# Phenotype and Adverse Quality of Life in Boys with Klinefelter Syndrome

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**Objectives** To characterize associations among psychosocial well-being, physical phenotype, and sex hormones in a sample of youth with Klinefelter syndrome (KS). We hypothesized that KS physical traits (phenotype) are associated with adverse psychosocial health measures and that testosterone levels are associated with adverse psychosocial health.

**Study design** Forty-three boys with KS (ages 8-18 years) participated in a cross-sectional study. Participants underwent physical examination, hormone analyses, and psychosocial health questionnaires.

**Results** Using an investigator-developed Klinefelter Phenotype Index Scale, the number of KS physical traits ranged from 1-13 (mean 5.1 ± 1.9). Pubertal boys presented with more KS traits compared with prepubertal boys (5.6 vs 4.2, $P = .01$). Boys diagnosed prenatally had a milder phenotype compared with those diagnosed postnatally. Gonadotropins were elevated without androgen deficiency in 45%. Psychosocial health scores indicated adverse quality of life (QOL) (67%), low self-esteem (38%), poor self-concept (26%), and risk for depression (16%) without a difference between pubertal groups. Linear regression showed that 22% of the variance in QOL ($P = .0001$) was explained by phenotype. Testosterone level was not associated with psychosocial health measures.

**Conclusions** Depending on the degree of phenotypic abnormality, boys with KS may be at risk for impaired QOL. Testosterone levels were not shown to influence psychosocial health. The Klinefelter Phenotype Index Scale may be a useful tool to characterize KS features in boys. *(J Pediatr 2015;167:650-7)*.

Klinefelter syndrome (KS) is a genetic condition caused by the presence of an extra X chromosome in the male karyotype. Tall stature, gynecomastia, small testes, androgen deficiency, elevated gonadotropins, and azoospermia typically characterize the condition.[1] KS is reported to be the most common sex chromosome aneuploidy with a prevalence of approximately 1 in 600 male births.[2] KS is also associated with physical, neurocognitive, and psychosocial comorbidities, including infertility and high risk for the development of cardiovascular disease, diabetes, osteoporosis, autoimmune disorders, and certain kinds of cancers.[3] Only 10% of affected individuals are diagnosed during childhood. It has been estimated that approximately 25% of affected individuals are diagnosed in adulthood, usually for infertility assessment, with the remaining 65% never receiving a diagnosis in their lifetime.[4] In adults, KS is associated with reproductive, neurocognitive, and psychosocial health problems that are believed to first emerge during childhood.[5] Affected individuals require long-term medical and mental health care needs that vary according to development and life stage.[6]

Although androgen deficiency is believed to underlie many KS-related abnormalities in both physical and emotional health,[7] large studies of boys with KS are uncommon, leading to poor understanding of how this genetic disorder affects growth and development during childhood. Testosterone concentration has been suggested to be associated with many physical and psychological symptoms in adult men. We sought to explore any relationships between testosterone and psychosocial health in children. The peripubertal period is presumed to be a sentinel time for the emergence of physical and psychosocial health issues associated with diminishing production of testosterone.[8] To gain insights into the range of KS traits and their impact on quality of life (QOL) during childhood, we studied the physical phenotype, associated reproductive hormones, and psychosocial health of peripubertal boys with KS.

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| BMI | Body mass index | KSphI | Klinefelter syndrome phenotype index |
| CDI | Children's Depression Inventory | LH | Luteinizing hormone |
| CV | Coefficient of variation | QOL | Quality of life |
| DHEAS | Dehydroepiandrosterone sulfate | TS | Tanner stage |
| FSH | Follicle stimulating hormone | U/L | Upper to lower body segment ratio |
| KS | Klinefelter syndrome | WC | Waist circumference |

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## Methods

The Columbia University Medical Center Institutional Review Board approved the research protocol. Data were collected between April 2010 and August 2011. The inclusion criteria included boys between the ages of 8 and 18 years with a confirmed karyotype of 47,XXY, or 46,XY/47,XXY, who were English speaking and able to read at the third grade level. Subjects were recruited from a pediatric endocrine clinic at Columbia University, local KS support groups, an online study website, a professional research recruitment website, and a social media website.

The study visit consisted of 3 components: physical examination, blood collection for hormone determinations with completion of 1 demographic questionnaire by the parent, and 4 questionnaires by the youth (QOL, self-esteem, self-concept, and risk for depression). Written informed consent was obtained from 18-year-old participants with parental informed consent; child assent was obtained from boys under the age of 18 years. Each subject received a $25 gift card as compensation for his/her time.

Clinical observations of physical traits, anthropometric measurements, and Tanner stage (TS) were assessed by 2 of the investigators, a pediatric nurse practitioner (S.C.) and a pediatric endocrinologist (I.F.). To characterize the KS physical phenotype, an investigator-developed assessment tool was used to quantify the number of KS physical traits including tall stature, eunuchoid body proportion, wide arm span, large waist circumference (WC), high body mass index (BMI), small testicular volume, short phallus, gynecomastia, skeletal abnormalities (pectus excavatum, pectus carinatum, scoliosis), high arched palate, clinodactyly, hand tremor, and hypertelorism. The KS phenotype index (KSphI) measurement tool was created and modeled after the Mainz Severity Score Index,[9] an instrument for quantifying the Anderson-Fabry disease phenotype. The KSphI score is a summed value that reflects the presence (score = 1) or absence (score = 0) of each physical trait with a total score ranging from 0 to 13. A higher score represents the presence of more KS physical features. Quality and accuracy of these measurements was assured with 90% agreement between the 2 raters (S.C. and I.F.). Height was measured to the nearest 0.1 cm in a standing position with either a Seca (Chino, California) fixed wall-mounted or a portable Charder HM200P clinical stadiometer (Charder, Taichun City, Taiwan). Subjects were positioned using the Frankfort horizontal plane, a horizontal plane represented in profile by a line between the lowest point on the margin of the orbit and the highest point on the margin of the auditory meatus. Height was measured 3 times. The average of the height measurements was used.[10] Reliability between the wall-mount and the portable stadiometers was measured by comparing heights in cm taken from 30 adult volunteers.

Weight was measured to the nearest 0.1 kg on a calibrated RLS (Rice Lake Weighing Systems, Rice Lake, Wisconsin) clinical digital scale (measurements at Columbia University Medical Center) or a calibrated portable UC-321 (A and D Medical, San Jose, California) digital scale (off-site measurements). Reliability between the clinical scale and the portable scale was measured by comparing weight in kg taken from 30 adult volunteers. Reliability between digital scales exceeded 98%.

WC was measured using a nonstretchable measuring tape according to the National Health and Nutrition Survey III guidelines.[11] Subjects were measured standing with legs together and arms at their sides with palms facing inward. The midpoint of the inferior margin (lowest point) of the last rib and the crest of the ilium was located. The subject was asked to exhale gently. WC was measured at just above the uppermost lateral border of the right ilium to the nearest 1 mm. Abnormal WC was defined as values $\geq$ the 90th percentile for age. BMI was calculated for height and age using the Centers for Disease Control BMI for Children online calculator.[12] BMI greater than the 85th percentile was used to determine overweight status.

Upper to lower body segment ratio (U/L) was measured with the subject in a standing position. The top of the pubic bone was palpated. The lower segment was measured from the top of the middle part of the pubic bone to the sole of the foot to the nearest 0.1 cm. The lower segment was subtracted from the total height to obtain the upper body segment measurement. The U/L was calculated by dividing upper body segment by the lower body segment. U/Ls less than 1.0 were considered abnormal.[13] Arm span was measured to the nearest 0.1 cm with the subject standing against a flat wall with arms outstretched to create a 90° angle with the torso. The distance between the tips of the right and left middle fingers were measured in cm using a nonstretchable measuring tape.[13] Hypertelorism was determined by measurement of the inner canthal distance using a disposable plastic ruler.[13] Inner canthal distance $\geq$2 SD was determined to be classified as hypertelorism.[13,14]

Sexual maturation was assessed by clinical observation of the presence and distribution of pubic hair, stretched phallic length, appearance of scrotum, and staged 1 to 5 according to the guidelines of Tanner.[15] Stretched phallic length was measured using a disposable wooden tongue blade pressed against the pubic ramus depressing the suprapubic fat pad as completely as possible.[13] Phallic length measurement to the nearest 1 mm was compared with the normal size range for chronological age using the normative measurements for age established by Schonfeld and Beebe.[16] Testicular volume was measured using Prader orchidometer beads. With the subject lying supine, testes were manually palpated and compared for size according to the technique of Prader. If testes were of different sizes, the average of the 2 testes were taken.[13] For purposes of this study, given that boys with KS characteristically have small testicular volume, the designation of prepubertal and pubertal status was made on the basis of pubic hair distribution. Gynecomastia was assessed using TS and bimanual palpation to distinguish between presence and absence of lipomastia or glandular tissue.[17] Subjects were assessed for the presence of skeletal abnormalities