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The Changing Face of Endogenous Cushing Syndrome: From Growth Failure in Childhood to Cardiometabolic Burden in Adulthood

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Abstract

Purpose

Endogenous Cushing syndrome (CS) demonstrates marked clinical heterogeneity, but age-related phenotypic differences across multiple etiologies remain insufficiently characterized. While pediatric CS is classically associated with growth failure and weight gain, adult disease is more often recognized through systemic metabolic complications. We compared the clinical, biochemical, auxological, metabolic, and etiological characteristics of pediatric/adolescent and adult patients with endogenous CS to characterize age-specific disease expression across a large real-world referral cohort.

Methods

This retrospective observational study included consecutive patients with confirmed endogenous CS evaluated at a high-volume tertiary endocrine referral center between January 2006 and December 2025. Patients were stratified into pediatric/adolescent (≤ 18 years) and adult (> 18 years) groups. Baseline demographic, clinical, anthropometric, biochemical, and etiological data were analyzed. An exploratory composite cardiometabolic burden score was constructed. Multivariable logistic regression assessed independent associations between age group and major clinical outcomes.

Results

A total of 281 patients were included (41 pediatric/adolescent, 240 adults). Pediatric/adolescent patients demonstrated a distinct auxological phenotype, with reduced height SDS (− 1.72 ± 1.21), elevated BMI SDS (+ 2.08 ± 0.91), impaired growth velocity in 83.3%, and delayed puberty/hypogonadism in 36.0%. Weight gain was nearly universal in younger patients (100% vs 81.0%, $P = 0.0008$), whereas adults had higher rates of diabetes mellitus, hypertension, proximal myopathy, fracture/osteoporosis, and greater cardiometabolic burden (*all* $P < 0.05$). Biochemical severity and etiological distribution were broadly comparable. Adult age remained independently associated with diabetes, hypertension, and high cardiometabolic burden.

Conclusions

Endogenous CS demonstrates clear age-dependent phenotypic heterogeneity. Pediatric/adolescent patients predominantly present with disproportionate weight gain, impaired growth, and pubertal disturbance, whereas adults have a greater cumulative cardiometabolic, myopathic, and skeletal burden. Recognition of these age-specific clinical patterns may support earlier diagnostic suspicion and more structured clinical evaluation.

Introduction

Endogenous Cushing syndrome (CS) is a rare but clinically important disorder caused by chronic exposure to excess endogenous glucocorticoids, resulting in substantial multisystem morbidity and increased mortality if diagnosis is delayed (1–3). The clinical manifestations of hypercortisolism are heterogeneous and may evolve insidiously, often leading to diagnostic delay, particularly in patients with non-classical or gradually progressive disease (2, 3). Although the biochemical diagnosis and etiological classification of CS are well established, the clinical expression of the disease varies considerably across patients, and factors influencing phenotypic heterogeneity remain incompletely understood.

Age is likely to be one of the most important modifiers of disease expression. In adults, endogenous CS is typically recognized through progressive weight gain, central obesity, hypertension, diabetes mellitus, proximal myopathy, neuropsychiatric symptoms, and skeletal complications (2–4). Large registry studies have consistently demonstrated the substantial cardiometabolic burden associated with adult CS, even before definitive diagnosis, reflecting prolonged systemic exposure to cortisol excess (5). However, many of these manifestations overlap with common metabolic disorders, which may reduce clinical suspicion and delay recognition. Recent contemporary reviews emphasize that the nonspecific and overlapping presentation of Cushing syndrome remains a major contributor to delayed diagnosis, particularly in patients presenting with common metabolic phenotypes rather than classical stigmata (6).

In contrast, pediatric and adolescent CS is uncommon, accounting for only a small proportion of endogenous CS cases, and differs biologically and clinically from adult disease (7, 8). In younger patients, the most characteristic clinical clue is not obesity alone, but disproportionate weight gain accompanied by impaired linear growth. Growth deceleration, delayed puberty, and altered body composition are considered hallmark features in pediatric hypercortisolism (7–9). Nevertheless, most available pediatric literature focuses predominantly on Cushing disease rather than the broader spectrum of endogenous CS, and direct comparisons between pediatric/adolescent and adult phenotypes remain limited.

Existing studies have largely examined individual manifestations of hypercortisolism rather than the broader age-dependent clinical phenotype. Moreover, most published cohorts originate from either exclusively adult endocrine practice or highly selected pediatric pituitary series, limiting generalizability across the full etiological spectrum of endogenous CS (5, 7–9). Whether age-related phenotypic differences simply reflect differences in disease etiology, or represent fundamentally distinct biological expressions of cortisol excess, remains insufficiently explored.

This distinction has practical clinical importance. Earlier recognition of pediatric CS requires heightened suspicion for abnormal growth trajectories rather than conventional metabolic red flags, whereas in adults, cumulative cardiometabolic complications may dominate presentation. Better characterization of age-specific phenotypes could therefore improve diagnostic suspicion, reduce time to diagnosis, and refine clinical assessment pathways.

In this study, we compared the clinical, biochemical, auxological, metabolic, and etiological characteristics of pediatric/adolescent and adult patients with endogenous CS managed at a high-volume tertiary endocrine center. We hypothesized that age significantly modifies the clinical expression of endogenous hypercortisolism, with younger patients demonstrating a predominantly auxological phenotype characterized by disproportionate weight gain and impaired growth, while adults exhibit a greater cardiometabolic and myopathic burden despite comparable biochemical severity of cortisol excess.

Materials and Methods

Study design and setting

This retrospective observational study was conducted at a high-volume tertiary referral center managing patients with complex endocrine disorders from a broad geographic catchment area. Consecutive patients with confirmed endogenous Cushing syndrome (CS) evaluated between January 2006 and December 2025 were screened for inclusion.

Clinical data were retrieved through systematic review of electronic medical records, inpatient case files, outpatient clinic documentation, laboratory databases, and radiological archives using a structured data extraction approach to ensure consistency in data collection.

The study was approved by the Institutional Ethics Committee. Given the retrospective observational design and use of anonymized clinical data, the requirement for informed consent was waived. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study population

Patients with biochemically confirmed endogenous CS and adequate baseline clinical and biochemical data were included. Both ACTH-dependent and ACTH-independent etiologies were eligible.

Diagnosis of endogenous Cushing syndrome was established using standard institutional diagnostic protocols consistent with contemporary guideline-based practice (3), requiring compatible clinical features together with biochemical confirmation using at least two abnormal tests where feasible, including elevated urinary free cortisol, failure of cortisol suppression following dexamethasone suppression testing, and/or loss of circadian cortisol rhythm, with plasma ACTH measurement used for etiological classification.

Patients were classified etiologically as having Cushing disease, ectopic ACTH syndrome, adrenal adenoma, adrenocortical carcinoma, bilateral adrenal disease including primary pigmented nodular adrenal disease (PPNAD), or unclassified disease where definitive localization remained inconclusive.

Patients with exogenous glucocorticoid exposure, pseudo-Cushing states, or incomplete baseline diagnostic data were excluded.

For age-stratified analyses, patients were categorized into pediatric/adolescent (≤ 18 years) and adult (> 18 years) groups. This threshold was selected to distinguish patients in whom growth and pubertal development remain clinically relevant from the adult population. Within the pediatric/adolescent cohort, patients were additionally described as children aged < 10 years and adolescents aged 10–18 years. This descriptive stratification was performed because the etiological spectrum and clinical presentation of endogenous CS may differ between younger children and adolescents. Formal comparative statistical testing between these pediatric subgroups was not performed because of the limited number of children.

Clinical and anthropometric assessment

Baseline demographic, clinical, anthropometric, biochemical, and etiological data were extracted in a standardized format.

Clinical variables included symptom duration, weight gain, obesity phenotype, hyperpigmentation, striae, easy bruising, proximal myopathy, hypertension, diabetes mellitus, acne, hyperandrogenic manifestations, menstrual dysfunction, mood disturbance, and skeletal complications including fracture or osteoporosis.

Hypertension was defined as a documented prior diagnosis, use of antihypertensive medication, or blood pressure ≥ 140/90 mmHg in adults. In pediatric/adolescent patients, hypertension was defined according to age-, sex-, and height-adjusted pediatric blood pressure criteria or documented treatment. Diabetes mellitus was defined as a documented prior diagnosis, use of glucose-lowering therapy, fasting plasma glucose ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL with symptoms, or HbA1c ≥ 6.5%.

Anthropometric parameters included height, weight, body mass index (BMI), and resting blood pressure measured during routine clinical assessment. Obesity phenotype was categorized as generalized or centripetal based on documented clinical examination findings. Generalized obesity was defined as diffuse overall adiposity on clinical assessment, whereas centripetal obesity referred to predominant truncal adiposity with relatively preserved peripheral habitus, based on documented physician examination findings.

Pediatric auxological assessment

Detailed auxological assessment was performed in pediatric/adolescent patients with sufficient available data. Height and BMI SDS were calculated using WHO age- and sex-specific reference standards. Short stature was defined as height SDS < − 2.

Where serial height measurements were available, annualized growth velocity was calculated. Growth velocity was interpreted relative to age- and sex-appropriate pediatric reference standards, with values below the expected range considered impaired. Delayed puberty or hypogonadism was assessed based on age-appropriate pubertal expectations and documented clinical evaluation.

Height–BMI SDS discordance was additionally examined as a marker of disproportionate weight gain relative to impaired linear growth.

Hormonal and biochemical assessment

Biochemical and hormonal parameters were measured in the institutional accredited central laboratory using standardized assay methods applicable during the study period. Serum cortisol was measured using electrochemiluminescence immunoassay (ECLIA; Cobas e411/e601, Roche Diagnostics, Mannheim, Germany) from 2009 onwards, and by radioimmunoassay (RIA) in the earlier study period. Plasma adrenocorticotropic hormone (ACTH) was measured using ECLIA (Elecsys; Roche Diagnostics, Germany) in later years and by RIA (Biosure Technologies, Belgium) previously. Assay performance was monitored through internal calibration procedures and routine quality assurance measures to ensure consistency across platforms. Although institutional quality control procedures were maintained, absolute hormonal values should be interpreted cautiously when comparing across eras.

Hormonal evaluation included morning serum cortisol, late-night serum cortisol, overnight dexamethasone suppression test (ONDST), low-dose dexamethasone suppression test (LDDST), high-dose dexamethasone suppression test (HDDST), plasma ACTH, and UFC, as clinically indicated. Additional biochemical assessment included serum potassium, renal function parameters, lipid profile, and glycated hemoglobin (HbA1c). Given the retrospective nature of the study and long study duration, not all investigations were available for all patients.

To facilitate comparison across assay platforms and reference ranges, UFC values were normalized relative to the upper limit of normal (× ULN).

Cardiometabolic burden assessment

As an exploratory measure of cumulative cardiometabolic and functional burden, we constructed a non-validated composite cardiometabolic burden score. One point was assigned for each of the following abnormalities: hypertension, diabetes mellitus, obesity, hypertriglyceridemia, and proximal myopathy. Hypertension was defined as a documented prior diagnosis, use of antihypertensive medication, or blood pressure ≥ 140/90 mmHg in adults; in pediatric/adolescent patients, hypertension was defined according to age-, sex-, and height-adjusted pediatric blood pressure criteria or documented treatment. Diabetes mellitus was defined as a documented diagnosis, use of glucose-lowering therapy, fasting plasma glucose ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL with symptoms, or HbA1c ≥ 6.5%. Obesity was defined as BMI ≥ 30 kg/m² in adults and BMI ≥ 95th percentile for age and sex in

pediatric/adolescent patients. Hypertriglyceridemia was defined as fasting triglycerides ≥ 150 mg/dL or documented lipid-lowering therapy for hypertriglyceridemia. Proximal myopathy was defined by documented clinical evidence of proximal muscle weakness on physician examination. The score ranged from 0 to 5, and high cardiometabolic burden was predefined as the presence of ≥ 3 abnormalities. Because this score has not been externally validated, it was used only as an exploratory descriptive measure.

Statistical analysis

Continuous variables were assessed for normality using visual inspection and the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD), while non-normally distributed variables are presented as median (interquartile range [IQR]). Categorical variables are presented as frequency (percentage).

Between-group comparisons between pediatric/adolescent and adult patients were performed using the independent samples t-test for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Multivariable logistic regression analysis was performed to evaluate independent associations between age group and clinically relevant outcomes, including diabetes mellitus, hypertension, generalized obesity, proximal myopathy, and high cardiometabolic burden. Covariates were selected a priori based on clinical relevance and potential confounding of age-related phenotype, including sex, BMI, etiological subtype, biochemical severity (morning cortisol concentration), and ACTH dependency status. Given the exploratory objective of the analysis, these variables were retained to account for major biological and disease-related determinants of phenotype.

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Missing data were handled using complete-case analysis. The extent of missingness varied by variable because of the retrospective design and differing documentation availability, particularly for pediatric auxological measures.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided, and a P value < 0.05 was considered statistically significant. Given the exploratory nature of subgroup analyses, findings should be interpreted as hypothesis-generating.

Results

A total of 281 patients with endogenous Cushing syndrome were included in the analysis, comprising 41 pediatric/adolescent patients (≤ 18 years) and 240 adults (> 18 years). Within the pediatric/adolescent cohort, 5 patients were children aged < 10 years and 36 were adolescents aged 10–18 years. Cushing disease was present in 2/5 children and 29/36 adolescents, whereas adrenal causes were relatively

more frequent among younger children. Because of the small number of children, these data were interpreted descriptively and are presented in **Supplementary Table 3.**

Baseline characteristics

Baseline demographic and anthropometric characteristics are summarized in Table 1. Pediatric/adolescent patients presented at a mean age of 15.2 ± 2.6 years, whereas adults presented at 34.8 ± 10.9 years. Female predominance was observed in both groups, although it was significantly greater among adults (72.5% vs 53.7%, P = 0.017). Sex-wise descriptive analysis showed that the pediatric/adolescent cohort had a relatively balanced distribution between males and females, whereas adults showed a stronger female predominance. The sex-wise distribution of major clinical features is shown in **Supplementary Table 4**.Adults also reported a longer symptom duration prior to diagnosis (24 [14–42] vs 18 [12–30] months, P = 0.041).

Table 1
Baseline demographic and anthropometric characteristics

Variable	Pediatric/adolescent (≤ 18 years) (n = 41)	Adults (> 18 years) (n = 240)	P value
Age, years	15.2 ± 2.6	34.8 ± 10.9	< 0.001
Female sex, n (%)	22 (53.7)	174 (72.5)	0.017
Symptom duration, months	18 (12–30)	24 (14–42)	0.041
Weight, kg	57.9 ± 16.7	70.6 ± 13.5	< 0.001
Height, cm	147.4 ± 14.1	159.0 ± 8.3	< 0.001
BMI, kg/m²	26.4 ± 4.0	28.0 ± 5.0	0.039
Systolic blood pressure, mmHg	126.7 ± 19.0	132.4 ± 19.1	0.140
Diastolic blood pressure, mmHg	82.2 ± 15.0	84.0 ± 15.0	0.564
Values are presented as mean ± SD, median (IQR), or n (%).			

Adults had significantly higher body weight (70.6 ± 13.5 vs 57.9 ± 16.7 kg, P < 0.001) and BMI (28.0 ± 5.0 vs 26.4 ± 4.0 kg/m², P = 0.039). In contrast, pediatric/adolescent patients were significantly shorter in stature (147.4 ± 14.1 vs 159.0 ± 8.3 cm, P < 0.001). Baseline systolic and diastolic blood pressure values did not differ significantly between the groups (Table 1).

Because of the retrospective design, availability of individual clinical and biochemical variables varied across patients; denominators are reported where applicable.

Auxological phenotype in pediatric/adolescent patients

Detailed auxological assessment of pediatric/adolescent patients is presented in Table 2. A distinct pattern of disproportionate weight gain with impaired linear growth was evident. Mean height SDS was −1.72 ± 1.21, whereas mean BMI SDS was + 2.08 ± 0.91, resulting in a marked height–BMI discordance.

Table 2
Auxological characteristics in pediatric/adolescent patients

Variable	Pediatric/adolescent patients (≤ 18 years)
Patients with available height/weight data	**31/41**
Height SDS	**−1.72 ± 1.21**
BMI SDS	**+ 2.08 ± 0.91**
Height SDS < − 2, n (%)	**12/31 (38.7)**
BMI ≥ 95th percentile, n (%)	**24/31 (77.4)**
BMI ≥ 99th percentile, n (%)	**10/31 (32.3)**
Height SDS–BMI SDS discordance	**3.80 ± 1.34**
Patients with serial height data	**18/41**
Growth velocity, cm/year	**2.1 ± 1.3**
Impaired growth velocity, n (%)	**15/18 (83.3)**
Delayed puberty / hypogonadism, n (%)	**9/25 (36.0)**

Abbreviations: BMI = body mass index; SDS = standard deviation score. Data are presented as mean ± standard deviation unless otherwise specified. Height SDS–BMI SDS discordance represents the absolute difference between BMI SDS and height SDS. Delayed puberty/hypogonadism was assessed only in evaluable patients.

Clinically significant short stature (height SDS < − 2) was present in 38.7% of evaluable patients, while 77.4% had obesity above the 95th percentile, including 32.3% with severe obesity (> 99th percentile). Among those with serial auxological data, mean growth velocity was substantially reduced (2.1 ± 1.3 cm/year), and impaired growth velocity was documented in 83.3%. Delayed puberty or hypogonadism was noted in 36.0% of evaluable patients (Table 2).

These findings highlight the characteristic pediatric presentation of endogenous Cushing syndrome, in which excess weight gain occurs alongside impaired somatic growth.

Clinical phenotype according to age

Age-related differences in clinical presentation are summarized in Table 3. Weight gain was nearly universal among pediatric/adolescent patients (100% vs 81.0%, P = 0.0008). Generalized obesity was significantly more frequent in younger patients (29.3% vs 10.1%, P = 0.002), whereas centripetal obesity occurred with similar frequency in both groups.

Table 3
Clinical phenotype according to age group

Clinical feature	Pediatric/adolescent (≤ 18 years)	Adults (> 18 years)	P value
Weight gain	39/39 (100)	192/237 (81.0)	0.0008
Obesity	35/41 (85.4)	178/238 (74.8)	0.167
Centripetal obesity	23/41 (56.1)	154/238 (64.7)	0.297
Generalized obesity	12/41 (29.3)	24/238 (10.1)	0.002
Pigmentation	27/40 (67.5)	144/233 (61.8)	0.596
Striae	30/40 (75.0)	136/236 (57.6)	0.054
Bruising	18/40 (45.0)	123/233 (52.8)	0.395
Proximal myopathy	18/40 (45.0)	150/235 (63.8)	0.034
Hypertension	20/40 (50.0)	179/235 (76.2)	0.001
Diabetes mellitus	11/41 (26.8)	150/235 (63.8)	< 0.001
Acne	17/40 (42.5)	80/227 (35.2)	0.379
Hirsutism / hyperandrogenism	16/36 (44.4)	72/205 (35.1)	0.284
Menstrual irregularity*	12/22 (54.5)	112/174 (64.4)	0.361
Mood disturbance	11/39 (28.2)	84/226 (37.2)	0.293
Fracture / osteoporosis	3/38 (7.9)	51/218 (23.4)	0.032

Abbreviations: Data are presented as n/N (%). Denominators vary because of incomplete retrospective clinical documentation. Generalized obesity denotes diffuse overall adiposity, whereas centripetal obesity denotes predominant truncal adiposity with relative peripheral sparing based on physician clinical assessment.

*Assessed in female patients only.

Adults demonstrated a more severe systemic phenotype. Hypertension was significantly more common among adults (76.2% vs 50.0%, P = 0.001), as was diabetes mellitus (63.8% vs 26.8%, P < 0.001). Adults also had higher rates of proximal myopathy (63.8% vs 45.0%, P = 0.034), skeletal complications including fracture or osteoporosis (23.4% vs 7.9%, P = 0.032), hypertriglyceridemia, and overall cardiometabolic burden (Fig. 1).

Cutaneous manifestations such as striae and bruising were common in both groups, without statistically significant differences. Similarly, acne, hyperandrogenic manifestations, menstrual irregularities, and mood disturbances were broadly comparable between age groups (Table 3).

Overall, pediatric/adolescent patients showed a phenotype dominated by abnormal growth and weight gain, whereas adults accumulated greater systemic metabolic and musculoskeletal morbidity.

Biochemical and metabolic profile

Biochemical and metabolic characteristics are summarized in Table 4. Despite marked phenotypic differences, no major between-group differences were observed in available biochemical indices of hypercortisolism. Morning serum cortisol, late-night cortisol, urinary free cortisol, and dexamethasone suppression test responses did not differ significantly.

Table 4
Biochemical and metabolic profile according to age group

Variable	Pediatric/adolescent (≤ 18 years)	Adults (> 18 years)	P value
Morning cortisol, nmol/L	848.7 ± 319.5	806.2 ± 458.4	0.478
Midnight cortisol, nmol/L	675.8 ± 275.7	692.2 ± 367.6	0.763
ONDST cortisol, nmol/L	558.2 ± 361.6	612.2 ± 419.8	0.456
LDDST cortisol, nmol/L	516.7 ± 381.8	501.1 ± 377.6	0.835
HDDST cortisol, nmol/L	288.8 ± 353.5	361.3 ± 377.6	0.293
Morning ACTH, pg/mL	73.8 ± 35.0	103.8 ± 43.1	0.029
UFC, × ULN	4.8 (2.6–8.2)	5.2 (2.8–9.6)	0.491
ACTH-dependent disease, n (%)	34/41 (82.9)	191/240 (79.6)	0.625
Potassium, mmol/L	4.10 ± 0.56	4.09 ± 0.65	0.928
Hypokalemia, n (%)	6/39 (15.4)	52/225 (23.1)	0.287
Triglycerides, mg/dL	136.2 ± 42.2	185.3 ± 110.6	0.001
Hypertriglyceridemia, n (%)	13/36 (36.1)	133/212 (62.7)	0.003
Fasting plasma glucose, mg/dL	112.6 ± 38.4	157.8 ± 68.5	< 0.001
HbA1c, %	5.43 ± 0.70	7.40 ± 2.06	< 0.001

Abbreviations: ACTH = adrenocorticotropic hormone; HbA1c = glycated hemoglobin; HDDST = high-dose dexamethasone suppression test; LDDST = low-dose dexamethasone suppression test; ONDST = overnight dexamethasone suppression test; UFC = urinary free cortisol; ULN = upper limit of normal. Data are presented as mean ± standard deviation, median (interquartile range), or n/N (%), as appropriate. Denominators vary because of incomplete retrospective biochemical data availability. UFC values are expressed as multiples of the assay-specific upper limit of normal to account for assay variation across the study period. Hypokalemia was defined as serum potassium <3.5 mmol/L, and hypertriglyceridemia as triglycerides ≥150 mg/dL.

Adults had significantly higher morning ACTH concentrations (103.8 ± 43.1 vs 73.8 ± 35.0 pg/mL, P = 0.029), although the overall proportion of ACTH-dependent disease was similar.

Metabolic abnormalities were considerably more pronounced in adults. Triglyceride levels were significantly higher (**185.3 ± 110.6 vs 136.2 ± 42.2 mg/dL, P = 0.001**), with hypertriglyceridemia present in nearly two-thirds of adults (**62.7% vs 36.1%, P = 0.003**). Glycemic burden was also substantially greater in adults. Fasting plasma glucose was higher in adults than in pediatric/adolescent patients

(157.8 ± 68.5 vs 112.6 ± 38.4 mg/dL, P < 0.001), and HbA1c values were also higher in adults (7.4 ± 2.1% vs 5.4 ± 0.7%, P < 0.001), consistent with the greater prevalence of overt diabetes mellitus. Additional metabolic laboratory parameters, including renal function and lipid fractions, are shown in Supplementary Table 2.

These findings suggest that differences in clinical phenotype are unlikely to be explained solely by differences in biochemical severity of cortisol excess.

Etiological distribution

The etiological distribution of endogenous Cushing syndrome was comparable between age groups (Table 5). Cushing disease was the predominant etiology in both pediatric/adolescent and adult patients (75.6% vs 73.3%, P = 0.761), followed by ectopic ACTH syndrome and adrenal causes.

Table 5
Etiological distribution of endogenous Cushing syndrome

Etiology	Pediatric/adolescent (≤ 18 years)	Adults (> 18 years)	P value
Cushing disease	31/41 (75.6)	176/240 (73.3)	0.761
Ectopic ACTH syndrome	3/41 (7.3)	15/240 (6.3)	0.734
Adrenal adenoma	4/41 (9.8)	31/240 (12.9)	0.582
Adrenocortical carcinoma	1/41 (2.4)	8/240 (3.3)	1.000
Bilateral adrenal disease / PPNAD	2/41 (4.9)	5/240 (2.1)	0.278
Unclassified / pending localization	0	5/240 (2.1)	1.000

Abbreviations: ACTH = adrenocorticotropic hormone; PPNAD = primary pigmented nodular adrenocortical disease. Data are presented as n/N (%). Etiological classification was based on integrated clinical, biochemical, imaging, and histopathological assessment, where available.

The proportions of adrenal adenoma, adrenocortical carcinoma, bilateral adrenal disease, and unclassified cases did not differ significantly (Table 5). This suggests that the observed age-related phenotypic differences were not attributable to major differences in underlying disease etiology.

Cardiometabolic burden

Overall cardiometabolic burden was substantially greater in adults, as shown in **Supplementary Table 1**. A high cardiometabolic burden score (≥ 3 metabolic complications) was significantly more frequent in adults (65.6% vs 39.5%, P = 0.003), with a higher median burden score (3 [2–4] vs 2 [2–3], P = 0.002).

This reinforces the observation that adults with endogenous Cushing syndrome present with a greater cumulative burden of metabolic and cardiovascular complications.

Multivariable analysis

Multivariable logistic regression analysis is presented in Table 6. After adjustment for sex, BMI, etiological subtype, morning cortisol levels, and ACTH dependency, adult age remained independently associated with diabetes mellitus (adjusted OR 3.21, 95% CI 1.47–7.02; P = 0.004), hypertension (adjusted OR 2.54, 95% CI 1.18–5.46; P = 0.017), and high cardiometabolic burden (adjusted OR 2.68, 95% CI 1.27–5.64; P = 0.010).

Table 6
Multivariable logistic regression analysis

Outcome	Predictor	Adjusted OR	95% CI	P value
Diabetes mellitus	Adult age group	3.21	1.47–7.02	0.004
Hypertension	Adult age group	2.54	1.18–5.46	0.017
Myopathy	Adult age group	1.89	0.93–3.82	0.078
Generalized obesity	Pediatric/adolescent age group	2.92	1.25–6.82	0.013
High cardiometabolic burden (≥ 3)	Adult age group	2.68	1.27–5.64	0.010

Abbreviations: ACTH = adrenocorticotropic hormone; CI = confidence interval; OR = odds ratio. Multivariable logistic regression models were adjusted for prespecified clinically relevant covariates, including sex, body mass index, etiological subtype, morning cortisol concentration, and ACTH dependency status. High cardiometabolic burden was defined as the presence of ≥ 3 of the following: hypertension, diabetes mellitus, obesity, hypertriglyceridemia, and proximal myopathy.

Conversely, pediatric/adolescent age was independently associated with generalized obesity (adjusted OR 2.92, 95% CI 1.25–6.82; P = 0.013) (Table 6**).**

Taken together, these findings demonstrate that age significantly modifies the clinical expression of endogenous Cushing syndrome (Fig. 2). Pediatric/adolescent patients predominantly exhibit an auxological phenotype characterized by disproportionate weight gain and impaired growth, whereas adults develop a more pronounced cardiometabolic and myopathic phenotype, despite comparable biochemical severity of hypercortisolism.

Discussion

In this large tertiary-care cohort of endogenous Cushing syndrome (CS), age significantly influenced clinical presentation. Pediatric/adolescent patients predominantly showed an auxological phenotype

with disproportionate weight gain, impaired linear growth, and pubertal disturbance, whereas adults had a greater burden of cardiometabolic and musculoskeletal complications, including diabetes, hypertension, hypertriglyceridemia, proximal myopathy, and skeletal fragility. These differences occurred despite broadly similar biochemical severity and etiological distribution, suggesting that age meaningfully shapes disease expression.

The adult phenotype in our cohort is consistent with prior studies highlighting the systemic metabolic burden of chronic cortisol excess (4, 5). Adults had significantly higher rates of diabetes mellitus, hypertension, hypertriglyceridemia, and proximal myopathy, with multivariable analysis confirming independent associations between adult age and both diabetes and hypertension. Similar findings have been reported in large registry cohorts, where hypertension, weight gain, skin manifestations, and myopathy are among the most common presenting features of adult Cushing syndrome (5). Chronic glucocorticoid excess contributes to insulin resistance, visceral adiposity, endothelial dysfunction, and dyslipidemia, thereby increasing cardiometabolic risk over time (4). The higher cardiometabolic burden observed in adults likely reflects cumulative cortisol exposure superimposed on age-related metabolic susceptibility. Contemporary reviews continue to emphasize the disproportionate cardiovascular and metabolic morbidity associated with untreated hypercortisolism, even in patients without florid classical presentation (6). Some of the observed differences may also reflect baseline age-related cardiometabolic risk independent of hypercortisolism, which cannot be fully disentangled in a retrospective comparison.

In contrast, the pediatric/adolescent phenotype was distinct. Although obesity and weight gain were common, the hallmark feature was disproportionate adiposity accompanied by impaired linear growth. Pediatric patients had lower height SDS, higher BMI SDS, marked height–BMI discordance, and significantly reduced growth velocity where serial auxological data were available. This pattern is well recognized in pediatric endocrine literature, where progressive weight gain with declining growth velocity is considered a key clinical clue to endogenous hypercortisolism (7–10). In routine practice, obesity alone may be attributed to lifestyle factors, but weight gain accompanied by impaired growth should prompt suspicion for pathological hypercortisolism.

Within the pediatric/adolescent cohort, descriptive stratification showed that most patients were adolescents aged 10–18 years, while children aged < 10 years constituted a smaller subgroup. Although formal subgroup comparison was limited by sample size, adrenal causes appeared relatively more frequent among younger children, whereas Cushing disease predominated among adolescents. This pattern is consistent with the recognized age-related etiological distribution of pediatric Cushing syndrome. Similarly, the pediatric/adolescent group showed a relatively balanced sex distribution, in contrast to the stronger female predominance observed among adults. These findings support the importance of considering age and developmental stage when interpreting the clinical phenotype of endogenous CS.

Recent pediatric screening recommendations similarly emphasize that declining growth velocity in the context of weight gain should trigger targeted evaluation for hypercortisolism, rather than attributing obesity solely to lifestyle factors (11).

Recent prospective pediatric data further support these observations. A large multicenter cohort of pediatric endogenous Cushing syndrome similarly identified growth deceleration, excess weight gain, and pubertal disturbance as dominant presenting features, reinforcing impaired linear growth as one of the most clinically discriminative clues in younger patients (9).

Delayed puberty or hypogonadism was observed in over one-third of evaluable pediatric/adolescent patients, highlighting the broader developmental impact of sustained cortisol excess. Glucocorticoid excess can impair growth hormone secretion, disrupt insulin-like growth factor-1 action, and suppress gonadotropin pulsatility, thereby affecting both linear growth and pubertal progression (10, 12). These consequences are particularly relevant in younger patients, in whom even relatively shorter disease duration may result in clinically evident endocrine dysfunction.

An important finding in our study was that these phenotypic differences were observed despite broadly comparable biochemical indices of hypercortisolism, including morning cortisol, late-night cortisol, urinary free cortisol, and dexamethasone suppression responses. This suggests that absolute biochemical severity alone may not fully explain the observed clinical heterogeneity. Adults may accumulate greater cumulative cortisol exposure before diagnosis despite similar biochemical values at presentation, while age-related differences in metabolic vulnerability and physiological response to cortisol excess may also contribute. The consequences of hypercortisolism during active growth are inherently different from those in metabolically mature adults. Together, these findings suggest that age and developmental stage meaningfully influence clinical phenotype (Fig. 2). This interpretation is also consistent with the recognized diagnostic complexity of Cushing syndrome, particularly in patients with variable or cyclic cortisol secretion, where single time-point biochemical values may not fully reflect cumulative exposure (13).

The similar etiological distribution between pediatric/adolescent and adult groups strengthens this interpretation. Cushing disease was the predominant etiology in both groups, with no significant differences in the proportions of pituitary, ectopic, or adrenal causes. This makes it less likely that the observed phenotypic differences were primarily driven by underlying disease etiology. Previous studies have shown that ectopic ACTH syndrome is often associated with a more severe metabolic phenotype, including greater hypokalemia, diabetes, and myopathy (5, 14). Given the comparable etiological distribution in our cohort, age appears to be a more plausible contributor to the observed clinical differences.

The higher burden of fracture and osteoporosis observed in adults is also notable. Chronic glucocorticoid excess adversely affects bone through impaired bone formation, increased bone resorption, and deterioration of trabecular microarchitecture (15). Although pediatric patients may also have impaired skeletal accrual, overt fragility events are less commonly recognized at presentation. In

adults, the greater burden likely reflects the combined effects of prolonged cortisol exposure and age-related baseline skeletal vulnerability.

Our findings have practical diagnostic implications. In adults, unexplained diabetes mellitus, resistant hypertension, dyslipidemia, or proximal myopathy should raise suspicion for hypercortisolism in the appropriate clinical setting. In contrast, in pediatric practice, the most important clue may be disproportionate weight gain accompanied by impaired linear growth rather than obesity alone. Delayed recognition remains a major challenge in Cushing syndrome, and diagnostic suspicion is often shaped by the clinician's perception of the "classical" phenotype (16). Our findings suggest that this clinical framework should be age-specific.

This study has several strengths. It includes a relatively large cohort from a high-volume tertiary endocrine referral center and captures multiple etiologies of endogenous Cushing syndrome rather than focusing solely on Cushing disease. Although several individual features of pediatric and adult CS are well recognized, direct comparative analyses across pediatric/adolescent and adult patients within the same real-world referral cohort remain limited. The present study therefore adds practical value by quantifying age-related differences across auxological, metabolic, myopathic, skeletal, biochemical, and etiological domains using a uniform institutional dataset. The inclusion of detailed pediatric auxological assessment, descriptive pediatric subgrouping, sex-wise analysis, and adjusted models further strengthens the clinical interpretation of the findings.

Certain limitations should be acknowledged. The retrospective design introduces the possibility of documentation bias and incomplete data capture, particularly for pediatric auxological variables. Not all biochemical investigations were uniformly available because of the long study period and evolving diagnostic practices, and hormonal assay platforms changed over time, which may affect comparability despite institutional quality control measures. Referral bias is also possible given the tertiary-care setting. The cardiometabolic burden score was exploratory and has not been externally validated; therefore, it should be interpreted as a descriptive measure of cumulative clinical burden rather than a prognostic tool. Age-related background risks for diabetes, hypertension, and skeletal disease may partly contribute to adult–pediatric differences and cannot be fully separated from the effects of hypercortisolism in this retrospective design. Given the relatively smaller pediatric subgroup, subgroup and multivariable analyses should be interpreted cautiously as exploratory and hypothesis-generating rather than confirmatory.

Nevertheless, our findings provide clinically relevant insight by showing that the presentation of endogenous Cushing syndrome varies meaningfully with age and developmental stage, rather than reflecting a uniform biochemical disorder with variable symptom burden. This distinction may help improve diagnostic recognition, particularly in younger patients, where delayed diagnosis can adversely affect growth and pubertal development (17, 18).

In conclusion, endogenous Cushing syndrome demonstrates clear age-dependent differences in clinical phenotype. Pediatric/adolescent patients predominantly present with disproportionate weight gain,

impaired growth velocity, short stature, increased BMI SDS, and pubertal disturbance, whereas adults exhibit a greater burden of diabetes mellitus, hypertension, hypertriglyceridemia, proximal myopathy, and skeletal complications despite broadly similar biochemical severity and etiological distribution. Descriptive pediatric subgrouping and sex-wise analysis further support the influence of age and developmental stage on disease expression. Recognition of these age-specific patterns may facilitate earlier diagnostic suspicion and more structured clinical evaluation in both pediatric and adult practice.

Declarations

Competing Interests

The authors declare that they have no competing financial or non-financial interests related to this work.

Funding

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Ethics Approval

The study was approved by the Institutional Ethics Committee, Postgraduate Institute of Medical Education and Research, Chandigarh, India (**INT/IEC/2017/85**) and conducted in accordance with the principles of the Declaration of Helsinki.

Consent to Participate

Informed consent was obtained from participants or waived due to the retrospective design, as per institutional guidelines.

Consent for Publication

Given the retrospective observational design and use of anonymized clinical data, the requirement for informed consent was waived by the Institutional Ethics Committee.

Availability of Data and Material

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

V.J. and R.P. contributed to conceptualization, data curation, formal analysis, and wrote the original draft of the manuscript. K.K. contributed to data curation, formal analysis, and interpretation of data. B.S. , J.J., C.A. and J.K. contributed to data curation and formal analysis. S.K.B. contributed to supervision and critically reviewed and edited the manuscript. R.W. contributed to conceptualization, supervision, critical revision, and final approval of the manuscript. All authors reviewed and approved the final manuscript.

Use of AI Tools

AI-assisted language editing tools were used only to improve grammar and readability. All scientific content, data analysis, interpretation, and final manuscript decisions were performed and verified by the authors, who take full responsibility for the integrity and accuracy of the work.

References

1. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM et al (2008) The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93(5):1526–1540
2. Gadelha M, Gatto F, Wildemberg LE, Fleseriu M (2023) Cushing's syndrome. Lancet 402(10418):2237–2252
3. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR et al (2021) Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 9(12):847–875
4. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A (2016) Complications of Cushing's syndrome: state of the art. Lancet Diabetes Endocrinol 4(7):611–629
5. Valassi E (2022) Clinical presentation and etiology of Cushing's syndrome: Data from ERCUSYN. J Neuroendocrinol 34(8):e13114
6. Reincke M, Fleseriu M (2023) Cushing Syndrome: A Review. JAMA 330(2):170–181
7. Lodish MB, Keil MF, Stratakis CA (2018) Cushing's Syndrome in Pediatrics: An Update. Endocrinol Metab Clin North Am 47(2):451–462
8. Ferrigno R, Hasenmajer V, Caiulo S, Minnetti M, Mazzotta P, Storr HL et al (2021) Paediatric Cushing's disease: Epidemiology, pathogenesis, clinical management and outcome. Rev Endocr Metab Disord 22(4):817–835
9. Tatsi C, Kamilaris C, Keil M, Saidkhodjaeva L, Faucz FR, Chittiboina P et al (2024) Paediatric Cushing syndrome: a prospective, multisite, observational cohort study. Lancet Child Adolesc Health 8(1):51–62
10. Stratakis CA (2016) Diagnosis and Clinical Genetics of Cushing Syndrome in Pediatrics. Endocrinol Metab Clin North Am 45(2):311–328

11. Chioma L, Patti G, Cappa M, Maghnie M (2025) Cushing syndrome in paediatric population: who and how to screen. J Endocrinol Invest 48(Suppl 1):7–19
12. Magiakou MA, Chrousos GP (2002) Cushing's syndrome in children and adolescents: current diagnostic and therapeutic strategies. J Endocrinol Invest 25(2):181–194
13. Nowak E, Vogel F, Albani A, Braun L, Rubinstein G, Zopp S et al (2023) Diagnostic challenges in cyclic Cushing's syndrome: a systematic review. Lancet Diabetes Endocrinol 11(8):593–606
14. Isidori AM, Lenzi A (2007) Ectopic ACTH syndrome. Arq Bras Endocrinol Metabol 51(8):1217–1225
15. Mancini T, Doga M, Mazziotti G, Giustina A (2004) Cushing's syndrome and bone. Pituitary 7(4):249–252
16. Ragnarsson O, Olsson DS, Papakokkinou E, Chantzichristos D, Dahlqvist P, Segerstedt E et al (2019) Overall and Disease-Specific Mortality in Patients With Cushing Disease: A Swedish Nationwide Study. J Clin Endocrinol Metab 104(6):2375–2384
17. Davies JH, Storr HL, Davies K, Monson JP, Besser GM, Afshar F et al (2005) Final adult height and body mass index after cure of paediatric Cushing's disease. Clin Endocrinol (Oxf) 62(4):466–472
18. Yordanova G, Martin L, Afshar F, Sabin I, Alusi G, Plowman NP et al (2016) Long-term outcomes of children treated for Cushing's disease: a single center experience. Pituitary 19(6):612–624

Figures

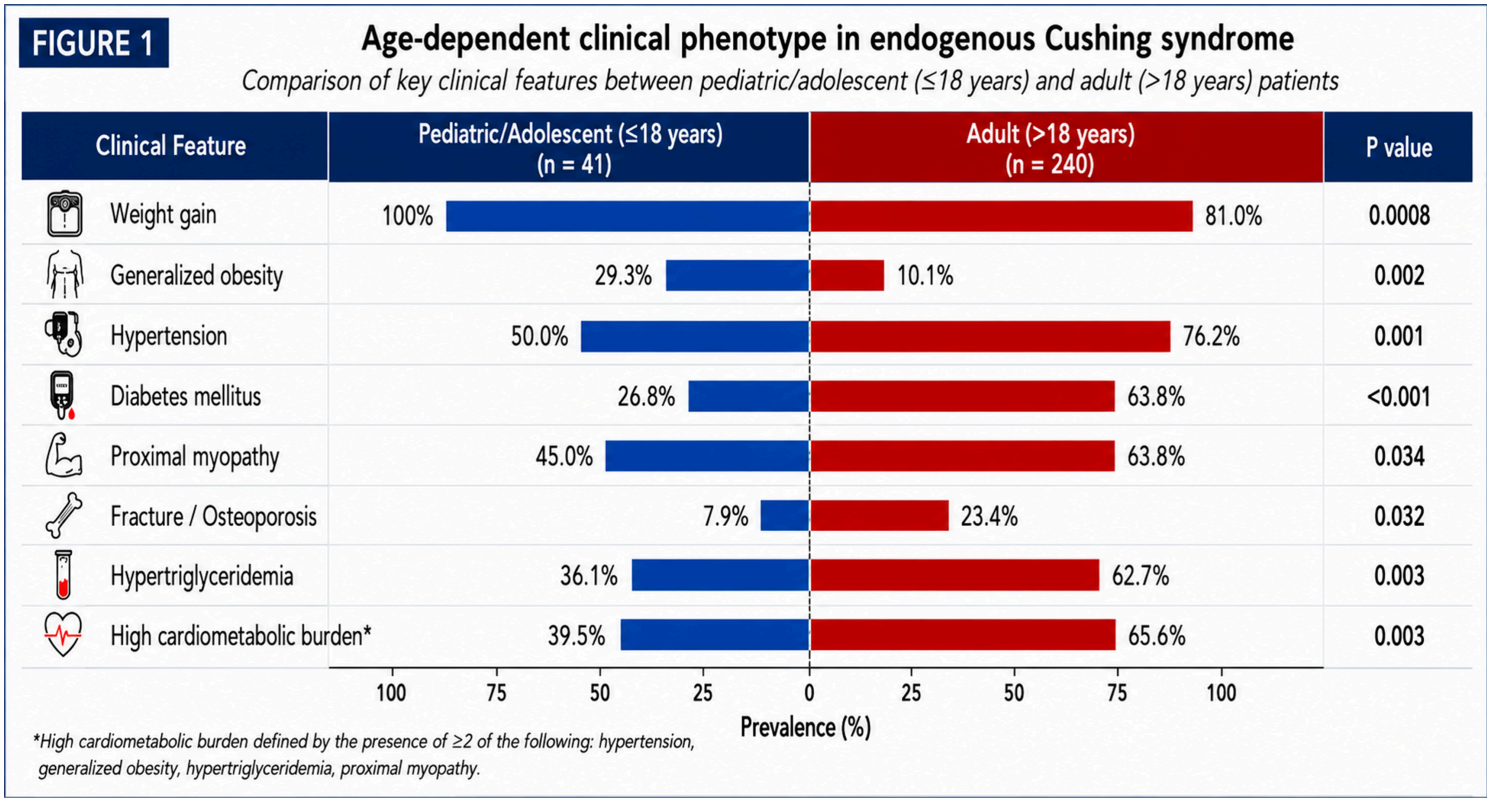


Figure 1

Age-dependent clinical phenotype in endogenous Cushing syndrome.
Comparison of the prevalence of key clinical manifestations between pediatric/adolescent patients (≤18 years; *n* = 41) and adults (>18 years; *n* = 240) with endogenous Cushing syndrome. Pediatric/adolescent patients more frequently presented with universal weight gain and generalized obesity, reflecting a predominantly auxological phenotype, whereas adults exhibited a higher burden of cardiometabolic and musculoskeletal complications, including hypertension, diabetes mellitus, proximal myopathy, hypertriglyceridemia, and fracture/osteoporosis. High cardiometabolic burden was defined as ≥3 of the following: hypertension, diabetes mellitus, obesity, hypertriglyceridemia, and proximal myopathy.

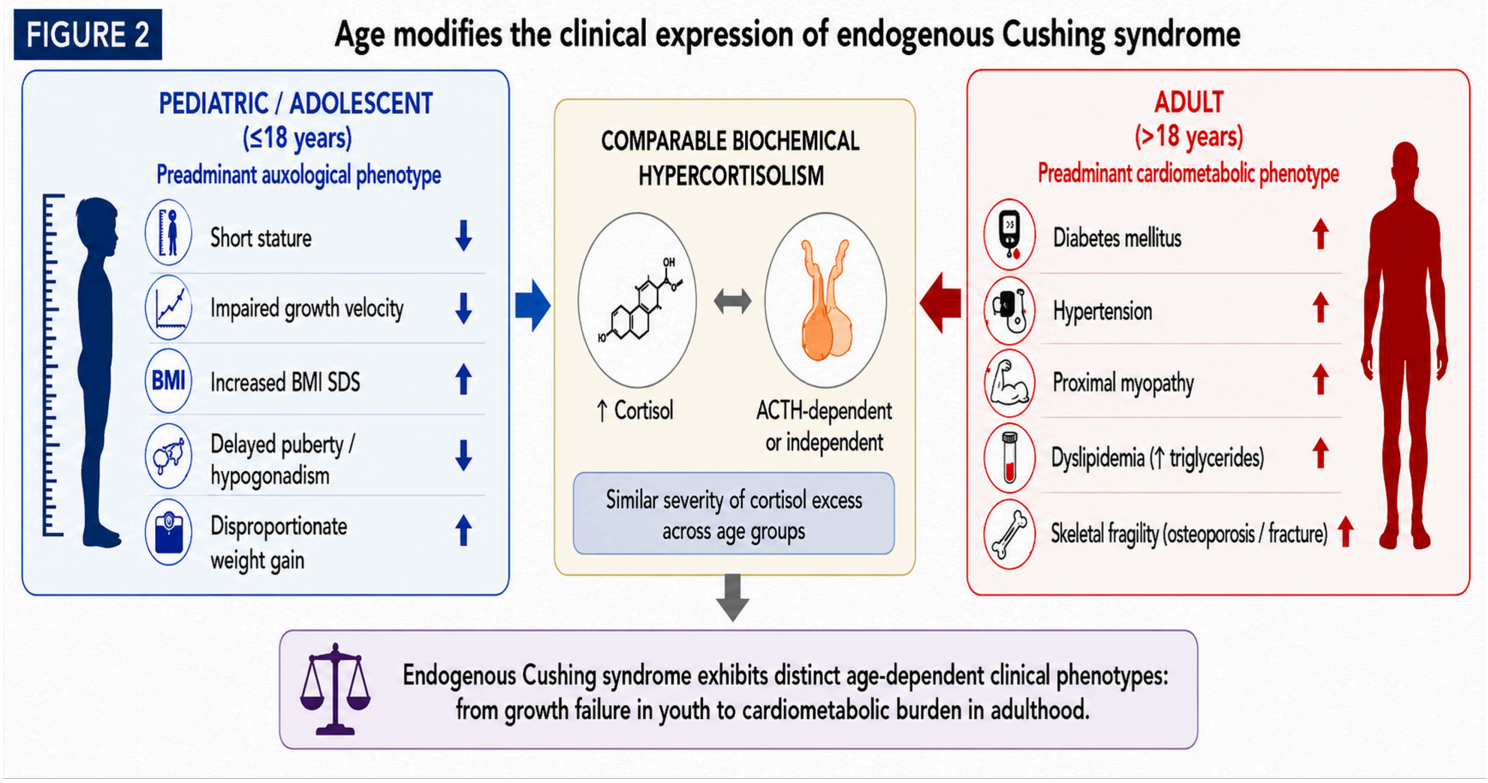


Figure 2

Conceptual illustration of age-dependent clinical expression in endogenous Cushing syndrome.
Schematic representation highlighting the differential clinical phenotype of endogenous Cushing syndrome across age groups despite no major differences in available biochemical severity indices of hypercortisolism. In pediatric/adolescent patients (≤18 years), the predominant phenotype is auxological, characterized by short stature, impaired growth velocity, increased BMI standard deviation score (SDS), delayed puberty/hypogonadism, and disproportionate weight gain. In contrast, adults (>18 years) demonstrate a predominant cardiometabolic and musculoskeletal phenotype, characterized by diabetes mellitus, hypertension, proximal myopathy, dyslipidemia (particularly hypertriglyceridemia), and skeletal fragility (osteoporosis/fractures). These findings emphasize that age significantly modifies the clinical expression of endogenous hypercortisolism, with growth impairment predominating in younger patients and systemic metabolic complications in adults.

Supplementary Files

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