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Comparing the use of CDC and WHO Growth Charts in Children with Cystic Fibrosis through Two Years of Age

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Abstract

Objective—To examine differences between use of WHO and CDC growth reference in children with cystic fibrosis (CF) up to 2 years of age.

Study design—Growth from 1–24 months in 2587 children, born 2003–2006 and recorded in the US CF Foundation Registry, was evaluated using WHO and CDC references.

Results—In both boys and girls with CF aged 1–24 months, use of WHO charts resulted in ~8 percentile lower length-for-age (LFA) and ~13% higher short stature rate (LFA<5th percentile). WHO weight-for-age was ~9 percentile lower prior to age 6 months, crossed at 6–7 months, and remained ~14 percentile higher at 8–24 months. WHO Weight-for-Length percentile (WFLp) was similar before 12 months but ~10 percentile higher at 12–24 months compared with CDC. When using WHO charts, 9% of children had underweight (WFLp<50th) classified differently and this rate varied with age: 4% in the first year, 7% at 12, 13% at 15, and 16% at 18 months, respectively. Weight status assessed by WHO BMI charts was different from WHO Weight-for-Length charts. At 24 months when switching back to CDC, 26% of children with normal WFLp on WHO charts appeared underweight on CDC charts. A 70th percentile of WHO BMIp was equivalent to the 50th percentile CDC BMIp.

Conclusion—Growth status in children with CF differed when using WHO and CDC references, particularly during the second year of life. These differences need to be considered for all uses of growth assessment in CF.

Keywords

cystic fibrosis; growth; 2000 CDC growth reference; 2006 WHO growth reference; infants; malnutrition

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Growth charts are important clinical tools to assess and monitor growth. For infants with cystic fibrosis (CF), the US CF Foundation (CFF) recommended age-specific daily weight gain values for growth monitoring.¹ A 50th percentile goal of weight-for-length (WFL) was also recommended. For those who are undernourished, increased rates of weight gain are targeted for catch-up growth. Since 2010, most CF pediatric clinics in the US have switched to the 2006 World Health Organization (WHO) growth reference² for children younger than 24 months to replace the use of the US Centers for Disease Control and Prevention (CDC) growth reference,³ in the wake of recommendations from both the CDC and the American Academy of Pediatrics.^{4, 5} The rationale for this recommendation is that the WHO reference represents the best possible growth potential from optimally fed babies (breastfed) residing in optimal living conditions in areas throughout the world. There are substantial anthropometric differences between the CDC and WHO reference population.^{6–9} Thus the impact of changing growth references on the interpretation of individual growth status, as well as population averages in CF, needs to be elucidated.

At age 24 months, when transitioning from WHO back to CDC reference, WFL status in children with CF with certain severe mutations was significantly better when using WHO charts compared with CDC charts.¹⁰ However, thorough comparisons prior to age 24 months for WFL, as well as for other anthropometric variables (ie, weight and length), are not available. Estimates of nutritional status by the two references vary by age, the chart used, and cutoff values applied in healthy children without CF.^{7–9} Similar results are expected in children with CF but the magnitude is unknown. In addition, a goal of 50th percentile of Body Mass Index (BMI, at age 24 months or older) or WFL (younger than 24 months) is recommended based on the CDC reference for children with CF.^{10,11} Because the CDC and WHO growth charts differ, the corresponding percentile cut-off value on WHO charts will also vary.

In children with CF who are at high risk of growth faltering,^{12–16} the switch from use of the CDC to WHO growth charts from 0–23.9 months, then back to the CDC charts at age 2, may be a significant source of confusion for care providers and potentially impart undue anxiety on families due to an appearance of abrupt decline in nutritional status caused by the switch. Overall, clarification in the population with CF is necessary because of the reliance on nutritional status indicators for evaluation of individual patient care, overall assessment of effectiveness of nutritional interventions in clinical care, and the performance of CF Centers with regard to nutritional management.

Therefore, the aim of this study is to apply the WHO and CDC growth reference, over 1–24 months of age in a representative population of children with CF, in order to (1) compare differences in weight and height status (ie weight-for-age percentile [WFAp], length-for-age percentile [LFAp], weight-for-length percentile [WFLp], BMI percentile [BMIp]); (2) compare prevalence of under-nutrition; and (3) identify WHO values equivalent to the 50th percentile of CDC BMI at 24 months, the age at which health care providers switch back to CDC charts.

METHODS

The CFF Patient Registry documents the diagnosis and follow-up evaluations of patients with CF who are seen at accredited centers in the United States. 2,954 children born between 2003–2006 were identified from the 1986–2008 CFF Patient Registry.¹⁷ Among them, 346 children (12%) who did not have weight and length measured in the first two years of life were excluded. Length, weight, and weight-for-length measurements that deviated more than 5 SD from the CDC medians were excluded because these values were likely outliers resulting from measurement or recording errors. Very few children (n=149, 5%) had weight and length information available in the first two weeks of life, therefore, comparisons between WHO and CDC growth charts at birth were not performed. The remaining 2,587 children with 23,481 observations were included for analyses. The study protocol was approved by the human subjects committee at the University of Wisconsin-Madison.

Growth evaluation using WHO and the CDC growth charts

Z-score and percentile values were calculated using code written for SAS and utilized reference values for the CDC's 2000 growth charts (downloaded from <http://www.cdc.gov/growthcharts>) and reference values for the WHO's 2006 growth charts (downloaded from <http://www.who.int/childgrowth/standards/en/>). A cutoff value of the 50th percentile of WFLp and BMIp was used to define underweight.^{10,11} Short stature was defined as LFAp less than the 5th percentile.¹⁸ For CDC BMIp calculations at 24 months of age, 0.7 cm was subtracted from recumbent length to obtain standing height.²

Computation of WHO WFLp and BMIp equivalents to the 50th percentile CDC BMI at age 24 months

WHO values equivalent to the 50th percentile of CDC BMI at 24 months were computed for boys and girls at a given stature (5th–95th percentile) as follows: First, the weight for the given height corresponding to the 50th percentile CDC BMI was identified; then the corresponding WFLp or WHO BMIp value corresponding to this height and weight was calculated. For instance, in boys at age 24 months, 11.14 kg body weight for a given height of 82.8 cm (the CDC 5th percentile) corresponded to the 50th percentile CDC BMI. For this weight and height, WHO BMIp was the 70th percentile, WHO WFLp was the 57th percentile and CDC WFLp was the 39th percentile.

Statistical analyses

SAS (version 9.4, SAS Institute, Inc., Cary NC, 2014) and R (<http://www.r-project.org>) statistical software were used for statistical analyses. To compare growth between use of WHO and CDC growth charts in the first two years, repeated measures were performed using PROC GENMOD procedure in SAS using generalized estimating equations (GEE) with a working assumption of independence among observations.¹⁹ The identity link was used for continuous outcomes and the logit link combined with the binomial variance function was used for dichotomous outcomes in GEE models. At 24 months, paired t-test and chi-square test were conducted to test the difference between the WHO and the CDC. The analyses were performed separately for boys and girls.

RESULTS

The study cohort (n=2,587) was comprised of the majority of children with CF (84%) born between 2003–2005 and reported in the 2008 US CFF patient registry. Among them, 1,301 (50%) were boys. 599 (23%) of them had meconium ileus (MI), 1,770 (68%) had pancreatic insufficiency without MI, and 218 (8%) were pancreatic sufficient. About one quarter of these children (n=658, 25%) were diagnosed through prenatal/neonatal screening, and another one third (n=965, 37%) were identified because of symptoms other than MI. In 2566 children with racial and ethnicity information available, the predominant racial background was non-Hispanic white (82%), Hispanic (11%), and non-Hispanic black (4%). The remaining 3% consisted of American Indian or Alaska Native, Asian, multi-races, and others.

Comparing Length-for-Age status between using WHO and CDC growth charts

In boys with CF, the WHO length-for-age percentile (LFAp) was consistently below the CDC's by an average of ~8 percentiles in the first two years of life (WHO 13 ± 28 vs. CDC $21 \pm 27^{\text{th}}$ percentile, $p < 0.0001$; Figure 1, A). As a result, more boys with CF were classified as short (LFAp $< 5^{\text{th}}$) using WHO charts compared with the CDC (WHO 35% vs. CDC 22%, $p < 0.0001$; Figure 1, B). Similar results were found in girls with CF (Figure 1, C and D). Overall, ~14% of the study population who had normal height on CDC charts appeared short (LFAp $< 5^{\text{th}}$) when using the WHO charts.

Comparing Weight-for-Age status between using WHO and CDC growth charts

In boys with CF, the WHO weight-for-age percentile (WFAp) was 9 percentiles lower than the CDC's prior to age 6 months (WHO 7 ± 24 vs. CDC $16 \pm 26^{\text{th}}$ percentile, $p < 0.0001$), crossed at age 6–7 months, then remained 14 percentiles higher from 8–24 months (WHO 32 ± 30 vs. CDC $18 \pm 26^{\text{th}}$ percentile, $p < 0.0001$; Figure 2, A). Similar results were observed in girls with CF (Figure 2, B).

Comparing Weight-for-Length status between using WHO and CDC growth charts

No difference in weight-for-length percentile (WFLp) was observed in boys between the WHO and CDC references prior to age 12 months (WHO 36 ± 30 vs. CDC $36 \pm 31^{\text{st}}$ percentile, $p = 0.88$). At 12–24 months of age, WHO WFLp was 11 percentiles higher than the CDC's (WHO 64 ± 28 vs. CDC $53 \pm 30^{\text{th}}$ percentile, $p < 0.0001$; Figure 2, C). As a result, underweight prevalence defined by WHO WFLp $< 50^{\text{th}}$ was similar to that defined by the CDC prior to age 12 months, though the comparison was statistically significant due to large sample size (WHO 60% vs. CDC 59%, $p < 0.0001$). At ages 12–24 months, the difference in underweight prevalence between the two references became notable (WHO 35% vs. CDC 46%, $p < 0.0001$; Figure 2, E). A similar trend was observed in girls with CF (Figure 2, D and F).

When using WHO WFL charts, ~9% of children had nutritional status classified differently in the first two years of life. And this rate varied with age: ~4% in the first year, compared with 7% at age 12 months, 13% at age 15 months, and 16% at age 18 months. Moreover, all the differently-classified subjects in the second year were underweight on CDC charts but

normal on WHO charts. In fact, 28% of children aged 12–24 months who were underweight on CDC charts appeared normal weight when using WHO charts.

Comparing WHO Weight-for-Length and WHO BMI status

WHO BMI curves are available for ages 0–24 months. Comparisons of WHO WFLp and WHO BMIp in children with CF revealed that the two were correlated ($\rho=0.96$, $p<0.0001$) but also significantly different from each other (Figure 2, C–F). In boys (Figure 2, C), BMIp was 13 percentiles lower prior to age 6 months (BMIp 16 ± 27 vs. WFLp $29 \pm 30^{\text{th}}$ percentile, $p<0.0001$), similar at ages 6–12 months (BMIp 40 ± 31 vs. WFLp $41 \pm 30^{\text{th}}$ percentile, $p<0.0001$), and 8 percentiles higher at ages 12–24 months (BMIp 72 ± 28 vs. WFLp $64 \pm 28^{\text{th}}$ percentile, $p<0.0001$), compared with WFLp. As a result, underweight prevalence based on WHO BMIp $<50^{\text{th}}$ was higher before age 6 months (BMIp 80% vs. WFLp 67%, $p<0.0001$), similar at ages 6–12 months (BMIp 57% vs. WFLp 56%, $p=0.009$), and lower at ages 12–24 months (BMIp 28% vs. WFLp 35%, $p<0.0001$), compared with WFLp $<50^{\text{th}}$ (Figure 2, E). Similar results were observed in girls with CF (Figure 2, D and F).

Comparing WHO and the CDC growth charts at age 24 months

1,027 children [$n=510$ boys (50%)] had both height and weight information available at age 24 months (range: 23.5–24.5 months). In boys, WHO LFAP was significantly lower, whereas WFAp, WFLp, and BMIp were significantly higher than CDC values (all $p<0.05$). Similar results were observed in girls. When transitioning back to CDC charts at age 24 months, 29% of children (56/192) who were short on WHO charts appeared normal on CDC charts; 27% (189/702) with WHO WFLp $>50^{\text{th}}$ were at CDC WFLp $<50^{\text{th}}$; 30% (204/685) with WHO BMIp $>50^{\text{th}}$ were at CDC BMIp $<50^{\text{th}}$.

WHO WFLp and BMIp equivalent to the 50th percentile CDC BMI at age 24 months

The 50th percentile CDC BMIp value corresponding to the computed equivalent WHO BMIp and WFLp values at age 24 months, across the range of statures (5th–95th percentile) for both boys and girls. Results indicate that the 50th percentile CDC BMI was equivalent to the ~70th percentile WHO BMIp (70th for boys and 67th for girls) regardless of various statures. However, no universal WFLp value was found corresponding to the 50th percentile CDC BMI. The equivalent WHO WFLp values increased with height, from ~60th for short statures up to ~70th percentile for tall statures.

DISCUSSION

WHO growth charts have been adopted to replace CDC growth charts in CF care for children younger than 24 months. Differences were observed when comparing the two growth charts in children with CF. Overall, using WHO growth charts in this population with CF resulted in a higher prevalence of shortness and a lower prevalence of underweight in the first two years of life, compared with values from CDC charts. The extent of disagreement varied by age, with a larger discrepancy occurring during the second year, especially for the underweight classification of WFLp $<50^{\text{th}}$ percentile. Using WHO WFL charts in the first year had little impact on the prevalence of underweight estimates, but in

the second year the prevalence was significantly lower according to WHO charts. When switching from WHO charts to CDC charts at 2 years of age, which is the current clinical practice, about one quarter of children with normal weight on WHO WFL charts will appear underweight on CDC charts, similar to the findings by Goday et al in children with certain severe CF genotypes.¹⁰

The discrepancy between use of the WHO and the CDC reference in children with CF is consistent with findings in healthy children without CF.^{7,8} However, the magnitude of the difference is rather large in children with CF, possibly due to cohort effect as well as differences in underweight cutoff values. For example, in healthy children without CF younger than 2 years of age, the prevalence of underweight decreased 2% after switching from CDC to WHO WFL charts when the 5th percentile cutoff was used,⁸ compared with a 10% decrease in children with CF using the 50th percentile cutoff. The prevalence of short stature in healthy children without CF increased 3.5% when switching to WHO charts using the 5th percentile cutoff,⁸ compared with a ~13% increase in children with CF when the same cutoff was applied. Large differences between the two growth references were also observed at age 24 months when transitioning back from the WHO to the CDC reference in children with CF. The implication of these differences is that individual assessment of growth, as well as estimation of nutritional status at the population level, will substantively change. In children with chronic illnesses affecting growth, such as CF, this is a particular concern given the intensive nutritional management of individual patients, and the routine evaluation of both the effectiveness of clinical practices in CF centers and CF center performance, which are all influenced by growth and nutritional status.

It is not clear how to interpret discrepant growth assessments when switching growth references and which nutrition/growth goal to use in CF infant care. These need to be examined carefully with respect to long-term disease outcomes. The aforementioned study by Goday et al briefly showed that at age 2 years, children with WFL_p≥50th on WHO but not on CDC charts had a lower but normal percent predicted forced expiratory volume in 1 second (FEV_{1p}) at age 6 years compared with those with WFL_p≥50th on CDC charts.¹⁰ WFL_p≥50th on WHO but not on CDC charts is likely to be in the range of 25–50th percentile on CDC charts. These results indicate that a lower WFL goal at age 2 years, i.e., CDC 25–50th percentile may be sufficient to achieve a normal FEV_{1p}. However, some critical issues need to be carefully addressed: 1) whether the lower but normal FEV_{1p} is clinically significant at age 6 years as well as in the long term; 2) how growth at 2–6 years modifies the associations; and 3) an assessment of concurrent and longitudinal associations with other pulmonary outcomes, i.e., chest X-ray scores, respiratory infections, and survival.

Many clinicians have been plotting growth data on both WHO and CDC growth charts for growth assessments. With the wide use of electronic medical records, this is easy to do, but does not solve the problem. It is still not clear how to interpret discrepant results and make clinical decisions. Another temporary solution is to use WHO cutoff values equivalent to the CDC's. The CFF recommends using the 50th percentile for its weight-related goal based on CDC growth reference.^{10,11} Our analysis shows that at age 24 months, ~70th WHO BMI percentile (67th in girls and 70th in boys) corresponds to the 50th percentile CDC BMI regardless of statures. With respect to WFL percentiles, there is no single WHO percentile

value that is equivalent to the CDC's BMI 50th. The equivalent WHO WFL percentile values increased with stature, from ~60th for short statures up to ~70th percentile for tall statures. In children younger than 2 years of age, WHO's median WFA reference curve is above the CDC's median prior to age 6 months, crosses at ~6 months, and remains below it from 6–24 months.² With this in mind, the WHO WFAp that is equivalent to the CDC's WFA 50th percentile is always above the 50th percentile after age 6 months, and is actually much higher at 12–24 months. However, it is important to note that the opposite is true before age 6 months (i.e. the WHO WFAp are below the CDC's 50th). WHO's WFL reference curves are similar in children shorter than 70 cm, but lower in children taller than 70 cm compared with the CDC's.² As expected, the WHO WFLp that is equivalent to the CDC's WFL 50th percentile is close to 50th percentile in the first year when average length is close to, or shorter than 70cm, and will be above 50th percentile at 12–24 months. Of note, however, is that BMIp and WFLp are correlated but not interchangeable for both growth references.^{9,20} Therefore, at age 24 months, using the WHO's WFL that matches the CDC WFL at the 50th percentile does not mean that it will also meet the 50th percentile BMI goal. Again, no sufficient scientific evidence is available to support this temporary solution of identifying WHO percentile values equivalent to CDC percentiles.

The differences between the WHO and CDC growth references in CF did not differ significantly by newborn screening, and race and ethnicity (data not shown). Weight and length status at birth was not evaluated in our study because of lack of data. As the majority of infants with CF are diagnosed beyond two weeks after birth, comparisons between the WHO and CDC growth reference at birth is less of a concern. Nevertheless, the WHO reference population weighs about 200 grams less, and is about 0.1 cm shorter at birth compared with the CDC reference.^{2,3} Therefore, using WHO charts at birth would result in higher WFAp and LFAp values. Consequently, fewer infants will be classified as short or underweight at birth using the WHO reference.

In conclusion, our study shows that growth status differed when using the WHO and CDC references, particularly during the second year of life. The switch from use of the CDC to WHO growth chart from 0–24 months of age, and then from the WHO to CDC growth chart at 2 years of age, is likely to be a source of confusion among CF care providers and families alike. It is unknown how the switch from the CDC to WHO growth charts may alter individual patient care and further influence short- and long-term clinical outcomes. In the long term, studies are necessary to determine the WHO growth percentile that is associated with optimal pulmonary outcomes. In the short term, it may be prudent to identify and use the WHO percentile that is equivalent to the CDC's 50th when reporting prevalence and values of nutritional status, and for researchers to be clear about which growth reference is used when evaluating associations between growth and other clinical outcomes.

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Abbreviations

CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
BMI	Body Mass Index
BMIp	Body Mass Index percentile
LFA	-for-Age
LFAP	-for-Age percentile
WFA	weight-for-age
WFAp	weight-for-age percentile
WFL	weight-for-length
WFLp	weight-for-length percentile
WHO	World Health Organization

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Figure 1.

Length status estimated by WHO and CDC growth charts in children with CF at ages 1–24 months. The analyses were performed separately for boys and girls with CF. Short stature was defined as LFAp < 5th percentile.

Figure 2.

Weight-for-Length and BMI status estimated by WHO and CDC growth charts in children with CF at ages 1–24 months. The analyses were performed separately for boys and girls with CF. Underweight was defined as WFLp < 50th percentile or BMIp < 50th percentile.