Reference Growth Charts for Children With 47,XXY/Klinefelter Syndrome

Shanlee M. Davis, MD, PhD,[1,2] Taylor E. Marshall, MD,[3] Karli S. Swenson, PhD,[1,2] Samantha Bothwell, MS,[1,2] Natalie J. Nokoff, MD, MS,[2] Amelia Middleton, BS,[1,2] Anna Furniss, MS,[4] Maram Alkhdour, MD,[5] Dimitri A. Christakis, MD, MPH,[6] Victoria A. Elliott, MD,[7] Jennifer Heeley, MD,[5] Chijioke Ikomi, MD,[8] Judith Ross, MD,[8] Stephen I. Stone, MD,[5] Maria G. Vogiatzi, MD,[9] Nicole R. Tartaglia, MD, MS[1,2]

abstract

BACKGROUND AND OBJECTIVES: Although tall stature is commonly associated with 47,XXY/Klinefelter syndrome (KS), detailed childhood growth patterns are not well-defined. This study aimed to develop KS-specific growth charts for stature-for-age, weight-for-age, weight-for-length (0–24 months), and body mass index (BMI)-for-age (2–18 years).

METHODS: We conducted a population-based secondary analysis using clinical data from 6 US pediatric centers. The cohort included 1279 males aged younger than 20 years with a diagnosis of KS and at least 1 outpatient measurement of height and/or weight. Nonparametric quantile regression was used to model age-related growth trajectories.

RESULTS: A median of 6 longitudinal growth data points per individual contributed to the creation of KS-specific curves. Key differences from standard reference growth charts included the following: (1) approximately 20% of boys with KS aged younger than 4 years were below the 5th percentile for height, whereas approximately 25% exceeded the 95th percentile by late childhood; (2) height velocity increased in midchildhood (after age 6 years), but without a distinct pubertal growth spurt; and (3) BMI distribution was broader, with approximately 10% of individuals below the 5th percentile and approximately 25% above the 95th percentile.

CONCLUSIONS: Boys with KS demonstrate distinct and variable growth trajectories compared with the general population. These KS-specific growth charts offer a valuable clinical tool for monitoring growth, guiding anticipatory counseling, and identifying atypical development patterns.

[1]*eXtraOrdinarY Kids Clinic and Research Program, Children's Hospital Colorado, Aurora, Colorado;* [2]*Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado;* [3]*Department of Pediatrics, University of California Los Angeles, Los Angeles, California;* [4]*University of Colorado Adult and Child Consortium for Health Outcomes Research & Delivery Sciences (ACCORDS), Aurora, Colorado;* [5]*Department of Pediatrics, Washington University School of Medicine, St Louis, Missouri;* [6]*Department of Pediatrics, Seattle Children's Hospital, Seattle, Washington;* [7]*Department of Endocrinology, Nationwide Children's Hospital, Columbus, Ohio;* [8]*Department of Pediatrics, Nemours Children's Health Delaware, Wilmington, Delaware; and* [9]*Department of Pediatrics, Division of Endocrinology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*

Corresponding author: Shanlee M. Davis, MD, PhD, Department of Pediatrics, University of Colorado School of Medicine, 13123 East 16th Ave B265, Aurora, CO 80045. Shanlee.davis@cuanschutz.edu

Dr Davis conceptualized and designed the study, oversaw data analysis, obtained funding, and reviewed and revised the manuscript. Drs Marshall and Swenson contributed to data analysis, drafted sections of the manuscript, and reviewed and revised the manuscript. Ms Bothwell performed data cleaning and analysis, drafted sections of the manuscript, and reviewed and revised the manuscript. Dr Nokoff, Ms Middleton, Ms Furniss, Drs Alkhdour, Christakis, Elliott, Heeley, Ikomi, Ross, Stone, Vogiatzi, and Tartaglia coordinated and contributed to data collection and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST DISCLOSURES: Dr Nokoff has consulted for Neurocrine Biosciences and served as an expert panel member for World Athletics. The other authors have no conflicts of interest relevant to this article to disclose.

WHAT'S KNOWN ON THIS SUBJECT: Children with 47,XXY are often described as tall, but detailed, population-based data on early growth patterns and body mass index distribution have been limited.

WHAT THIS STUDY ADDS: This study provides the first Klinefelter syndrome–specific growth charts, highlighting early short stature, midchildhood height acceleration, absence of a pubertal growth spurt, and wide body mass index variability.

To cite: Davis SM, Marshall TE, Swenson KS, et al. Reference Growth Charts for Children With 47,XXY/Klinefelter Syndrome. *Pediatrics.* 2025;156(6):e2025072193

INTRODUCTION

Height, weight, and body mass index (BMI) are core vital signs in pediatric clinical care, serving as critical indicators to identify children who may require further evaluation or intervention.[1,2] In the United States, growth is typically monitored using standardized curves from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC). However, these reference charts do not reflect the growth patterns of individuals with genetic conditions that affect growth trajectories. For children with known genetic syndromes, condition-specific growth charts are essential. They provide clinicians with a meaningful context for interpreting growth data, enabling more accurate anticipatory guidance, reducing unnecessary workups, and identifying deviations that may signal comorbid conditions.[2,3] Such charts have been developed for several genetic syndromes known to affect growth, including Trisomy 21, Turner syndrome, Noonan syndrome, and Marfan syndrome.[4–6]

Klinefelter syndrome (KS), caused by the presence of an extra X chromosome (47,XXY), occurs in 1 in approximately 600 males.[7] Despite its prevalence, fewer than 20% of youth with KS are diagnosed, although this is beginning to shift with the widespread adoption of noninvasive prenatal screening for aneuploidy.[8] KS presents with variable clinical features that evolve over time. Classic characteristics include tall stature, obesity, hypogonadism, and infertility, as well as a range of neurodevelopmental and medical comorbidities. On average, adult height in KS is 5 to 7 cm taller than the general population[9,10] and 4 to 8 cm taller than midparental height.[10] Increased height velocity in childhood has also been described.[11] In addition, individuals with KS are at an increased risk of overweight and obesity.[12,13] Despite these well-documented associations with altered growth, no KS-specific growth charts currently exist. As a result, clinicians lack appropriate tools to monitor growth in this population, leaving a gap in both clinical care and research.

The goal of this study was to develop reference growth charts specific to infants, children, and adolescents with KS. Using a large, multisite data set of longitudinal clinical records along with data from a prospective natural history study, we constructed KS-specific charts for weight-for-age, stature-for-age, weight-for-length (0–24 months), and BMI-for-age (2–18 years). These charts are intended to be a clinical tool to monitor growth in children and adolescents with KS.

METHODS

Data Sources

This study primarily used data from PEDSnet, a pediatric clinical research network that integrates electronic health records (EHRs) from multiple US children's hospital systems using common data elements.[14] We obtained deidentified clinical data for all individuals with a male sex and billing diagnosis of KS (Concept ID C0022735 or ICD10 Q98.4) who had at least 1 outpatient encounter between 2009 and 2019 at 1 of the 6 health systems participating in PEDSnet. The age of KS diagnosis was defined as the age at the first encounter with a KS billing diagnosis. To isolate growth trajectories specific to KS, we excluded patients with any diagnosis of a genetic condition other than KS, high-grade sex chromosome aneuploidy (eg, 48,XXYY), metabolic disorder, cerebral palsy, malignancy, and complex congenital malformation (see Figure 1). Additionally, for analyses involving children under 2 years of age, prematurity (defined as gestational age <37 weeks) was an exclusion criterion. This protocol was reviewed by the Colorado Multiple Institutional Review Board (COMIRB 18-0887) and determined to be nonhuman subjects research.

To validate the PEDSnet data set, we overlaid growth parameters from the eXtraordinarY Babies Study, a prospective natural history study of infants with prenatally identified sex chromosome trisomies,[15] onto the preliminarily PEDSnet-generated generated curves. Although the eXtraordinarY Babies data aligned well with the PEDSnet-generated curves for ages 2 to 18 years, a discrepancy was observed in the 0- to 24-month cohort: PEDSnet-based percentile lines were systematically lower than those from the eXtraordinarY Babies Study. This difference suggested possible bias in the PEDSnet infant data, likely due to overrepresentation of infants with more complex medical needs receiving early care in tertiary settings. As a result, for the final 0- to 24-month growth curves, we incorporated growth data from both sources, assigning equal weight (50/50) to the PEDSnet and eXtraordinarY Babies data sets. For the 2- to 18-year curves, we used only PEDSnet data, as the eXtraordinarY Babies participants are still largely under 8 years of age and in smaller numbers at older ages, and their data fit well with the PEDSnet-derived trajectories.

Infants in the eXtraordinarY Babies Study are confirmed to have nonmosaic 47,XXY and no comorbid conditions affecting growth or neurodevelopment. Anthropometric data are collected at in-person visits at 2, 6, 12, and 24 months of age, with length measured to the nearest 0.1 cm using an infantometer and weight measured to the nearest 0.1 kg by trained research personnel. Written informed consent was obtained from parents, and the study protocol is approved by the Colorado Multiple Institutional Review Board (COMIRB 17-0118).

Data Processing

We began by reviewing scatter plots of raw growth parameter data by age to identify potential errors and outliers. Height measurements were assessed for duplicates; for individuals aged younger than 16 years, identical successive height values were removed, assuming these were likely carried forward without new measurement. In contrast, duplicate values were retained for individuals older

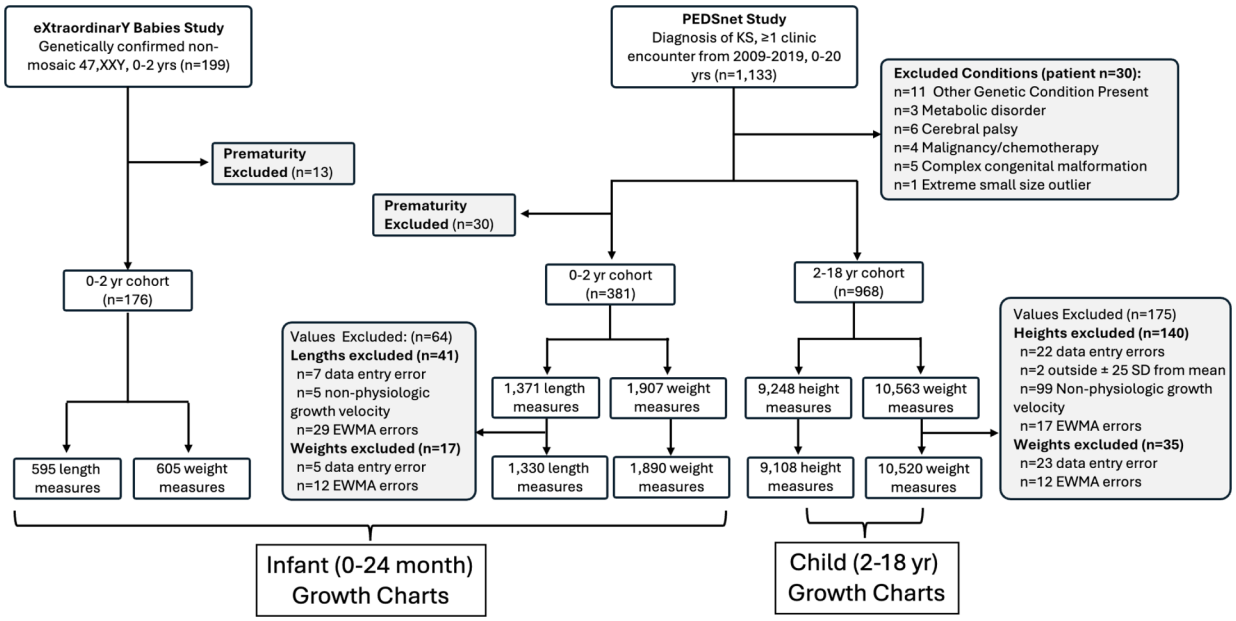

FIGURE 1.
Flow of inclusion diagram.
Abbreviations: EWMA, exponentially weighted moving average; KS, Klinefelter syndrome.

than 16 years, reflecting the possibility of true growth cessation due to epiphyseal closure. For patients older than 30 days, height measurements recorded within a 5-day window were averaged into a single data point. We then implemented the growthcleanr R package[16] to identify patient-specific outliers with an exponentially weighted moving average (EWMA)-based algorithm. Inputs to the package included subject identifier, sex (male), parameter type (specified as either height [cm] or weight [kg]), age in days at measurement, and the recorded value. All default package settings were used, except that for allowing duplicates to be carried forward as specified above. All first entries from site 1 (n = 61 measurements) were removed due to confirmed data entry errors, including 16 from the 0- to 24-month cohort and 45 from the 2- to 18-year cohort. Additional detectable errors flagged using the growthcleanr R package were removed (n = 187 measurements), including values outside ±25 SD from the mean (n = 2 measures; both heights for ages 2–18 years), nonphysiologic growth velocity patterns (n = 114 measures; 6 lengths for ages 0–24 months and 108 heights for ages 2–18 years), and EWMA-identified anomalies (n = 71; 7 weights and 29 lengths for ages 0–24 months as well as 8 weights and 27 heights for ages 2–18 years). Weight-for-length and BMI values were calculated from cleaned height and weight data, and no additional outliers were identified.

Statistical Analysis

We used nonparametric quantile regression, implemented via the quantregGrowth R package,[17,18] to model the effect of age on growth parameters with penalized P-splines in age. Quantile regression was selected to avoid assumptions about underlying distribution of the response variable, allow for heteroscedasticity, accommodate nonnormal residuals, and incorporate covariates. The spline basis imposes smoothness across adjacent ages, such that centiles for a given age bin are informed not only by observations in that bin but also by neighboring ages. Although we report the minimum number of observations per bin (1 month for 0- to 2-year-old charts and 6 months for 2- to 18-year-old charts), quantile estimates are not calculated independently within bins but are instead derived from the fitted smooth function across the full age span. To ensure valid centile ordering, monotone rearrangement was applied across quantiles at each age. We transformed the fitted quantiles into pseudo–Lambda-Mu-Sigma (LMS) parameters solely to facilitate EHR integration; the estimation itself does not rely on a Box-Cox normality assumption. We included 2 covariates in the model: (1) a normalized measure frequency per patient, calculated by the reciprocal of the absolute difference from the median to reduce bias from individuals with more or fewer data points, and (2) testosterone prescription status (Anatomical Therapeutic Chemical Classification G03B) to account for the known impact of exogenous androgens on growth. Predicted quantiles from the regression models were used to generate KS-specific length-for-age, weight-for-age, and weight-for-length for 0 to 24 months of age, and stature-for-age, weight-for-age, BMI-for-age growth chart for 2 to 18 years-of-age, using 1-month increments for ages 0 to

24 months and 6-month increments for 2 to 18 years. Each chart was generated with the 5th, 10th, 25th, 50th, 75th, and 95th percentiles. To support curve smoothing extremes, we included all data between ages 1.5 and 20.5 years in modeling the 2- to 18-year charts and then trimmed data outside of the target age range for final visualizations. For visual comparison, the WHO (ages 0–24 months) and the CDC (ages 2–18 years) curves were overlaid as 5 to 95 percentile bands. To quantify differences, we compared mean height and weight values at each year of age between the KS cohort and WHO/CDC reference data by computing the difference between intercept estimates from linear regressions, adjusted for testosterone, and the reference mean. Although WHO and CDC curves may not perfectly represent contemporary US pediatric populations, they remain the standard clinical reference for growth monitoring. To facilitate integration with EHR systems, LMS csv files were generated using the LMSfit function within the sitar R package[19] (version 1.4.0) in 1-month increments for ages 0 to 24 months and 6-month increments for ages 2 to 18 years. All analyses were performed in R version 4.4.0.

RESULTS

Growth parameters from 1279 unique individuals with KS were included in the analysis, comprising 11 033 height/length measurements and 13 015 weight measurements, with a median of 6 measurements per individual (Table 1; Figure 1). Within the PEDSnet cohort, the median age of KS diagnosis was 9.8 years, with the first and last growth measurements occurring at median ages of 5.5 and 13 years, respectively. Compared with PEDSnet, the eXtraordinarY Babies Study cohort included a higher proportion of non-Hispanic white participants and a greater number of infants treated with testosterone. KS-specific growth curves are shown in Figures 2–4, with WHO and CDC 5th to 95th percentile reference bands overlaid for visual comparison. Clean versions of the KS-only curves, as well as LMS tables for EHR integration, are provided in the Supplemental Material. Statistical comparisons to reference data by age are presented in Table 2.

Infancy (0–2 Years)

Among infants with KS, 25% of length and 10% of weight measurements fell below the WHO 5th percentile (Figure 2). In contrast, the 95th percentile values were comparable to WHO norms, indicating greater variability toward the lower end of the distribution. Mean length and weight in this age group were significantly lower than reference values (Table 2). Weight-for-length data showed a higher prevalence of underweight status (<5th percentile) in the first year of life, with normalization occurring by approximately 12 months.

Childhood and Adolescence (2–18 Years)

Early childhood height trends extended from infancy, with approximately 20% of boys aged 2 to 4 years below the

TABLE 1. Demographic Characteristics of Youth With Klinefelter Syndrome Included in Growth Curve Development

Demographic Characteristics	Included in 0- to 24-Month Set (N = 557)		Included in 2- to 18-Year Set (N = 968)
	PEDSnet (N = 381)	eXtraordinarY Babies Study (N = 176)	PEDSnet Only
Age at KS Diagnosis, years [IQR]	0.77 [0.24–4.1]	All Prenatal	9.8 [4.1–14]
Ever on testosterone, n (%)	22 (5.8%)	117 (66.5%)	223 (23.0%)
Race, n (%)			
White non-Hispanic	227 (59.6%)	141 (80.1%)	645 (66.6%)
Hispanic/Latinx	56 (14.7%)	27 (15.3%)	109 (11.3%)
Asian non-Hispanic	7 (1.8%)	4 (2.3%)	36 (3.7%)
Black non-Hispanic	41 (10.8%)	2 (1.1%)	88 (9.1%)
Other non-Hispanic	17 (4.5%)	2 (1.1%)	33 (3.4%)
Not available	33 (8.7%)	0 (0%)	57 (5.9%)
Age at first measurement, years [IQR]	0.20 [0–0.7]	0.25 [0.2–1.0]	8.0 [1.6–13]
Age at last measurement, years [IQR]	1.1 [0.2–1.9]	1.1 [0.98–2.0]	14 [8.5–18]
Number of height measurements			
Total, N	1330	595	9248
Per person, n [IQR]	2 [1–3]	4 [3–4]	5.0 [2–11]
Total number of weight measurements			
Total, N	1890	605	10 520
Per person, n [IQR]	2 [1–4]	4 [3–4]	6.0 [2–12]

Data are expressed as count (%) or median [IQR]. Abbreviations: N, total population; n, subgroup of total population.

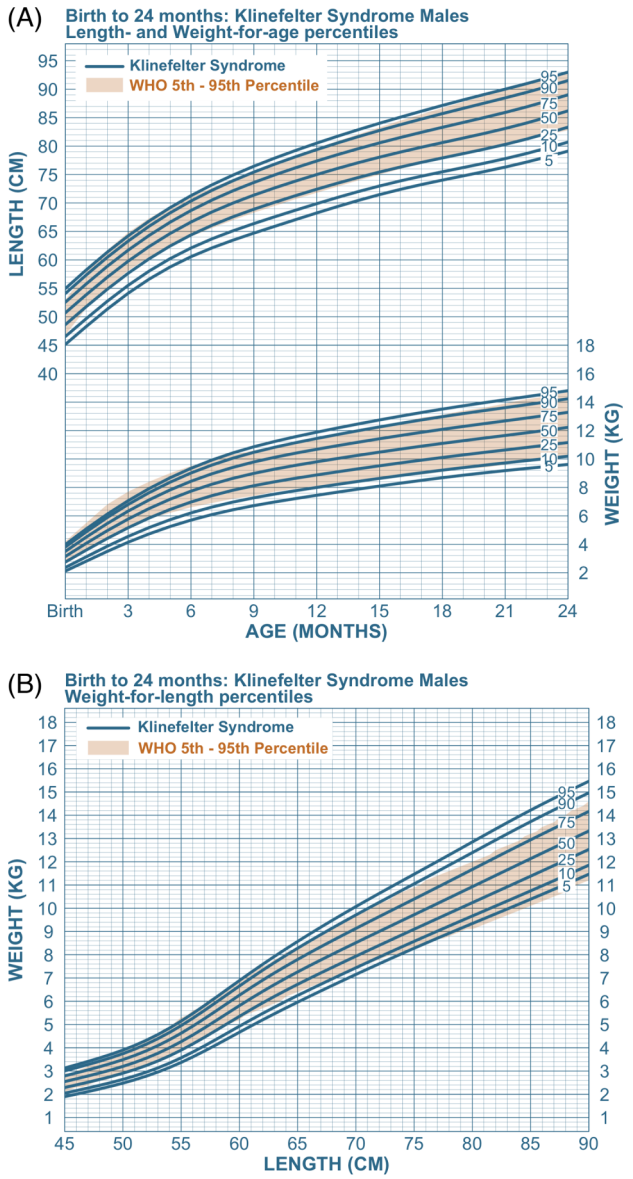

FIGURE 2.
(A) Length- and weight-for-age growth curves and (B) weight-for-length percentiles for Klinefelter syndrome from birth to age 24 months, with the 5th to 95th percentile bands from WHO reference curves overlaid for comparison. Growth curves were estimated using 1-month age bins for ages 0 to 24 months and 6-month age bins for ages 2 to 18 years.
Abbreviation: WHO, World Health Organization.

CDC 5th percentile for stature (Figure 3). By age 5 years, height began to diverge upward, with tall stature (>95th percentile) seen in 10% at age 5 years, 25% by age 10 years, and 20% by age 15 years. The largest mean height differences were observed between ages 11 to 13 years, where youth with KS were on average 8 cm taller than peers ($P < .001$). At age 20 years, the mean height remained elevated by 4.7 cm compared with CDC norms ($P < .001$).

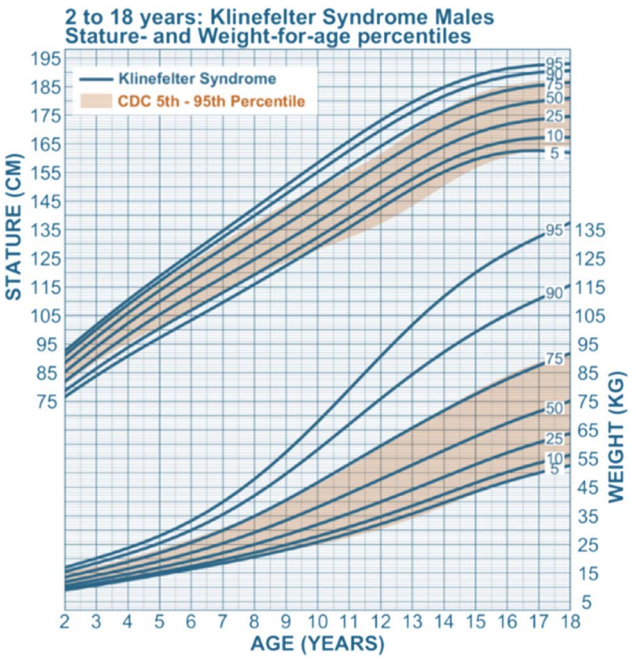

FIGURE 3.
Stature- and weight-for-age growth curves for Klinefelter syndrome from 2 to 18 years old with the CDC 5th to 95th percentile bands overlaid for comparison. Growth curves were estimated using 6-month age bins for ages 2 to 18 years.
Abbreviation: CDC, Centers for Disease Control and Prevention.

Height velocity in KS was significantly higher than expected during midchildhood (ages 7–12 years), averaging 7.2 ± 0.6 cm/y compared with 5.5 ± 0.5 cm/y in the reference population ($P < .001$). However, no clear pubertal growth spurt was observed. From ages 12 to 15 years, mean growth velocity in KS (6.1 ± 0.3 cm/y) was lower than CDC estimates (7.0 ± 0.7 cm/y; $P < .001$). Testosterone treatment status had minimal impact on overall growth trajectories (Supplemental Figure 1). A sensitivity analysis removing duplicated height measures after the age of 16 years resulted in minimal changes in height curves.

Weight and BMI (2–18 Years)

By early childhood, approximately 10% of boys with KS exceeded the CDC 95th percentile for weight-for-age, increasing to 25% by midchildhood and remaining elevated through adolescence (Figure 3). BMI distributions in KS spanned a broader range than the CDC reference (Figure 4). Although median BMI was similar to norms, approximately 35% of youth older than 4 years fell into the overweight category (≥85th percentile), and approximately 20% met criteria for obesity (≥95th percentile). By age 18 years, 5% of individuals had a BMI exceeding 42 kg/m^2, consistent with class III (severe) obesity. Conversely, approximately 10% were underweight (<5th percentile).

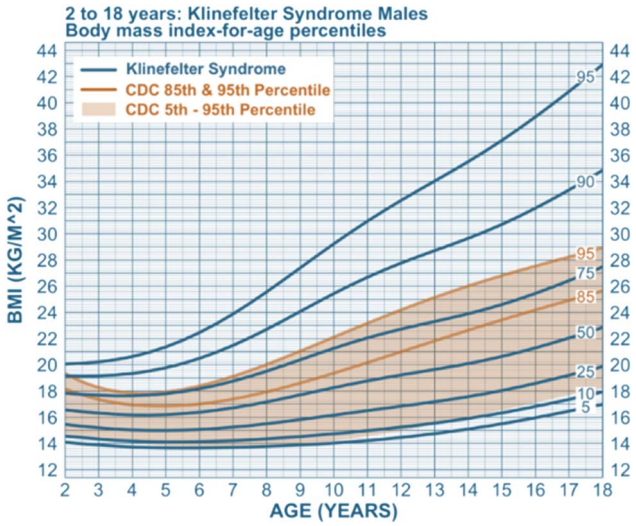

FIGURE 4.
Body mass index-for-age growth curve for Klinefelter Syndrome from ages 2 to 18 years with the CDC 5th to 95th percentile bands overlaid for comparison. The CDC 85th and 95th percentile lines indicate overweight and obesity, respectively. Growth curves were estimated using 6-month age bins for ages 2 to 18 years.
Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention.

DISCUSSION

We used clinical data from 1279 children to develop the first KS-specific growth charts, illustrating the distinct growth trajectories of this population. Although tall stature and obesity are well-recognized features of KS in both the medical and lay literature, our findings demonstrate greater variability in growth than has previously been appreciated. These reference curves provide a valuable tool to support individualized care, enabling clinicians to offer anticipatory guidance, determine when further evaluation is warranted, and assess the impact of clinical interventions on growth outcomes.

Tall stature in KS has primarily been attributed to an additional copy of the short-stature homeobox (*SHOX*) gene located on the pseudoautosomal region of the X chromosome.[20,21] *SHOX* escapes X chromosome inactivation; therefore, individuals with KS (47,XXY) express 3 copies of this gene. Its protein product promotes growth by regulating endochondral ossification at the growth plate.[22] The increased prepubertal height velocity demonstrated by that observed in our cohort is congruent with the *SHOX* gene-dosage hypothesis. However, the lack of distinct growth acceleration in puberty and continued growth at 18 to 20 years suggests gonadal steroids may also contribute to

TABLE 2. Age-Delineated Height and Weight of Patients With Klinefelter Syndrome Compared to the Reference Male Population

Age, years	N, Ht	Mean (SD) Height of KS, cm	Mean (SD) Height of RP, cm	*P* Value	N, Wt	Mean (SD) Weight of KS, cm	Mean (SD) Weight of RP, cm	*P* Value
0–1	1167	60.1 (8.8)	65.1 (2.1)	<.001[a]	1508	5.8 (2.5)	7.2 (0.8)	<.001[a]
1–2	574	79.3 (5.1)	81.6 (2.7)	<.001[a]	705	10.8 (1.7)	10.8 (1.2)	.439
2–3	400	89.5 (5.7)	90.6 (3.7)	.001[a]	490	13.2 (2.4)	13.4 (1.5)	.030[a]
3–4	405	98.5 (5.6)	98.7 (4.0)	.717	454	16.1 (3.3)	15.3 (1.8)	<.001[a]
4–5	378	105.3 (6.3)	105.6 (4.4)	.719	422	18.4 (3.7)	17.3 (2.2)	<.001[a]
5–6	366	112.8 (7.0)	112.2 (4.8)	.076	406	21.5 (5.0)	19.5 (2.6)	<.001[a]
6–7	376	119.6 (7.3)	118.6 (5.2)	.009[a]	418	24.7 (5.9)	21.9 (3.2)	<.001[a]
7–8	333	126.8 (7.8)	124.9 (5.6)	<.001[a]	378	28.2 (7.6)	24.3 (3.7)	<.001[a]
8–9	369	133.3 (9.2)	130.7 (6.0)	<.001[a]	420	33.0 (9.3)	27.1 (4.4)	<.001[a]
9–10	472	140.6 (9.2)	136.1 (6.4)	<.001[a]	531	38.9 (11.7)	30.2 (5.3)	<.001[a]
10–11	457	147.4 (8.7)	141.1 (6.8)	<.001[a]	497	43.6 (15.1)	33.9 (6.4)	<.001[a]
11–12	571	154.7 (9.2)	146.2 (7.2)	<.001[a]	640	50.0 (18.1)	38.1 (7.5)	<.001[a]
12–13	556	160.8 (9.9)	152.4 (7.6)	<.001[a]	620	56.4 (18.9)	43.0 (8.6)	<.001[a]
13–14	626	167.3 (10.1)	160.0 (8.0)	<.001[a]	677	59.3 (20.7)	48.3 (9.5)	<.001[a]
14–15	651	173.3 (8.9)	167.1 (8.0)	<.001[a]	737	66.5 (22.0)	53.7 (10.1)	<.001[a]
15–16	620	177.4 (8.4)	171.9 (7.7)	<.001[a]	719	72.1 (23.6)	58.7 (10.5)	<.001[a]
16–17	629	179.1 (8.8)	174.5 (7.4)	<.001[a]	696	77.7 (25.4)	62.8 (10.7)	<.001[a]
17–18	650	180.3 (9.5)	175.8 (7.2)	<.001[a]	697	79.9 (28.8)	66.0 (10.9)	<.001[a]
18–19	418	180.0 (9.9)	176.4 (7.1)	<.001[a]	410	83.9 (26.4)	68.2 (11.1)	<.001[a]
19–20	198	181.4 (9.2)	176.7 (7.1)	<.001[a]	204	86.8 (27.6)	69.9 (11.3)	<.001[a]

Data are presented as mean (SD) with *P* values reflecting the difference in means between KS and RP measurements at each age time frame, after adjusting for testosterone status (World Health Organization for ages 0–2 years and CDC for ages 2–18 years).
Abbreviations: Ht, height; KS, Klinefelter syndrome; RP, reference male population; Wt, weight.

altered growth in KS. In typical male puberty, testosterone stimulates growth hormone and insulin-like growth factor 1 to drive the pubertal growth spurt with peak aggregate height velocity corresponding with Tanner 3 to 4.[23] Epiphyseal maturation and growth cessation follows, mediated by the aromatization of testosterone to estradiol.[24] In KS, testosterone insufficiency may explain both the lack of pubertal growth acceleration and continued growth into adulthood. Intervention studies have found that androgen treatment in KS does impact growth velocity and epiphyseal maturation.[25] Although we did not observe a strong effect of testosterone treatment on growth patterns in our data set, bone age, treatment dose, and adherence could not be assessed; therefore, we are limited in the conclusions we can draw regarding the impact of exogenous testosterone on growth.

In addition to linear growth, men with KS have a high prevalence of obesity and obesity-related disorders, contributing to long-term morbidity and mortality.[13,26] Abnormal lipid metabolism and hypogonadism have been proposed to underlie this phenotype.[27] Our findings support prior research suggesting that overweight/obesity in KS often begin in childhood and increases with age, not dissimilar from the general population.[28] However, given the known obesity-associated morbidity in adults with KS, these early trends underscore the importance of promoting healthy lifestyle interventions from a young age. Conversely, low BMI also affects a subset of patients. If pathologic conditions are ruled out, counseling should still focus on promoting balanced nutrition and physical activity.

Our data also highlight that a substantial proportion of infants and young children with KS fall below the 5th percentile for height and weight. Although smaller birth size has been associated with KS,[29,30] data on early postnatal growth are limited. Our findings suggest that clinicians can offer reassurance for a child with KS falling below the general population reference curve but tracking appropriately on the KS given the expected catch-up growth in later childhood. However, some conditions that negatively impact growth have been reported in KS, including early feeding difficulties, growth hormone deficiency,[31–33] thyroid dysfunction,[34] and eosinophilic esophagitis,[35] so patients deviating from these KS growth curves should be evaluated for causes of poor growth. Future research should investigate the biologic mechanisms that may contribute to reduced intrauterine and early postnatal growth in XXY.

This study has several limitations. First, a diagnosis of KS in PEDSnet has not been independently validated. However, prior research from our group found a 95% accuracy rate for a single diagnosis code of Turner syndrome in PEDSnet, and the reasons for false positives were not applicable to KS,[36] so we expect similar reliability here. PEDSnet data also reflect a clinically ascertained KS population seen within tertiary care networks and will not capture individuals with undiagnosed KS or those not engaged in specialty care. Additional limitations include lack of gestational age, unknown measurement conditions (eg, recumbent vs standing height, clothed vs unclothed), and potential minor data inaccuracies despite cleaning. Although our quantile regression approach smooths across ages and supports robust percentile estimation, sample sizes remain smaller particularly at the younger ages, which may increase uncertainty in extreme percentiles. In contrast, the eXtraordinarY Babies Study provided high-quality, prospectively collected anthropometric data, but it is currently limited to infants and young children and includes a more homogeneous sample. Despite these limitations, this work offers the first clinically relevant reference growth curves for children and adolescents with KS in the United States, built from a large, diverse data set.

CONCLUSIONS

We have developed KS-specific growth charts for infants and youth using a large clinical US data set. Although many children with KS fall within broad general population growth ranges, their overall growth trajectory is distinct. These novel reference curves provide a valuable clinical tool to support individualized assessment, monitoring, and counseling for children and adolescents with KS.

FUNDING: NIH/NICHD R01HD091251, R03 HD102773/HD/NICHD NIH HHS/United States. The study sponsors are not involved in the study design, data collection, analysis, or interpretation of the data, the writing or the report, nor the decision to submit the manuscript for publication.

Accepted for Publication Date: September 4, 2025

https://doi.org/10.1542/peds.2025-072193

REFERENCES

1. Hermanussen M. Auxology: an update. *Horm Res Paediatr.* 2010;74(3):153–164. PubMed doi: 10.1159/000317440
2. de Onis M, Wijnhoven TM, Onyango AW. Worldwide practices in child growth monitoring. *J Pediatr.* 2004;144(4):461–465. PubMed doi: 10.1016/j.jpeds.2003.12.034
3. Ranke MB. Disease-specific standards in congenital syndromes. *Horm Res.* 1996;45 Suppl 2(2):35–41.
4. Pyeritz RE. Papadatas CJ BC. *Endocrine Genetics and Genetics of Growth.* Alan R Liss, Inc; 1985.
5. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. *Arch Dis Child.* 1985;60(10):932–935. PubMed doi: 10.1136/adc.60.10.932
6. Cronk C, Crocker AC, Pueschel SM, et al. Growth charts for children with Down syndrome: 1 month to 18 years of age. *Pediatrics.* 1988;81(1):102–110. PubMed doi: 10.1542/peds.81.1.102
7. Visootsak J, Graham JM Jr. Klinefelter syndrome and other sex chromosomal aneuploidies. *Orphanet J Rare Dis.* 2006;1:42. PubMed doi: 10.1186/1750-1172-1-42
8. Groth KA, Skakkebæk A, Høst C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome—a clinical update. *J Clin Endocrinol Metab.* 2013;98(1):20–30. PubMed doi: 10.1210/jc.2012-2382
9. Davis SM, Teerlink C, Lynch JA, et al. Prevalence, morbidity, and mortality of men with sex chromosome aneuploidy in the Million Veteran Program cohort. *JAMA Netw Open.* 2024;7(3):e244113. PubMed doi: 10.1001/jamanetworkopen.2024.4113
10. Gravholt CH, Chang S, Wallentin M, Fedder J, Moore P, Skakkebæk A. Klinefelter syndrome: integrating genetics, neuropsychology, and endocrinology. *Endocr Rev.* 2018;39(4):389–423. PubMed doi: 10.1210/er.2017-00212
11. Aksglaede L, Skakkebaek NE, Juul A. Abnormal sex chromosome constitution and longitudinal growth: serum levels of insulin-like growth factor (IGF)-I, IGF binding protein-3, luteinizing hormone, and testosterone in 109 males with 47,XXY, 47,XYY, or sex-determining region of the Y chromosome (SRY)-positive 46,XX karyotypes. *J Clin Endocrinol Metab.* 2008;93(1):169–176. PubMed doi: 10.1210/jc.2007-1426
12. Davis SM, Nokoff NJ, Furniss A, et al. A population-based assessment of cardiometabolic-related diagnosis in youth with Klinefelter syndrome: a PEDSnet study. *J Clin Endorinol Metab.* 2022;107(50):e1850–e1859. PubMed doi: 10.1210/clinem/dgac056
13. Bojesen A, Kristensen K, Birkebaek NH, et al. The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care.* 2006;29(7):1591–1598. PubMed doi: 10.2337/dc06-0145
14. Forrest CB, Margolis PA, Bailey LC, et al. PEDSNet: a national pediatric learning health system. *J Am Med Inform Assoc.* 2014;21(4):602–606. PubMed doi: 10.1136/amiajnl-2014-002743
15. Tartaglia N, Howell S, Davis S, et al. Early neurodevelopmental and medical profile in children with sex chromosome trisomies: background for the prospective eXtraordinarY babies study to identify early risk factors and targets for intervention. *Am J Med Genet C Semin Med Genet.* 2020;184(2):428–443. PubMed doi: 10.1002/ajmg.c.31807
16. Daymont C, Ross ME, Russell Localio A, Fiks AG, Wasserman RC, Grundmeier RW. Automated identification of implausible values in growth data from pediatric electronic health records. *J Am Med Inform Assoc.* 2017;24(6):1080–1087. PubMed doi: 10.1093/jamia/ocx037
17. Muggeo V, Sciandra M, Tomasello A, Calvo S. Estimating growth charts via nonparametric quantile regression: a practical framework with application in ecology. *Environ Ecol Stat.* 2013;20(4):519–531. doi: 10.1007/s10651-012-0232-1
18. Muggeo V, Torretta F, Eilers PHC, Sciandra M, Attanasio M. Multiple smoothing parameters selection in additive regression quantiles. *Stat Model.* 2021;21(5):428–448. doi: 10.1177/1471082X20929802
19. Cole N. *Super Imposition by Translation and Rotation Growth Curve Analysis.* R Package Version 140; 2023.
20. Ogata T, Matsuo N. Sex chromosome aberrations and stature: deduction of the principal factors involved in the determination of adult height. *Hum Genet.* 1993;91(6):551–562. PubMed doi: 10.1007/BF00205079
21. Ottesen AM, Aksglaede L, Garn I, et al. Increased number of sex chromosomes affects height in a nonlinear fashion: a study of 305 patients with sex chromosome aneuploidy. *Am J Med Genet A.* 2010;152A(5):1206–1212. PubMed doi: 10.1002/ajmg.a.33334
22. Marchini A, Ogata T, Rappold GA. A track record on SHOX: from basic research to complex models and therapy. *Endocr Rev.* 2016;37(4):417–448. doi: 10.1210/er.2016-1036
23. Soliman A, Sanctis VD, Elalaily R, Bedair S. Advances in pubertal growth and factors influencing it: can we increase pubertal growth? *Indian J Endocrinol Metab.* 2014;18(Suppl 1):S53–S62. doi: 10.4103/2230-8210.145075
24. Weise M, De-Levi S, Barnes KM, Gafni RI, Abad V, Baron J. Effects of estrogen on growth plate senescence and epiphyseal fusion. *Proc Natl Acad Sci U S A.* 2001;98(12):6871–6876. PubMed doi: 10.1073/pnas.121180498
25. Davis SM, Cox-Martin MG, Bardsley MZ, Kowal K, Zeitler PS, Ross JL. Effects of oxandrolone on cardiometabolic health in boys with Klinefelter syndrome: a randomized controlled trial. *J Clin Endocrinol Metab.* 2017;102(1):176–184. PubMed doi: 10.1210/jc.2016-2904
26. Bojesen A, Gravholt CH. Morbidity and mortality in Klinefelter syndrome (47,XXY). *Acta Paediatr.* 2011;100(6):807–813. PubMed doi: 10.1111/j.1651-2227.2011.02274.x
27. Davis SM, Urban R, D'Alessandro A, et al. Unique plasma metabolite signature for adolescents with Klinefelter syndrome reveals altered fatty acid metabolism. *Endocr Connect.* 2023;12(5):e220523. doi: 10.1530/EC-22-0523
28. Davis SM, DeKlotz S, Nadeau KJ, Kelsey MM, Zeitler PS, Tartaglia NR. High prevalence of cardiometabolic risk features in adolescents with 47,XXY/Klinefelter syndrome. *Am J Med Genet C Semin Med Genet.* 2020;184(2):327–333. PubMed doi: 10.1002/ajmg.c.31784

29. Tartaglia N, Davis S, Howell S, et al. Medical findings in infants prenatally identified with sex chromosome trisomy in year one of life. *Pediatrics*. In Press.

30. Dotters-Katz SK, Humphrey WM, Senz KL, Lee VR, Shaffer BL, Caughey AB. The impact of prenatally diagnosed Klinefelter syndrome on obstetric and neonatal outcomes. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:173–176. PubMed doi: 10.1016/j.ejogrb.2016.05.006

31. Gonzales-Ellis BA, Pingul MM, Reddy S, Boney CM, Wajnrajch MP, Quintos JB. Growth hormone deficiency and central precocious puberty in Klinefelter syndrome: report of a case and review of KIGS database. *J Pediatr Endocrinol Metab*. 2013;26(3–4):361–364. PubMed doi: 10.1515/jpem-2012-0333

32. Bahíllo-Curieses MP, Fournier-Carrera M, Morán-López J, Martínez-Sopena MJ. Klinefelter syndrome and short stature: an unusual combination. *Endocrine*. 2011;39(3):294–295. PubMed doi: 10.1007/s12020-011-9454-5

33. Ramesh J, Nagasatyavani M, Venkateswarlu J, Nagender J. An unusual combination of Klinefelter syndrome and growth hormone deficiency in a prepubertal child. *J Clin Res Pediatr Endocrinol*. 2014;6(3):187–189. PubMed doi: 10.4274/jcrpe.1225

34. Tahani N, Ruga G, Granato S, et al. A combined form of hypothyroidism in pubertal patients with non-mosaic Klinefelter syndrome. *Endocrine*. 2017;55(2):513–518. PubMed doi: 10.1007/s12020-016-1130-3

35. Howell S, Buchanan C, Davis SM, et al. Eosinophilic esophagitis in individuals with sex chromosome aneuploidies: clinical presentations and management implications. *Mol Genet Genomic Med*. 2021;9(12):e1833. PubMed doi: 10.1002/mgg3.1833

36. Huang SD, Bamba V, Bothwell S, et al. Development and validation of a computable phenotype for Turner syndrome utilizing electronic health records from a national pediatric network. *Am J Med Genet A*. 2024;194(4):e63495. PubMed doi: 10.1002/ajmg.a.63495