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Weight for Age Charts for Children With Achondroplasia

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To develop accurate weight for age charts for individuals with achondroplasia. These novel weight for age, gender-specific growth curves for achondroplasia patients from birth through 16 years were constructed from a longitudinal, retrospective, single observer cohort study of 334 individuals with achondroplasia. Weight for age data from 301 subjects in this achondroplasia cohort, constituting 1,964 total weight measurements, are presented in these weight for age curves. Percentiles (5, 25, 50, 75, 95th) were estimated across the age continuum by gender, using a 1 month window (±0.5 months) around each time point of interest. Percentiles were smoothed using a quadratic, penalized smoother by a semi-parametric model approach. Raw weight data from the achondroplasia cohort are compared to that of average stature children presented in the current CDC growth curves, divided into 0–36 months and 2–16 years. There was overlap of birth weight between achondroplasia and average stature infants. This statistical modeling method can be applied to other anthropometric parameters collected from this achondroplasia cohort (e.g., length, BMI), other skeletal dysplasia diagnoses, and to syndromic, non-skeletal dysplasia diagnoses which may benefit from standardization of weight for age. © 2007 Wiley-Liss, Inc.

Key words: achondroplasia; weight; anthropometry; growth; FGFR3

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INTRODUCTION

Achondroplasia is the most common short stature skeletal dysplasia with an estimated incidence of 1:26,000–1:40,000 [Gardner, 1977; Oberklaid et al., 1979; Martinez-Frias et al., 1991]. Clinical features include disproportionate short stature with rhizomelic shortening of the limbs, midface hypoplasia with relative macrocephaly and frontal bossing, trident hand conformation and lordosis. Achondroplasia is an autosomal dominant disorder caused by mutations in fibroblast growth factor receptor 3 (*FGFR3*). Potential serious, though rare complications for individuals with achondroplasia include: (1) cervical spinal cord compression ± hydrocephalus due to a small foramen magnum causing peripheral neurologic impairment, central sleep apnea and death, (2) lumbar nerve root and/or cord compression with vascular compromise due to vertebral wedging and stenosis often manifesting as bowel or bladder dysfunction and claudication, and (3) lower extremity varus deformity potentially causing pain and limited ambulation, treated by osteotomy. Carrying excessive body weight exacerbates the potential orthopedic and neurologic complications in the lumbar spine and lower extremities in patients with achondroplasia. Excessive body weight can also worsen pre-existing mechanical obstructive sleep apnea caused by relatively smaller airways, relative macroglossia and mid-face hypoplasia typically found in achondroplasia [Francomano and Muenke, 2002; Pauli, 2005; Francomano, 2006]. For these reasons, it is imperative to monitor and maintain a healthy body weight for people with achondroplasia.

Up to this point, there have been no weight for age growth charts for achondroplasia for clinical use. The charts presented here can be used in conjunction with current height for age [Horton et al., 1978] and

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weight for height charts for achondroplasia [Hunter et al., 1996] to optimize routine healthcare for these patients. It is essential to have a weight reference for achondroplasia in order to detect deviation from the expected growth pattern, both positive and negative, which may be attributable to co-morbid conditions (e.g. gastroesophageal reflux, obesity).

The data used to construct these weight for age charts are unique from prior anthropometric efforts for achondroplasia patients in that they constitute a larger, longitudinal dataset, and measurements were obtained by a single observer (C.I.S). Furthermore, new non-parametric statistical modeling methods were employed with more powerful computational capabilities [Venables and Ripley, 2002; Ruppert et al., 2003; Wand et al., 2005]. Thus the weight for age curves presented here are the most accurate representation of the true percentile estimates in this population available today.

With these charts, we will be able to offer better anticipatory guidance to our patients and potentially ascertain the impact of weight on the orthopedic and neurologic complications of achondroplasia through future longitudinal clinical studies. Furthermore, these methods can be applied to construct weight for age charts for people with other skeletal dysplasias and other well defined syndromic diagnoses.

MATERIALS AND METHODS

This study was approved by the Institutional Review Boards (IRB) of the Johns Hopkins Medical Institution of Baltimore, Maryland, and AI DuPont Hospital for Children in Wilmington, Delaware. An achondroplasia anthropometry database was created from data originally collected by a single observer (C.I.S.) over the course of 37 years (1967–2004) of clinical practice. Retrospective accounts of birth parameters (height, weight, and/or head circumference) from as early as 1931 were also included in the database. Birth parameters were the only anthropometric value not directly measured, but considered reliable, by C.I.S. Data analyzed for this study were extracted from the clinical records of this author's patients at the AI DuPont facility. All data included in the database were retrospective from point of IRB approval and anonymized by the individual performing the primary data collection.

All skeletal dysplasia diagnoses were made by a single observer (C.I.S.) by clinical, radiographic and/or molecular means. Only subjects in whom there was no ambiguity of diagnosis were included in this database, having also benefited from longitudinal observation of the well-established natural history of achondroplasia. All anonymized demographic and anthropometric data as outlined below were entered into a Stata 8.0 database [StataCorp, 2003], stored, and analyzed using R for Windows [Wand et al., 2005] at the Johns Hopkins Medical Institution and Bloomberg School of Public Health.

The following demographic and anthropometric parameters were included in this analysis: date of birth, date of each visit (thus age at visit calculated by difference), weight at each clinical visit, gender, birth weight, and gestational age at birth. Additional parameters were collected (including birth length and head circumference, gestational age, and length, head circumference, upper segment, lower segment, arm span, inner canthal distance, outer canthal distance, chest circumference, hand length, and middle digit length at each clinic visit) and will be presented separately. Centiles (5, 25, 50, 75, and 95th) were estimated across the age continuum (0–16 years) for each parameter by gender. A 1 month window ($\pm$0.5 months around each time point of interest) was used for each estimate and the centiles smoothed using a quadratic, penalized smoother.

Normative weight data for average stature individuals from birth through 6 years were obtained from data tables published online in conjunction with the 2000 CDC/NCHS growth curves [Kuczmarski et al., 2000, 2002]. These data were derived from US Vital Statistics 1968–1980 and 1985–1994, and National Health and Nutrition Examination Survey (NHANES) I, II, and III. For 6 through 16 years, normative values for average stature individuals excluded NHANES III but included National Health Examination Survey (NHES) I and II data. The goal of this project was to create new weight for age charts for achondroplasia which conformed to the current CDC/NCHS curve structure for average stature individuals; one chart for ages 0–36 months and another for 2–20 years for each gender. A relative paucity of achondroplasia data from 17–20 years necessitated truncation of the achondroplasia curves at 16 years for males and females.

Data for birth weight by gestational age in average stature individuals was obtained from the CDC/NCHS growth curves [Kuczmarski et al., 2000, 2002] and the Canadian Perinatal Surveillance System [Kramer et al., 2001] for comparison to the achondroplasia cohort. Achondroplasia subjects born prior to 35 weeks gestation were not included in the 0–36 month weight for age charts, but they were included in the 2–16 year charts.

RESULTS

The sample size of achondroplasia data are presented in Table I. There were 334 total individuals included in the achondroplasia anthropometry database. Of these 334, weight data from 301 individuals, including 1,964 data points, were available for this analysis.

Raw data for achondroplasia weight for age by gender from 0 to 36 months and 2 to 16 years are presented in Figures 1 and 2. Average stature

TABLE I. Sample of Male and Female Subjects With Achondroplasia From Whom Weight for Age Centile Curves were Derived

	Males	Females	Combined
0–36 months			
Number of subjects	145	114	259
Number of weight measurements	424	365	789
Average number of weight measurements per person	2.9	3.2	3.0
Range in number of weight measurements per person	1–9	1–8	
2–16 years			
Number of subjects	136	111	247
Number of weight measurements	670	651	1321
Average number of weight measurements per person	4.9	5.9	5.3
Range in number of weight measurements per person	1–18	1–20	

isopleths included in Figures 1 and 2 for comparison are from the 2000 CDC/NCHS Growth Charts for the United States [Kuczmarski et al., 2000, 2002].

Weight for age charts for achondroplasia for clinical use by gender for 0–36 months (Fig. 3) and 2–16 years (Fig. 4) are presented with 5th, 25th, 50th, 75th and 95th centile isopleths. Within the 0–36 month interval analysis, we observed more variability in the raw data values over the latter half of this interval as the youngest achondroplasia subjects aged. Thus widening of the 5th and 95th centile lines in this region is due to greater raw data variability, not a byproduct of data paucity or the result of artificial smoothing methods. On the 2–16 year curves, widening of the 5th and 95th centiles occurs at approximately 10–12 years; this may also be due to greater variability in raw data or, in contrast to the widening in the younger cohort, may be a reflection of relative data paucity in this region or a combination of both.

Figure 1 indicates significant overlap of birth weight between our achondroplasia cohort and average stature individuals from the CDC/NCHS cohort. Thus, information on gestational age and birth weight was explored (Table II). Of the 261 achondroplasia patients with available birth weight, 210 were reportedly born at "term" (defined as $\geq$37 weeks gestation), 31 were reportedly born preterm, and gestational age was not specified in 20 individuals. Although we could not confirm that patients for whom gestational age was not known were born at term, we reasoned that a premature delivery would have been more likely reported than a term delivery in medical records. It should be noted that inclusion of the weight data from these "gestation unknown" individuals may have unintentionally shifted our achondroplasia weight curves to slightly lower values if unidentified preterm infants were inadvertently included in these curves.

However, as shown in Table II, the average birth weight of these "gestation unknown" individuals was not significantly different than that of term average stature or achondroplasia individuals. Therefore, weight data from these 20 individuals were retained in both the 0–36 months and 2–16 year growth curves.

In Table II, mean birth weight for achondroplasia subjects by gender and gestational age are compared to normative average stature data. Among the male achondroplasia infants, average birth weight of those born at 35 and 36 weeks gestation was not significantly lower than that of male achondroplasia subjects born at 37 weeks gestation (3.12 ± 0.6 kg); thus weight data from these 13 males was included in the weight curves. Weight data from females born at 35 and 36 weeks gestation were also included in the weight curves as these average values were also within 2 SD of the birth weight for achondroplasia females born at 37 weeks gestation (3.10 ± 0.5 kg). To be consistent among males and females and retain as many data points as possible, 35 weeks gestation was the minimum gestational age for inclusion in the growth charts from 0 to 36 months. All other weight data from achondroplasia subjects with unknown gestational age and those known to be born $\leq$34 weeks gestation were included in the 2–16 year curves as the influence of their gestational age should have diminished sufficiently for inclusion by that age.

DISCUSSION

These novel weight for age charts were created to meet a basic clinical need—to monitor the weight of patients with achondroplasia. Excessive body weight is detrimental to the general health of all individuals, known to increase the risk of heart disease, hypertension and diabetes. However, it is the belief of these authors, and often echoed by other healthcare providers and members of this patient population directly, that excessive body weight is additionally and particularly damaging to the orthopedic and neurologic sequelae of achondroplasia.

On the other end of the weight spectrum, it is equally important to recognize failure to gain appropriate weight, particularly in infancy and early childhood, in these patients. Young achondroplasia patients are at risk for general pediatric co-morbid conditions such as psychosocial failure to thrive, gastroesophageal reflux, and malabsorption.

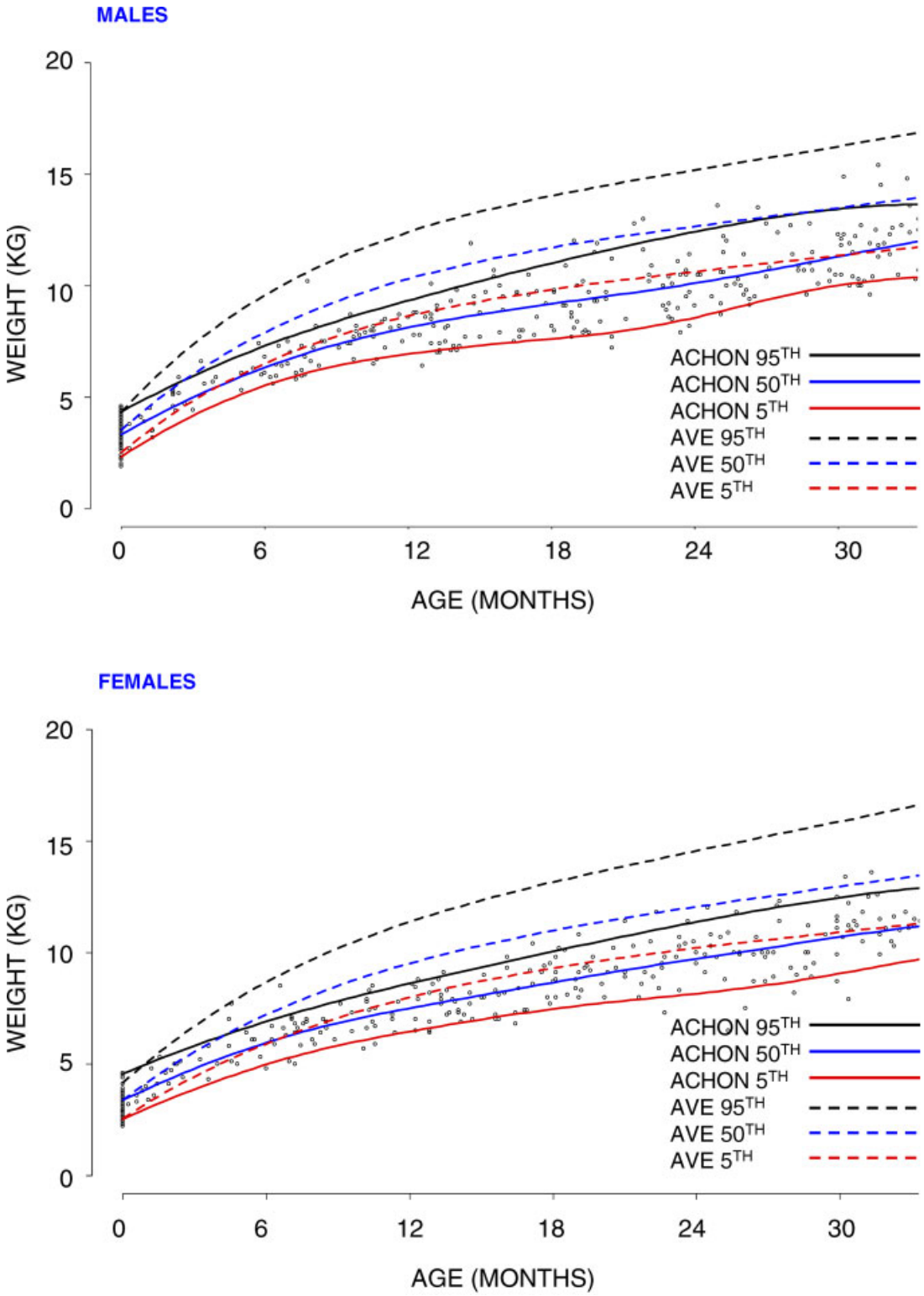

FIG. 1. Raw data with 5th, 50th, and 95th centiles of weight for age in achondroplasia (ACHON, solid lines) and average stature (AVE, dotted lines) males and females, 0–36 months. Average stature curves for 0–36 months from 2000 NCHS/CDC growth curves [Kuczmarski et al., 2000, 2002]. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

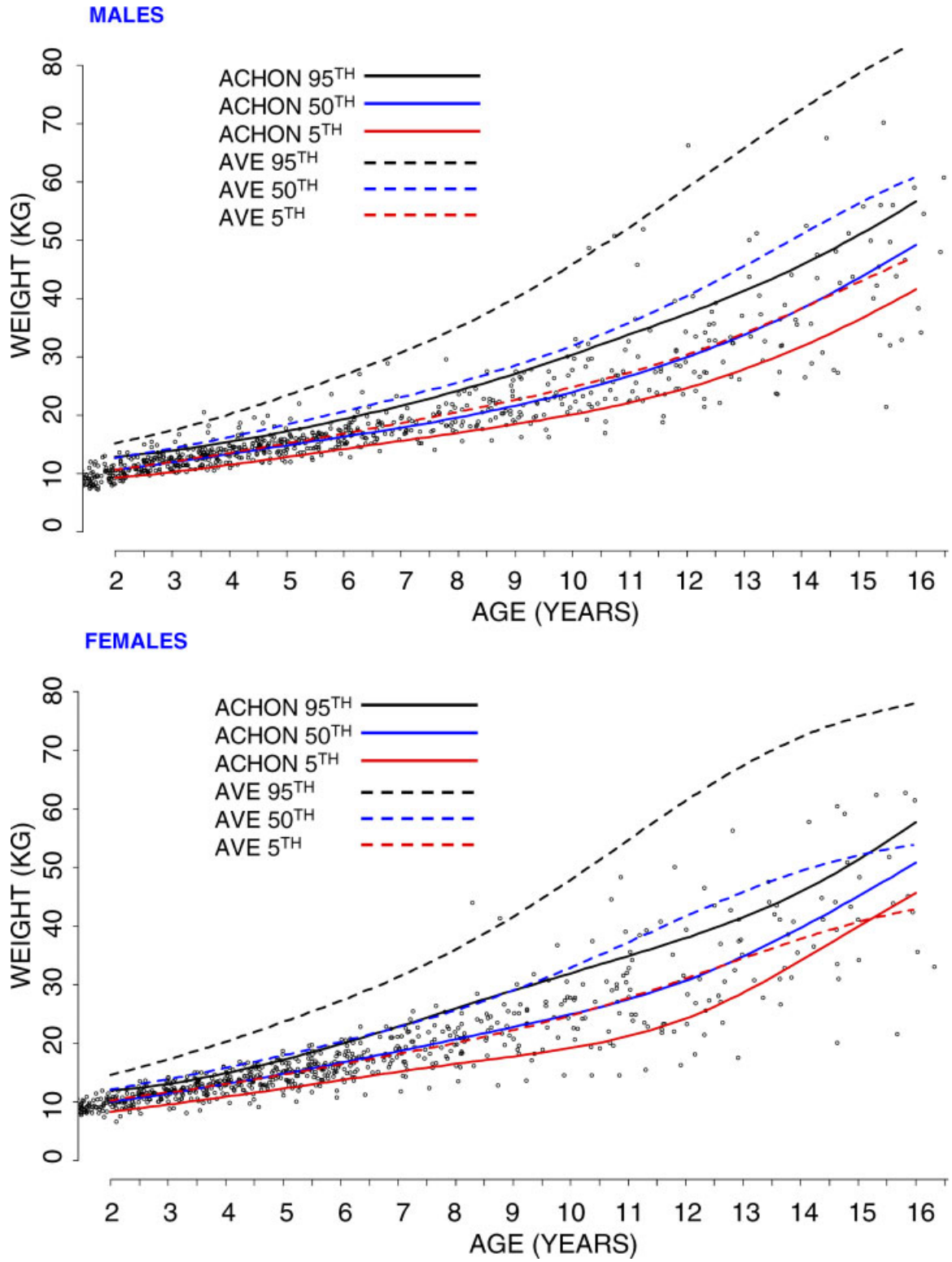

FIG. 2. Raw data with 5th, 50th, and 95th centiles of weight for age in achondroplasia (ACHON, solid lines) and average stature (AVE, dotted lines) males and females, 2–16 years. Average stature curves for 2–20 years from 2000 NCHS/CDC growth curves [Kuczmarski et al., 2000, 2002], truncated at 16 years for comparison to achondroplasia cohort. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

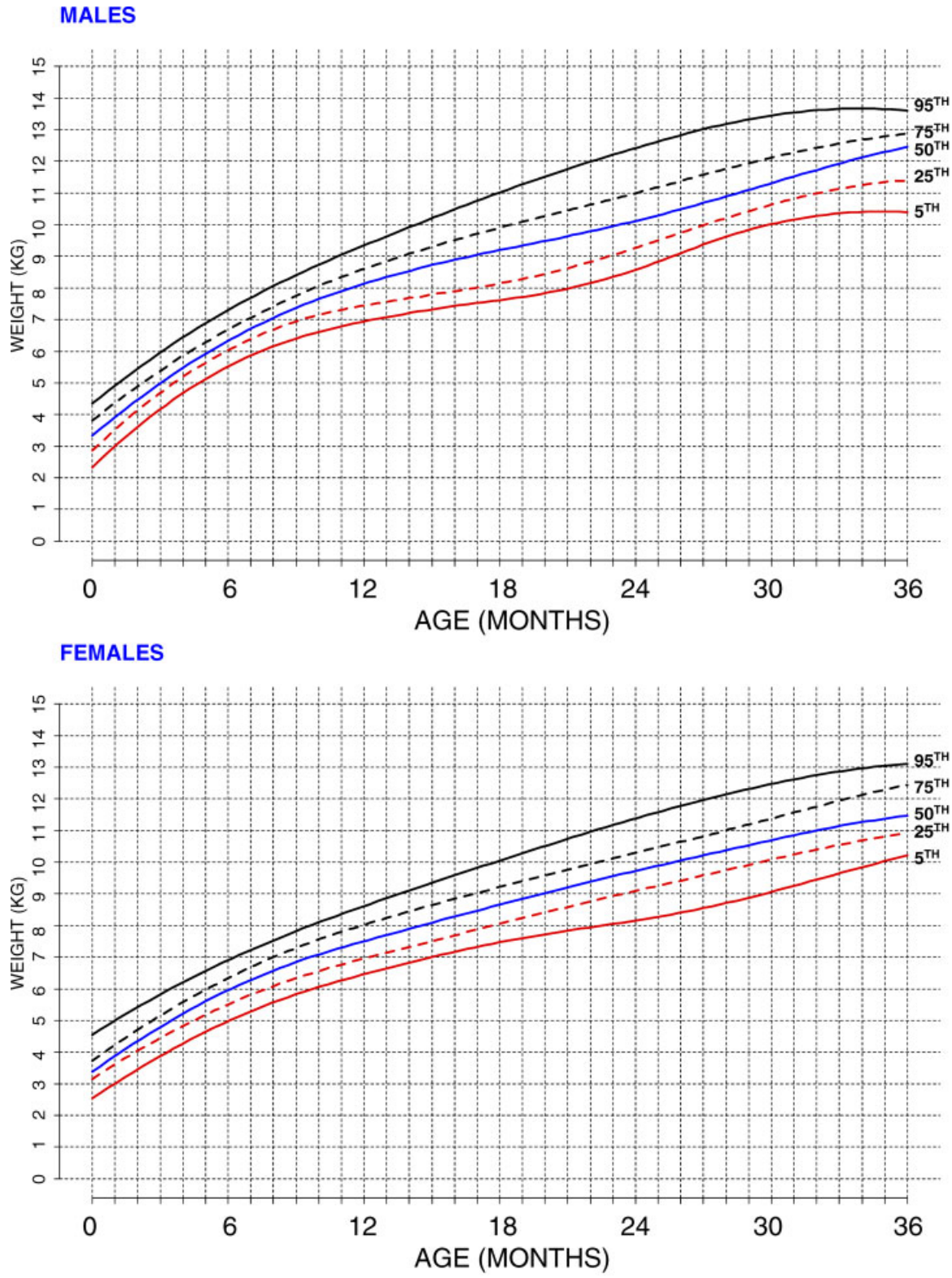

FIG. 3. Weight for age curves for achondroplasia with 5th, 25th, 50th, 75th, and 95th centiles for males and females, 0–36 months. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

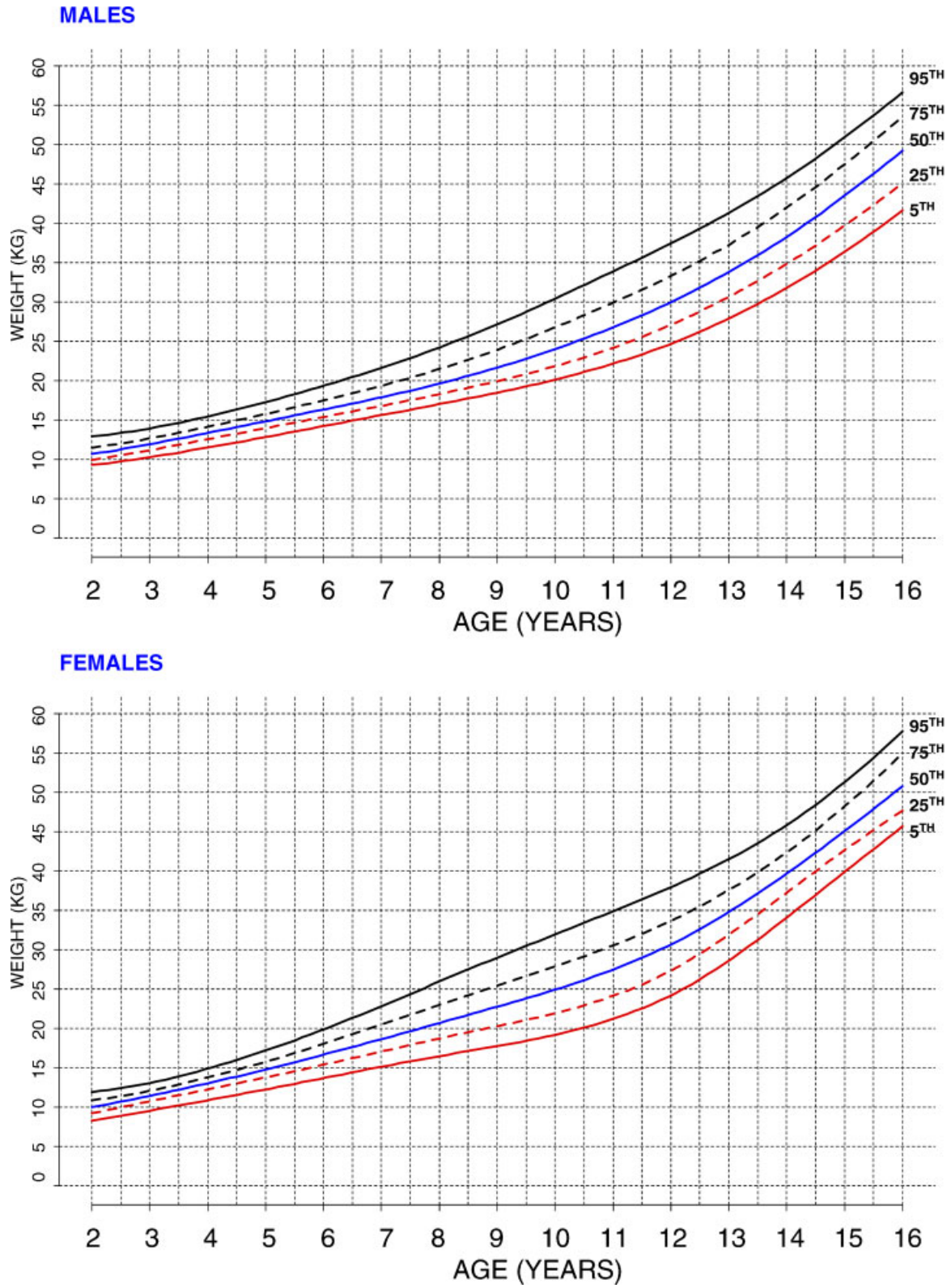

FIG. 4. Weight for age curves for achondroplasia with 5th, 25th, 50th, 75th, and 95th centiles for males and females, 2–16 years. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II. Birth Weight by Gender and Gestational Age in Achondroplasia Patients and Average Stature Individuals

	Males Birth weight (kg)[a]			Females Birth weight (kg)[a]		
Gestational age (weeks)	n	Achondroplasia	*Average stature reference*	n	Achondroplasia	*Average stature reference*
≥37 (term)	116	3.5 ± 0.5	*3.4 ± 0.6*[b]	94	3.3 ± 0.5	*3.3 ± 0.5*[b]
36	10	2.7 ± 0.5	*2.9 ± 0.4*[c]	3	3.4 ± 1.0	*2.8 ± 0.4*[c]
35	3	2.7 ± 0.1	*2.6 ± 0.4*[c]	1	2.2	*2.5 ± 0.4*[c]
<35	8	2.4 ± 0.7		6	2.2 ± 0.5	
Unknown	9	3.3 ± 0.4		11	3.3 ± 0.5	
Total	146			115		

[a]Mean ± SD.
[b]Kuczmarski et al. 2000, Kuczmarski et al., 2002[2002].
[c]Kramer et al. [2001].

Additionally, they are also at risk for rare yet serious complications associated with achondroplasia, including restrictive lung disease and obstructive sleep apnea with hypoxia, both of which can hinder adequate weight gain [Stokes et al., 1983; Pauli, 2005; Trotter and Hall, 2005]. As outlined by Rimoin [1995], failure to thrive is a key feature his group considers (in combination with the presences of axial and/or appendicular hypotonia, apnea, absence of CSF flow around the cord and/or intracord lesions by T2 MRI) to determine which achondroplasia patients need cervicomedullary decompression. These new curves should be useful in the clinical setting over the entire weight spectrum to identify patients who deserve further evaluation to determine the etiology of their deviation from the achondroplasia weight norm.

These new weight for age charts also benefit from the longitudinal nature of this large, uniformly measured cohort of subjects, analyzed with statistical modeling techniques not available for previous achondroplasia growth curves. Until further analysis of other anthropometric parameters from this unique achondroplasia cohort are complete, we anticipate these weight for age charts will be used in conjunction with current weight for height [Hunter et al., 1996] and height for age charts [Horton et al., 1978] to optimize direct patient care and provide better anticipatory guidance in terms of weight management. With standardization of achondroplasia weight, prospective studies to examine the influence of weight on neurologic and orthopedic complications of achondroplasia should now be pursued. Furthermore, now that this methodology has been established, it can be applied to other non-skeletal dysplasia, syndromic diagnoses that could benefit from the establishment of weight norms.

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