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Low Weight, Morbidity, and Mortality in Children With Cerebral Palsy: New Clinical Growth Charts

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KEY WORDS
growth charts, cerebral palsy, mortality, morbidity

ABBREVIATIONS
CDC—Centers for Disease Control and Prevention
GMFCS—Gross Motor Function Classification System
CDER—Client Development Evaluation Report

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WHAT'S KNOWN ON THIS SUBJECT: Weight-for-age percentiles of children with cerebral palsy are lower than in the general population. This is especially true in children with more severe motor dysfunction. Poor growth, loosely defined, is associated with increased hospitalization and school absences.

WHAT THIS STUDY ADDS: This article reports evidence-based thresholds for low weight and provides estimates of associated increases in mortality risk. These estimates are illustrated on new clinical growth charts for children with cerebral palsy, stratified according to gender and Gross Motor Function Classification System levels.

abstract

OBJECTIVE: To determine the percentiles of weight for age in cerebral palsy according to gender and Gross Motor Function Classification System (GMFCS) level and to identify weights associated with negative health outcomes.

PATIENTS AND METHODS: This study consists of a total of 102 163 measurements of weight from 25 545 children with cerebral palsy who were clients of the California Department of Developmental Services from 1988 through 2002. Percentiles were estimated using generalized additive models for location, scale, and shape. Numbers of comorbidities were compared using *t* tests. The effect of low weight on mortality was estimated with proportional hazards regression.

RESULTS: Weight-for-age percentiles in children with cerebral palsy varied with gender and GMFCS level. Comorbidities were more common among those with weights below the 20th percentile in GMFCS levels I through IV and level V without feeding tubes ($P < .01$). For GMFCS levels I and II, weights below the 5th percentile were associated with a hazard ratio of 2.2 (95% confidence interval: 1.3–3.7). For children in GMFCS levels III through V, weights below the 20th percentile were associated with a mortality hazard ratio of 1.5 (95% confidence interval: 1.4–1.7).

CONCLUSIONS: Children with cerebral palsy who have very low weights have more major medical conditions and are at increased risk of death. The weight-for-age charts presented here may assist in the early detection of nutritional issues or other health risks in these children. *Pediatrics* 2011;128:e299–e307

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Growth charts are standard tools for monitoring pediatric growth, development, and overall health. They contain estimated weight-for-age percentiles based on a reference population. If a child's weight falls well outside age norms, it may raise clinical concern. The standard charts in pediatric practices are those of the Centers for Disease Control and Prevention (CDC) for boys and girls in the US general population.[1] These charts may not be helpful for children with cerebral palsy, whose growth patterns may be markedly different from those of the general pediatric population.[2–15]

Krick et al[2] produced the first cerebral palsy–specific growth charts based on the weight and stature of children with severe quadriplegia. The North American Growth in Cerebral Palsy Research Collaboration has produced curves for several other growth parameters, including weight, knee height, upper-arm length, mid–upper arm muscle area, triceps skinfold, and subscapular skinfold.[3] Recently, Day et al[4] constructed a series of height, weight, and BMI charts stratified by motor and feeding skills.

Some researchers and practitioners have raised concerns over the usefulness of growth charts as diagnostic or prognostic tools. One concern is that existing charts are descriptive references rather than prescriptive standards, showing how a particular group of children grew rather than how a particular child should grow. Recently, the World Health Organization attempted to address this concern by constructing growth charts based on a select sample of "healthy children living under conditions likely to favor achievement of their full genetic growth potential [and whose mothers] engaged in fundamental health-promoting practices, namely breastfeeding and not smoking."[16] Whether the resulting World Health Organization charts are truly prescriptive or in any sense more useful than the descriptive CDC reference curves is an open question.[17]

Whether such a select sample for cerebral palsy growth curves would be helpful is far from clear. Cerebral palsy growth patterns are dependent on the severity of disabilities,[4] and children with more severe disabilities are likely to have significant comorbidities. Thus, defining a "healthy" cerebral palsy population becomes a difficult and somewhat arbitrary task. Perhaps a more reasonable approach to growth-chart construction is to begin with a clinically appropriate reference population to the construct charts then analyze empirical data to determine growth thresholds that are associated with good or bad health outcomes in that population. This approach was taken by Stevenson et al[3] and Samson-Fang et al,[5] who showed that poor growth, measured by a combination of weight and other parameters, was associated with increased health care use and decreased social-participation outcomes.

The following were the goals of the present study:

1. Estimate reference weight-for-age percentiles for children with cerebral palsy at each Gross Motor Function Classification System (GMFCS) level.
2. Test for associations between weight for age and morbidity and mortality and quantify those that are significant.
3. Construct cerebral palsy growth charts that clearly illustrate potentially unhealthy low weights.
4. Design the charts to mimic the CDC charts so that they may easily be integrated into existing clinical practice.

METHODS

Inclusion and Exclusion Criteria

The study population included children with cerebral palsy who were clients of the California Department of Developmental Services between January 1988 and December 2002. Clients of the Department of Developmental Services are assessed annually with the Client Development Evaluation Report (CDER).[18] This report contains over 200 medical, functional, behavioral, and cognitive items. For each client, a team headed by a pediatric neurologist makes medical diagnoses, including the assessment of cerebral palsy, whereas functional items (crawling, walking, and feeding, etc) may be assessed by other professionals familiar with that aspect of the client's development.

Children who had a CDER with an *International Classification of Disease, Ninth Revision*[19] code for any of several degenerative conditions or conditions acquired after infancy were excluded from all analyses. The inclusion-exclusion algorithm is shown in Fig 1.

Gross Motor Classification

Growth patterns in children with cerebral palsy vary with motor and feeding abilities.[4] The classification system for motor disability in children with cerebral palsy used most commonly in clinical and research settings is the 5-level GMFCS[20]:

I. Walks without limitations
II. Walks with limitations
III. Walks using a hand-held mobility device
IV. Self-mobility with limitations, may use powered mobility
V. Transported in a manual wheelchair

The specific criteria for each level are age dependent and were developed with the intent that children would

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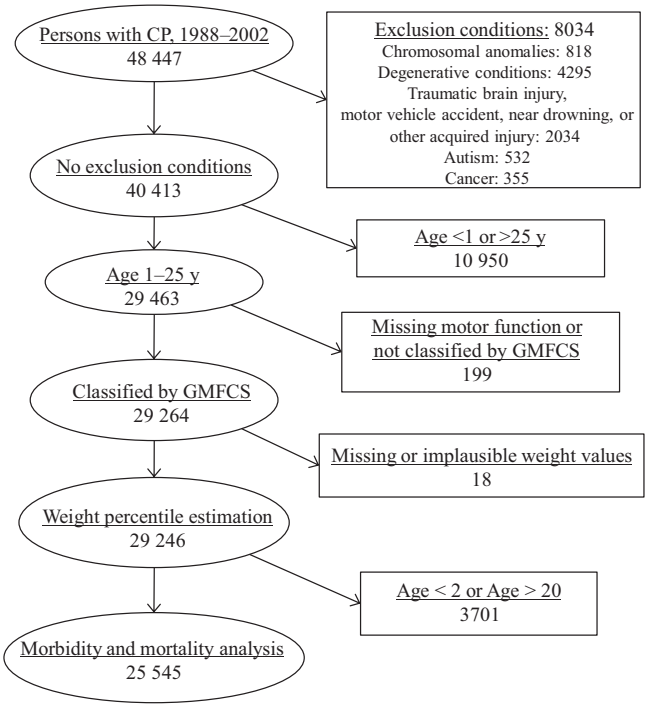

FIGURE 1
Study population inclusion-exclusion algorithm. CP indicates cerebral palsy.

maintain the same GMFCS level throughout childhood and adolescence. Wood and Rosenbaum[21] documented the reliability of GMFCS from the age of 2 to 12 years to be 0.79.

For the present study, the age-specific GMFCS criteria were approximated with functional items from the CDER based on the classification algorithm used in Krach et al.[25] Functional-item data have been independently validated[22–24] and have interrater reliability exceeding 0.85.[24] Because the presence of a feeding tube may affect growth, GMFCS level V was subdivided into children who fed orally without a feeding tube (GMFCS V-NT) and those who had a feeding tube (GMFCS V-TF). The vast majority of feeding tubes (well over 90%) are gastrostomy tubes. In the United States, nasogastric feeding is rarely used for extended periods.

Some children gained or lost abilities and were represented in 1 or more GMFCS levels over the course of the study. A relatively small number of children (<1%) were not assigned to any GMFCS level because they had missing functional assessments or because they had rare combinations of abilities and disabilities. These children were excluded from additional analysis.

Weight-for-Age Growth Curves

Weight measures for the CDER were taken directly or, in some cases, reported by a parent or other caregiver. Discrepancies between weights recorded on the CDER and those in an individual's actual medical records were found in 9% of a random sample, but these were small enough to be ignored as immaterial.[22]

For approximately one-third of the assessments, weight values were carried over from a previous CDER. Because such observations do not accurately represent age-specific weights, we excluded them from additional analysis. Few individuals had recorded weights that were well above or below biologically plausible limits. In addition, some assessments suggested extreme rates of weight change; for example, a 5-year-old child gaining 50 pounds during a 1-year period. Together, all such doubtful observations made up less than 0.1% of our study sample and were excluded from additional consideration.

Gender- and GMFCS-specific reference percentiles (growth curves) were estimated for children with cerebral palsy who were aged 2 to 20 years (data on children aged 1 to 25 years were used to improve the precision of weight percentiles at ages 2 and 20). This age range was selected to match the standard CDC charts. Percentiles were estimated with generalized additive models for location, scale, and shape (GAMLSS), with a Box-Cox power exponential distribution. This is a semiparametric statistical-modeling technique that allows estimation of age-specific percentiles and *z* scores.[26] Models were fit in accordance with World Health Organization methodology using cubic smoothing splines. Model selection was based on penalized maximum likelihood.[27]

Morbidity

Separately for each GMFCS level, the mean number of chronic major medical conditions was calculated within weight-for-age quintiles. According to the Department of Developmental Services, chronic major medical conditions are "major, chronic medical problems that limit or impede the client or significantly impact the provision of service" and "include, but are not limited to, diabetes mellitus, hypertension, congenital or arteriosclerotic heart disease, upper respiratory infections, etc."[18] Differences in the mean number of chronic major medical conditions, for people in the extreme

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TABLE 1 Study Population

	GMFCS Level					
	I	II	III	IV	V-NT[a]	V-TF[b]
No. of assessments	14 030	31 808	13 994	24 744	11 919	5668
Male, %	61	57	55	57	54	54
Age, median (interquartile range), y	4.5 (1.7–6.8)	4.5 (2.7–6.4)	4.6 (3.2–6.5)	4.4 (2.6–6.4)	3.9 (2.2–6.3)	4.1 (2.4–6.4)
Has a feeding tube, %	1	2	5	9	0	100
Orally fed by others, %	1	2	11	33	85	0
Has severe (IQ 20–34) or profound (IQ < 20) mental retardation, %	11	22	34	50	68	84
Low birth weight (<2500 g) or preterm labor (<37 wk), %	25	28	35	31	23	22
Weight, median (interquartile range), kg	28 (16–50)	27 (19–44)	26 (18–39)	21 (15–32)	18 (13–26)	23 (16–31)

Observations are 102 163 CDERs from 25 545 subjects with cerebral palsy, who received services from the California Department of Developmental Services between 1988 and 2002. Some children contributed observations to more than 1 group.

[a] Is fed orally.

[b] Dependent on a feeding tube.

weight quintiles versus those in the 3 middle quintiles were assessed with *t* tests.

Mortality

Electronic death records were obtained from the California Department of Health Services. Individuals surviving 3 or more years after their last weight measure were censored at 3 years. All individuals surviving to December 31, 2002, were administratively censored at that date.

We used Cox proportional hazards regression analysis with time-varying covariates[28] to relate survival time to weight percentiles. This enabled us to control for other variables, such as feeding skills, that might confound or modify the effect of low weight on mortality. Separate models were fit for GMFCS levels I and II and GMFCS levels III through V because children in these groups tend to be different with respect to functional skills beyond gross motor function, feeding and cognition, age-specific weight values, age-specific mortality patterns, and secular trends. Low-weight cutoffs were selected on the basis of maximum likelihood. Data were managed in SAS version 9.12,[29] and analyzed by using R version 2.9.[30]

RESULTS

Descriptive Statistics

The study population included 25 545 children (56% male, aged 2–20 years) who contributed 102 163 weight measurements (Table 1). Age, gender, prematurity or low birth weight, and calendar year of CDER did not vary significantly by GMFCS level. The most frequent level in our study population was GMFCS level II (31%). This was followed by levels IV (24%), V (17%), I (14%), and III (14%). The proportion with severe feeding and cognitive disabilities increased with increasing GMFCS level. For example, 2% of children in GMFCS level I were either tube fed or orally fed by others compared with 42% of children in GMFCS level IV and 90% in GFMCS level V. Eleven percent of children in GMFCS level I had severe or profound mental retardation compared with 50% of children in GMFCS level IV and 73% in GFMCS level V.

Weight-for-Age

In all but the most severe group (GMFCS level V), weight-for-age data exhibited nonlinear dependence on age, with a visible growth spurt between ages 9 and 13 years and plateau in late adolescence. For each GMFCS level, weight-for-age percentiles for boys and girls were similar up to about the age of 15 years. Girls plateaued earlier than boys, and between the ages of 15 and 20 years boys tended to weigh more than girls. Gender differences were smaller in the more severely affected groups. For example, at age 20 years the difference in median weights for boys and girls in GMFCS level I was 7.3 kg; the difference was only 1.8 kg in the GMFCS V-TF group. Figure 2A shows a scatter plot of weight-for-age data in boys from GMFCS level I, along with estimated weight-for-age percentiles and the CDC percentiles for boys in the general population. The 90th percentile in GMFCS level I closely tracked that of the general population. The median was lower, and the difference in medians increased with age. The 10th percentile was markedly lower at all ages. Children in GMFCS level V exhibited more linear growth patterns (ie, no growth spurt), with a plateau in late adolescence (Fig 2B).

Morbidity

The mean number of chronic major medical conditions increased modestly with GMFCS level. The most striking marker for chronic medical conditions was the presence of a feeding tube. For example, children in GMFCS V-TF had, on average, twice as many

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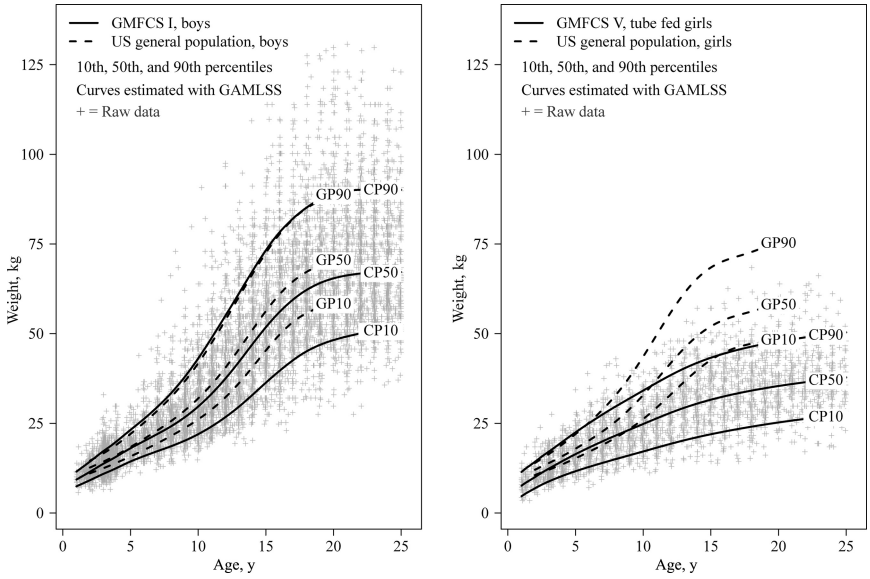

FIGURE 2
Weight-for-age data and fitted percentiles.

major medical conditions as those in GMFCS V-NT (Fig 3). Among children in the GMFCS levels I through IV and the level V-NT groups, those with weights below the 20th percentile had more major medical conditions than children whose weights fell in the middle 60% ($P < .01$). In contrast, children in GMFCS V-TF who had weights below the 20th percentile had fewer major medical conditions than the middle 60% ($P < .0001$). The mean number of major medical conditions for children with weights above the 80th percentile was not significantly different from that of children with weights in the middle 60%.

Mortality

Study participants contributed a total of 166 327 person-years of follow-up time. There were 1496 deaths, for an overall mortality rate of 9 deaths per 1000 person-years. For GMFCS levels III through V, children with weight for age below the 20th percentile had significantly higher mortality rates compared with children with weight for age in the 20th to 80th percentile range ($P < .01$) (Fig 4). The excess death rate in this lowest quintile increased steadily with GMFCS level (0.3 per 1000 person-years [GMFCS level I] up to 26 per 1000 person-years [GMFCS V-TF]). Weight above the 80th percentile was not associated with differential mortality.

Because mortality rates in children with cerebral palsy vary strongly with the severity of disabilities, for modeling purposes the data were divided into 2 groups: mild to moderate (GMFCS levels I and II) and severe (GFMCS levels III through V). Within each group, we fit unadjusted Cox proportional hazard regression models and also more complex models with baseline hazard functions stratified by GMFCS level and adjusted for time-varying covariates, including age, gender, mobility, feeding, mental retardation, low birth weight or prematurity, and calendar year. Unadjusted and adjusted hazard ratios from the models are given in Tables 2 and 3. For GMFCS levels I and II, weight below the 5th percentile was associated with an adjusted hazard ratio of 2.2 (95% confidence interval: 1.3–3.7). For GMFCS levels III through V, weight below the 20th percentile was associated with increased mortality (adjusted hazard ratio: 1.5 [95% confidence interval: 1.4–1.7]). The relative mortality risk associated with low weight did not vary with gender, age, or calendar year. Sensitivity analyses confirmed that the pattern of missing age-specific weights were noninformative with respect to survival and therefore did not influence these results.

These mortality risk research findings are illustrated on newly developed

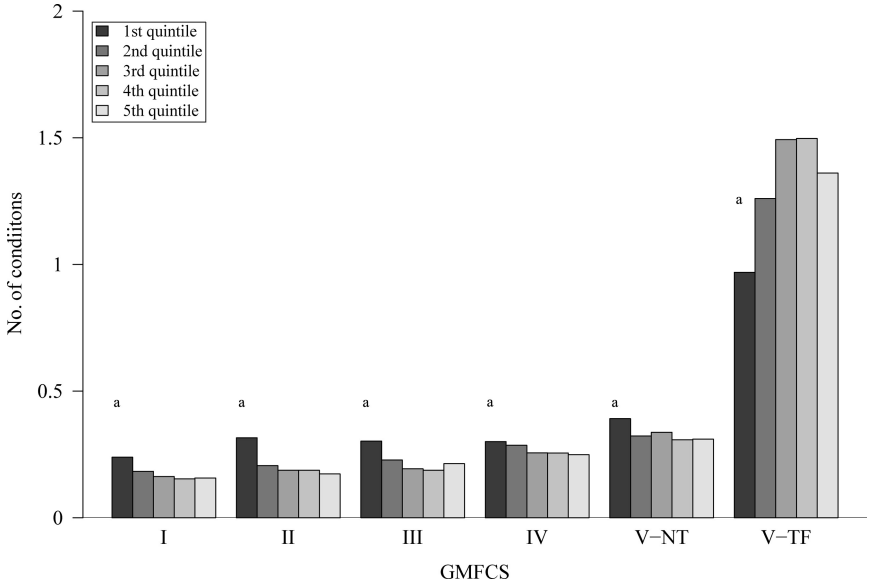

FIGURE 3
Mean number of chronic major medical conditions according to weight quintile. [a] Significant difference from the middle 3 quintiles ($P < .01$).

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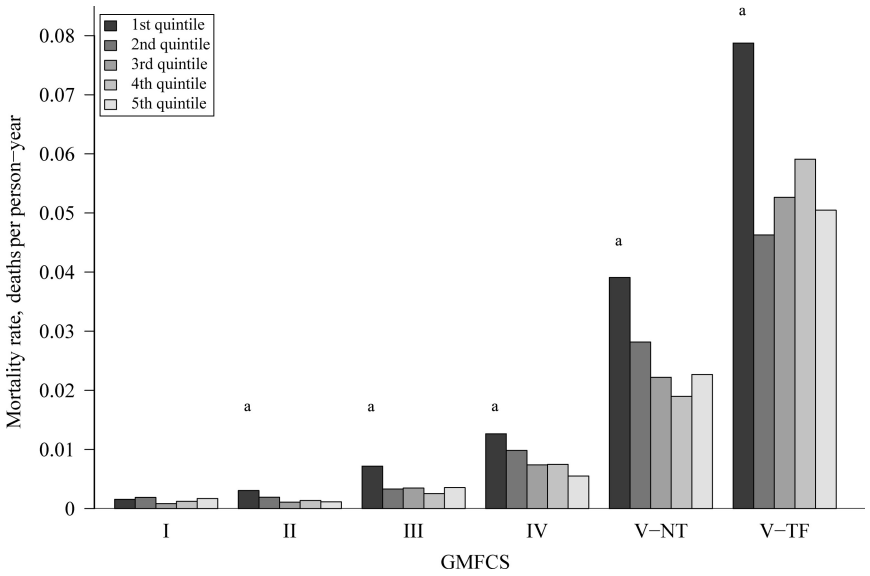

FIGURE 4
Crude mortality rates according to weight quintile. [a] Significant difference from the middle 3 quintiles ($P < .05$).

TABLE 2 Cox Regression Results for Children in GMFCS Levels I and II

	Hazard Ratio for Death and 95% Confidence Interval	
	Unadjusted	Adjusted[a]
Weight below the 5th percentile[b]	3.2 (1.9–5.3)	2.2 (1.3–3.7)

Based on 45 838 evaluations of 13 118 individuals in GMFCS levels I or II. The cohort experienced 125 deaths over 76 733 person-years of follow-up.
[a] Adjusted for gender, age, stair climbing ability, mental retardation, feeding, and low birth weight or prematurity.
[b] GMFCS- and age-specific 5th percentile.

TABLE 3 Cox Regression Results for Children in GMFCS Levels III Through V

	Hazard Ratio for Death and 95% Confidence Interval	
	Unadjusted	Adjusted[a]
Weight below the 20th percentile[b]	1.6 (1.4–3.8)	1.5 (1.4–1.7)

Both models account for functional skills that vary over time (ie, time-varying covariates). The baseline hazard functions were stratified by GMFCS level. Based on 56 325 evaluations of 14 688 individuals in GMFCS levels III through V. The cohort experienced 1371 deaths over 89 594 person-years of follow-up.
[a] Adjusted for gender, age, head-lifting ability, feeding, mental retardation, low birth weight or prematurity, and calendar year.
[b] GMFCS- and age-specific 20th percentile.

growth charts with shaded weight-for-age values where mortality risk is significantly increased. Fig 5 shows weight-for-age charts for girls in GMFCS level IV and boys in GMFCS level V who are tube fed. The new charts are styled after the standard CDC charts and include designated areas to record patient name, dates, parental height and weight, and general notes. The full set of growth charts is available at www.lifeexpectancy.org/articles/newgrowthcharts.shtml.

DISCUSSION

Among children in GMFCS levels I through IV, and level V who are not tube fed, low weight was, as expected, associated with an increase in the number of concurrent chronic major medical conditions. Why very low weight is associated with fewer major medical conditions for children in the GMFCS V-TF group is unclear. It may be that some very-low-weight children have feeding tubes placed strictly to address weight issues even in the absence of comorbidities, whereas heavier children have feeding tubes to reduce risks from aspiration pneumonias or to address other medical issues. Additional research is necessary to fully understand this.

The concept of failure to thrive is used frequently in general pediatric practice without much evidence regarding its associations with health outcomes.[31] It is interesting to note that our evidence-based GMFCS levels I and II low-weight threshold (ie, the 5th percentile) is broadly consistent with anthropometric failure-to-thrive criteria.[32] This threshold also is consistent with studies of the general population that have found the 10th percentile of adult BMI to be associated with modestly increased mortality.[33,34] That the low-weight percentile threshold for GMFCS levels I and II is lower than that for GMFCS levels III through V (5th versus 20th percentile) reflects the fact that children in GMFCS levels I and II weigh more than those in GMFCS levels III through V.

It may seem counterintuitive that high weights were not associated with increased mortality or morbidity, particularly because obese children may be subject to additional comorbidities and may require modified care regimes. The most likely explanation may be that the effects of overweight or obesity do not noticeably increase mortality risk until adulthood. The impact of childhood obesity on adult outcomes in people with developmental disabilities remains an open question.

The proper clinical interpretation of the risks discussed here deserves additional comment. A practicing clinician may ask, "Do these risks apply to

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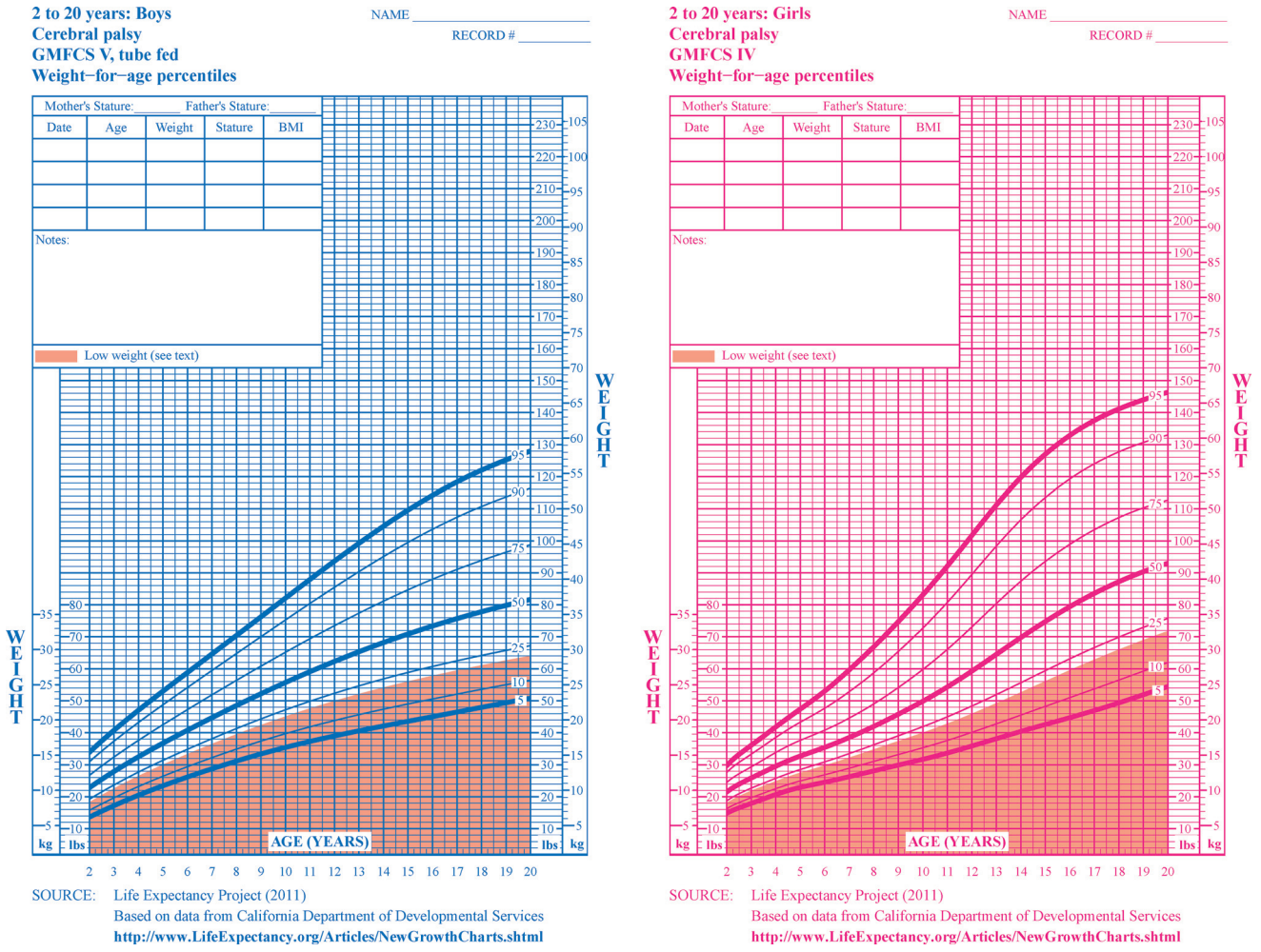

FIGURE 5
Clinical growth charts for children with cerebral palsy.

my patient? And, if so, for how long?" The evidence presented here is generally applicable to all children with cerebral palsy, but additional patient-specific features should always be considered. One potentially benign reason for low weight may simply be small parental stature. In cases where benign etiology has been ruled out, the excess risks associated with low weight should be interpreted as persistent for as long as the child remains in the low-weight category. On the other hand, for the reasons stated above clinicians should not take the findings of this study to infer that overweight is not a significant health risk in children with cerebral palsy.

The primary limitation of the study is the lack of information regarding the etiology of low weight. Low weight is a known marker for nutritional deficits and general frailty, which is a reasonable mechanism for increased morbidity and mortality. On the other hand, children may lose weight or have trouble gaining it as a result of chronic or acute illness. A secondary limitation is the apparent underrepresentation of GMFCS level I (14%) in our study population. In other population-based cerebral palsy registries, the proportion of those in level I ranged from 30% to 40%.[35–37] It may be that the most mildly affected individuals in California disproportionately choose not to seek long-term services from the Department of Developmental Services because of a perceived lack of need. Thus, our GMFCS level I findings may be valid only for children with ongoing needs for services.

The study has a number of strengths. The findings represent the first evidence-based link between low weight and mortality risk in children with cerebral palsy. The large sample size allowed percentile estimates that are robust to modeling assumptions. For example, the charts presented here have estimated weight-for-age percentiles that are consistent with those in Day et al.[4] The GAMLSS growth chart methodology used here is consistent with that of both the CDC and World Health Organization. It al-

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lows for the calculation of both percentiles and *z* scores, which have become popular in both the research and clinical communities. Finally, the use of a simple and reliable measure, weight, may have practical benefits over using a more detailed but possibly unreliable combination of measures, for example stature or skinfold thickness, in children with cerebral palsy.

CONCLUSIONS

Evidence-based decision-making is crucial in clinical and care-planning settings. Without sound empirical evidence to rely on, clinicians may be forced to make important treatment decisions on the basis of subjective impressions. The extent to which today's clinicians can practice evidence-based medicine depends largely on the availability of tools designed with these principles in mind.

The new cerebral palsy growth charts presented here are the first to give a visual indication of potentially unhealthy weights. GMFCS is relatively stable throughout childhood and adolescence and thus provides a useful stratification scheme from which to monitor a particular child's growth. To facilitate integration into current clinical practice, our growth charts are styled in accordance with those of the CDC and include designated areas to record patient characteristics and clinical notes. Ultimately, the utility of the charts will become more apparent as they are used in clinical practice.

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Jordan Brooks, Steven Day, Robert Shavelle and David Strauss

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