Age-appropriate body mass index in children with achondroplasia: interpretation in relation to indexes of height[1–3]

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ABSTRACT

Background: Achondroplasia is the most common short stature skeletal dysplasia, with an estimated worldwide prevalence of 250 000. Body mass index (BMI)–for-age references are required for weight management guidance for children with achondroplasia, whose body proportions are unlike those of the average stature population.

Objective: This study used weight and height data in a clinical setting to derive smoothed BMI-for-age percentile curves for children with achondroplasia and explored the relation of BMI with its components, weight and height.

Design: This was a longitudinal observational study of anthropometric measures of children with achondroplasia from birth through 16 y of age.

Results: The analysis included 1807 BMI data points from 280 children (155 boys, 125 girls) with achondroplasia. As compared with the BMI of peers of average stature, the BMI in children with achondroplasia is higher at birth, lacks a steep increase in infancy and a later nadir between 1 and 2 y of age, and remains substantially higher through 16 y of age in both sexes. Patterns of change in height and weight in children with achondroplasia are unique in that there is no overlap in the height distribution after 6 mo of age and no spike in height velocity during infancy or puberty—the 2 periods of greatest linear growth in individuals of average stature.

Conclusions: Sex- and age-specific BMI curves are available for children with achondroplasia (birth to 16 y of age) for health surveillance and future research to determine associations with health outcomes (eg, cardiovascular disease, diabetes, and indication for and outcome of surgery).   *Am J Clin Nutr* 2008;88:364–71.

INTRODUCTION

Achondroplasia is the most common short stature-skeletal dysplasia, occurring in ≥ 1 of 20 000 births (1–4). Sporadic mutations in fibroblast growth factor receptor 3 (FGFR3) cause $\approx 80\%$ of achondroplasia cases, with 98% of all cases attributable to one mutation (G1138A). Clinical features of this metaphyseal dysplasia include rhizomelia, macrocephaly, frontal bossing, midface hypoplasia, lumbar lordosis and stenosis, and a small foramen magnum (5). Acceptable terms to describe these patients are Little People (LPs), short stature, or dwarf.

Excess weight has severe consequences for the health and well-being of all people, but can especially exacerbate common medical problems for achondroplastic patients, including obstructive sleep apnea, genu varus, spinal stenosis, and lordosis.

Data from a recent 40-y morbidity and mortality study show that cardiovascular disease–related deaths in achondroplasia are higher than expected compared with age- and sex-matched individuals of average stature, which suggests an influence of central adiposity (6).

Because there is a recognized problem in this population, there is a need to better evaluate appropriate body mass starting in childhood (7, 8). Weight-for-height curves published in 1996 were the first effort to facilitate simultaneous assessment of weight and height in the clinical setting (7). We recently published age- and sex-specific weight curves for children with achondroplasia (9), which were comparable with those available for children of average stature and intended to complement age- and sex-specific height curves in longtime clinical use (10).

Average-stature pediatric BMI-for-age curves have existed for several years, with BMI values beyond the 95th percentile indicating overweight (11). Current recommendations of the American Academy of Pediatrics to monitor body mass include BMI calculation at all routine well-child health visits and throughout the school years (12). Because of the unique body proportions in persons with achondroplasia, however, average-stature BMI norms are inappropriate for use in this population. Moreover, in children of average stature, distinct BMI patterns occur during growth and may predict sentinel events of puberty (13–15) and risk adult obesity (16), but the relevance of these patterns to the achondroplasia population is unknown.

This article reports the first BMI-for-age growth curves for children with achondroplasia using data obtained longitudinally over decades of clinical practice; such reference curves will be applicable to routine medical care in this population. We also present data on height velocity, previously described in only a small number of children with achondroplasia using hand-smoothing techniques (10). Furthermore, relations of BMI

during childhood to weight, height, height velocity, and upper-to-lower body segment ratios in these children are explored.

SUBJECTS AND METHODS

An achondroplasia anthropometry database was created from longitudinal data extracted from the clinical records of patients seen by one of the authors (CIS) over the course of clinical practice from 1967 to 2004. Retrospective accounts of birth variables from these individuals included in this analysis dated back to 1956. Additional information about this database is described in a prior publication (9). This study was approved by the Institutional Review Boards of the Johns Hopkins Medical Institution (Baltimore, MD) and AI DuPont Hospital for Children (Wilmington, DE).

Anthropometric measures of interest in this study were weight, height, lower segment (measured as the standing distance from pubic bone to ground at instep), and upper segment (measured as sitting height or calculated as the difference between height and lower segment length). BMI was calculated at every point at which there was a simultaneous weight and length or height value available for all achondroplasia patients [weight (kg)/height^2 (m)]. Growth velocity for each individual was calculated as the change in height over the time interval between every 2 consecutive height values, provided the time interval between measurements was >3 mo but <18 mo. The midpoint of the age interval between 2 height measurements was considered the age at which that velocity was achieved; thus, velocity was plotted at that time point.

Scatter plots of all the variables of interest (weight, height, BMI, upper-to-lower body segment ratio, and height velocity) were produced using R (Vienna, Austria) (17–19), from which percentiles (5th, 50th, and 95th) were estimated across the age continuum (0–16 y) by sex. Given the paucity of data beyond 16 y, smoothed curves could not be reliably derived for children beyond that age. For all measures except height velocity, empirical percentiles were estimated at each time point (in 1-mo increments) by taking the observed variable percentile value for all observations within ± 1 mo of the time point. Scatter plot smoothing was then used to estimate the mean percentile values for each variable as a function of age. A semiparametric approach (18) was used to select smoother df, and the resulting smooth functions were weighted based on the concentration of data points used to estimate variable percentiles at each time point. Because of height velocity data paucity issues in older ages, empirical percentiles for this measure were estimated by taking the observed percentile value for all values within ± 3 mo of the time point, and the smoothing df were reduced relative to the values chosen by the semiparametric approach.

For comparison purposes, reference data for weight, height, and BMI for individuals of average stature from birth to 16 y were obtained from data tables published in conjunction with the 2000 Centers for Disease Control and Prevention/National Center for Health Statistics growth curves (20, 21). Sex-specific height velocity figures for children of average stature were estimated from curves published by Brandt (22) for 0–3 y and by Tanner and Davies (23) for 3–16 y. Upper-to-lower body segment ratios for average stature were estimated from curves published by Headings (24) and recently compiled in the *Handbook of Physical Measurements* (25). Average-stature birth length data were referenced from Lubchenco et al (26). Data from achondroplastic

patients born before 35 wk of gestation (28 boys, 11 girls) were not included in the analyses involving the first 2 y of life, although data acquired from these premature individuals after 2 y of life were included in the reference curves.

RESULTS

The sample size of achondroplastic patient data are presented in **Table 1**. There were 334 individuals included in the original achondroplasia database. Of these 334 patients, 1807 BMI data points were included from 280 subjects and 1516 height velocity points are presented from 202 subjects. Twenty-three BMI data points >35 from 5 male and 5 female subjects were excluded from the analysis because unusually high component weight values could not be confirmed as accurate.

Reference curves for clinical use for evaluating BMI-for-age in children with achondroplasia, from birth to 16 y of age, are shown in **Figure 1**. *See* Supplement Figure 1, A and B, under "Supplemental data" in the online issue for the raw data from which these clinical curves were derived.

Smoothed percentile curves for BMI for children with achondroplasia from birth through 16 y of age, with available normative data from boys and girls of average stature superimposed, are shown in **Figure 2**. As compared with the BMI of peers of average stature, the BMI in children with achondroplasia is higher at birth and lacks a steep increase in the first 6 mo of life and a later nadir between 1 and 2 y of age. Rather, the BMI in patients with achondroplasia increases steadily to a plateau of ≈20 at ≈2 y of age compared with a mean BMI of ≈16 in males and females of average stature at this same age. From ≈3 to 8 y of life, nearly the entire BMI distribution for achondroplastic patients (5th to 95th percentiles) appears to be above the 95th percentile of that for the children of average stature. Thereafter, and up to 16 y of age, only the lower half of the achondroplasia BMI distribution (ie, up to the 50th percentile) overlaps the upper half of the average-stature BMI distribution (ie, above the 50th percentile). By visual inspection, median BMI is observed to remain at or above 20 beyond 2 y of age in children with achondroplasia.

To explore the rationale for differences in the magnitude and patterning of BMI-for-age between children with achondroplasia and children of average stature, the components of BMI (ie, height and weight) are explored in **Figure 3**. Considerable overlap exists in weight-for-age between children of average stature and those with achondroplasia. As shown previously, birth weight is comparable between our achondroplasia cohort and

TABLE 1
Number of data points from which the anthropometric normative curves were derived in subjects with achondroplasia from birth through 16 y of age

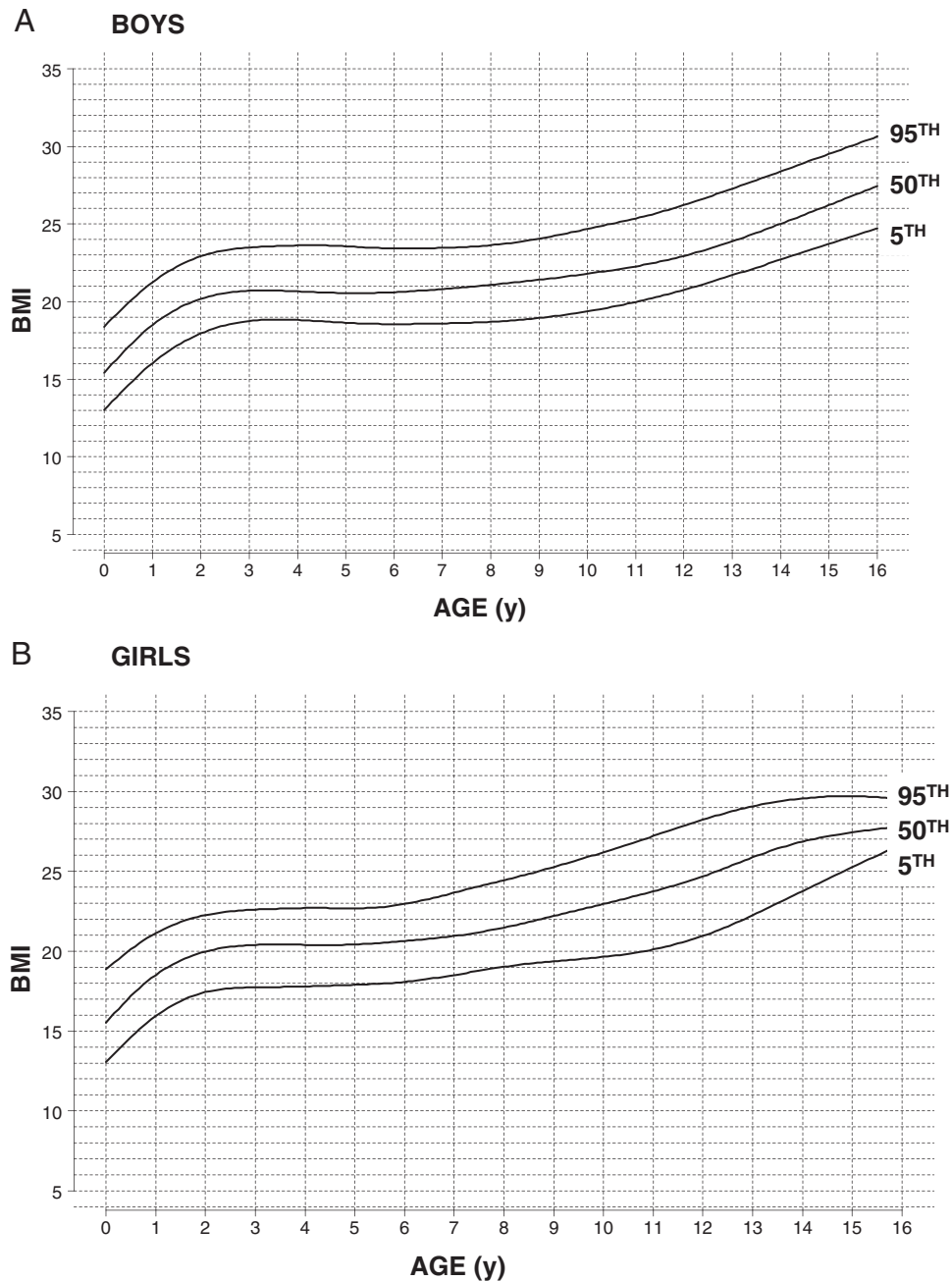|	Boys	Girls	Data points	No. of patients (M/F)
BMI (kg/m^2)	937	870	1807	280 (155/125)
Height (cm)	1018	937	1955	293 (162/131)
Weight (kg)	960	893	1853	293 (155/128)
Upper-to-lower body ratio	629	584	1213	226 (130/96)
Height velocity (cm/y)	764	752	1516	202 (107/95)

A   **BOYS**

B   **GIRLS**

FIGURE 1. BMI curves (5th, 50th, and 95th percentiles) from 0 to 16 y of age in boys and girls with achondroplasia.

term infants of average stature (9). After infancy, the 95th percentile of weight in achondroplastic children appears comparable with the median weight-for-age in children of average stature, and the median weight-for-age in achondroplastic children is similar to the 5th percentile in peers of average stature. This overlap in weight between our achondroplastic cohort and average-stature norms remains over this entire distribution. Thus, ≈50% of the children with achondroplasia have body weights comparable with the lower 50% of their average-stature peers from birth through 16 y of age.

Height, however, differs substantially between children with achondroplasia and those of average stature from birth through 16 y of age for both boys and girls (Figure 3). Despite the appearance in Figure 3 that the mean birth length of the term

individuals in our achondroplasia cohort is quite similar to that of infants of average stature, there is a statistically significant difference ($P < 0.0001$) in birth length between achondroplastic infants (47.4 ± 0.2 cm; $n = 242$) and term infants of average stature (48.5 ± 0.1; $n = 595$) (26). From birth, infants of average stature experience much more rapid linear growth than do achondroplastic infants, with no overlap in height distributions after 6 mo of age. The disparity in height between individuals of average stature and those with achondroplasia becomes more pronounced in both sexes as both approach the pubertal years.

Distinct patterns of linear growth are driven by differences in height velocity between achondroplasia and average stature children, as shown in **Figure 4**. Differences in height velocity are particularly apparent during infancy and puberty, both of which
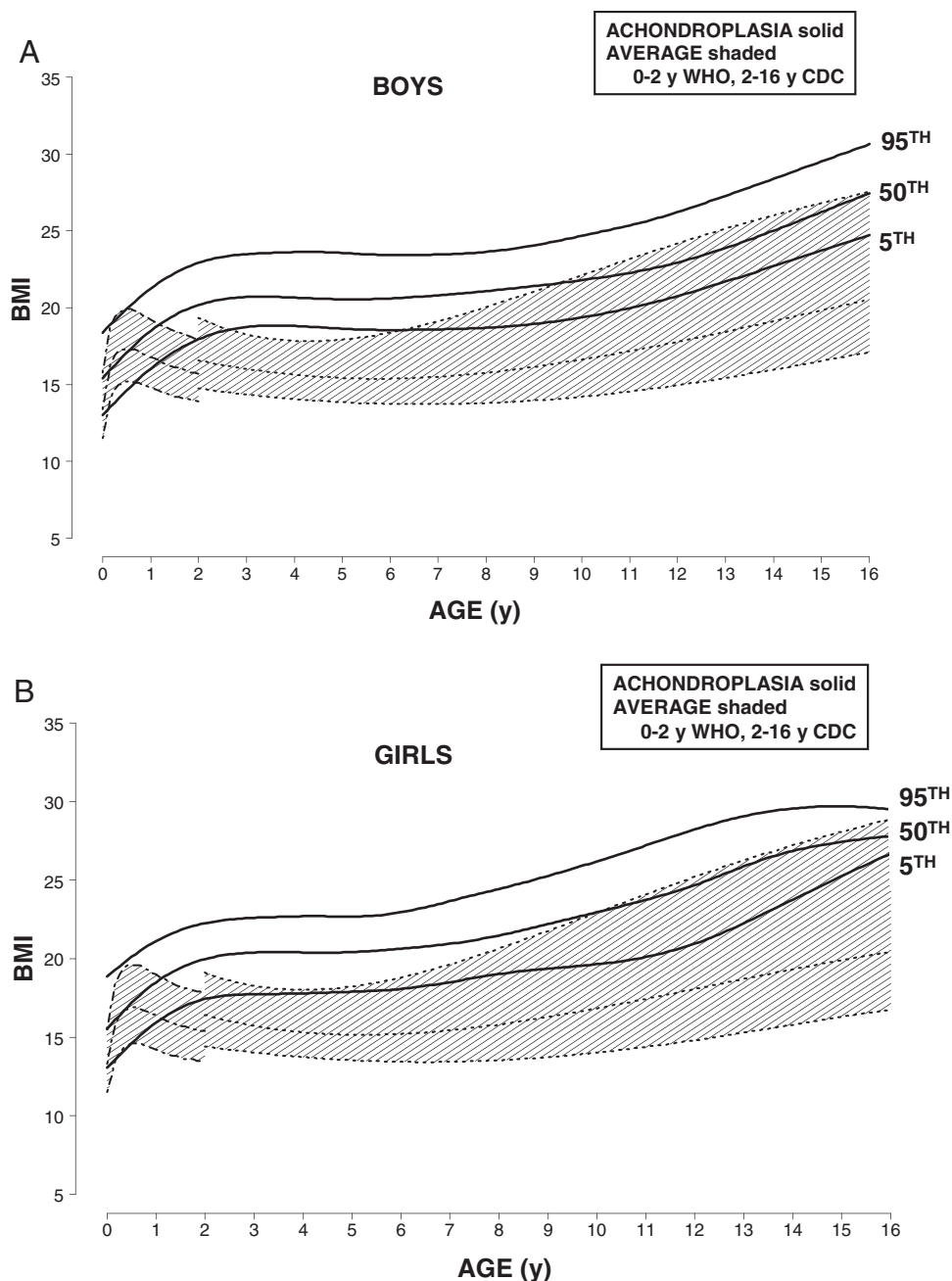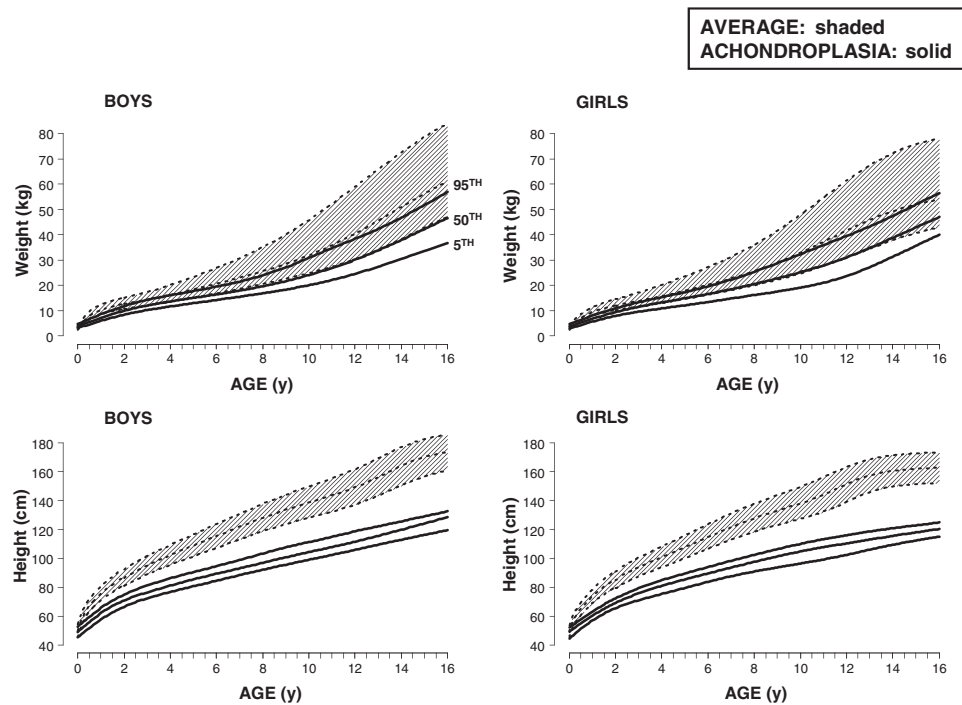
FIGURE 2. BMI curves (5th, 50th, and 95th percentile) from 0 to 16 y of age in boys and girls with achondroplasia (solid lines) and superimposed World Health Organization (WHO; from 0 to 2 y of age) and Centers for Disease Control and Prevention (CDC; from 2 to 16 y) reference curves (dotted and shaded section).

are periods of rapid linear growth in individuals of average stature. Whereas the median height velocity in infants of average stature shortly after birth was ≈3.7 cm/mo (44 cm/y), that in our achondroplastic infants (boys and girls combined) was ≈1.7 cm/mo (20 cm/y). By 1 y of life, median height velocity decreased to ≈1.2 cm/mo (14.4 cm/y) in children of average stature, whereas that in our achondroplastic cohort at 1 y of life is 0.8 cm/mo (10 cm/y). The difference in height velocity between children of average stature and our achondroplastic cohort during childhood (ie, ages 2–10 y) is not nearly as dramatic. The median height velocity in children of average stature older than 10 years ranges from ≈5.5 cm/y to just under 7 cm/y, whereas the median

height velocity of our achondroplastic cohort remained steady at ≈5 cm/y from 2 to 10 y of age. However, unlike males and females of average stature, there is no evidence of a pubertal linear growth spurt in children with achondroplasia. Rather, median height velocities throughout the pubertal years remain at ≈5 cm/y in boys and girls through the age of 16 y. This is in stark contrast with the median height velocity curves shown in Figure 4 for children of average stature with a median peak height velocity of 9.3 cm/y in boys at 13.5 y of life and of 8.3 cm/y in girls at 12 y of life. Thus, gains in height are particularly limited in achondroplastic subjects during what would be expected to be periods of greatest linear growth: both infancy and puberty.
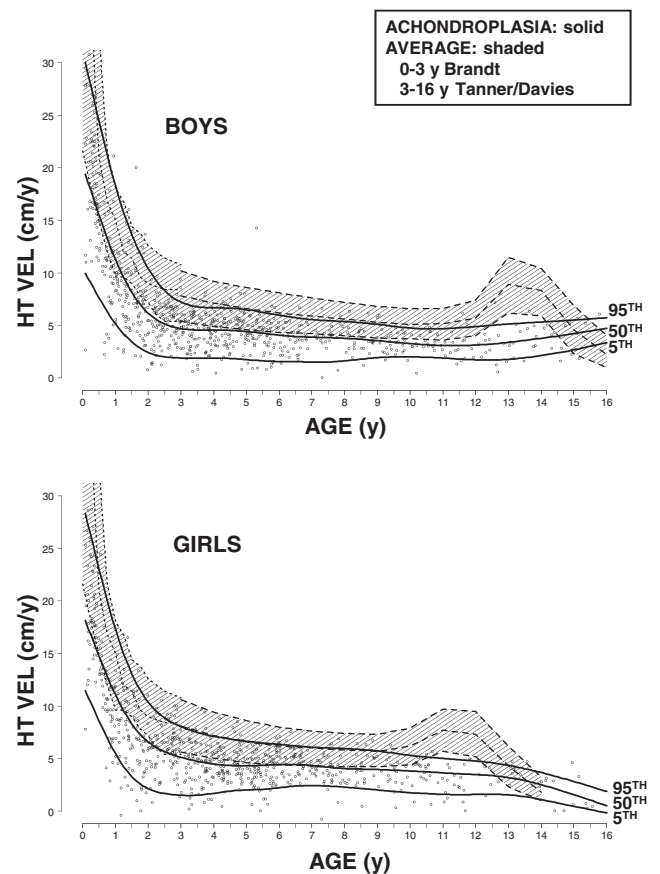
AVERAGE: shaded
ACHONDROPLASIA: solid

FIGURE 3. Height and weight percentiles (5th, 50th, and 95th) for age (from 0 to 16 y) and sex for the achondroplasia cohort (solid) compared with children of average stature (dotted and shaded section) (20, 21).

The relative contribution of upper and lower segment length over childhood in children with achondroplasia compared with that of their peers of average stature is shown in **Figure 5**. In children of average stature, this ratio falls to 1 by 10 y of age as the long bones lengthen relative to the trunk. Because the growth of the extremities is limited in achondroplasia relative to the normal growth of the trunk, the ratio of upper to lower extremities never reaches 1 in persons with achondroplasia.

DISCUSSION

Although skeletal dysplasias are relatively rare, it is estimated that >250 000 individuals worldwide have achondroplasia—the most prevalent form of dwarfism (27). The novel pediatric BMI-for-age curves presented here can be used in daily clinical care as a screening tool to identify children with achondroplasia who are at the extremes of the population distribution of body mass, thereby prompting more intensive nutritional and physical assessment and intervention. Achondroplasia-specific BMI charts are essential to meet current basic medical care recommendations to screen all children for obesity by calculating BMI. The general population trend toward increasing obesity rates may have particular consequences for short-statured individuals. With less body area on which to distribute a greater body mass, even a minor increase in weight may potentially worsen ambulation, cause or worsen obstructive sleep apnea, or contribute to cardiovascular disease (6, 28). These BMI curves should also be applied in future research to describe the relations between body mass in children and later health outcomes, such as adult obesity, cardiovascular disease, and orthopedic and neurosurgical indications and outcomes. Finally, whereas general pediatric anticipatory guidance is currently focused on the detection and treatment of obesity, it should be noted that these BMI-for-age curves are also useful in screening for underweight individuals.

ACHONDROPLASIA: solid
AVERAGE: shaded
  0–3 y Brandt
  3–16 y Tanner/Davies

FIGURE 4. Height velocity (HT VEL) curves (5th, 50th, and 95th percentiles) from 0 to 16 y of age in boys and girls with achondroplasia (solid lines) compared with data for children of average stature (dotted and shaded section) from Brandt (22; 0–3 y; 10th, 50th, and 90th percentiles) and Tanner/Davies (23; 3–16 y; 3rd, 50th, and 97th percentiles).

ACHONDROPLASIA: solid
AVERAGE: dotted, 50TH percentile
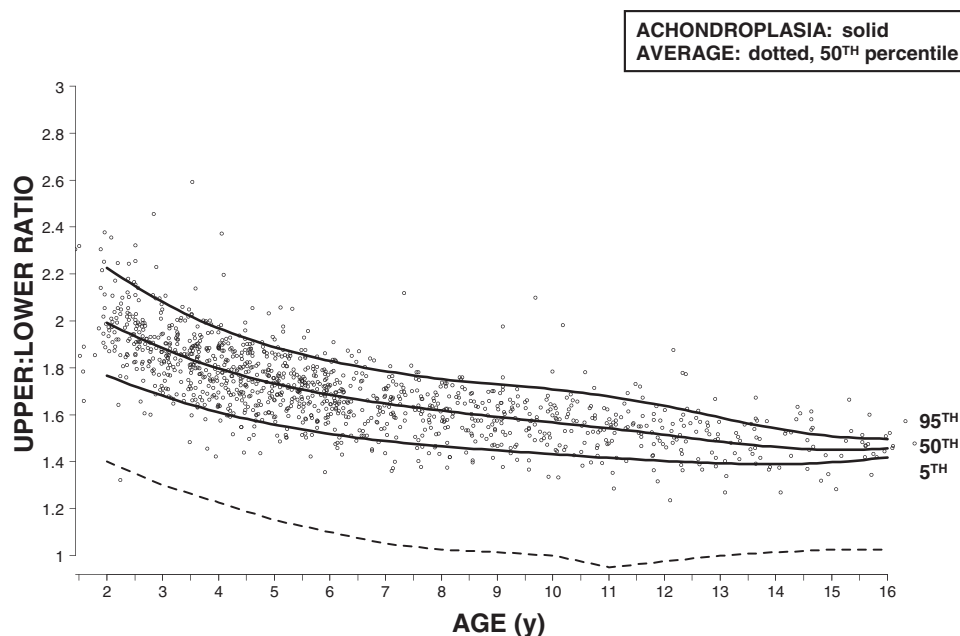
FIGURE 5. Upper-to-lower body segment ratios in boys and girls with achondroplasia (solid lines) and in children of average stature (24, 25; 50th percentile; dashed line).

The data set from which these growth curves are derived also allows for further exploration of typical growth patterns in achondroplasia. Measures were obtained by a single observer under standardized conditions, and the growth curves were derived largely from longitudinal data. Although collected at a single clinic site, data are likely to be representative of the larger achondroplastic population, in that patterns in the data are similar to those observed previously in a smaller cross-sectional study of BMI in achondroplasia (8). However, the large sample size and novel smoothing technique are unique to this study. Additionally, the statistical approach used here could be applied to other skeletal dysplasia or syndromic populations with anthropometric features that warrant monitoring and potential medical intervention.

Two major observations emerged from our examination of the BMI curves in this achondroplasia population: *1*) BMI is substantially higher in children with achondroplasia than in their peers of average stature, and *2*) patterns of change in BMI with age differ between individuals with achondroplasia and their peers of average stature.

References for BMI derived from children of average stature are inapplicable to the achondroplastic population because of the dramatic differences in body proportions, such that nearly all children with achondroplasia would be considerably overweight if evaluated against the norm of those with an average stature. In fact, population-based studies in adults of average stature from a variety of subgroups with unique anthropometric characteristics have shown that BMI overestimates body fatness in populations with disproportionately long trunk and short limb length, as in some Asian and Inuit populations (29). Conversely, body fatness is underestimated by BMI in populations with long limbs, such as Australian aboriginals (30, 31). Achondroplasia represents an extreme of the former body type, thus justifying condition-specific BMI curves.

A review of the literature found only 2 other studies in which BMI was assessed in achondroplasia. As noted, Hecht et al (8)

showed that BMI was elevated relative to the norm of children with average stature. Secondary analysis of data presented by Owen et al (32) showed that BMI was strongly correlated with body fat assessed by densitometry ($r = 0.86$, $P < 0.0001$), although, as would be expected, application of equations derived in a population of average stature to predict body fat percentage from BMI substantially overestimated actual body fat in achondroplastic individuals. It will be particularly important in future studies to clarify the relation between BMI and body composition (ie, fat and lean mass) in children with achondroplasia. Dual-energy X-ray absorptiometry is perhaps the most practical approach in the pediatric population to define the relative contribution of fat and lean mass to total body mass and their relation to BMI. In the population with an average stature, BMI is less strongly correlated with body fat in children than in adults (33, 34); perhaps this is the case in achondroplasia as well.

Patterns of change in BMI across the ages are also different between children with achondroplasia and those of average stature. The BMI of children with achondroplasia increases through 2 y of age before reaching a plateau at ≈20, which lasts until gains begin again at ≈8 y of age. A peak during infancy (≈6 mo) and nadir during childhood (≈6 y), as observed in children of average stature (20, 21, 35), are absent among children with achondroplasia. Furthermore, the BMI inflection points are not sex or percentile dependent in timing or magnitude among children with achondroplasia as they are among children of average stature. However, the differences in patterns of BMI are associated with very different weight and height growth trajectories between achondroplastic children and those of average stature. Although the upper half of the body weight distribution for children with achondroplasia overlaps the lower half of the body weight distribution of children of average stature throughout childhood, this is not the case for stature. Although the distribution of body length between achondroplasia and children of average stature overlaps at birth, linear growth in children with achondroplasia lags behind their peers of average stature almost

immediately, such that by 6 mo of age the length distributions are entirely distinct.

Different patterns of linear growth are captured in the height velocity curves presented here. Linear growth has been defined as being composed of 3 components—infancy, childhood, and puberty—each under unique hormonal control, with childhood driven by the growth hormone–insulin-like growth factor axis and puberty being additionally driven by sex steroids, and infant growth less well understood (36, 37). Height velocity among children with achondroplasia is particularly compromised during what would typically be the periods of most rapid growth—infancy and puberty. Our findings are similar to those reported by Horton et al (10) in 61 children followed longitudinally, with the exception that a minor teenage growth spurt was suggested in their hand-smoothed data. The fact that patients with achondroplasia are smaller at birth, have lower height velocity in infancy and throughout puberty, and do not normalize or sustain modestly increased height velocity with the use of exogenous growth hormone (38–42) indicates that the dominant negative effect of the mutated FGFR3 gene product on chondrocyte proliferation and maturation overrides the ability of an otherwise healthy intrauterine environment, endogenous growth hormone and sex hormones to produce normal linear growth.

That BMI increases over the peripubertal and pubertal years (ie, 8 y and beyond), when the linear growth rate remains static, also suggests that the increasing BMI over this time may be predominantly due to gains in body fat. However, body fat depots and the link between gains in fat and onset of pubertal development have not previously been explored in children with achondroplasia. This is in contrast with children of average stature, in whom the timing and magnitude of the pubertal linear growth spurt is preceded and may be predicted by the "adiposity rebound" of early childhood (13–16). As noted, both this rebound and the subsequent pubertal linear growth spurt are absent in children with achondroplasia, such that sentinel markers of pubertal development are not observed in this population, and the characteristics and timing of pubertal development are in need of further elucidation. Moreover, better understanding of the pattern, composition, and timing of weight acquisition in achondroplasia in future studies may reveal periods of development during which diet and exercise could be manipulated to optimize lean mass acquisition and avoid fat acquisition.

The BMI-for-age charts presented herein represent a first step in the assessment and clinical management of body mass in children with achondroplasia into their teenage years. Further research to describe the association of BMI with body fat deposition throughout childhood and into adulthood, when consequences of overweight in this population are severe, are required.

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