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Pubertal timing, tempo and growth through puberty in children with hypophosphataemic rickets: a single-centre retrospective cohort study

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Abstract

Background

Children with hypophosphataemic rickets (HR) remain short despite conventional treatment. It is still debated when height is lost, and pubertal timing and tempo have rarely been compared with population references. We compared both with Turkish references and described growth through puberty in children with HR of mixed aetiology.

Methods

This exploratory retrospective single-centre study included 33 children with HR first seen in 1994–2025. Ages at pubertal onset (breast stage 2 or testicular volume ≥ 4 mL; interval-censored analysis of all patients) and at menarche were compared with Turkish references. Height standard deviation scores (SDS) across pubertal stages were analysed with a linear mixed model, excluding growth hormone-treated children.

Results

Mean onset age was 9.68 years in girls and 9.75 years in boys; the differences from the reference were − 0.42 years (95% confidence interval [CI] − 1.25 to 0.38) and − 1.85 years (− 2.86 to − 0.86). Menarche (n = 10, mostly whole-year ages) was 0.95 years (0.40 to 1.49) later than the reference, mainly in girls first seen after onset. In five girls followed from before puberty, the difference in age at menarche was + 0.48 years (− 0.32 to 1.28), and their mean interval from breast stage 2 to menarche was at least 2.80 years (difference from the reference + 1.00 years, − 0.47 to 2.47). In 12 patients with ≥ 2 measurements from stage 2 onwards, height SDS fell by 0.82 (0.44 to 1.19) between stage 2 and near-final height (NFH), yet the five measured at both points gained 14.2–32.4 cm, within or above the reference range. NFH was − 2.88 ± 1.56 SDS (mean ± standard deviation; n = 12) and 1.70 SDS (0.58 to 2.82) below target height (n = 8).

Conclusions

Pubertal onset was not delayed and may be early in boys; a slower tempo in girls needs confirmation. In this small cohort, height SDS fell through puberty despite height gains in centimetres within or above the reference range, and NFH remained well below target height.

Background

Hypophosphataemic rickets (HR) comprises disorders of renal phosphate wasting. In X-linked hypophosphataemia (XLH), pathogenic *PHEX* variants lead to excess fibroblast growth factor 23 (FGF23)

[1]. XLH accounted for most genetically confirmed cases in a Turkish national cohort, in which *DMP1* and *SLC34A3* variants were also found [2]. Conventional treatment of XLH combines oral phosphate with active vitamin D [3], whereas FGF23-independent forms differ in mechanism and treatment. Burosumab, an anti-FGF23 antibody, improved rickets and growth more than conventional treatment in a randomised trial [4] and was associated with greater gains in height standard deviation score (SDS) in a real-world study [5]. It is now recommended as first-line treatment for children with XLH and rickets [3].

Adults with XLH remain short. In a French cohort of 398 adults, mean final height SDS was − 2.08 in men and − 1.70 in women [6]. Earlier treatment is associated with better growth [7], but it is still debated when height is lost. Steendijk and Hauspie described a normal pubertal spurt that did not restore the earlier deficit [8], and Sochett et al. found nearly normal pubertal height gain in six girls [9]. Others reported a slower pubertal spurt, with only a short spurt in limb growth [10], a fall in height SDS after 13 years of age [11] and, in a Turkish *PHEX*-positive cohort, lower height SDS during puberty than before it, without an observable pubertal spurt [12].

Pubertal timing and tempo have received less attention and have rarely been compared with population references. We therefore compared them with Turkish references in children with HR of mixed aetiology followed at a single centre, and described height through puberty in both SDS and centimetres.

Methods

Study design and participants

This retrospective cohort study included all children with HR whose first visit to the Department of Paediatric Endocrinology, Istanbul Faculty of Medicine, was between 1994 and 2025. HR was diagnosed by clinical and/or radiological signs of rickets together with hypophosphataemia for age, renal phosphate wasting (tubular reabsorption of phosphate [TRP] or ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate [TmP/GFR] inappropriately low for the serum phosphate concentration), elevated alkaline phosphatase, and normal serum calcium and 25-hydroxyvitamin D concentrations. Twenty patients had genetic testing: *PHEX* was first analysed by Sanger sequencing and multiplex ligation-dependent probe amplification, followed by clinical exome sequencing when no *PHEX* variant was found. Of 34 patients identified, one with Dent disease (*CLCN5* variant) was excluded, leaving 33 (18 girls, 15 boys) for the analyses of pubertal timing (Fig. 1). The three patients treated with growth hormone (GH; one girl and two boys, all prepubertal when GH was started) were excluded from the growth analyses, leaving a growth cohort of 30; a sensitivity analysis included them (Additional file 1: Table S1). In the text and figures, girls are numbered 1–18 and boys 19–33, each in order of age at the first visit. Some patients may have been included in the national cohort study, which did not report pubertal data [2]. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13] (Additional file 2).

Data collection

We extracted family history, genetic results, FGF23 and 1,25-dihydroxyvitamin D where measured, TRP and TmP/GFR, treatment and its earliest documented start, physician-recorded adherence, GH or burosumab use, orthopaedic surgery, nephrocalcinosis, nephrolithiasis, parathyroid adenoma, and bone age where recorded (Greulich–Pyle method, read by paediatric endocrinologists [14]). Disease was classified as FGF23-mediated (pathogenic *PHEX* variant or elevated FGF23), FGF23-independent (pathogenic *SLC34A3* or *SLC34A1* variant, or low FGF23 with elevated 1,25-dihydroxyvitamin D) or unclassified.

Anthropometry

Height was measured with a wall-mounted Harpenden stadiometer and expressed as SDS using Turkish references [15], and sitting height/height ratio as SDS using Turkish references [16]; body mass index (BMI) was expressed as SDS using the same references as height [15]. Because the references end at 18 years, 18-year values were used for older patients. Target height was the sex-adjusted mid-parental height ([father's height + mother's height ± 13 cm]/2) [17], expressed as SDS with the 18-year reference. Near-final height (NFH) was height at ≥ 18 years, or at ≥ 15 years in girls and ≥ 16 years in boys once height velocity over at least 1 year was below 2 cm/year [18].

Pubertal assessment and reference data

Pubertal stage was assessed by paediatric endocrinologists according to Marshall and Tanner [19, 20], with testicular volume measured by Prader orchidometer. Onset was defined as breast stage 2 in girls and testicular volume ≥ 4 mL in boys; for brevity, both are called stage 2. Because stages were recorded at visits, onset was known only to lie within an interval: between the last documented prepubertal assessment and the visit at which stage 2 was first recorded (onset observed), before the first visit (pubertal at the first visit) or after the last visit (prepubertal at the last visit). Age at menarche was reported by the patients. Girls who were prepubertal at the first visit are described as followed from before puberty, and those already pubertal at the first visit as first seen after pubertal onset.

Onset was compared with a mixed-longitudinal cohort of Istanbul children from high socioeconomic backgrounds examined in 1989–2002 (girls, 10.1 ± 1.0 years [21]; boys, 11.6 ± 1.2 years [22]). For menarche, the same cohort was the primary reference (reference A, 12.2 ± 0.9 years [21]). Secondary references were a survey in Denizli (B, 12.41 years, by recall [23]) and probit medians from surveys of Istanbul schoolgirls published in 2011 (C, 12.74 years [24]) and conducted in 2022 (D, 12.04 years [25]). Reference values for the interval from breast stage 2 to menarche (1.8 ± 0.6 years) and for total pubertal height gain from onset to final height (girls 16.0 ± 3.9 cm, boys 26.4 ± 4.3 cm) came from the children of this cohort who were followed longitudinally to final height: 101 girls, whose mean age at breast stage 2 was 10.6 ± 0.9 years, and 30 boys [21, 22].

Statistical analysis

Data are mean ± standard deviation (SD) or median (interquartile range [IQR] or range). The study was exploratory: there was no sample size calculation or correction for multiple comparisons, and estimates are given with 95% confidence intervals (CIs).

For each sex, mean onset age was estimated by maximum likelihood from the onset intervals of all patients, assuming a normal distribution with the reference SD, with profile-likelihood CIs and likelihood-ratio tests against the reference mean. Sensitivity analyses varied or estimated the SD, excluded GH-treated patients or one twin, and used a nonparametric (Turnbull) estimate; in girls, onset was also compared with the probit median of Istanbul schoolgirls (9.65 years [24]). We also compared the age at which stage 2 was first recorded, an upper bound for onset, with the reference mean. Recorded menarche ages were compared with the references by one-sample t-tests (primary analysis) and between the two groups of girls by Welch t-test; in sensitivity analyses, 0.5 years was added to whole-year ages and girls without menarche were treated as censored. The interval from breast stage 2 to menarche was calculated from both ends and from the midpoint of the onset interval.

Height SDS at the first recorded stages 2–5 and at NFH was analysed with a linear mixed model (pubertal stage as fixed effect, random intercept per patient; restricted maximum likelihood, Satterthwaite degrees of freedom [26, 27]) in growth-cohort patients with at least two such measurements. A measurement recorded at both stage 5 and NFH was counted once, as NFH. Height SDS at each stage was taken from the stage-specific records of the database; in two patients in the model (nos. 17 and 31), these records came from a later visit than the first at that stage, and using the first-visit values instead changed the estimates by less than 0.02 SDS. Two stage 4 entries that conflicted with the first-visit record (nos. 15 and 17) and all measurements after limb lengthening were excluded. The stage effect was tested by likelihood ratio, and the model was checked against a within-patient (patient fixed-effects) estimator with F-tests, by a patient-level bootstrap (2000 resamples) and by leaving out one patient at a time; sex was examined only as an exploratory interaction. The change from the first (prepubertal) visit to stage 2 was analysed separately by paired t-test, and height gain in centimetres from stage 2 to NFH was expressed as SDS of the reference gain. NFH was compared with target height by paired t-test and related to age at the first visit by Spearman correlation with an exact p value.

The main analyses were repeated after excluding FGF23-independent disease and in FGF23-mediated disease alone. Exact Wilcoxon signed-rank and Mann–Whitney tests were used as nonparametric checks. Missing data were not imputed, and two-sided $p < 0.05$ was considered significant. Analyses used Python 3.11 (SciPy, statsmodels; quartiles by linear interpolation) and R 4.3 (lme4, lmerTest). An artificial intelligence assistant (Claude, Anthropic) wrote and ran the Python and R code, cross-checked the results with separately written code and helped draft and edit the text. The authors checked all analyses and the text and take full responsibility for the content.

Results

Patients

At the first visit, median age was 8.5 years (IQR 3.7–13.3) and median height SDS − 2.23 (IQR − 3.75 to − 1.39) (Table 1). Disease was FGF23-mediated in 10 patients, FGF23-independent in 7 and unclassified in 16 (13 not tested genetically). Phosphate was given with calcitriol to 21 patients and alone to 7; it was started at a median age of 10.6 years (IQR 3.3–13.7), and before 5 years of age in nine.

Table 1
Characteristics of the 33 patients with hypophosphataemic rickets

Characteristic	All (n = 33)	Girls (n = 18)	Boys (n = 15)
Age at first visit, years, median (IQR)	8.5 (3.7–13.3)	7.7 (3.0–11.5)	8.5 (6.4–14.2)
Documented follow-up, years, median (IQR)[a]	2.8 (0.0–7.3)	1.2 (0.0–7.8)	3.3 (0.7–5.6)
Height SDS at first visit, median (IQR)	−2.23 (− 3.75 to − 1.39)	−2.29 (− 3.31 to − 1.51)	−2.00 (− 3.95 to − 1.09)
BMI SDS at first visit, median (IQR)[b]	0.83 (− 0.11 to 1.44)	0.83 (0.43–1.23)	0.95 (− 1.24 to 1.48)
Pubertal stage at first visit, n (%)			
Prepubertal	20 (61)	11 (61)	9 (60)
Stage 2–4[c]	9 (27)	5 (28)	4 (27)
Stage 5	4 (12)	2 (11)	2 (13)
Consanguinity, n/N (%)	10/32 (31)	4/18 (22)	6/14 (43)
Affected parent documented, n (%)	4 (12)	2 (11)	2 (13)
Genetic result, n (%)			
Pathogenic *PHEX* variant	8 (24)	6 (33)	2 (13)
Pathogenic *SLC34A3* variant	4 (12)	3 (17)	1 (7)
Pathogenic *SLC34A1* variant	1 (3)	0 (0)	1 (7)
No variant detected	7 (21)	1 (6)	6 (40)
Not tested	13 (39)	8 (44)	5 (33)
Disease mechanism, n (%)[d]			
FGF23-mediated	10 (30)	6 (33)	4 (27)
FGF23-independent	7 (21)	3 (17)	4 (27)
Unclassified	16 (48)	9 (50)	7 (47)
TRP, %, median (IQR)[e]	76 (69–87)	74 (69–88)	80 (70–87)
TmP/GFR, mg/dL, median (IQR)[e]	2.00 (1.63–2.29)	2.11 (1.75–2.80)	1.98 (1.63–2.17)
Conventional treatment, n (%)			
Phosphate and calcitriol	21 (64)	12 (67)	9 (60)

Characteristic	All (n = 33)	Girls (n = 18)	Boys (n = 15)
Phosphate alone	7 (21)	4 (22)	3 (20)
Vitamin D only	1 (3)	0 (0)	1 (7)
None	3 (9)	1 (6)	2 (13)
Not recorded	1 (3)	1 (6)	0 (0)
Age at phosphate start, years, median (IQR)[f]	10.6 (3.3–13.7)	10.6 (3.3–12.4)	10.1 (5.3–14.3)
Phosphate started before 5 years of age, n (%)	9 (27)	6 (33)	3 (20)
Adherence as recorded by the physician, n (%)			
Good	15 (45)	10 (56)	5 (33)
Poor	9 (27)	4 (22)	5 (33)
Unknown or not recorded	9 (27)	4 (22)	5 (33)
Growth hormone treatment, n (%)[g]	3 (9)	1 (6)	2 (13)
Orthopaedic surgery, n (%)			
Deformity correction only	10 (30)	6 (33)	4 (27)
Limb lengthening	3 (9)	2 (11)	1 (7)
Nephrocalcinosis, n (%)	13 (39)	7 (39)	6 (40)
Nephrolithiasis, n (%)	2 (6)	1 (6)	1 (7)
Parathyroid adenoma, n (%)	2 (6)	1 (6)	1 (7)

Percentages are of the column total unless a denominator is given. [a]From the first to the last visit with anthropometric data; 10 patients had data from a single visit. [b]Recorded in 27 patients (15 girls, 12 boys). [c]Includes one boy with pubic hair stage 3 whose genital examination was declined. [d]FGF23-mediated: pathogenic *PHEX* variant or elevated FGF23; FGF23-independent: pathogenic *SLC34A3* or *SLC34A1* variant, or low FGF23 with elevated 1,25-dihydroxyvitamin D. [e]Measured at variable ages; TRP in 28 and TmP/GFR in 22 patients. [f]Earliest documented start, in 28 patients. [g]Included in the analyses of pubertal timing and excluded from the growth analyses. Two further patients received burosumab and were included in all analyses: a boy, for 3 months from 13.3 years, and a girl with FGF23-mediated disease, whose age at the start of burosumab was not recorded. BMI body mass index; FGF23 fibroblast growth factor 23; IQR interquartile range; SDS standard deviation score; TmP/GFR ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate; TRP tubular reabsorption of phosphate

Pubertal timing

Onset was observed in 12 patients (6 girls, 6 boys); 13 were already pubertal at the first visit, and eight were still prepubertal at their last visit, all younger than 8 years at that visit (Fig. 1). Mean onset age was 9.68 years (95% CI 8.85 to 10.48) in girls, not significantly different from the reference (− 0.42 years, 95% CI − 1.25 to 0.38; p = 0.30), and 9.75 years (8.74 to 10.74) in boys, 1.85 years (0.86 to 2.86) earlier than the reference (p < 0.001) (Table 2, Fig. 2a). Without the GH-treated patients, onset was earlier than the reference in both sexes (girls − 0.98 years, p = 0.033; boys − 2.87 years, p < 0.001). In boys, the difference persisted with other assumed or estimated SDs (p ≤ 0.019) and without one twin (− 1.65 years, − 2.72 to − 0.60; p = 0.002). The age at which stage 2 was first recorded, however, did not differ significantly from the reference in either sex (girls + 0.30 years, p = 0.67; boys − 0.98 years, p = 0.32). In FGF23-mediated disease alone, the differences were − 0.87 years (95% CI − 2.31 to 0.63) in six girls and − 2.62 years (− 4.11 to − 1.13) in four boys (Additional file 1: Table S1).

Table 2
Pubertal timing and tempo compared with Turkish reference data

Measure	n	Patients	Reference, mean ± SD	Difference (95% CI)	p
Pubertal onset, girls (breast stage 2)					
Onset observed / pubertal at first visit / prepubertal at last visit	18	6 / 7 / 5			
Mean age at onset, interval-censored estimate (95% CI)[a]	18	9.68 (8.85–10.48)	10.1 ± 1.0 [21]	−0.42 (− 1.25 to 0.38)	0.30
Without growth hormone-treated patients	17	9.12 (8.20–10.02)		−0.98 (− 1.90 to − 0.08)	0.033
Age at which stage 2 was first recorded, mean ± SD[b]	6	10.40 ± 1.64		+ 0.30 (− 1.42 to 2.03)	0.67
Nonparametric estimate: interval containing the median[c]	18	9.41–10.44			
Pubertal onset, boys (testicular volume ≥ 4 mL)					
Onset observed / pubertal at first visit / prepubertal at last visit	15	6 / 6 / 3			
Mean age at onset, interval-censored estimate (95% CI)[a]	15	9.75 (8.74–10.74)	11.6 ± 1.2 [22]	−1.85 (− 2.86 to − 0.86)	< 0.001
Without growth hormone-treated patients	13	8.73 (7.55–9.90)		−2.87 (− 4.05 to − 1.70)	< 0.001
Age at which stage 2 was first recorded, mean ± SD[b]	6	10.63 ± 2.17		−0.98 (− 3.25 to 1.30)	0.32
Nonparametric estimate: interval containing the median[c]	15	8.66–9.43			
Menarche					
All girls with menarche, mean ± SD	10	13.15 ± 0.76	12.2 ± 0.9 [21][d]	+ 0.95 (0.40 to 1.49)	0.003
Followed from before puberty	5	12.68 ± 0.64		+ 0.48 (− 0.32 to 1.28)	0.17

Measure	n	Patients	Reference, mean ± SD	Difference (95% CI)	p
Pubertal onset, girls (breast stage 2)					
First seen after pubertal onset[e]	5	13.61 ± 0.59		+ 1.41 (0.68 to 2.14)	0.006
Difference between the two groups				+ 0.93 (0.03 to 1.83)	0.044
All girls, censored estimate (95% CI)[f]	18	13.35 (12.82–13.88)		+ 1.15 (0.62 to 1.68)	< 0.001
Breast stage 2 to menarche, girls followed from before puberty[g]					
From the first recorded stage 2 (shortest possible)	5	2.80 ± 1.18	1.8 ± 0.6 [21]	+ 1.00 (− 0.47 to 2.47)	0.13
From the midpoint of the onset interval	5	3.47 ± 0.95		+ 1.67 (0.50 to 2.85)	0.017
From the last prepubertal assessment (longest possible)	5	4.15 ± 0.72		+ 2.35 (1.46 to 3.25)	0.002

Ages and intervals in years; differences are patients minus reference. Unless stated otherwise, all 33 patients, including the 3 treated with growth hormone. [a]Normal distribution with the SD fixed at the reference SD; each patient contributes the interval known to contain onset (patients pubertal at the first visit an upper bound, those prepubertal at the last visit a lower bound); profile-likelihood 95% CI and likelihood-ratio p. [b]Patients documented as prepubertal at an earlier visit; this age is an upper bound for onset, and the last prepubertal assessment was a median of 1.6 years earlier (range 0.6–3.4); one-sample t-test. [c]Turnbull estimate; estimated proportion with onset by the reference mean age, girls 0.36–0.89 and boys 0.86. [d]Reference A, primary analysis; comparisons with three further Turkish references are given in Additional file 1: Table S1. [e]3 of the 5 recalled a menarche that preceded their first visit. [f]Sensitivity analysis: normal distribution with SD 0.9 years; the 8 girls without menarche were censored at their last visit (3 of them pubertal, at 11.19, 11.22 and 14.96 years). [g]The onset interval runs from the last prepubertal assessment to the first recorded stage 2, so the true interval lies between the first and last rows. One-sample t-tests unless stated otherwise; Welch t-test for the difference between the two groups. CI confidence interval; SD standard deviation

In the growth cohort, bone age was behind chronological age by a median of 1.02 years at the last prepubertal reading (n = 7) and by 0.30 years at the first pubertal reading (n = 16); the difference decreased in all four patients with both readings.

Menarche occurred at 13.15 ± 0.76 years (n = 10), 0.95 years (95% CI 0.40 to 1.49; p = 0.003) later than reference A (Table 2, Fig. 2b); 7 of the 10 ages were whole years. The difference was larger in girls first seen after pubertal onset (13.61 ± 0.59 years; +1.41 years, 95% CI 0.68 to 2.14; p = 0.006), three of whom

recalled a menarche before their first visit, than in girls followed from before puberty (12.68 ± 0.64 years; +0.48 years, 95% CI − 0.32 to 1.28; p = 0.17). The two groups differed by 0.93 years (0.03 to 1.83; p = 0.044). In sensitivity analyses that took whole-year ages as completed years, menarche was later than reference A in girls followed from before puberty as well (p = 0.021). Treating girls without menarche as censored gave a mean of 13.35 years (12.82 to 13.88), and excluding FGF23-independent disease gave a difference of + 1.01 years (0.42 to 1.60; n = 8). References B and D gave similar results, whereas reference C differed only from girls first seen after onset (Additional file 1: Table S1).

In the five girls followed from before puberty, the mean interval from breast stage 2 to menarche lay between 2.80 years (shortest possible values) and 4.15 years (longest possible values), against 1.8 years in the reference (+ 1.00 years, 95% CI − 0.47 to 2.47; p = 0.13 for the shortest values and p = 0.017 for the midpoints) (Table 2, Fig. 2c). The two girls with the earliest onset intervals (nos. 3 and 4) also had the longest times from the first recorded stage 2 to menarche. The GH-treated girl had not reached menarche 1.96 years after stage 2 was first recorded.

Height through puberty

Twelve patients (7 girls, 5 boys) contributed 41 measurements at stages 2–5 and NFH. Relative to stage 2, height SDS fell progressively; the difference at NFH was − 0.82 (95% CI − 1.19 to − 0.44; likelihood-ratio p < 0.001; Table 3, Fig. 3a). The within-patient estimator (− 0.81, − 1.19 to − 0.43), leaving out one patient at a time (− 0.91 to − 0.70) and other sensitivity analyses gave similar results (Additional file 1: Table S1). Only adding the two GH-treated patients, whose height SDS rose after stage 2, reduced the difference to − 0.33 (95% CI − 0.84 to 0.18). In FGF23-mediated disease alone (6 patients, 20 measurements), the difference at NFH was − 0.89 (− 1.59 to − 0.18). A sex difference was not supported: the change from stage 2 to NFH differed by − 0.55 SDS between boys and girls (boys minus girls; 95% CI − 1.40 to 0.30; interaction p = 0.20).

Table 3
Height standard deviation score through puberty in children not treated with growth hormone

Pubertal stage or interval	Patients, n	Height SDS	Difference or change (95% CI)	p
Linear mixed model, by pubertal stage[a]		*Model mean (95% CI)*	*Difference from stage 2*	
Stage 2	7	−1.66 (− 2.43 to − 0.89)	Reference	
Stage 3	6	−1.95 (− 2.74 to − 1.17)	−0.30 (− 0.68 to 0.09)	0.13
Stage 4	10	−2.25 (− 3.01 to − 1.48)	−0.59 (− 0.94 to − 0.23)	0.002
Stage 5	9	−2.37 (− 3.13 to − 1.60)	−0.71 (− 1.09 to − 0.33)	< 0.001
Near-final height	9	−2.48 (− 3.24 to − 1.71)	−0.82 (− 1.19 to − 0.44)	< 0.001
Change within the same patients[b]		*Earlier / later mean*	*Change*	
First (prepubertal) visit to first recorded stage 2[c]	10	−1.54 / −1.09	+ 0.46 (− 0.01 to 0.93)	0.055
First recorded stage 2 to near-final height	5	−1.22 / −2.04	−0.83 (− 1.36 to − 0.29)	0.013

[a]Patients with at least two measurements at stages 2–5 or near-final height (12 patients, 41 measurements; 7 girls, 5 boys); measurements after limb lengthening and two inconsistent stage 4 entries (nos. 15 and 17) excluded. Random intercept per patient, REML, Satterthwaite degrees of freedom; likelihood-ratio test for pubertal stage p < 0.001. Within-patient (patient fixed-effects) estimates of the difference from stage 2: stage 3 − 0.30 (p = 0.13), stage 4 − 0.57 (p = 0.003), stage 5 − 0.70 (p < 0.001) and near-final height − 0.81 (95% CI − 1.19 to − 0.43; p < 0.001). Leaving out one patient at a time, the near-final height estimate ranged from − 0.91 to − 0.70 (largest likelihood-ratio p = 0.008); patient-level bootstrap 95% CI − 1.11 to − 0.52. [b]Mean height SDS at the earlier and the later time point; change with 95% CI and paired t-test. [c]Patients documented as prepubertal at the first visit and later recorded at stage 2. Height gain in centimetres for each patient is shown in Fig. 3b. CI confidence interval; REML restricted maximum likelihood; SDS standard deviation score

Before puberty, height SDS rose by a mean of 0.46 (95% CI − 0.01 to 0.93; p = 0.055) between the first visit and the first recorded stage 2 in the 10 patients with observed onset (Table 3). It rose in all five girls (mean + 0.85) and in three of the five boys (mean + 0.06). In the five patients measured at both the first recorded stage 2 and NFH, height increased by 14.2–32.4 cm, within or above the reference range (SDS of the reference gain − 0.46 to + 4.21), while height SDS fell by 0.24–1.46 (Fig. 3b).

Near-final height

NFH was reached by 12 patients (7 girls, 5 boys; two after limb lengthening; nine also in the mixed model) at 18.6 ± 1.7 years; three girls were assessed before 18 years (Table 4). NFH SDS was − 2.88 ± 1.56. All eight patients with target height were below it (mean − 1.70 SDS, 95% CI − 2.82 to − 0.58; p = 0.009) (Fig. 3c). NFH tended to be lower in patients first seen at an older age (r_s = − 0.57; p = 0.056; n = 12), but this could not be separated from sex and treatment. Of those who reached NFH, the boys had been first seen at a median age of 16.2 years and none had started phosphate before 13.5 years, whereas the girls had been first seen at a median age of 8.7 years and three had started phosphate before 5 years. NFH SDS was − 3.28 ± 0.69 in boys and − 2.59 ± 1.98 in girls (exploratory Mann–Whitney p = 0.11; Additional file 1: Table S1).

Table 4
Near-final height in children not treated with growth hormone

Measure	All (n = 12)	Girls (n = 7)	Boys (n = 5)
Age, years, mean ± SD	18.6 ± 1.7	17.7 ± 1.6	19.8 ± 0.9
Height, cm, mean ± SD	151.1 ± 10.1	147.6 ± 11.8	155.9 ± 4.4
Height SDS, mean ± SD	−2.88 ± 1.56	−2.59 ± 1.98	−3.28 ± 0.69
Near-final minus target height SDS, mean (range) [n]	−1.70 (− 4.37 to − 0.14) [8]	−0.92 (− 1.56 to − 0.14) [5]	−3.00 (− 4.37 to − 2.06) [3]
Age at first visit, years, median	12.4	8.7	16.2
Phosphate started before 5 years of age, n	3	3	0
Sitting height/height SDS, mean ± SD [n]	0.23 ± 1.10 [9]	0.02 ± 1.26 [6]	0.66 ± 0.68 [3]

Includes two patients after limb lengthening (one girl, one boy). Three girls were assessed before 18 years: at 17.96 years (no growth over the preceding 1.6 years), 15.96 years (1.2 cm/year over the preceding 3.7 years) and 15.18 years (0.6 cm/year over the preceding 1.9 years). SD standard deviation; SDS standard deviation score

Discussion

In this cohort, pubertal onset was not delayed and may have been early in boys. Menarche was later than the reference, mainly in girls first seen after pubertal onset, and in five girls followed from before puberty the interval from breast stage 2 to menarche appeared prolonged. Height SDS fell by about 0.8 between stage 2 and NFH, even though height gain in centimetres was within or above the reference range in the five patients measured at both points, and NFH was 1.7 SDS below target height.

We found no earlier study that compared pubertal onset, menarche and tempo together with population references in children with HR. Because onset is known only to lie between visits, we analysed the intervals of all patients rather than the age at first recorded stage 2, which overestimates onset and ignores patients already pubertal at their first visit. Onset in girls was then close to the reference mean,

but earlier once the GH-treated girl was excluded; in boys it was earlier, also after excluding one twin. This finding in boys, however, rests on six boys with observed onset and on orchidometry by several examiners. Bone age was delayed before puberty, as reported in XLH, particularly in boys [28], yet onset was not delayed. The Istanbul reference cohort was examined in 1989–2002, and menarche has since become earlier in Istanbul [25]; secular and population differences may therefore affect these comparisons, including the early onset in boys.

Menarche was later in girls first seen after pubertal onset, who were shorter at the first visit than girls followed from before puberty (mean height SDS − 3.87 vs − 1.88), had started treatment later (median 14.3 vs 3.5 years) and, in three cases, recalled their menarche; disease severity, late treatment and recall may all contribute. In girls followed from before puberty, however, the interval from breast stage 2 to menarche appeared longer than in the reference. With five girls and mostly whole-year ages, this remains a hypothesis. Moreover, the interval is longer when breast development starts earlier [29], and the two girls with the earliest onset intervals had the longest times from the first recorded stage 2 to menarche, so timing may explain part of the difference. We found no previous report of a slow tempo of female puberty in HR; metabolic control may deteriorate during puberty [9, 12], but the mechanism remains to be studied.

The fall in height SDS between stage 2 and NFH agrees with the decline after 13 years of age in a German multicentre study that did not analyse growth by pubertal stage [11] and with the lower pubertal than prepubertal height SDS in a Turkish *PHEX*-positive cohort [12]. Unlike that cohort, in which no pubertal spurt was observed, our five patients measured at both stage 2 and NFH gained 14.2–32.4 cm, within or above the reference range; this is a lower bound, as onset preceded the first recorded stage 2. The pattern resembles the normal spurt that did not restore the earlier deficit [8] and the nearly normal pubertal gain in girls [9]. An earlier onset within the normal range is associated with lower final height [30], which may contribute to the fall in boys. Before puberty, height SDS tended to rise, mainly in girls treated from early childhood, in line with the benefit of early treatment [7].

Mean NFH SDS was lower in boys than in girls, but the difference was not significant. Height SDS was also lower in men than in women in a French adult cohort [6] and in males than in females in a cohort with hereditary hypophosphataemic rickets [10], whereas paediatric cohorts have not shown a consistent sex difference [31, 32]. In our cohort, however, four of the five boys who reached NFH had first been seen in adolescence, none had started phosphate before 13.5 years, and the data did not support a sex difference in the fall of height SDS during puberty. Sex therefore cannot be separated from treatment history.

Current recommendations advise more frequent visits during periods of rapid growth [3]. Our findings suggest that pubertal stage and growth velocity should be followed closely through puberty, with bone age as indicated, and that the effect of burosumab on pubertal growth and tempo should be assessed in FGF23-mediated disease; in adolescents with XLH, burosumab was associated with better growth [5].

Strengths and limitations

Strengths include references from the same city, an interval-based analysis of onset that uses all patients, separate analysis of prepubertal and pubertal changes in height, pubertal growth in centimetres and display of individual data in the figures. However, this retrospective cohort is small and heterogeneous in aetiology, age at diagnosis and treatment, reflecting tertiary referral over three decades. Genetic testing was incomplete and 16 patients could not be classified by mechanism, so the findings cannot be attributed to XLH alone, although the main estimates pointed in the same direction in FGF23-mediated disease. Onset was observed in only 12 patients, within intervals of up to 3.4 years, and menarche was self-reported and mostly recorded in whole years. The mixed model rests on 12 patients, only five of whom were measured at both stage 2 and NFH. Bone age was available at few visits; alkaline phosphatase, parathyroid hormone and treatment doses were not recorded systematically during follow-up; and the references differ in design and period. Two patients received burosumab, a boy for 3 months and a girl from an unrecorded age; both were included in all analyses. We also did not take BMI into account: median BMI SDS at the first visit was 0.83, all five boys not treated with GH whose onset was observed had a BMI SDS of at least 0.9 at the first recorded stage 2, and overweight is associated with earlier puberty in both sexes, although by only a few months [33]. All analyses were exploratory.

Conclusions

In this small cohort of children with HR of mixed aetiology, pubertal onset was not delayed and may be early in boys, and the interval from breast stage 2 to menarche may be prolonged. Height SDS fell through puberty, although height gain in centimetres was within or above the reference range in the five patients measured at both points. NFH remained well below target height and tended to be lower in patients first seen at an older age, which could not be separated from sex and treatment. Pubertal progress and growth should be monitored closely, and prospective multicentre studies are needed.

Abbreviations

BMI: body mass index; CI: confidence interval; FGF23: fibroblast growth factor 23; GH: growth hormone; HR: hypophosphataemic rickets; IQR: interquartile range; NFH: near-final height; SD: standard deviation; SDS: standard deviation score; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TmP/GFR: ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate; TRP: tubular reabsorption of phosphate; XLH: X-linked hypophosphataemia

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (approval no. 2886057, 24 September 2024) and conducted in accordance with the Declaration of

Helsinki. Written informed consent for the use of clinical data was obtained from the parents or legal guardians of participants who were minors at the time of consent, and directly from participants who had reached the age of majority. Clinical trial number: not applicable.

Consent for publication

Consent for the publication of de-identified individual data, as presented in this article, was obtained from the patients or their parents or legal guardians.

Availability of data and materials

The dataset analysed during the current study is not publicly available because it contains clinical data from a small number of patients with a rare disease, which could allow identification. De-identified data and the analysis code are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TK contributed to study design and interpretation, performed and checked the statistical analyses and drafted the manuscript, both with the assistance described in Methods. OBD and CK collected and processed the data. ADK conceived and supervised the study, revised the manuscript and is the corresponding author. MY, SP, FD and FB contributed substantially to the analysis and interpretation of the data and to drafting and revising the manuscript. All authors read and approved the final manuscript.

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Figures

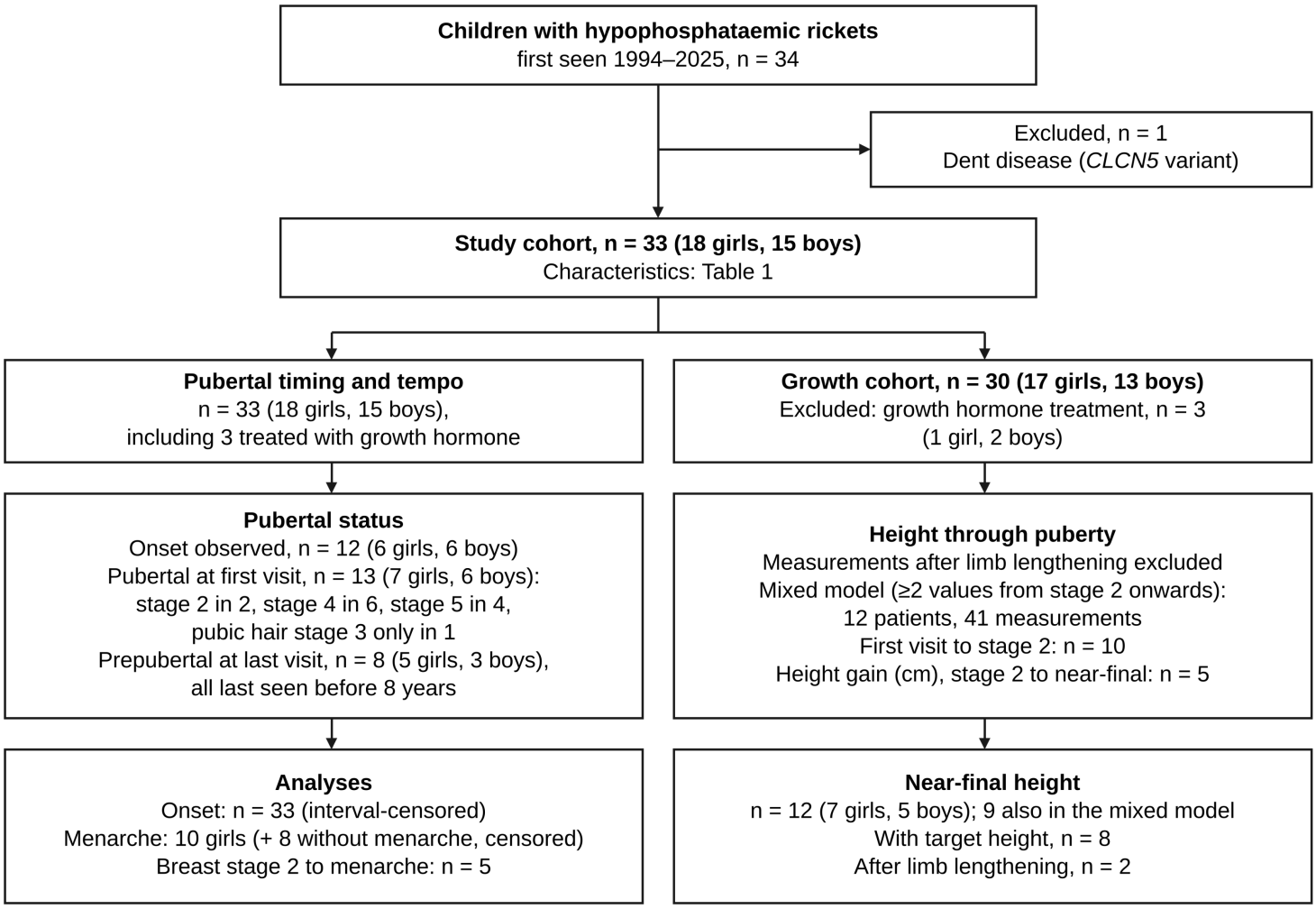


Figure 1

Flow of patients through the study. Groups overlap; each analysis used every patient with the required data.

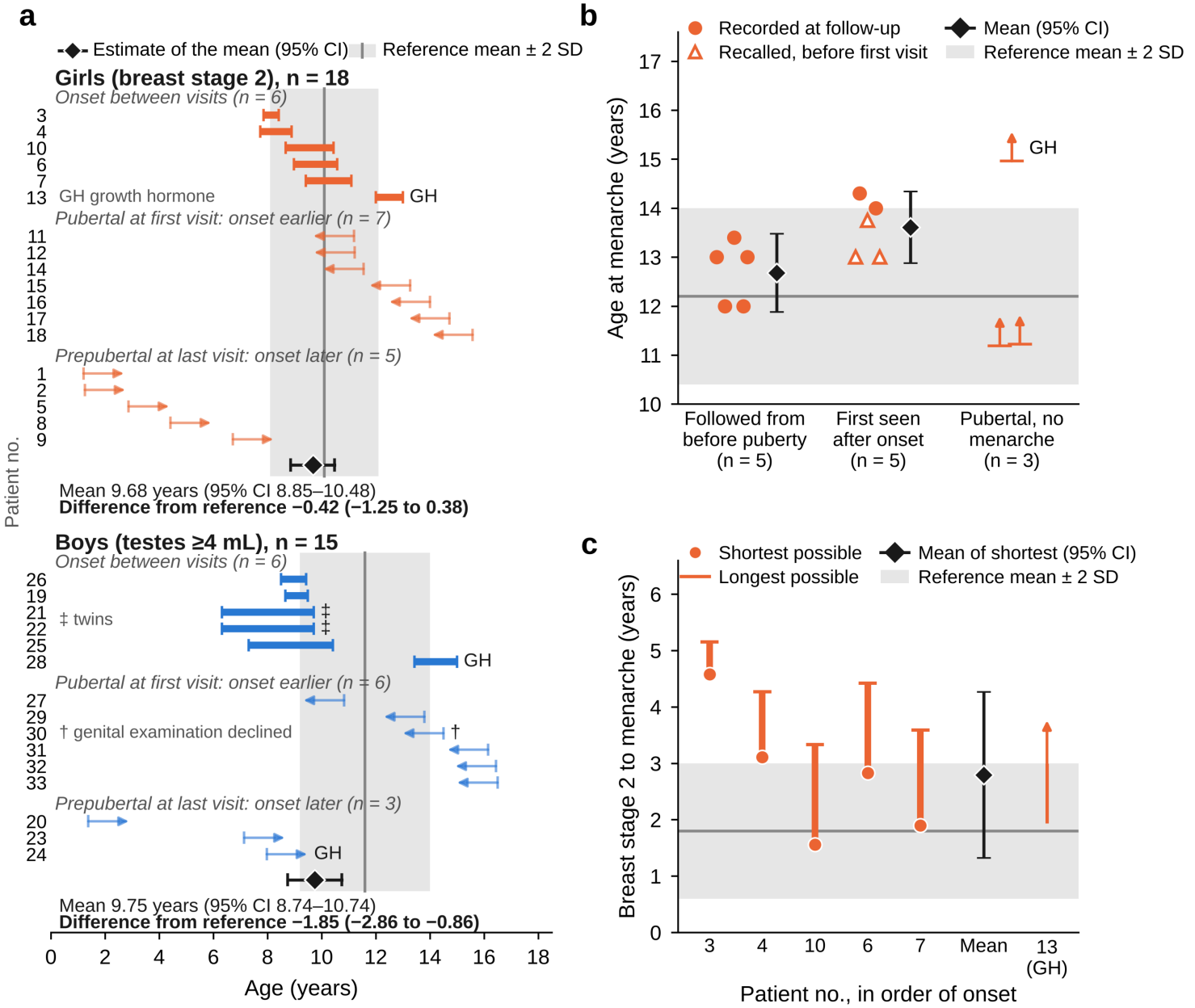


Figure 2

Pubertal timing and tempo compared with Turkish references. (a) Interval known to contain the age at pubertal onset (breast stage 2 in girls, testicular volume ≥4 mL in boys) in all 33 patients (numbered as in Methods), grouped by how onset was observed. Bars run from the last prepubertal assessment to the visit at which stage 2 was first recorded; arrows mark patients who were already pubertal at their first visit (onset before that age) or still prepubertal at their last visit (onset after that age), and their length has no meaning. Grey bands and vertical lines show the mean ± 2 SD and mean of the Istanbul references [21, 22]. Diamonds with bars show the interval-censored estimate of the mean (95% CI); the estimate and its difference from the reference are printed below. The boy marked † had pubic hair stage 3. (b) Age at menarche by group, with group means and 95% CIs. Arrows mark the last visit of three pubertal girls without menarche; five girls still prepubertal at their last visit are not shown. The grey band and line show the mean ± 2 SD and mean of the primary reference (reference A [21]). (c) Interval from

breast stage 2 to menarche in the five girls followed from before puberty, in order of onset. Because onset lies between the last prepubertal assessment and the first recorded stage 2, each bar spans the possible values, from the shortest (dot) to the longest. The diamond shows the mean of the shortest values with its 95% CI. The arrow shows the GH-treated girl, who had not reached menarche at her last visit (lower bound). The grey band and line show the reference mean ± 2 SD and mean [21]. CI confidence interval; GH growth hormone; SD standard deviation

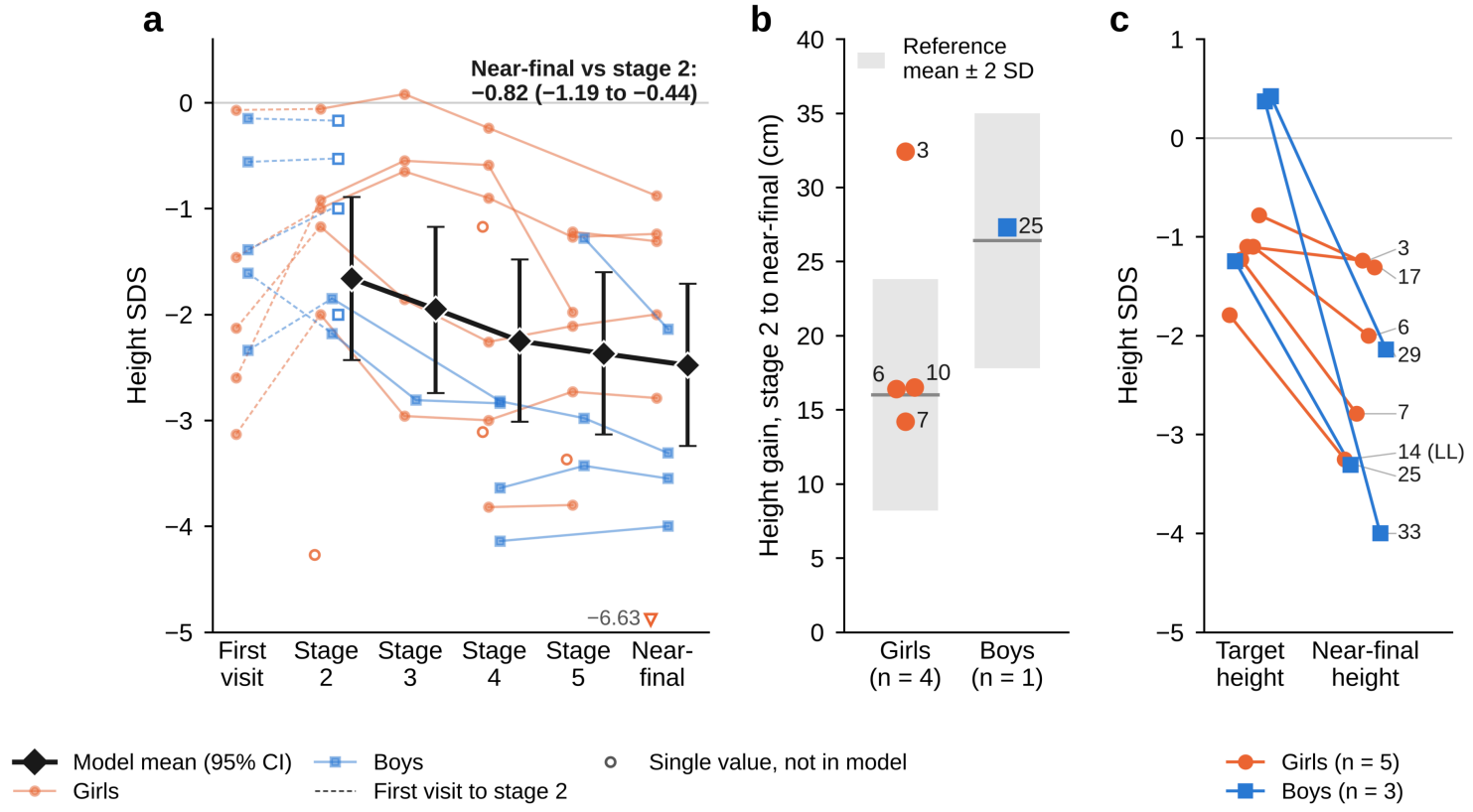


Figure 3

Height through puberty in children not treated with growth hormone. (a) Height SDS at the first (prepubertal) visit, at the first recorded Tanner stages 2–5 and at near-final height, as used in the analyses; measurements after limb lengthening are not shown. Black diamonds with bars, joined by a line, show the means and 95% CIs estimated by the mixed model for its 12 patients, with the model estimate of the change from stage 2 to near-final height; these means differ from the near-final height mean in Table 4, which includes other patients. Thin lines join measurements of the same patient, with girls and boys offset horizontally. Open symbols are patients with a single measurement from stage 2 onwards, who were not in the model; one value below the axis is marked with its value. (b) Height gain from the first recorded stage 2 to near-final height, labelled with the patient number used in Fig. 2a; because stage 2 was first recorded after onset, the gains are lower bounds. Grey bands and lines show the mean ± 2 SD and mean total pubertal height gain of healthy Turkish children [21, 22]. (c) Target and near-final height SDS in the eight patients with both, labelled with patient number. CI confidence interval; LL limb lengthening; SD standard deviation; SDS standard deviation score

Supplementary Files

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