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Comparison of WHO and CDC Growth Charts in Predicting Pulmonary Outcomes in Cystic Fibrosis

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Abstract

Objectives—The relation of weight-for-length (WFL) and weight-for-age (WFA) measurements with pulmonary function in patients with cystic fibrosis (CF) using the World Health Organization (WHO) growth standards has not been evaluated. The objective of the present study was to show that the relation of WFL and WFA measurements at 2 years with forced expiratory volume in 1 second (FEV₁) at 6 to 8 years differs when using the WHO versus the Centers for Disease Control and Prevention (CDC) growth charts.

Methods—We assessed 1155 patients in the CF Foundation Patient Registry born between 2001 and 2004. Comparisons were made between the CDC and WHO growth charts.

Results—The WFL percentiles are significantly higher for the WHO growth standards compared with those for the CDC growth charts (median and interquartile range [IQR] WHO—64.8 [41.7–84.9], CDC—48.1 [23.7–75.7], $P < 0.0001$). WFL and WFA percentiles at 2 years on both charts are strongly associated with FEV₁ at 6 to 8 years of age. The FEV₁ at 6 to 8 years was statistically significantly lower for children who were classified as reaching a WFL 50th percentile at 2 years by WHO standards alone versus those who qualified by both growth charts (median and IQR 103 [94–115] vs 107 [96–117], $P < 0.05$). Continued weight gain between 2 and 6 years was associated with a higher lung function at age 6 to 8 years.

Conclusions—Although children attaining the 50th WFL percentile on the WHO growth chart by age 2 years have a lower FEV₁ at 6 years than children attaining the same percentile on the CDC chart, both groups of children attain clinically normal FEV₁. Further studies are needed to determine whether this difference is clinically meaningful.

Keywords

CDC; FEV₁; nutrition; pulmonary function; WHO

Early nutritional status as measured by weight-for-age (WFA) or weight-for-length (WFL) has been correlated with progression of lung disease and survival in cystic fibrosis (CF) (1–4). Furthermore, better nutrition status at 3 to 4 years of life is associated with better lung function, fewer complications, and better survival (5,6). Malnutrition is usually the earliest manifestation in infants with CF (1); however, recovery of birth weight *z* score within 2 years of diagnosis of CF has been shown to be positively associated with a better lung function status at 6 years (7). After the age 2 years, a higher baseline body mass index (BMI), WFA maintenance above the tenth percentile, and/or a slower rate of decline in BMI are associated with a slower rate of decline in lung function (5,8).

Because of the importance of nutrition on growth, and hence pulmonary function, the Cystic Fibrosis Foundation (CFF) issued a clinical practice guideline in 2008 recommending early detection and aggressive treatment for undernutrition (9) and that children reach a WFL status 50th percentile by age 2 years on the traditional 2000 Centers for Disease Control and Prevention (CDC) growth charts (10). Since that time, the American Academy of Pediatrics and the CDC have recommended using the 2006 World Health Organization (WHO) growth charts (11) to monitor growth of all of the children from birth to 2 years of age (12). The 2 charts differ markedly, and children ages >3 months with similar anthropometric measurements appear better nourished on the WHO charts than when plotted on the CDC growth charts. Thus, we examined implications on pulmonary function outcomes using the WHO growth charts while maintaining the current CFF recommendation of 50th percentile for WFL status.

The primary objective of the present study was to examine pulmonary function outcomes at 6 years stratified by growth at 2 years using the different growth standards. Specifically, we examined the association between WFL and WFA at 2 years and the percent predicted forced expiratory volume in 1 second (FEV_{1p}) at 6 years when using the WHO versus CDC percentiles. Secondary objectives included examining the association between weight change from ages 2 to 6 years and maximum FEV_{1p} and other factors associated with maximum FEV_{1p}.

METHODS

We obtained data from the CFF Patient Registry of a cohort of patients born between 2001 and 2004 and studied those patients for at least 6 years. Patients diagnosed by genetic testing as having CF and with the following mutations, which are known to be associated with a more severe phenotype, were included: F508del/F508del, F508del/G542X, F508del/G551D, F508del/N1303K, F508del/R553X, and F508del/W1282X. All of the patients were on supplemental enzymes and presumed to be pancreatic insufficient. In addition, they had to have an encounter within 2 months of their second birthday with recorded weight and height and a valid spirometric examination between the ages of 6 and 8 years. The maximum

FEV_{1p} was recorded (henceforth, FEV_{1p} refers to the maximum value obtained between ages 6 and 8 years).

Patients with weight and/or height values ± 4 z scores were individually reviewed and excluded if the recorded value appeared erroneous in relation to one before and/or after that visit. Likewise, patients with FEV_{1p} <50% were excluded because this was >3 standard deviations (SD) below the mean and was attributed to poor effort.

Other variables of interest included sex, total number of hospital admissions (for a CF-related complication), and total duration on antibiotics (inpatient and outpatient days) before the maximum FEV_{1p}. Records were also searched for positive cultures for *Burkholderia cepacia complex* (BCCO), methicillin-resistant *Staphylococcus aureus* (MRSA), nontuberculous mycobacteria, *Stenotrophomonas maltophilia* (SM), and *Pseudomonas aeruginosa* (PA) before their maximum FEV_{1p}.

The WFA and WFL percentiles on the CDC and WHO charts were calculated using SAS version <http://www.who.int/childgrowth/software/en> for the WHO growth charts and <http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm> for the CDC growth charts. Patients were categorized into 3 groups: 10th percentile, >10th but <50th percentile, and 50th percentile, based on their WFA and WFL status by both the CDC and WHO growth charts. The tenth percentile was chosen as the lower cutoff because children with CF who were above the tenth percentile were considered to be adequately nourished until 2005 (13). Because children with a CDC WFL 50th percentile at age 2 years will always be 50th percentile on the WHO WFL chart, a comparison of FEV_{1p} between children who were <50th percentile on the CDC charts but 50th percentile on the WHO charts and children who were 50th percentile on both the CDC and WHO charts was made.

Weight change between 2 years and time of FEV_{1p} was evaluated using the CDC WFA percentiles. Group comparisons were made based on whether patients were above or below the 50th percentile at their second birthday and at the time of FEV_{1p}.

To determine a WHO WFL percentile that would correspond to a CDC WFL at the 50th percentile at 2 years, we used the weight-for-recumbent length data table (birth to 36 months) from the CDC charts for each sex (14). The CDC WFL 50th percentiles for 80.5 to 93.5 cm (which encompass the span between the 3rd and the 97th percentile for both sexes) were chosen to represent 2 years. Weights at 50th percentile for specific lengths were extracted, and based on the WHO standard, WFL was calculated. The present study was approved by the institutional review board of Children's Hospital of Wisconsin, Milwaukee (IRB 341418-2).

Data Analysis

Descriptive characteristics were used to summarize sample characteristics and are expressed as median and interquartile range (IQR) or mean $\pm$ SD. A nonparametric Mann-Whitney test was used to compare the continuous variables by grouping variables. A signed rank test was used to compare WFL/WFA based on WHO and CDC. Analysis of variance was performed to examine the differences between the CDC and WHO chart WFA and WFL categories in

FEV_{1p}, and Tukey-Kramer test was used for multiple comparisons adjustment. A stepwise regression was used to model dependence of FEV_{1p} on important covariates. The following variables were included in the model: WFL percentile at age 2 years, number of hospital admissions, total duration on antibiotics, sex, age at diagnosis, and a history of infection with BCCO, MRSA, nontuberculous mycobacteria, SM, or PA. Total duration on antibiotics was log transformed to ensure fit. All of the statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) software. A significance level (α) of 0.05 was used for all of the tests.

RESULTS

The CFF Patient Registry had 1814 patients born between 2001 and 2004 who met the search criteria. Patients were excluded for a variety of reasons but most commonly for lack of weight or height measurements (Fig. 1). Complete data were available for 1155 patients including weight and height at ages 2 and 6 years and a valid FEV_{1p} and were included in the analysis. A summary of the patient characteristics is presented in Table 1. More than 85% of the patients were homozygous F508del.

Comparison of WHO Versus CDC Charts at 2 Years of Age

A comparison of the WHO and CDC growth percentiles at 2 years of age showed that the WFL percentiles are significantly higher for the WHO growth charts compared with those for the CDC growth charts (median and IQR WHO—64.8 [41.7–84.9], CDC—48.1 [23.7–75.7], $P < 0.0001$).

Cross-tabulating patients at age 2 years, by WFA (Table 2) and WFL (Table 3), on both the CDC and WHO charts, demonstrates that patients shift to higher percentiles on the WHO charts. For example, of the 450 (39%) patients categorized as being WFL >10th but <50th percentile by CDC charts, 194 (43%) are categorized as being WFL 50th percentile on the WHO charts.

Comparison of FEV_{1p} in Patients With WFL Category 50th Percentile

The FEV_{1p} at 6 years was lower for children who were classified as reaching a WFL 50th percentile at 2 years by the WHO charts alone ($n = 194$) versus those who were 50th percentile on both the CDC and WHO ($n = 564$) growth charts (median and IQR 103 [94–115] vs 107 [96–117], $P < 0.05$). There was no difference in FEV_{1p} ($P > 0.12$) by WFA percentiles.

Factors Associated With FEV_{1p} at 6 to 8 Years

Stepwise regression analysis to identify the important factors associated with FEV_{1p} at 6 years of age was performed with aforementioned covariates (Table 4). Sex was not a significant variable. WHO WFL percentile at 2 years, total duration on antibiotics before their FEV_{1p}, and a history of BCCO were determined to be significant covariates of FEV_{1p} at 6 years. One unit increase in log(total duration on antibiotics) is associated with a 1.48% decrease in FEV_{1p}, whereas a 1-U increase in WHO WFL percentiles at 2 years of age is

associated with 0.08% increase in FEV_{1p} at 6 years. Patients with a positive culture for BCCO (n = 24) had a lower FEV_{1p} compared with patients without.

Weight Change Between 2 and 6 Years of Age

Sustained weight between ages 2 and 6 years at 50th percentile was strongly associated with a higher FEV_{1p} at 6 years. Patients whose WFA was <50th percentile at age 2 years but improved to 50th percentile by age 6 years had a significantly higher FEV_{1p} compared with patients who remained <50th percentile at both times (median [IQR] 107 [95–118] vs 102 [91–112], $P = 0.003$). Patients whose WFA was 50th percentile at both age 2 and 6 years had a significantly higher FEV_{1p} compared with patients who were below the 50th percentile at both time periods (median [IQR] 109 [99–119] vs 102 [91–112], $P < 0.0001$) (Fig. 2).

WHO WFL Corresponding to the CDC WFL at 50th Percentile

The CDC WFL 50th percentiles at 2 years for lengths 80.5 to 93.5 cm with corresponding weights were used to calculate the WHO WFL percentiles. For boys, a WHO WFL corresponding to CDC WFL at the 50th percentile ranges from 55.6 to 65.2 percentiles, whereas for girls, it ranges from 53.2 to 70.2 percentiles.

DISCUSSION

Our analysis demonstrates that there is a shift to higher percentiles by WFL status at age 2 years on the 2006 WHO growth charts (12,15,16) compared with the traditional 2000 CDC growth charts (17), giving the impression of a better nutritional status. These results also provide additional evidence that a higher WFL at the age 2 years is associated with a better pulmonary function at 6 years (3,5,18,19). Current CFF guidelines recommend that children reach a WFL status 50th percentile by age 2 years (10); however, the present study shows that children attaining a WFL status of <50th percentile on the CDC growth charts but are classified as 50th percentile on the WHO standards will have a lower (but clinically normal) FEV_{1p} compared with children reaching a WFL status 50% on both charts. This would suggest that if clinicians were to switch to using the WHO growth charts for monitoring growth from birth to 2 years and maintaining the 50th percentile recommendation by age 2 years, they may be targeting a lower weight and the implications would be a lower FEV_{1p} at 6 years.

The important question is whether this 4% median difference in FEV_{1p} is clinically significant at age 6 years and in the long term. Children with a higher FEV_{1p} at baseline are more likely to have a higher FEV_{1p} up to 15 years later compared with individuals with a lower baseline FEV_{1p} (20). Furthermore, FEV_{1p} is a surrogate marker of lung health and a higher FEV_{1p} is commonly associated with being relatively healthy. In 2011, >87% of children ages 6 to 17 years in the CFF Patient Registry had an FEV_{1p} 70% (21). This mirrors the gradual improvement in median BMI, which has a strong association with better lung function. The 2011 US CF registry annual report demonstrates a progressive decline of FEV_{1p} after the ages of 6 to 8 years into adulthood (21), and in the Epidemiologic Study of Cystic Fibrosis, children ages 6 to 8 years had a slower rate of decline in FEV_{1p} compared

with older children (22). Additionally, decreased morbidity, higher FEV_{1p}, and improved survival in CF have been achieved through aggressive management with the use of adjunctive treatments. Dornase alfa therapy has been associated with an improvement in FEV_{1p} by up to 5.6% (23), whereas hypertonic saline compared with placebo showed a short-term improvement in FEV_{1p} by a mean difference of 4.15 (24). Although both therapies resulted in only small improvements in FEV_{1p}, they are now standard of care in CF because of the cumulative benefits. Taken together, any significant increment in FEV_{1p} by age 6 years, through a higher target WHO WFL percentile, may be clinically meaningful and may lead to a higher FEV_{1p} being maintained at later ages in spite of the inevitable decline.

On the contrary, this 4% median difference is clouded by the within-subject coefficients of variation for FEV_{1p} for stable out-patients, with CF reported to be 5.3% to 5.8% occurring <2 weeks apart (25). This variation is significantly greater in patients with CF compared with that in normal patients. Based on our analysis, WHO WFL percentiles above the 50th percentile would correspond to the 50th percentile on the CDC WFL chart in regard to achieving a similar FEV_{1p}. It is yet unclear whether there is an added clinical benefit that is to be obtained by using the CDC-WFL >50th percentile criterion instead of adopting the WHO-WFL >50th percentile criterion and hence a higher median FEV_{1p} (107% vs 103%). In addition, our data indicate that the lower ends of IQR were at 94% (WHO 50th percentile) and 96% (CDC 50th percentile), indicating that >75% of children with WFL >50th percentile on either growth charts had “normal” FEV_{1p}. This means that of the 194 patients with WHO-WFL >50th percentile but CDC-WFL <50th percentile, fewer than 25% of patients had FEV₁ <94%. The key issue is whether this 25% would have a higher FEV_{1p} at age 6 to 8 years if they are monitored on CDC charts at age 2 years (hence would be treated more aggressively because their WFL would be below the 50th percentile) instead of being monitored on the WHO charts at age 2 years. Our data also mirror the data from children without CF in which children who are reclassified as being of normal weight on the WHO growth charts from being underweight on the CDC growth charts may be affected by morbidities associated with being underweight (26). Although longer-term data have associated improved pulmonary and survival outcomes with weight at age 4 years (6), we do not believe that the available data answer this specific question, and perhaps prospective observational or interventional studies would be needed.

Nutritional status at 3 years in a cohort of 931 patients and pulmonary outcomes at 5.5 to 7.5 years using the CDC growth percentiles for comparison have been described by Konstan et al (5). Shorter measurement intervals in the WHO charts result in a better tool for monitoring the rapid and changing rate of growth in early infancy (27). Our study looked at a large cohort of 1155 patients and compared pulmonary function outcomes at age 6 years with growth indicators plotted on both the WHO and CDC growth charts at 2 years of age (the time that one would transition to the CDC growth charts). Based on our analysis, we suggest that the 50th WHO WFL percentile may be used to monitor adequacy of growth at age 2 years in children with CF; however, additional benefit in FEV_{1p} may be achieved through a higher target on the WHO growth chart.

In our study, sustained weight gain that maintains the child at a CDC WFA 50th percentile between 2 and 6 years was associated with a higher pulmonary function, whereas poor weight gain that reduces CDC WFA to <50th percentile was associated with a lower pulmonary function. A study also demonstrated that patients who achieved a WFA percentile >50% at age 4 years attained a much higher height-for-age percentile early in life, which was also associated with fewer pulmonary exacerbations and a higher FEV_{1p} (6). Thus, lung functions at later ages are variably dependent on nutritional status and growth beyond 2 years (8,28,29), underscoring the importance of continued nutritional surveillance and aggressive management of weight loss.

In the regression model, a higher WFL status at 2 years of age was associated with a higher FEV_{1p}. Additionally, children who acquire BCCO before age 6 years and those requiring prolonged or recurrent antibiotics had a significantly lower FEV_{1p} at 6 years. The most common infections in our study were caused by PA, SM, and MRSA. Although the incidence of infection was high, most infections were transient and do not reflect chronic infection status. Furthermore, we presume that antibiotics were administered because of suspected or culture-proven infections and the cumulative duration on treatment for a CF-related complication was reflective of recurrent transient or chronic infection and was associated with FEV_{1p} at 6 years. This underscores the importance of early eradication of bacterial infections and hence prevention of recurrent pulmonary exacerbations.

The present study has certain limitations. Foremost is the genotypic selection, which limits our ability to generalize our results to the CF population with mutations associated with less severe phenotypic expression; however, the majority of patients in the CFF Patient Registry are homozygous F508del, which is associated with pancreatic insufficiency (21). Additionally, we cannot ascertain the accuracy of obtained measurements in registry data. Careful attention was, however, paid to extreme values with exclusion of patients with apparent erroneous entries. Multiple other independent predictors of decline in FEV_{1p}, such as chronic infection status, socioeconomic status, birth weight, and weight at diagnosis, were not evaluated in the present study (22,30). Our database lacked good proxy indicators of socioeconomic status such as parental income and health insurance status because they changed often for a majority of patients. Lastly, we could not ascertain the primary indication for receiving antibiotics, and it was presumed to be because of a pulmonary exacerbation or other bacterial infection resulting in a CF exacerbation.

CONCLUSIONS

In summary, our findings demonstrate that nutritional status in children with CF at age 2 years and sustained growth is strongly associated with pulmonary function at age 6 years. Furthermore, although a higher FEV_{1p} is achieved in children with a CDC WFL status of 50% as opposed to children achieving this percentile only on the WHO chart, both groups of children attain a clinically normal FEV_{1p}. This suggests that at age 2 years, the WHO WFL at the 50th percentile can be used as a target for children with CF; however, additional benefit in FEV_{1p} may be achieved through a higher target on the WHO growth chart. Although different percentile values may be obtained on different growth charts despite similar growth indicators, evaluating the child as a whole as opposed to paying attention

only to the WFL percentiles is optimal. In addition, infection prevention and aggressive early management are associated with better pulmonary outcomes. Further studies are required to determine whether the changes in FEV_{1p} seen when children attain the 50th percentile on the CDC versus the WHO growth chart are clinically meaningful.

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FIGURE 1.
Summary of reasons for patient exclusion.

FIGURE 2.

Relation between change in CDC weight-for-age percentile between 2 and 6 years (change in WFA across the 50th percentile at 2 and 6 years of age based on the CDC growth reference data). WFL percentile <50 at 2 years, ≥ 50 at 6 years, $n = 195$ (17%); WFL percentile <50 at 2 years, <50 at 6 years, $n = 615$ (53%); WFL percentile ≥ 50 at 2 years, ≥ 50 at 6 years, $n = 247$ (21%).

TABLE 1

Characteristics of 1155 children with cystic fibrosis *

Characteristic	n (%)
Male sex	555 (48)
Mean weight (kg) at 2 y (SD)	11.70 (1.36)
Mean height (cm) at 2 y (SD)	84.44 (3.63)
Homozygous F508del	981 (85)
History of at least 1 admission	819 (71)
MRSA positive	394 (34)
SM positive	481 (42)
BCCO positive	24 (2)
PA positive	900 (78)
NTM positive	14 (1)
Median number of admits (IQR)	2 (0–3)
Median duration on antibiotics (IQR) [†]	13 (0–37)
Median maximum percent predicted FEV ₁ (IQR) [‡]	105 (94–115)

BCCO = *Burkholderia cepacia complex*; FEV₁ = forced expiratory volume in 1 second; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; NTM = nontuberculous mycobacteria; PA = *Pseudomonas aeruginosa*; SD = standard deviation; SM = *Stenotrophomonas maltophilia*.

* Values at 6 years of age unless stated otherwise.

[†] Cumulative number of days on inpatient/outpatient antibiotics.

[‡] Represents the maximum recorded FEV_{1p} between 6 and 8 years.

TABLE 2

Cross-tabulation for weight-for-age at age 2 years; CDC versus WHO growth charts

CDC WFA	WHO WFA			Total
	10th percentile	>10th but <50th percentile	50th percentile	
10th percentile	108	196	0	304
>10th but <50th percentile	0	339	171	510
50th percentile	0	0	341	341
Total	108	535	512	1155

The numbers represent patient distribution on the CDC and WHO growth charts based on their percentile groups at 2 years. Cross-tabulating WFA by CDC and WHO growth percentiles shows that WHO percentiles are higher and that there is redistribution of patients toward higher percentiles on the WHO growth chart. CDC = Centers for Disease Control and Prevention; WFA = weight-for-age; WHO = World Health Organization.

TABLE 3

Cross-tabulation for weight-for-length at age 2 years; CDC versus WHO growth charts

CDC WFL	WHO WFL			Total
	10th percentile	>10th but <50th percentile	50th percentile	
10th percentile	37	104	0	141
>10th but <50th percentile	0	256	194	450
50th percentile	0	0	564	564
Total	37	360	758	1155

The numbers represent patient distribution on the CDC and WHO growth charts based on their percentile groups at 2 years. Cross-tabulating WFL by CDC and WHO growth percentiles shows that WHO percentiles are higher and that there is redistribution of patients toward higher percentiles on the WHO growth chart. CDC = Centers for Disease Control and Prevention; WFL = weight-for-length; WHO = World Health Organization.

TABLE 4Linear regression analysis of factors associated with maximum percent predicted FEV₁ at 6 years

Variable	Estimate	SE	P
Intercept	95.49	3.68	<0.0001
WHO weight-for-length percentile at 2 y	0.08	0.02	<0.0001
log LOA *	-1.48	0.24	<0.0001
<i>Burkholderia</i> (negative)	6.69	3.38	0.048

LOA = length of time on antibiotics; SE = standard error; WHO = World Health Organization.

* Log(total number of days on antibiotics).