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Exploring the cardiovascular impact of functioning pituitary tumours

Fábio Pereira Dinis

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TÍTULO DISSERTAÇÃO

Exploring the cardiovascular impact of fumet'amyg p. lu. bay human

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Eu, Fábio Pereira Dinis, abaixo assinado, nº mecanográfico 201905665, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 15/03/2025

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Fábio Pereira Dinis

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Trabalho de acordo com as normas da revista: "Endocrinology Insights"

Research Article

Exploring the cardiovascular impact of functioning pituitary tumours

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Keywords: Pituitary neoplasms, cardiovascular disease, acromegaly, Cushing disease, prolactinoma

Abstract

Objective: This study aimed to assess the cardiovascular burden in patients with functioning pituitary tumours.

Methods: Retrospective analysis of 257 patients with functioning pituitary tumours (137 acromegaly, 94 Cushing's disease, 26 prolactinoma) who underwent surgery. Cardiovascular events, tumour characteristics, age at diagnosis, and tumour activity status were evaluated. We also evaluated the relationship between the achievement of remission after surgery and the use of hormonal control therapy with cardiovascular events.

Results: Cerebrovascular and cardiovascular disease occurred in 10.9%, 8.5%, and 3.8% of patients with acromegaly, Cushing's disease and prolactinoma, respectively. Significant differences were found in the prevalence of diabetes/pre-diabetes (p=0.008) and hypertension (p=0.045) among tumour types – higher in patients with acromegaly and Cushing's disease and lower in patients with prolactinomas. Dyslipidaemia was highly prevalent across all groups. In acromegaly, patients diagnosed after 50 years had higher rates of diabetes, cerebrovascular and cardiovascular disease and hypertension. Cushing's disease patients diagnosed after 50 years had significantly higher rates of hypertension and dyslipidaemia. Disease duration and tumour control status showed no correlation with cardiovascular outcomes. Patients with Cushing's disease who did not achieve remission postoperatively had more cardiovascular and cerebrovascular events (p=0.002).

Conclusion: Patients with functioning pituitary tumours demonstrate a high cardiovascular burden even after tumour control. The impact varies among tumour types. In patients with Cushing's disease, remission in the immediate postoperative period is associated with fewer cardiovascular and cerebrovascular events. These findings highlight the need for long-term cardiovascular monitoring and management in these patients, regardless of tumour control status.

Introduction

Pituitary tumours are neoplasms originating from the cells of the adenohypophysis, the anterior portion of the pituitary gland. They can be classified into two categories, functioning and non-functioning, based on the presence or absence of secretory function and according to the type of hormones secreted [1]. Among the different types, lactotroph tumours (53 % of pituitary tumours), somatotroph tumours (12%) and corticotroph tumours (4%) stand out [2].

Although histologically benign, functional tumours are associated with high morbidity, for several reasons: their anatomical location and consequent proximity to critical neurovascular structures due to the hypersecretion or hormonal deficiencies, from the compressive effects of the tumour or by complications of surgery or radiotherapy [3]. Despite the often-florid clinical picture, the diagnosis delay is still frequent in patients with functioning pituitary tumours, i.e., 5.5 years for acromegaly and ~3 years for patients with hypercortisolism, and this is associated with increased morbidity and mortality [4, 5].

In addition to diagnostic delay, several other factors may impact the cardiovascular health of patients with pituitary tumours, such as hormonal hypersecretion, hormonal failures, and radiotherapy [6-9]. Patients with acromegaly, in addition to a high prevalence of cardiovascular risk factors, have a specific type of cardiomyopathy, characterised by biventricular hypertrophy, left ventricular systolic and diastolic dysfunction, valvular insufficiency, aortic root dilatation, and arrhythmias [10]. In patients with Cushing's disease, the prevalence of metabolic syndrome is prominent and carotid intima-media thickness is increased. A common consequence of these two types of abnormalities is the incidence of cerebrovascular events, which has already been reported in previous studies [11]. Prolactinomas are associated with obesity, dysregulation of glucose and lipid metabolism as well as endothelial dysfunction [12, 13, 8].

Current management strategies primarily focus on achieving tumour and biochemical control through surgery and/or medical therapy, but it is unclear whether achieving hormonal remission consistently translates into a reduction in cardiovascular risk. Moreover, variability in treatment response suggests that additional clinical markers may be needed to identify patients at higher risk of persistent cardiovascular complications, even after disease control.

In this study, we aim to evaluate the cardiovascular burden associated with functioning pituitary tumours by assessing clinical outcomes and treatment strategies in a retrospective cohort of 257 patients who underwent surgery.

Methods

This study employed a retrospective design to assess the cardiovascular burden in patients with functioning pituitary tumours. We conducted a comprehensive review of medical records from Coimbra Local Health Unit for patients diagnosed with functioning pituitary tumours between 14/07/1986 and 09/01/2024. Informed consent was obtained from individuals using protocols approved by local research ethics committees (OBS.SF.165/2021). All patient data were anonymised to ensure confidentiality. Inclusion criteria encompassed adult patients (≥18 years) with a confirmed diagnosis of functioning pituitary tumour who have undergone surgery, including prolactinomas, acromegaly, and Cushing's disease. Exclusion criteria included patients <18 years, with non-functioning pituitary tumours, who have not undergone surgery or had incomplete medical records.

Data collection was done by extracting the relevant information from electronic medical records, including demographic characteristics, tumour type and size, endocrine function tests, cardiovascular risk factors, and cardiovascular outcomes. Specifically, we collected data on age, sex, lipid profile, duration of the disease since diagnosis, number of surgeries performed, achievement of remission in the immediate post-operative period, completion of medical therapy in the postoperative period, number of surgeries performed, completion of radiotherapy, tumour control status, insufficiencies at diagnosis and in the immediate post-operative period and whether they were under medical therapy at the time of the last medical record available. Cardiovascular outcomes of interest included hypertension, dyslipidaemia, diabetes mellitus, coronary artery disease, heart failure, cardiac arrhythmia, valvular disease and cerebrovascular events. Besides assessing each individual, we also analysed them by groups: i) (patients with cardiovascular-cerebrovascular pathology (CVD -CV), which includes the cardiovascular events analysed (arrhythmia, coronary heart disease, heart failure, valvular heart disease and strokes and transient ischaemic strokes), ii) patients with just cardiovascular pathology (CVD) (which includes only arrhythmia, coronary heart disease, heart failure, valvular heart disease), iii) patients with just as cerebrovascular pathology, (CV) which includes only strokes and transient ischaemic strokes).

Endocrine function was assessed through hormone measurements specific to each tumour type. For prolactinomas, serum prolactin levels were recorded. In cases of GH-secreting tumours, we documented GH and insulin-like growth factor 1 (IGF-1) levels. For ACTH-secreting tumours, we noted serum cortisol and ACTH levels, as well as results from dexamethasone suppression tests and urinary-free cortisol where available. Cardiovascular assessment included echocardiographic data, electrocardiogram findings, and results from any additional cardiovascular imaging studies (e.g., coronary angiography, cardiac MRI) were recorded where available. Treatment modalities, including

medical therapy, surgery, and radiotherapy, were documented along with their timing relative to cardiovascular outcomes.

Statistical analysis was performed using SPSS Statistics version 30. Descriptive statistics were used to summarise patient characteristics and cardiovascular outcomes. Continuous variables were expressed as means ± standard deviations or medians with interquartile ranges, depending on the distribution. Categorical variables were presented as frequencies and percentages. Comparisons between tumour types were made using appropriate statistical tests (e.g., chi-square test for categorical variables, t-test or Mann–Whitney for continuous variables). All tests were one-sided, and a p-value <0.05 was considered statistically significant.

Results

Basal characteristics of the sample

A total of 257 functional pituitary tumours that underwent surgery (137 cases of acromegaly, 94 cases of Cushing's disease and 26 cases of prolactinoma) were analysed, including 181 women (average age of 59.7 ± 14.6 years) and 76 men (average age of 56.9 ± 14.3 years). Of the female study population, 90 had acromegaly (65.7% of all acromegaly patients analysed), 79 had Cushing's disease (84% of all Cushing's disease patients analysed), and 12 had prolactinoma (46.2% of all prolactinoma patients analysed). Of the male study population, 47 had acromegaly (34.3% of all acromegaly patients analysed), 15 had Cushing's disease (16% of all Cushing's disease patients analysed), and 14 had prolactinoma (53.8% of all prolactinoma patients analysed). We also characterised for age at diagnosis for each tumour subtype (45.3 ± 13.7 for acromegalia; 41.9 ± 14.0 for Cushing disease and 41.4 ± 14.2 for prolactinoma), duration of disease (normality was assessed by the Shapiro-Wilk and Kolmogorov-Smirnov test, which showed differences between groups, so the non-parametric test, Kruskal-Wallis, was used for analysis by tumour subtype), which revealed a median duration of 12 years (range 1-48 years) for acromegalic patients, 10 years for patients with Cushing's disease (range 2-38 years) and 17 years for prolactinoma (range 6-35 years). We also characterised the presence or absence of medical therapy for hormonal control, the number of transsphenoidal surgeries, whether they had undergone radiotherapy, disease control status and for pituitary insufficiencies present at the time of diagnosis and in the last clinical record, which are depicted in Table 1.

Cardiovascular burden in patients with functioning pituitary tumours

Regarding the cardiovascular events analysed, there were no statistically significant differences between the different types of tumours and CVD (p= 0.600), nor for CV pathology (p=0.556), as shown in Table 2. For CVD-CV pathology, the results were 10.9%, 8.5% and 3.8% respectively. In the assessment of diabetes/pre-diabetes (38.7% of acromegalic patients, 30.9% of patients with Cushing's disease and 7.7% of patients with prolactinoma), there were statistically significant differences (p=0.008), as for hypertension (50.7% of acromegalic patients, 48.9% of patients with Cushing's disease and 24% of patients with prolactinoma), (p=0.045). Although the differences were not statistically significant, the prevalence of dyslipidaemia was high in all tumour types (58.1% in patients with acromegaly, 54.3% in patients with Cushing's disease and 65.4% in patients with prolactinoma).

For each subtype of tumour, we assessed the relationship between cardiovascular events and years of disease duration, divided into subgroups (<5 years duration, 5-10 years, 10-15 years, 15-20 years, >20

years , as well as for age above and below the cut-off point (<5/>5 years, <10/>10 years; <15/>15; <20/>20 years), tumour activity status (in remission, controlled with medical therapy/radiotherapy, not controlled despite medical therapy/radiotherapy), age at diagnosis before or after 50 years, post-operative remission and use of post-operative medical therapy. This data can be found in the supplementary tables 1-25.

Cardiovascular burden in patients with acromegaly

When cardiovascular events were analysed and compared with age at diagnosis before and after the age of 50 for patients with acromegaly, there was a higher prevalence of diabetes (53.7% in patients diagnosed after the age of 50, 25.7% in patients under the age of 50, p=0.003), cerebrovascular and cardiovascular pathology (17.1% in patients diagnosed after the age of 50 and 5.4% in patients under the age of 50, p=0.042) and arterial hypertension (36,1% in patients diagnosed under the age of 50, 65,9% in patients after the age of 50, p=0.002). For the CVD pathology analysed, there were 3 events before the age of 50 (4.1%) and 5 after the age of 50 (12.2%), p-value = 0.100).

When comparing cardiovascular events with tumour activity status (in remission, controlled with medical therapy/radiotherapy, uncontrolled disease medical therapy/radiotherapy), significant differences were only observed for dyslipidaemia (79.5% in patients with controlled disease, 49.1% in patients in remission and 43.5% of patients with uncontrolled disease, p=0.004). For the cerebrovascular and cardiovascular pathology analysed, there were 6 events in patients in remission (12.9%), 6 events in patients with disease controlled with medical therapy/radiotherapy (14%) and no events in patients with uncontrolled disease (p=0.164).

Regarding the analysis of disease duration, for all the stratified groups, no statistical differences were found. For cardiovascular and cerebrovascular pathology, there was 1 event in the group with <5 years of disease, 3 events in the group with 5-10 years of disease, 2 events in the group with 10-15 years of disease, 2 events in the group with 15-20 years of disease and 5 events in the group with more than 20 years of disease (p= 0.936).

Analysing for age above and below the cut-off point, statistically significant differences were found for the duration of illness for more than 15 years for ischaemic heart disease, 3 events after 15 years of disease and 0 events with less than 15 years of disease (p=0.048).

When assessing the achievement of biochemical remission after surgery and the use of medical therapy in the immediate post-op period, there were no significant differences for any of the outcomes analysed

Cardiovascular burden in patients with Cushing's disease

In patients with Cushing's disease, whose diagnosis was made after 50 years of age, differences with statistical significance were disclosed for arterial hypertension (92.3% in patients diagnosed after 50 years of age, 34.3% in patients diagnosed under the age of 50, $p<0.001$) and dyslipidaemia (84.6% in patients diagnosed after 50 years of age, 51.4% in patients diagnosed under the age of 50).

When comparing cardiovascular events with tumour activity status (in remission, controlled with medical therapy/radiotherapy), there were no significant differences between groups for any of the outcomes assessed.

Regarding the analysis of disease duration, for all the stratified groups, no differences were found.

Analysing for age above and below the cut-off point, statistically significant differences were found for ischaemic heart disease, with patients with the disease for less than 5 years having more events than those with the disease for more than 5 years (20.0% and 1.7%, respectively, 1 event in the group with less than 5 years of disease, 1 event in the group with more than 5 years of disease) ($p= 0.023$).

When we assessed the achievement of biochemical remission after surgery, shown in Table 5, there were statistically significant differences for cardiovascular events, specifically for ischaemic heart disease (3 events in the group that did not achieve remission and 0 events in the group that achieved remission, p-value = 0.019) and for cerebrovascular pathology (3 events in the group that did not achieve remission, 0 events in the group that achieved remission, p-value = 0.019).

The use of medical therapy in the post-operative period did not translate into significant differences between all events, as shown in Table 6.

Cardiovascular burden in patients with prolactinoma

When cardiovascular events were analysed and compared with age at diagnosis before and after the age of 50, for prolactinoma no differences were found between the groups. For the cardiovascular and

cerebrovascular pathology analysed, there were 1 event before the age of 50 and 0 events after the age of 50 (5.9% % of patients under the age of 50, p-value =0.725).

When comparing cardiovascular events with tumour activity status (in remission, controlled with medical therapy/radiotherapy, there were no significant differences between groups for any of the outcomes assessed. For the cerebrovascular and cardiovascular pathology analysed, there were 1 event in patients in remission (11.1 % of all patients with disease in remission), 0 events in patients with disease controlled with medical therapy/radiotherapy and 0 events in patients with uncontrolled disease (p=0.374).

Regarding the analysis of disease duration, no significant differences were found. For cardiovascular and cerebrovascular pathology, there were 0 events in the group with 5-10 years of disease, 0 events in the group with 10-15 years of disease, 0 events in the group with 15-20 years of disease, 1 event in the group with >20 years of disease (p=0.668).

Analysing for age above and below the cut-off point, statistically significant differences were found for dyslipidaemia, with patients with more than 10 years of illness presenting more frequently dyslipidaemia than patients with less than 10 years of disease (15 and 2, respectively, p value=0.037).

When assessing the achievement of biochemical remission after surgery and the use of medical therapy in the immediate post-op period, there were no significant differences for any of the outcomes analysed.

Discussion

Our study is in line with the results of previous studies that have revealed a high prevalence of cardiovascular events in patients with pituitary tumours. Diabetes/pre-diabetes and hypertension were more prevalent in patients with Cushing's disease and acromegaly, while dyslipidaemia was more prevalent in patients with prolactinoma, although these events were ubiquitously present in all three types of tumours. These differences possibly reflect distinct pathophysiological mechanisms with different metabolic and cardiovascular impacts, in particular the action of GH in Acromegalia, which promotes increased resistance to the action of insulin and a decrease in its secretion, as well as stimulation of fluid retention due to its anti-natriuretic effect, promoting hypertension [14] and the action of cortisol, which promotes central obesity, dyslipidaemia and hypertension [15]. Prolactin exerts its effects by acting on the orexigenic-anorexigenic systems, leading to changes in appetite that increase the risk of obesity and to LDL and low HDL levels in these patients [9].

The ubiquitous presence of cardiovascular pathology and risk in these patients is not only justified by their age. In patients with acromegaly, there were statistically significant differences, with a predominance of diabetes, arterial hypertension and cerebrovascular and cardiovascular pathology events after 50 years. In the analysis of disease duration, statistically significant differences were only found for ischaemic heart disease in patients with more than 15 years of disease. However, in the analysis of disease duration for the different subgroups, it is possible to see a clear progression in the increase of events as the years of disease activity increase. This suggests that the cardiovascular events and their consequences in these patients possibly result from a long period of time under the influence of high GH levels in the tissues [16], which is favoured by the fact that many of these tumours can manifest with unspecific symptoms and signs, often leading to a delayed time without a definitive diagnosis, with all the negative impact that this period entails in cardiovascular terms for these patients and is not clear to what extent and what damage may be reversible with disease control [10], reinforcing the importance of early diagnosis in reducing the risk of complications.

In patients with Cushing’s disease diagnosed after the age of 50, there were only statistically significant differences for arterial hypertension and dyslipidaemia, and these results could show much of the role of aging in terms of cardiovascular risk. Although there were no significant differences, the majority of cerebrovascular-cardiovascular events occurred in patients under 50 years old. Previous studies have described the maintenance of atherosclerosis and various clinical and biochemical abnormalities typical of the active phase of Cushing's disease, such as obesity, hypertension, impaired glucose tolerance, and hyperlipidaemia 5 years after remission [17]. This alerts us to the possibility of an earlier manifestation of the cardiovascular consequences of the active phase of the disease in these patients.

In patients with prolactinoma, there are no differences in the various outcomes in patients diagnosed before age 50 or later. It was also associated with fewer cardiovascular and cerebrovascular events when compared with acromegaly and Cushing's disease but, with a predominance of metabolic alterations such as systemic arterial hypertension dyslipidaemia, atherosclerosis, insulin resistance, hyperglycaemia, and obesity [8].

In patients with Cushing's disease who did not achieve remission in the immediate post-operative period, a cardiovascular or cerebrovascular event occurred in 15.6% of these patients (while there were no events in the group that went into remission in the immediate post-operative period), which indicates that achieving biochemical remission in the immediate postoperative period was associated with a lower risk of cardiovascular and cerebrovascular events in these patients. Although less studied than in acromegaly, the incidence of cerebrovascular and cardiovascular events in patients with Cushing's disease is documented in the literature, despite the fact that in many studies these have been excluded by the presence of any other form of Cushing syndrome and not only patients with ACTH-dependent pituitary tumours [11]. This may suggest that the risk of cardiovascular events in patients with Cushing's disease is particularly increased in the early years of the disease and that more incisive hormonal control from the post-operative period onwards may have an impact on mitigating these events. More studies will be needed to confirm this association and to ascertain the benefit of administering medical hormone suppression therapy in these patients, regardless of their functional status after surgery.

Another important point that may draw attention to the complex relationship between the control of cardiovascular events in these patients was the fact that the status of disease activity/control did not reveal any difference between groups, reflecting that biochemical control of hormone hypersecretion alone is not enough to decrease the risk of cardiovascular events in these patients. For patients with acromegaly, the only result with statistical significance revealed contradictory data, showing a predominance of dyslipidaemia in patients in remission or controlled by medical therapy, which may reveal poorer cardiovascular control in these patients or an overestimation of the effect of tumour remission/control in cardiovascular morbidity, reinforcing the need for continued vigilance and control of risk factors.

Pituitary tumours are rare pathologies, but they can have consequences, particularly in cardiovascular and metabolic terms, if they go unnoticed. However, as well as being more prompt in identifying these tumours at an early stage, there is a need for greater vigilance and control of cardiovascular risk factors in these patients[18].

The study demonstrates several strengths, including a large sample size of 257 patients with functioning pituitary tumours, providing a substantial dataset for analysis. It offers a comprehensive examination of multiple tumour types (acromegaly, Cushing's disease, and prolactinoma) and various cardiovascular outcomes, allowing for a broad understanding of the cardiovascular burden. The long-term follow-up, including patients diagnosed between 1986 and 2024, enables the assessment of long-term cardiovascular outcomes. The researchers collected extensive data on patient demographics, tumour characteristics, treatment modalities, and cardiovascular risk factors, providing detailed patient characteristics. However, the study also has limitations. Its retrospective design may be subject to selection bias and incomplete data, e.g., lack of a prospective protocol to evaluate the cardiovascular system in these patients. As a single-centre study, the data's generalisability to other populations or healthcare settings may be limited. The uneven distribution of tumour types (137 acromegaly cases, 94 Cushing's disease cases, but only 26 prolactinoma cases) may affect the statistical power for comparisons between tumour types. The lack of a healthy control group makes it difficult to determine the excess cardiovascular risk attributable to pituitary tumours. The study may not have accounted for all potential confounding factors that could influence cardiovascular outcomes. While it examined post-operative remission and medical therapy, the analysis of specific treatment modalities and their impact on cardiovascular outcomes was limited.

Conclusions

Pituitary tumours have a significant cardiovascular impact, which differs depending on the type of tumour. This study shows that biochemical control may not be sufficient alone to reduce risk factors and cardiovascular events in this patient population and that strict control of cardiovascular risk factors is necessary regardless of the degree of disease activity. In patients with Cushing's disease, achieving biochemical remission in the immediate postoperative period was associated with a lower risk of cardiovascular and cerebrovascular events in these patients. More studies are needed to confirm this association and to ascertain the background cardiovascular risk after remission or disease control.

Statements

Acknowledgement (optional)

None.

Statement of Ethics

This study was reviewed and approved by the Ethics Committee of Local Health Unit of Coimbra, approval number OBS.SF.165/2021 and written informed consent was obtained from participants in the study.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

FPD was responsible for extracting patient data, analysing, and writing the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Figure Legends

Table 1- Characterization of the patient sample

Variable	Acromegalia (N= 137)	Cushing disease (N= 94)	Prolactinoma (N=26)	p-value
Sex, n (%)	47 (34.3)			
Masculine	90 (65.7)	15 (16.0)	14 (53.8)	
Feminine		79 (84.0)	12 (46.2)	<0.001
Age (years), mean ± SD	45.3 ± 13.7	41.9 ± 14.0	41.4 ± 14.2	0.090
Duration of disease (years), median (IQR)	12 (1-48)	10 (2-38)	17 (6-35)	0.055
Tumor type, n (%)				
Functioning	127 (92.7)	90 (95.7)	25 (96.2)	
Non-Functioning	10 (7.3)	4 (4.3)	1 (3.8)	0.563
Medical Therapy, n (%)				
Yes	65 (47.4)	12 (12.8)	17 (65.4)	
No	72 (52.6)	82 (87.2)	9 (34.6)	<0.001
Number of surgeries, n (%)				
1	104 (75.9)	68 (72.3)	25 (96.2)	
2	19 (13.9)	18 (19.1)	1 (3.8)	
3	13 (9.5)	8 (8.5)	0 (0.0)	
4	4 (0.7)	0 (0.0)	0 (0.0)	0.222
Radiotherapy, n (%)				
Yes	16 (11.9)	9 (9.6)	0 (0.0)	
No	118 (88.1)	85 (90.4)	26 (100.0)	0.173
Disease Control, n (%)				
Remission	70 (51.1)	80 (85.1)	9 (34.6)	
Controlled with medical therapy/radiotherapy	43 (31.4)	9 (9.6)	14 (53.8)	
Not controlled with medical therapy/radiotherapy	24 (17.5)	5 (5.3)	3 (11.5)	<0.001
Insufficiency at diagnosis, n (%)				
Yes	33 (30.0)	6 (13.6)	1 (25.0)	
No	77 (70.0)	38 (86.4)	3 (75.0)	0.108
Insufficiency type, n (%)				
Gonadal Insufficiency	32 (29.4)	6 (13.6)	1 (25.0)	0.126
Adrenal Insufficiency	10 (9.1)	2 (4.5)	0 (0.0)	0.532
Thyroid Insufficiency	11 (10.1)	5 (11.4)	0 (0.0)	0.771
Diabetes insipidus	0 (0.0)	1 (2.3)	0 (0.0)	0.272
Current insufficiency, n (%)				
Yes	58 (42,6)	40 (42,6)	15 (57,7)	
No	78 (57.4)	54 (57.4)	11 (42.3)	0.340

Insufficiency type, n (%)				
Gonadal Insufficiency	41 (30.1)	6 (6.4)	11 (42.3)	<0.001
Adrenal Insufficiency	30 (22.1)	28 (29.8)	4 (15.4)	0.219
Thyroid Insufficiency	38 (27.9)	31 (33.0)	10 (38.5)	0.486
Diabetes insipidus	2 (1.5)	1 (1.1)	1 (3.8)	0.594

Table 2- Statistical analysis of the relationship between cardiovascular events and types of pituitary tumours

Cardiovascular risk factor/event	**Acromegalia (N= 137)**	**Cushing disease (N= 94)**	**Prolactinoma (N=26)**	**p-value**
Cardiovascular and Cerebrovascular disease, n (%)				
Yes	15 (10.9)	8 (8.5)	1 (3.8)	
No	122 (89.1)	86 (91.5)	25 (96.2)	0.491
Cardiovascular disease, n (%)				
Yes	11 (8.0)	5 (5.3)	1 (3.8)	
No	126 (92.0)	89 (94.7)	25 (96.2)	0.600
Personal history diabetes/pre-diabetes, n (%)	53 (38.7)	29 (30.9)	2 (7.7)	
Yes	84 (61.3)	65 (69.1)	24 (92.3)	0.008
No				
Personal History arterial hypertension, n (%)	68 (50.7)	46 (48.9)	6 (24.0)	
Yes	66 (49.3)	48 (51.1)	19 (76.6)	0.045
No				
Dyslipidemia, n (%)				
Yes	68 (58.1)	51 (54.3)	17 (65.4)	
No	49 (41.9)	43 (45.7)	9 (34.6)	0.582
Ischaemic heart disease, n (%)				
Yes	4 (2.9)	3 (3.2)	1 (3.8)	
No	133 (97.1)	91 (96.8)	25 (96.2)	0.968
Cerebrovascular disease, n (%)				
Yes	6 (4.4)	4 (4.3)	0 (0.0)	
No	131 (95.6)	90 (95.7)	26 (100.0)	0.556
Arrhythmias, n (%)				
Yes	8 (5.8)	1 (1.1)	0 (0.0)	
No	129 (94.2)	93 (98.9)	26 (100.0)	0.090
Valvular Disease, n (%)				
Yes	1 (0.7)	0 (0.0)	0 (0.0)	
No	136 (99.3)	94 (100.0)	26 (100.0)	0.0644
Heart failure, n (%)				
Yes	1 (0,7)	1 (1,1)	0 (0)	0,858
No	136 (99,3%)	93 (98,9)	26 (100)	

Table 3- Relationship between tumour control status and cardiovascular events in Acromegalia

Acromegalia	Remission	Controlled with medical therapy/radiotherapy	Not controlled despite with medical therapy/radiotherapy	p-value
Cardiovascular and Cerebrovascular disease, n (%)				
Yes	61 (87.1)	6 (14.0)	0 (0.0)	
No	9 (12.9)	37 (86.0)	24 (100.0)	0.164
Dyslipidemia, n (%)				
Yes	27 (49.1)	31 (79.5)	10 (43.5)	
No	28 (50.9)	8 (20.5)	13 (56.5)	0.004
Personal History arterial hypertension, n (%)				
Yes	37 (55.2)	21 (48.8)	10 (41.7)	
No	30 (44.8)	22 (51.2)	14 (58.3)	0.499
Personal history diabetes/pre-diabetes, n (%)				
Yes	28 (40.0)	14 (32.6)	11 (45.8)	
No	42 (60.0)	29 (67.4)	13 (54.2)	0.536

Table 4- Relationship between tumour control status and cardiovascular events in Cushing Disease

Cushing	Remission	Controlled with medical therapy/radiotherapy	Not controlled despite with medical therapy/radiotherapy	p-value
Cardiovascular and Cerebrovascular disease, n (%)				
Yes	7 (8.8)	1 (11.1)	0 (0.0)	
No	73 (91.3)	8 (88.9)	5 (100.0)	0.760
Dyslipidemia, n (%)				
Yes	42 (52.5)	6 (66.7)	2 (40.0)	
No	38 (47.5)	3 (33.3)	3 (60.0)	0.696
Personal History arterial hypertension, n (%)				
Yes	38 (47.5)	4 (44.4)	4 (80.0)	
No	42 (52.5)	5 (55.6)	1 (20.0)	0.355
Personal history diabetes/pre-diabetes, n (%)				
Yes	24 (30.0)	3 (33.3)	2 (40.0)	
No	56 (70.0)	6 (66.7)	3 (60.0)	0.883

Table 5- Relationship between immediate post-operative remission and cardiovascular events in Cushing disease

Variable	No immediate post-operative remission	Immediate post-operative remission	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	5 (15.6)	0 (0)	
No	27 (84.4)	57 (100)	0.002
Dyslipidemia, n (%)			
Yes	21 (65.6)	28 (49.1)	
No	11 (34.4)	29 (50.9)	0.133
Personal History arterial hypertension, n (%)			
Yes	16 (50)	27 (47.4)	
No	16 (50)	30 (52.6)	0.812
Personal history diabetes/pre-diabetes, n (%)			
Yes	12 (37.5)	16 (28.1)	0,358
No	20 (62.5)	41 (71.9)	
Cardiovascular disease, n (%)			
Yes	3 (9.4)	0 (0)	
No	29 (90.6)	57 (100)	0,019
Ischemic Heart disease, n (%)			
Yes	3 (9.4)	0 (0)	
No	29 (90.6)	57 (100)	0.019
Cerebrovascular Disease, n (%)			
Yes	3 (9.4)	0 (0)	
No	29 (90.6)	57 (100)	0.019

Table 6- Relationship between use of medical therapy in the immediate post-operative period and cardiovascular events in Cushing disease

Variable	No medical therapy post-surgery	Medical therapy post-surgery	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	5 (7%)	1 (4.8)	0.710
No	66 (93%)	20 (95.2)	
Dyslipidemia, n (%)			
Yes	37 (52.1)	12 (57.1)	
No	34 (47.9)	9 (42.9)	0.685
Personal History arterial hypertension, n (%)			
Yes	34 (47.9)	11 (52.4)	
No	37 (52.1)	10 (47.6)	0.717
Personal history diabetes/pre-diabetes, n (%)	19 (26.8)	9 (42.9)	0.159
Yes	52 (73.2)	12 (57.1)	
No			
Cardiovascular disease, n (%)			
Yes	4 (5.6)	0 (0)	
No	67 (94.4)	21 (100)	0.266
Heart Failure			
Yes	1 (1.4)	0 (0)	
No	70 (98.6)	21 (100)	0.584
Ischemic Heart disease, n (%)			
Yes	3 (4.2)	0 (0)	
No	68 (95.8)	21 (100)	0.338
Cerebrovascular Disease, n (%)			
Yes	2 (2.8)	1 (4.8)	
No	69 (97.2)	20 (95.2)	0.659

Supplementary tables

Supplementary table 1- Relation between cardiovascular events and age at diagnosis of acromegaly (<50 vs. ≥50 years)

Acromegalia	Diagnosis before 50 years	Diagnosis after 50 years	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	4 (5.4)	7 (17.1)	0.042
No	70 (94.6)	34 (82.9)	
Dyslipidemia, n (%)			
Yes	40 (59.7)	17 (54.8)	
No	27 (40.3)	14 (45.2)	0.650
Personal History arterial hypertension, n (%)			
Yes	26 (36.1)	27 (65.9)	0.002
No	46 (63.9)	14 (34.1)	
Personal history diabetes/pre-diabetes, n (%)			
Yes	19 (25.7)	22 (53.7)	0.003
No	55 (74.3)	19 (46.3)	
Cardiovascular Pathology, n (%)	3 (4.1)	5 (12,2)	
Yes			
No	71 (95.9)	36 (87;8)	0.100

Supplementary table 2- Relation between cardiovascular events and age at diagnosis of Cushing disease (<50 vs. ≥50 years)

Cushing Disease	Diagnosis before 50 years	Diagnosis after 50 years	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	3 (8.6)	1 (7.7)	
No	32 (91.4)	12 (92.3)	0.922
Dyslipidemia, n (%)			
Yes	18 (51.4)	11 (84.6)	0.037
No	17 (48.6)	2 (15.4)	
Personal History arterial hypertension, n (%)			
Yes	12 (34.3)	12 (92.3)	<0.001
No	23 (65.7)	1 (7.7)	
Personal history diabetes/pre-diabetes, n (%)			
Yes	8 (22.9)	5 (38.5)	0.280
No	27 (77.1)	8 (61.5)	

Supplementary table 3- Relation between cardiovascular events and age at diagnosis of Prolactinoma (<50 vs. ≥50 years)

Prolactinoma	Diagnosis before 50 years	Diagnosis after 50 years	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	1 (5.9)	2 (100.0)	
No	16 (94.1)	0 (0.0)	0.725
Dyslipidemia, n (%)			
Yes	10 (58.8)	2 (100.0)	
No	7 (41.2)	0 (0.0)	0.253
Personal History arterial hypertension, n (%)			
Yes	2 (12.5)	1 (50.0)	
No	14 (87.5)	1 (50.0)	0.180
Personal history diabetes/pre-diabetes, n (%)			
Yes	1 (5.9)	0 (0.0)	
No	16 (94.1)	2 (100.0)	0.725

Supplementary table 4- Relation between cardiovascular events and the use of medical therapy in acromegaly

Acromegalia	No medical therapy	Medical therapy	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	9 (12.5)	6 (9.2)	
No	63 (87.5)	59 (90.8)	0.541
Dyslipidemia, n (%)			
Yes	28 (49.1)	40 (66.7)	
No	29 (50.9)	20 (33.3)	0.055
Personal History arterial hypertension, n (%)			
Yes	37 (53.6)	31 (47.7)	
No	32 (46.4)	34 (52.3)	0.493
Personal history diabetes/pre-diabetes, n (%)			
Yes	29 (40.3)	24 (36.9)	
No	43 (59.7)	41 (63.1)	0.687

Supplementary table 5- Relation between cardiovascular events and the use of medical therapy in Cushing disease

Cushing	No medical therapy	Medical therapy	p-value

Cardiovascular and Cerebrovascular disease, n (%)			
Yes	8 (9.8)	0 (0.0)	
No	74 (90.2)	12 (100.0)	0.258
Dyslipidemia, n (%)			
Yes	43 (52.4)	8 (66.7)	
No	39 (47.6)	4 (33.3)	0.355
Personal History arterial hypertension, n (%)			
Yes	38 (46.3)	8 (66.7)	
No	44 (53.7)	4 (33.3)	0.188
Personal history diabetes/pre-diabetes, n (%)			
Yes	25 (30.5)	4 (33.3)	
No	57 (69.5)	8 (66.7)	0.842

Supplementary table 6- Relation between cardiovascular events and the use of medical therapy in Prolactinoma

Prolactinoma	**No medical therapy**	**Medical therapy**	**p-value**
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	1 (11.1)	0 (0.0)	
No	8 (88.9)	17 (100.0)	0.161
Dyslipidemia, n (%)			
Yes	7 (77.8)	10 (58.8)	
No	2 (22.2)	7 (41.2)	0.344
Personal History arterial hypertension, n (%)			
Yes	3 (33.3)	3 (18.8)	
No	6 (66.7)	13 (81.3)	0.412
Personal history diabetes/pre-diabetes, n (%)			
Yes	0 (0.0)	15 (88.2)	
No	9 (100.0)	2 (11.8)	0.284

Supplementary table 7- Relationship between tumour control status and cardiovascular events in Prolactinoma

Prolactinoma	Remission	Controlled with medical therapy/radiotherapy	Not controlled despite with medical therapy/radiotherapy	p-value
Cardiovascular and Cerebrovascular disease, n (%)				
Yes	1 (11.1)	14 (100.0)	0 (0.0)	
No	8 (88.9)	0 (0.0)	3 (100.0)	0.374
Dyslipidemia, n (%)				
Yes	7 (77.8)	8 (57.1)	2 (66.7)	
No	2 (22.2)	6 (42.9)	1 (33.3)	0.597
Personal History arterial hypertension, n (%)				
Yes	3 (33.3)	3 (23.1)	0 (0.0)	
No	6 (66.7)	10 (76.9)	3 (100.0)	0.501
Personal history diabetes/pre-diabetes, n (%)				
Yes	0 (0.0)	2 (14.3)	0 (0.0)	
No	9 (100.0)	12 (85.7)	3 (100.0)	0.395

Supplementary table 8- Relationship between duration of illness and cardiovascular events in acromegalic patients, all age groups

Cardiovascular risk factor/event	<5 years	5-10 years	10-15 years	15-20 years	>20 years	p-value
Cardiovascular and cerebrovascular disease, n (%)						
Yes	1 (5.6)	3 (9.7)	2 (9.5)	2 (13.3)	5 (12.5)	
No	17 (94.4)	28 (90.3)	19 (90.5)	13 (86.7)	35 (87.5))	0,936
Cardiovascular disease, n (%)						
Yes	0 (0)	2 (6.5)	2 (9.5)	2 (13.3)	4 (10)	
No	18 (100)	29 (93.5)	19 (90.5)	13 (86.7)	36 (90)	0,639
Personal history diabetes/pre-diabetes, n (%)						
Yes	6 (33.3)	12 (38.7)	8 (38.1)	9 (60)	13 (32.5)	0.442
No	12 (66.7)	19 (61.3)	13 (61.9)	6 (40)	27 (67.5)	
Personal History arterial hypertension, n (%)						
Yes	7 (38.9)	14 (45.2)	8 (38.1)	8 (57.1)	22 (56.4)	0.542
No	11 (61.1)	17 (54.8)	13 (61.9)	6 (42.9)	17 (43.6)	
Dyslipidemia, n (%)						
Yes	9 (56.3)	12 (52.2)	12 (66.7)	9 (75)	20 (52.6)	
No	7 (43.8)	11 (47.8)	6 (33.3)	3 (25)	18 (47.4)	0.597
Cerebrovascular disease, n (%)						
Yes	1 (5.6)	1 (3.2)	0 (0)	0 (0)	2 (5)	0.748
No	17 (94.4)	30 (96.8)	21 (100)	15 (100)	38 (95)	
Arrhythmias, n (%)						0.776
Yes	0 (0)	2 (6.5)	2 (9.5)	1 (6.7)	2 (5)	
No	18 (100)	29 (93.5)	19 (90.5)	14 (93.3)	38 (05)	

Supplementary table 9- Relationship between duration of illness and cardiovascular events in acromegalic patients, by age cut-of limits (<5, > 5years)

Cardiovascular risk factor/event	< 5years	> 5 years	p-value

Cardiovascular and cerebrovascular disease, n (%)			
Yes	1 (5.6)	12 (11.2)	
No	17 (94.4)	95 (88.8)	0.467
Cardiovascular disease, n (%)			
Yes	0 (0)	10 (9.3)	
No	18 (100)	97 (90.7)	0.176
Personal history diabetes/pre-diabetes, n (%)			
Yes	6 (33.3)	42 (39.3)	0.633
No	12 (66.7)	65 (60.7)	
Personal History arterial hypertension, n (%)			
Yes	7 (38.9)	52 (49.5)	0.404
No	11 (61.1)	53 (50.5)	
Dyslipidemia, n (%)			
Yes	9 (56.3)	53 (58.2)	0.882
No	7 (43.8)	38 (41.8)	
Cerebrovascular disease, n (%)	1 (5.6)	3 (2.8)	
Yes	17 (94.4)	104 (97.2)	0.539
No			
Arrhythmias, n (%)			
Yes	0 (0)	7(6.4)	0.264
No	18 (100)	100 (93.5)	
Ischemic Cardiopathy, n (%)			
Yes	0 (0)	3 (2.8)	
No	18 (100)	104 (97.2)	0.472

Supplementary table 10- Relationship between duration of illness and cardiovascular events in acromegalic patients, by age cut-of limits (<10, >10 years)

Cardiovascular risk factor/event	< 10 years	> 10 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	4 (8.2)	9 (11.8)	0.511
No	45 (91.8)	67 (88.2)	
Cardiovascular disease, n (%)			
Yes	2 (4.1)	8 (10.5)	
No	47 (95.9)	68 (89.5)	0.195
Personal history diabetes/pre-diabetes, n (%)			
Yes	18 (36.7)	30 (39.5)	
No	31 (63.3)	46 (60.5)	0.759
Personal History arterial hypertension, n (%)			
Yes	21 (42.9)	38 (51.4)	0.356
No	28 (57.1)	36 (48.6)	
Dyslipidemia, n (%)			
Yes	21 (53.8)	41 (60.3)	0.516
No	18 (46.2)	27 (39.7)	
Cerebrovascular disease, n (%)	2 (4.1)	2 (2.6)	
Yes	47 (95.9)	74 (97.4)	0.653
No			
Arrhythmias, n (%)			
Yes	2 (4.1)	5 (6.6)	
No	47 (95.9)	71 (93.4)	0.553
Ischemic Cardiopathy, n (%)			
Yes	0 (0)	3 (3.9)	
No	49 (100)	73 (96.1)	0.159

Supplementary table 11- Relationship between duration of illness and cardiovascular events in acromegalic patients, by age cut-of limits (<15, >15 years)

Cardiovascular risk factor/event	< 15 years	> 15 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	6 (8.6)	7 (12.7)	
No	64 (91.4)	48 (87.3)	0.450
Cardiovascular disease, n (%)			
Yes	4 (5,7)	6 (10.9)	
No	66 (94.3)	49 (89.1)	0.288
Personal history diabetes/pre-diabetes, n (%)			
Yes	26 (37.1)	22 (40)	0.744
No	44 (62.9)	33 (60)	
Personal History arterial hypertension, n (%)			
Yes	29 (41.4)	30 (56.6)	0.095
No	41 (58.6)	23 (43.4)	
Dyslipidemia, n (%)			
Yes	33 (57.9)	29 (58)	0.991
No	24 (42.1)	21 (42)	
Cerebrovascular disease, n (%)	2 (2.9)	2 (3.6)	
Yes	68 (97.1)	53 (96.4)	0.806
No			
Arrhythmias, n (%)			
Yes	4 (5.7)	3 (5.5)	
No	66 (94.3)	52 (94.5)	0.950
Ischemic Cardiopathy, n (%)			
Yes	0 (0)	3 (5.5)	
No	70 (100)	52 (94.5)	0.048

Supplementary table 12- Relationship between duration of illness and cardiovascular events in acromegalic patients, by age cut-of limits (<20, >20 years)

Cardiovascular risk factor/event	< 20 years	> 20 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	8 (9.4)	5 (12.5)	
No	77 (90.6)	35 (87.5)	0.598
Cardiovascular disease, n (%)			
Yes	6 (7.1)	4 (10)	
No	79 (92.9)	36 (90)	0.572
Personal history diabetes/pre-diabetes, n (%)			
Yes	35 (41.2)	13 (32.5)	
No	50 (58.8)	27 (67.5)	0.352
Personal History arterial hypertension, n (%)			0,202
Yes	37 (44)	22 (56.4)	
No	47 (56)	17 (43.6)	
Dyslipidemia, n (%)			
Yes	42 (60.9)	22 (52.6)	
No	27 (39.1)	18 (47.4)	0.409
Cerebrovascular disease, n (%)	2 (2.4)	2 (5)	
Yes	83 (97.6)	38 (95)	0.433
No			
Arrhythmias, n (%)			
Yes	5 (5.9)	2 (5)	
No	80 (94.1)	38 (95)	0.841
Ischemic Cardiopathy, n (%)			
Yes	1 (1.2)	1 (5)	
No	84 (98.8)	38 (95)	0.193

Supplementary table 13- Relationship between duration of illness and cardiovascular events in Cushing disease patients, al groups

Cardiovascular risk factor/event	<5 years	5-10 years	10-15 years	15-20 years	>20 years	p-value
Cardiovascular and cerebrovascular disease, n (%)						0.344
Yes	1 (20)	1 (3.8)	0 (0)	0 (0)	2 (13.3)	
No	4 (80)	25 (96.2)	11 (100)	8 (100)	13 (86.7)	
Cardiovascular disease, n (%)						
Yes	1 (20)	0 (0)	0 (0)	0 (0)	1 (6.7)	0.142
No	4 (80)	26 (100)	11 (100)	8 (100)	14 (93.3)	
Personal history diabetes/pre-diabetes, n (%)						
Yes	3 (60)	6 (33.3)	4 (36.4)	0 (0)	5 (33.3)	0.159
No	2 (40)	20 (76.9)	7 (63.6)	8 (100)	10 (66.7)	
Personal History arterial hypertension, n (%)						
Yes	4 (80)	10 (38.5)	6 (54.5)	1 (12.5)	8 (53.3)	0.127
No	1 (20)	16 (61.5)	5 (45.5)	7 (87.5)	7 (46.7)	
Dyslipidemia, n (%)						
Yes	4 (80)	15 (57.7)	6 (54.5)	3 (37.5)	9 (24.3)	0.661
No	1 (20)	11 (42.3)	5 (45.5)	5 (62.5)	6 (40)	
Ischaemic heart disease, n (%)	1 (20)	0 (0)	0 (100)	0 (0)	1 (6,7)	0.142
Yes	4 (80)	26 (100)	11 (100)	8 (100)	14 (93.3)	
No						
Cerebrovascular disease, n (%)	1 (20)	1 (3.8)	0 (0)	0 (0)	1 (6.7)	
Yes	4 (80)	25 (96.2)	11 (100)	8 (100)	14 (93.3)	0.436
No						

Supplementary table 14- Relationship between duration of illness and cardiovascular events in Cushing disease patients, by age cut-of limits (<5, >5 years)

Cardiovascular risk factor/event	< 5 years	> 5 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	1 (20)	3 (5)	
No	4 (80)	57 (95)	0.180
Cardiovascular disease, n (%)			
Yes	1 (20)	1 (1.7)	
No	4 (80)	59 (98.3)	0.023
Personal history diabetes/pre-diabetes, n (%)			
Yes	3 (60)	15(25)	
No	2 (40)	45 (75)	0.093
Personal History arterial hypertension, n (%)			
Yes	4 (80)	25 (41.7)	
No	1 (20)	35 (58.3)	0.098
Dyslipidemia, n (%)			
Yes	4 (80)	33 (55)	
No	1 (20)	27 (45)	0.278
Cerebrovascular disease, n (%)			
Yes	1 (20)	2 (3.3)	
No	4 (80)	58 (96.7)	0.088
Ischemic Cardiopathy, n (%)			
Yes	1 (20)	1 (1.7)	
No	4 (80)	59 (98.3)	0.023

Supplementary table 15- Relationship between duration of illness and cardiovascular events in Cushing disease patients, by age cut-of limits (<10, >10 years)

Cardiovascular risk factor/event	< 10 years	> 10 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	2 (6.5%)	2 (5.9)	
No	29 (93.5%)	32 (94.1)	0.924
Cardiovascular disease, n (%)			
Yes	1 (3.2)	1 (2.9)	
No	30 (96.8)	33 (97.1)	0.947
Personal history diabetes/pre-diabetes, n (%)			
Yes	9 (29)	9 (26.5)	
No	22 (71)	25 (73.5)	0.818
Personal History arterial hypertension, n (%)			
Yes	14 (45.2)	15 (44.1)	
No	17 (54.8)	19 (55.9)	0.933
Dyslipidemia, n (%)			
Yes	19 (61.3)	18 (52.9)	
No	12 (38.7)	16 (47.1)	0.497
Cerebrovascular disease, n (%)			
Yes	2 (6.5)	1 (2.9)	
No	29 (93.5)	33 (97.1)	0.500
Ischemic Cardiopathy, n (%)			
Yes	1	1	
No	30	33	0,947

Supplementary table 16- Relationship between duration of illness and cardiovascular events in Cushing disease patients, by age cut-of limits (<15, >15 years)

Cardiovascular risk factor/event	< 15 years	> 15 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			0.528
Yes	2	2	
No	40	21	
Cardiovascular disease, n (%)			
Yes	1 (2.4)	1 (4.3)	
No	41 (97.6)	22 (95.7)	0.661
Personal history diabetes/pre-diabetes, n (%)			
Yes	13 (32)	5 (21,7)	
No	29 (69)	18 (78.3)	0.427
Personal History arterial hypertension, n (%)			
Yes	20 (47.6)	9 (39.1)	
No	22 (52.4)	14 (60.9)	0.510
Dyslipidemia, n (%)			
Yes	25 (59.5)	12 (52.2)	0.567
No	15 (40.5)	11 (48.4)	
Cerebrovascular disease, n (%)	2 (4.8)	1 (4.3)	
Yes	40 (95.2)	22 (95.7)	0.939
No			
Ischemic Cardiopathy, n (%)	1 (2.4)	1 (4.3)	0.661
	41 (97.6)	22 (95.7)	

Supplementary table 17- Relationship between duration of illness and cardiovascular events in Cushing disease patients, by age cut-of limits (<20, >20 years)

Cardiovascular risk factor/event	< 20 years	> 20 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	2 (4)	2 (13.3)	
No	48 (96)	13 (86.7)	0.187
Cardiovascular disease, n (%)			
Yes	1 (2)	1 (6.7)	

No	49 (98)	14 (93.3)	0.359
Personal history diabetes/pre-diabetes, n (%)			
Yes	13 (26)	5 (33.3)	
No	37 (74)	10 (66.7)	0.578
Personal History arterial hypertension, n (%)			
Yes	21 (42)	8 (53.3)	
No	29 (58)	7 (46.7)	0.439
Dyslipidemia, n (%)			
Yes	28 (56)	9 (60)	
No	22 (44)	6 (40)	0.784
Cerebrovascular disease, n (%)			
Yes	2 (4)	1 (6.7)	
No	48 (96)	14 (93.3)	0,666
Ischemic Cardiopathy, n (%)			
Yes	1 (2)	1 (6.7)	
No	49 (98)	14 (93.3)	0,359

Supplementary table 18- Relationship between duration of illness and cardiovascular events in prolactinoma, al groups

Cardiovascular risk factor/event	5-10 years	10-15 years	15-20 years	>20 years	p-value
Cardiovascular and cerebrovascular disease, n (%)					
Yes	0 (0)	0 (0)	0 (0)	1 (10)	0.668
No	6 (100)	4 (100)	5 (100)	9 (90)	
Cardiovascular disease, n (%)					
Yes	0 (0)	0 (0)	0 (0)	1 (10)	0.668
No	6 (100)	4 (100)	5 (100)	9 (90)	
Personal history diabetes/pre-diabetes, n (%)					
Yes	1 (16.7)	1 (25)	0 (0)	0 (0)	0.322
No	5 (83.7)	3(75)	5 (100)	10 (100)	
Personal History arterial hypertension, n (%)					
Yes	1 (20)	1 (25)	2 (40)	2 (20)	
No	4 (80)	3 (75)	3 (60)	8 (80)	0.849
Dyslipidemia, n (%)					
Yes	2 (33.3)	3 (75)	4 (80)	8 (80)	
No	4 (66.7)	1 (25)	1 (20)	2 (20)	0.222
Ischaemic heart disease, n (%)					
Yes	0 (0)	0 (0)	0 (0)	1 (10)	0.668
No	6 (100)	5 (100)	4 (100)	9 (90)	

Supplementary table 19- Relationship between duration of illness and cardiovascular events in Prolactinoma, by age cut-of limits (<10, >10 years)

Cardiovascular risk factor/event	< 10 years	> 10 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			
Yes	0 (0)	1 (5.3)	0.566
No	6 (100)	18 (94.7)	

Cardiovascular disease, n (%)			
Yes	0 (0)	1 (5.3)	
No	6 (100)	18 (94.7)	0.566
Personal history diabetes/pre-diabetes, n (%)			
Yes	1 (16.7)	1 (5.3)	0.369
No	5 (83.3)	18 (94.7)	
Personal History arterial hypertension, n (%)			
Yes	1 (20)	5 (26.3)	0.772
No	4 (80)	14 (73.7)	
Dyslipidemia, n (%)			0.037
Yes	2 (33.3)	15 (78.9)	
No	4 (66.7)	4 (21.1)	
Ischemic Cardiopathy, n (%)			0.566
Yes	0 (0)	1 (5.3)	
No	6 (100)	18 (94.7)	

Supplementary table 20- Relationship between duration of illness and cardiovascular events in Prolactinoma by age cut-of limits (<15, >15 years)

Cardiovascular risk factor/event	**< 15 years**	**> 15 years**	**p-value**
Cardiovascular and cerebrovascular disease, n (%)			

Yes	0 (0)	1 (93.3)	0.405
No	10 (100)	14 (6.7)	
Cardiovascular disease, n (%)			
Yes			
No	0 (0)	1 (6.7)	0.405
	10 (100)	14 (93.3)	
Personal history diabetes/pre-diabetes, n (%)			
Yes	2 (20)	0 (0)	
No	8 (80)	15 (100)	0.071
Personal History arterial hypertension, n (%)	2 (22.2)	4 (26.7)	0.808
Yes	7 (77.8)	11 (73.3)	
No			
Dyslipidemia, n (%)			
Yes	5 (50)	12 (80)	
No	5 (50)	3 (20)	0.115
Ischemic	0 (0)	1 (6.7)	
Cardiopathy, n (%)	10 (100)	14 (93.7)	0.405

Supplementary table 21- Relationship between duration of illness and cardiovascular events in Prolactinoma patients, by age cut-of limits (<20, >20 years)

Cardiovascular risk factor/event	< 20 years	> 20 years	p-value
Cardiovascular and cerebrovascular disease, n (%)			0.211
Yes	0 (0)	1 (10)	
No	15 (100)	9 (90)	
Cardiovascular disease, n (%)			
Yes	0 (0)	1 (10)	
No	15 (100)	9 (90)	0.211
Personal history diabetes/pre-diabetes, n (%)			0.229
Yes	2 (13.3)	0 (0)	
No	13 (86.7)	10 (100)	
Personal History arterial hypertension, n (%)			
Yes	4 (28.6)	2 (20)	
No	10 (71.4)	8 (80)	0.633
Dyslipidemia, n (%)			
Yes	9 (60)	8 (80)	0.294
No	6 (40)	2 (20)	
Ischemic Cardiopathy, n (%)	0 (0)	1 (10)	0.211
	15 (100)	9 (90)	

Supplementary table 22- Relationship between use of medical therapy in the immediate post-operative period and cardiovascular events in Acromegalia

Variable	No medical therapy post-surgery	Medical therapy post-surgery	p-value
Cardiovascular and Cerebrovascular disease, n (%)			0.798
Yes	4 (9.5)	10 (11)	
No	38 (90.5)	81 (89)	
Dyslipidemia, n (%)			
Yes	17 (53.1)	50 (60.2)	
No	15 (46.9)	33 (39.8)	0,488
Personal History arterial hypertension, n (%)	22 (52.4)	46 (51.1)	0.892
Yes	20 (47.6)	44 (48.9)	
No			
Personal history diabetes/pre-diabetes, n (%)	15 (35.7)	37 (40.7)	0.587
Yes	27 (64.3)	54(59.3)	

No			
Cardiovascular disease, n (%)	3 (7.1)	8 (8.8)	
Yes	39 (92.8)	83 (91.2)	
No			0.748
Heart Failure			
Yes	0 (0)	1 (1.1)	
No	42 (100)	90 (98.9)	0.495
Valvular Disease			
Yes	0 (0)	1 (1.1)	
No	42 (100)	90 (98.9)	0.495
Ischemic Heart disease, n (%)			
Yes	0 (0)	4 (4.4)	
No	42 (100)	87 (95.6)	0.168
Cerebrovascular Disease, n (%)	1 (2.4)	4 (4.4)	
Yes	41 (97.6)	87 (95.6)	
No			0.570
Arritmia, n (%)			
Yes	3 (7.1)	5 (5.5)	
No	39 (92.8)	86 (94.5)	0.710

Supplementary table 23- Relationship between immediate post-operative remission and cardiovascular events in Acromegalia

Variable	No immediate post-operative remission	Immediate post-operative remission	p-value
Cardiovascular and Cerebrovascular disease, n (%)	9 (11.4)	4 (11.1)	
Yes	70 (88.6)	32 (88.9)	0.965
No			
Dyslipidemia, n (%)			
Yes	44 (61.1)	15 (50.6)	
No	28 (38.8)	12 (44.4)	0.616
Personal History arterial hypertension, n (%)			
Yes	37 (46.8)	19 (52.8)	
No	42 (53.2)	17 (47.2)	0.554
Personal history diabetes/pre-diabetes, n (%)			
Yes	44 (61.1)	15 (56.6)	
No	28 (38.9)	12 (44.4)	
			0.616
Cardiovascular disease, n (%)			0.926
Yes	7 (8.9)	3 (8.3)	

No	72 (91.1)	33 (91.7)	
Heart Failure			
Yes	0 (0)	1 (2.8)	
No	79 (100)	35 (97.2)	0.137
Valvular Disease			
Yes	0 (0)	1 (2.8)	
No	39 (100)	35 (97.2)	0.137
Ischemic Heart disease, n (%)			
Yes	3 (3.8)	1 (2.8)	
No	76 (96.2)	35 (97.2)	0.782
Cerebrovascular Disease, n (%)			
Yes	3 (3.8)	2 (5.6)	
No	76 (96.2)	74 (94.4)	0.668
Arritmia, n (%)			
Yes	4 (5.1)	3 (8.3)	
No	75 (94.8)	33 (91.7)	0.496

Supplementary table 24- Relationship between use of medical therapy in the immediate post-operative period and cardiovascular events in Prolactinoma

Variable	No medical therapy post-surgery	Medical therapy post-surgery	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	1 (12.5)	0 (0)	
No	7 (87.5)	18 (100)	0.126
Dyslipidemia, n (%)			
Yes	5 (62.5)	12 (66.7)	
No	3 (37.5)	6 (33.3)	0.837
Personal History arterial hypertension, n (%)			
Yes	2 (25)	4 (23.5)	
No	6 (75)	13 (76.5)	0.936
Personal history diabetes/pre-diabetes, n (%)			
Yes	1 (12.5)	1 (5.6)	
No	7 (87.5)	17 (94.4)	0.540
Cardiovascular disease, n (%)			
Yes	1 (12.5)	0 (0)	
No	7 (87.5)	18 (100)	0.126
Ischemic Heart disease, n (%)			
Yes	1 (12.5)	0 (0)	
No	7 (87.5)	18 (100)	0.126

Supplementary table 25- Relationship between immediate post-operative remission and cardiovascular events in Prolactinoma

Variable	No immediate post-operative remission	Immediate post-operative remission	p-value
Cardiovascular and Cerebrovascular disease, n (%)			
Yes	0 (0)	1 (7.1)	0.388
No	10 (100)	13 (92.9)	
Dyslipidemia, n (%)			
Yes	6 (60)	11 (78.6)	
No	4 (40)	3 (21.4)	0.324
Personal History arterial hypertension, n (%)			
Yes	2 (22.2)	4 (28.6)	
No	7 (77.8)	10 (71.4)	0.375
Personal history diabetes/pre-diabetes, n (%)			
Yes	1 (10)	0 (0)	
No	9 (90)	14 (100)	0.227
Cardiovascular disease, n (%)			
Yes	0 (0)	1 (7.1)	0.388
No	10 (100)	13 (92.9)	
Ischemic Heart disease, n (%)			
Yes	0 (0)	1 (7.1)	
No	10 (100)	13 (92.9)	0.388

Apêndices

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Original research article Página:10:" This study employed a retrospective design to assess the cardiovascular burden in patients with functioning pituitary tumours Página 8: "Retrospective analysis of 257 patients with functioning pituitary tumours (137 acromegaly, 94 Cushing's disease, 26 prolactinoma) who underwent surgery. Cardiovascular events, tumour characteristics, age at diagnosis, and tumour activity status were evaluated. We also evaluated the relationship between the achievement of remission after surgery and the use of hormonal control therapy with cardiovascular events. ." "Patients with functioning pituitary tumours demonstrate a high cardiovascular burden even after tumour control." "In patients with Cushing's disease, remission in the immediate postoperative period is associated with fewer cardiovascular and cerebrovascular events."
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Página 9: "Current management strategies primarily focus on achieving tumour and biochemical control through surgery and/or medical therapy, but it is unclear whether achieving hormonal remission consistently translates into a reduction in cardiovascular risk. Moreover, variability in treatment response suggests that additional clinical markers may be needed to identify patients at higher risk of persistent cardiovascular complications, even after disease control.
Objectives	3	State specific objectives, including any prespecified hypotheses	"Página 9: "In this study, we aim to evaluate the cardiovascular burden associated with functioning pituitary tumours by assessing clinical outcomes and treatment strategies in a retrospective cohort of 257 patients who underwent surgery."
Methods			

Study design	4	Present key elements of study design early in the paper	Página 10: "We conducted a comprehensive review of medical records from Coimbra Local Health Unit for patients diagnosed with functioning pituitary tumours between 14/07/1986 and 09/01/2024" Página 10: "Data collection was done by extracting the relevant information from electronic medical records, including demographic characteristics, tumour type and size, endocrine function tests, cardiovascular risk factors, and cardiovascular outcomes."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Página 10: "We conducted a comprehensive review of medical records from Coimbra Local Health Unit for patients diagnosed with functioning pituitary tumours between 14/07/1986 and 09/01/2024."
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	Página 10: "Inclusion criteria encompassed adult patients (≥18 years) with a confirmed diagnosis of functioning pituitary tumour who have undergone surgery, including prolactinomas, acromegaly, and Cushing's disease. Exclusion criteria included patients with non-functioning pituitary tumours, who have not undergone surgery and incomplete medical records." Not applicable in the context of this study
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic	Página 10: "Specifically, we collected data on age, sex, lipid profile, duration of the disease since diagnosis, number of surgeries performed, achievement of remission in the immediate post-operative period, completion of medical therapy in the postoperative period, number of surgeries performed, completion of radiotherapy, tumour control status, insufficiencies at diagnosis and in the immediate post-operative period and whether they were under medical therapy at the time of the last medical record available. Cardiovascular outcomes of interest included hypertension, dyslipidaemia, diabetes mellitus, coronary artery disease,

		criteria, if applicable	heart failure, cardiac arrhythmia, valvular disease and cerebrovascular events. Besides assessing each individual, we also analysed them by groups: i) (patients with cardiovascular-cerebrovascular pathology (CVD -CV), which includes the cardiovascular events analysed (arrhythmia, coronary heart disease, heart failure, valvular heart disease and strokes and transient ischaemic strokes), ii) patients with just cardiovascular pathology (CVD) (which includes only arrhythmia, coronary heart disease, heart failure, valvular heart disease), iii) patients with just as cerebrovascular pathology, (CV) which includes only strokes and transient ischaemic strokes)."
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Página 10,11: "Endocrine function was assessed through hormone measurements specific to each tumour type. For prolactinomas, serum prolactin levels were recorded. In cases of GH-secreting tumours, we documented GH and insulin-like growth factor 1 (IGF-1) levels. For ACTH-secreting tumours, we noted serum cortisol and ACTH levels, as well as results from dexamethasone suppression tests and urinary-free cortisol where available. Cardiovascular assessment included echocardiographic data, electrocardiogram findings, and results from any additional cardiovascular imaging studies (e.g., coronary angiography, cardiac MRI) were recorded where available. Treatment modalities, including medical therapy, surgery, and radiotherapy, were documented along with their timing relative to cardiovascular outcomes."
Bias	9	Describe any efforts to address potential sources of bias	Página 18: "large sample size of 257 patients with functioning pituitary tumours, providing a substantial dataset for analysis. It offers a comprehensive examination of multiple tumour types (acromegaly, Cushing's disease, and prolactinoma) and various cardiovascular outcomes, allowing for a broad understanding of the cardiovascular burden." Consecutive, random selection of patients from the endocrine pathology consultation with pituitary tumours
Study size	10	Explain how the study size was arrived at	Página 12: A total of 257 functional pituitary tumours that underwent surgery (137 cases of acromegaly, 94 cases of Cushing's disease and 26 cases of prolactinoma) were analysed, including 181 women (average age of 59.7 ± 14.6 years) and 76 men (average age of 56.9 ± 14.3 years).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which	Página 11: Descriptive statistics were used to summarise patient characteristics and cardiovascular outcomes. Continuous variables were expressed as means ± standard deviations or medians with interquartile ranges, depending on the distribution. Categorical variables were presented as frequencies and percentages. Comparisons between tumour types were made using appropriate statistical tests (e.g., chi-square test for categorical variables, t-test or Mann–Whitney for continuous variables).

		groupings were chosen and why	All tests were one-sided, and a p-value <0.05 was considered statistically significant.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Página 11: "Comparisons between tumour types were made using appropriate statistical tests (e.g., chi-square test for categorical variables, t-test or Mann–Whitney for continuous variables). All tests were one-sided, and a p-value <0.05 was considered statistically significant. Página 12: "normality was assessed by the Shapiro-Wilk and Kolmogorov-Smirnov test, which showed differences between groups, so the non-parametric test, Kruskal-Wallis, was used for analysis by tumour subtype), which revealed a median duration of 12 years (range 1-48 years) for acromegalic patients, 10 years for patients with Cushing's disease (range 2-38 years) and 17 years for prolactinoma (range 6-35 years)."
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	All patients with missing information were excluded from the study
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Página 12: "A total of 257 functional pituitary tumours that underwent surgery (137 cases of acromegaly, 94 cases of Cushing's disease and 26 cases of prolactinoma) were analysed"

		(b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	All patients with missing information were excluded from the study
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Página 10: "We conducted a comprehensive review of medical records from Coimbra Local Health Unit for patients diagnosed with functioning pituitary tumours between 14/07/1986 and 09/01/2024." Página 12: "A total of 257 functional pituitary tumours that underwent surgery (137 cases of acromegaly, 94 cases of Cushing's disease and 26 cases of prolactinoma) were analysed, including 181 women (average age of 59.7 ± 14.6 years) and 76 men (average age of 56.9 ± 14.3 years). Of the female study population, 90 had acromegaly (65.7% of all acromegaly patients analysed), 79 had Cushing's disease (84% of all Cushing's disease patients analysed), and 12 had prolactinoma (46.2% of all prolactinoma patients analysed). Of the male study population, 47 had acromegaly (34.3% of all acromegaly patients analysed), 15 had Cushing's disease (16% of all Cushing's disease patients analysed), and 14 had prolactinoma (53.8% of all prolactinoma patients analysed). We also characterised for age at diagnosis for each tumour subtype (45.3 ± 13.7 for acromegalia; 41.9 ± 14.0 for Cushing disease and 41.4 ± 14.2 for prolactinoma), duration of disease (normality was assessed by the Shapiro-Wilk and Kolmogorov-Smirnov test, which showed differences between groups, so the non-parametric test, Kruskal-Wallis, was used for analysis by tumour subtype), which revealed a median duration of 12 years (range 1-48 years) for acromegalic patients, 10 years for patients with Cushing's disease (range 2-38 years) and 17 years for prolactinoma (range 6-35 years)."
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	Página 10: "between 14/07/1986 and 09/01/2024"
Outcome data	15*	Report numbers of outcome events or summary measures over time	Página 8: "Cerebrovascular and cardiovascular disease occurred in 10.9%, 8.5%, and 3.8% of patients with acromegaly, Cushing's disease and prolactinoma, respectively. Significant differences were found in the prevalence of diabetes/pre-diabetes (p=0.008) and hypertension (p=0.045) among tumour types – higher in patients with acromegaly and Cushing's disease and lower in patients with prolactinomas. Dyslipidaemia was highly prevalent across all groups. In acromegaly, patients diagnosed after 50 years had higher rates of diabetes, cerebrovascular and cardiovascular disease and hypertension. Cushing's disease patients diagnosed after 50 years had significantly higher rates of hypertension and dyslipidaemia.

	Disease duration and tumour control status showed no correlation with cardiovascular outcomes. Patients with Cushing's disease who did not achieve remission postoperatively had more cardiovascular and cerebrovascular events (p=0.002).”

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Página 8: "Cerebrovascular and cardiovascular disease occurred in 10.9%, 8.5%, and 3.8% of patients with acromegaly, Cushing's disease and prolactinoma, respectively. Significant differences were found in the prevalence of diabetes/pre-diabetes (p=0.008) and hypertension (p=0.045) among tumour types – higher in patients with acromegaly and Cushing's disease and lower in patients with prolactinomas. Dyslipidaemia was highly prevalent across all groups. In acromegaly, patients diagnosed after 50 years had higher rates of diabetes, cerebrovascular and cardiovascular disease and hypertension. Cushing's disease patients diagnosed after 50 years had significantly higher rates of hypertension and dyslipidaemia. Disease duration and tumour control status showed no correlation with cardiovascular outcomes. Patients with Cushing's disease who did not achieve remission postoperatively had more cardiovascular and cerebrovascular events (p=0.002)."
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable in the context of this study
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Página 12 e 13: " For each subtype of tumour, we assessed the relationship between cardiovascular events and years of disease duration, divided into subgroups (<5 years duration, 5-10 years, 10-15 years, 15-20 years, >20 years , as well as for age above and below the cut-off point (<5/>5 years, <10/>10 years; <15/>15; <20/>20 years), tumour activity status (in remission, controlled with medical therapy/radiotherapy, not controlled despite medical therapy/radiotherapy), age at diagnosis before or after 50 years, post-operative remission and use of post-operative medical therapy. This data can be found in the supplementary tables 1-25." "
Discussion			

Key results	18	Summarise key results with reference to study objectives	Página 8: “Patients with functioning pituitary tumours demonstrate a high cardiovascular burden even after tumour control. The impact varies among tumour types. In patients with Cushing's disease, remission in the immediate postoperative period is associated with fewer cardiovascular and cerebrovascular events. These findings highlight the need for long-term cardiovascular monitoring and management in these patients, regardless of tumour control status.”
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Página 18: “However, the study also has limitations. Its retrospective design may be subject to selection bias and incomplete data, e.g., lack of a prospective protocol to evaluate the cardiovascular system in these patients. As a single-centre study, the data's generalisability to other populations or healthcare settings may be limited. The uneven distribution of tumour types (137 acromegaly cases, 94 Cushing's disease cases, but only 26 prolactinoma cases) may affect the statistical power for comparisons between tumour types. The lack of a healthy control group makes it difficult to determine the excess cardiovascular risk attributable to pituitary tumours. The study may not have accounted for all potential confounding factors that could influence cardiovascular outcomes. While it examined post-operative remission and medical therapy, the analysis of specific treatment modalities and their impact on cardiovascular outcomes was limited.”
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Página 18: “Pituitary tumours have a significant cardiovascular impact, which differs depending on the type of tumour. This study shows that biochemical control may not be sufficient alone to reduce risk factors and cardiovascular events in this patient population and that strict control of cardiovascular risk factors is necessary regardless of the degree of disease activity. In patients with Cushing's disease, achieving biochemical remission in the immediate postoperative period was associated with a lower risk of cardiovascular and cerebrovascular events in these patients.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Página 18: “As a single-centre study, the data's generalisability to other populations or healthcare settings may be limited. The uneven distribution of tumour types (137 acromegaly cases, 94 Cushing's disease cases, but only 26 prolactinoma cases) may affect the statistical power for comparisons between

			tumour types. The lack of a healthy control group makes it difficult to determine the excess cardiovascular risk attributable to pituitary tumours"
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Página 19: "This study was not supported by any sponsor or funder."

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Research Article

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