Brummelman P, Dullaart RP, van den Berg G, van der Klauw MM, Kerstens MN, Stegeman CA, Muller Kobold AC, Kema IP et al (2016) Effects of hydrocortisone on the regulation of blood pressure: results from a randomized controlled trial. J Clin Endocrinol Metab 101(10):3691–3699
23. Staufenbiel SM, Andela CD, Manenschijn L, Pereira AM, van Rossum EF, Biermasz NR (2015) Increased hair cortisol concentrations and BMI in patients with Pituitary-Adrenal disease on hydrocortisone replacement. J Clin Endocrinol Metab 100(6):2456–2462
24. Bengtsson D, Ragnarsson O, Berinder K, Dahlqvist P, Eden Engstrom B, Ekman B, Hoybye C, Jaras J, Valdemarsson S, Burman P et al (2022) Increased mortality persists after treatment of cushing's disease: A matched nationwide cohort study. J Endocr Soc 6(6):bvac045
25. Arnold F, Kappes J, Rottmann FA, Westermann L, Welte T (2024) HbA1c-dependent projection of long-term renal outcomes. J Intern Med 295(2):206–215