

# Pubertal Height Growth and Adult Height in Cystic Fibrosis After Newborn Screening

Zhumin Zhang, PhD,<sup>a</sup> Mary J. Lindstrom, PhD,<sup>b</sup> Philip M. Farrell, MD, PhD,<sup>c</sup> HuiChuan J. Lai, PhD, RD,<sup>a,b,c</sup> with the Wisconsin Cystic Fibrosis Neonatal Screening Group

abstract

**BACKGROUND:** To examine long-term growth benefit of newborn screening (NBS), adolescent peak height velocity (PHV), and adult height were compared between the screened (diagnosed early via NBS) and the control (identified generally by symptoms) in the Wisconsin Randomized Clinical Trial.

**METHODS:** Data from 107 children born in 1985–1994 and followed through 2012 were analyzed. PHV was estimated by a semiparametric growth curve model and compared with Tanner reference.

**RESULTS:** Meconium ileus (MI;  $n = 25$ ) was associated with the worst pubertal growth and adult height, including 1 child who did not experience apparent PHV; children with pancreatic sufficiency ( $n = 18$ ) achieved the best growth (normal PHV and adult height). In children with pancreatic insufficiency without meconium ileus ( $n = 64$ ), the subgroup most likely to benefit from NBS, screened children had similar PHV but better adult height compared with controls. Specifically, in boys, the screened group ( $n = 22$ ) achieved normal PHV (9.5 cm at 13.5 years); the control group ( $n = 19$ ) had similar onset age (13.6 years) but 0.6-cm lower magnitude ( $P = .08$ ). In girls, the screened group ( $n = 10$ ) had somewhat later (12.5 years vs 11.7 years,  $P = .12$ ) and lower PHV (7.3 cm vs 7.9 cm,  $P = .33$ ) than the controls ( $n = 13$ ), coinciding with later menarche (13.6 years vs 12.2 years,  $P = .10$ ). Adult height was taller in the screened than the control (50th vs 29th percentile,  $P = .02$ ), even after adjusted for genetic potential (32nd vs 15th percentile,  $P = .006$ ). Differences in adult height were primarily attributable to NBS and better prepubertal growth.

**CONCLUSIONS:** Early linear growth benefits of NBS were sustained through puberty, leading to better adult height in cystic fibrosis.



Departments of <sup>a</sup>Nutritional Sciences, <sup>b</sup>Biostatistics and Medical Informatics, and <sup>c</sup>Pediatrics, University of Wisconsin–Madison, Madison, Wisconsin

Dr Zhang conceptualized and designed the study, carried out the initial analyses, and drafted the initial manuscript; Dr Lindstrom carried out the growth curve modeling and reviewed and revised the manuscript; Dr Farrell designed and carried out the Wisconsin CF Newborn Screening Randomized Clinical Trial and critically reviewed and revised the manuscript; Dr Lai conceptualized and designed the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to HuiChuan J. Lai, PhD, RD, Department of Nutritional Sciences, University of Wisconsin–Madison, Madison, WI 53706. E-mail: hlai@wisc.edu

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**WHAT'S KNOWN ON THIS SUBJECT:** Children with cystic fibrosis (CF) diagnosed early through newborn screening (NBS) have better nutritional status and growth with greater height percentiles in the first decade of life compared with those diagnosed by traditional methods after signs/symptoms and then received similar standard nutritional therapies.

**WHAT THIS STUDY ADDS:** Early growth benefits of expedited diagnosis through NBS in children with CF sustain long-term through adolescence leading to better adult height, indicating there are persistent benefits when the disease is identified in newborns and treated with nutritional support.

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Short stature or stunting, an indicator of chronic malnutrition, is a persistent problem in children with cystic fibrosis (CF)<sup>1</sup> and also a prognostic factor.<sup>2,3</sup> Despite improved nutritional status and median survival age, many individuals with CF still fail to reach average height for their age<sup>4</sup> and/or genetic potential for height.<sup>5</sup> Nevertheless, findings from the Wisconsin Randomized Clinical Trial of Neonatal Screening for CF (RCT)<sup>6,7</sup> begun in 1985 demonstrate that children with CF diagnosed early through newborn screening (NBS) were more likely to respond to treatment initiation, recover from growth faltering,<sup>8,9</sup> and maintain near average height status through the first decade of life,<sup>10</sup> when compared with those generally diagnosed by conventional methods through signs and symptoms. However, whether such growth benefits of NBS are sustained long-term through adolescence has remained uncertain.

Adolescence is a critical time period for pubertal growth. Malnutrition occurring before or during this period may cause irreversible damages. Impaired pubertal growth is common in children with CF<sup>11-22</sup> and may be associated with stunting<sup>21,22</sup> and/or lung function deterioration.<sup>19,21</sup> With advances in new therapies and comprehensive nutrition management, peak height velocity (PHV) in children with CF born mid-1980 reported in the US CF Foundation Patient Registry (CFFPR) was improved compared with the older cohort but still remained below the average.<sup>22</sup> Early diagnosis of CF through NBS provides unequivocal nutritional benefits in early childhood.<sup>10</sup> Whether NBS-associated diagnosis and early therapy leads to normal pubertal growth and adult height is of great interest to the CF community.

We hypothesized that prepubertal growth benefits of NBS sustain long-term through adolescence leading to

better adult height in children with CF. Specific objectives were (1) to characterize PHV in children with CF enrolled in RCT; (2) to examine whether children with CF diagnosed early through NBS had improved PHV compared with those diagnosed through signs and symptoms; and (3) to examine whether screened children had better height status than the control, before and after adjusting genetic potential for height.

## METHODS

### Study Population

The study population consisted of 107 children with CF who were enrolled and followed through puberty in the Wisconsin RCT project, a prospective longitudinal investigation initiated in 1985 to assess the benefits and risks of CF NBS.<sup>6,7</sup> The design of the Wisconsin RCT project was described in detail elsewhere.<sup>6</sup> Briefly, children born in 1985–1994 in Wisconsin were randomly assigned to the screened and control arm. For children assigned to the screened arm, early diagnosis of CF was established through NBS, whereas in the control arm the diagnosis of CF was generally established by traditional methods (ie, through signs and symptoms of CF). In addition, some controls were identified by our unique “unblinding” method done to avoid selection bias, as described in detail elsewhere.<sup>10</sup> The Wisconsin RCT project was discontinued when the youngest subject reached age ~18 years. Anthropometric measurements were obtained according to a standardized protocol and performed by trained research nurses and dietitians.<sup>7,23</sup> Height and weight data at 2 to 18 years were used for the analyses. Age- and gender-specific z score/percentile values for height and BMI were computed by using the 2000 Centers for Disease Control and Prevention (CDC) growth charts.<sup>24</sup>

In these 107 children, 1 child with meconium ileus (MI) was excluded from all the comparisons because he did not experience a typical linear growth spurt with a flat curve. The study protocol was approved by the Human Subjects Committee at the University of Wisconsin and the Research and Publications Committee/Human Rights Board at Children’s Hospital of Wisconsin in 1983 and randomization of newborns occurred April 15, 1985 to June 30, 1994.

### Identifying PHV by Growth Curve Modeling

A semiparametric shape-invariant model was used to estimate PHV.<sup>25</sup> Conceptually, this method assumes that all individuals of the same gender have a common shape for their age versus height curve, which is estimated by using data from all children by a nonlinear mixed effects model with regression spline that has 2 continuous analytical derivatives. Each child’s individual height curve is then determined by shifting and scaling this common curve to obtain the best fit for his/her data. Once an individual’s height curve is fitted, the calculated first derivatives of this curve are used to determine the height velocity (HV) curve. Using this approach, age and magnitude of PHV were identified for each individual patient.

### Defining Late and Impaired PHV

Longitudinal standards of PHV for North American children developed by Tanner and Davies<sup>26</sup> were used to define normal PHV because they provide reference values for children with different growth tempo. On average, PHV occurs at 13.5 years with a magnitude of 9.5 cm/year in boys, and 11.5 years with a magnitude of 8.3 cm/year in girls. Late PHV was defined as PHV age at 2 SD later than average, namely, after 15.3 years in boys and 13.3 years in girls; attenuated PHV was defined as PHV magnitude below the fifth

percentile. Using these criteria, 3 PHV categories were defined: normal (PHV neither late nor attenuated), late (late PHV but not attenuated), and impaired PHV (PHV attenuated regardless of the onset age).

### Defining CF Phenotypes and Prepubertal Growth

MI was retrieved from the medical record. Pancreatic functional status - pancreatic sufficiency (PS) or pancreatic insufficiency (PI), was monitored as described<sup>23</sup> during the first 4 years of life, and the final determination occurred at age 4 years.

Growth at age 7 years was used to reflect prepubertal nutritional status, as the age of puberty take-off in healthy girls with early PHV was 6.5 years,<sup>26</sup> and none of the children in our study entered puberty before age 7 years. Growth at age 7 years was indicated by height and BMI z scores/percentiles, calculated by using the 2000 CDC growth charts.<sup>24</sup>

### Height Adjusted for Genetic Potential

Height adjusted for genetic potential was estimated from parental stature by using the Himes method.<sup>27</sup> This method predicts the child's genetic potential for height by eliminating the influence of tall and short parental stature and generating an "adjusted height" that represents the child's height as if his/her parents had average stature. The following steps are used to calculate Himes adjusted height: (1) calculate midparental height; (2) find the Himes adjustment value based on the child's gender, age, height, and midparent height; and (3) apply the adjustment value to the child's actual height to obtain the adjusted height.

Of the 106 patients, 93 (88%) had self-reported parental height data available. No significant differences were found between those with and those without parental heights regarding NBS (52% vs 31% screened,  $P = .24$ ), gender (57% vs

85% boys,  $P = .07$ ), phenotype (24% MI, 62% PI, and 14% PS vs 15% MI, 46% PI, and 38% PS,  $P = .11$ ), and adult height (38th vs 40th percentile at age 18 years,  $P = .88$ ). Himes-adjusted heights were calculated as described above. Parental height z scores/percentiles were calculated by using the 2000 CDC growth charts at age 20 years.<sup>24</sup>

### Statistical Analysis

Shape invariant modeling of height and HV curves<sup>25</sup> was performed by using the R nlme package (<http://www.r-project.org>). SAS (version 9.4; SAS Institute, Inc, Cary, NC) was used for other analyses. Student's *t* test or Wilcoxon rank test was used for 2-group comparisons of continuous variables. One-way ANOVA with Fisher's Least Significant Difference test was used for multiple-group comparisons of continuous variables.  $\chi^2$ /Fisher's exact test was used to compare categorical variables. Children with PI, who were most likely to benefit from NBS, were selected for comparisons between the screened and the controls. Repeated-measure analysis was performed to assess the difference in height status 2 to 18 years between the screened and the controls. Multiple regression models were used to assess the effects of various factors on adult height.

### RESULTS

Children enrolled in the Wisconsin RCT were typical children with CF in the United States.<sup>28</sup> Specifically, 23% of them were MI, 60% were PI, and 17% were PS (Table 1). Children with PS were less likely to be F508del homozygotes than those with MI and PI. As expected, the screened children were diagnosed earlier than the controls. Self-reported parental heights were above the average.

### Pubertal Linear Growth in RCT Cohort

Children in RCT experienced the typical growth spurt similar to Tanner reference.<sup>26</sup> When compared with Tanner reference, PHV in boys with CF occurred at the similar age with a reduced magnitude (0.1 year later and 0.4 cm shorter); PHV in girls with CF occurred later and was attenuated (0.5 years later and 0.7 cm shorter; Table 2). Approximately 82% of children had normal, 8% had late, and 10% had impaired PHV, respectively. This distribution did not differ by gender,  $P = .23$ .

With respect to CF phenotype, children with PS achieved normal PHV (boys: 9.6 cm/year at 13.3 years; girls: 8.3 cm/year at 11.5 years) similar to Tanner reference and normal adult height (boys, 52nd percentile; girls, 64th percentile). Children with MI had significant reduction in PHV magnitude compared with children with PS (shorter by 1.1 cm/year in boys and 1.2 cm/year in girls;  $P = .04$ ), and shorter adult height (boys, 34th percentile; girls, 17th percentile;  $P = .02$ ). PHV in children with PI (below the normal) appeared somewhat in between. More children with PS reached their midparental height percentile than children with MI and PI,  $P = .009$ .

### Comparisons of PHV Between the Screened and Controls in PI

In 64 children with PI, the subgroup most likely to benefit from NBS, the screened group apparently had similar PHV compared with the controls. In boys, the screened achieved normal PHV (9.5 cm/year at 13.5 years); the controls had similar onset age (13.6 years) but insignificantly smaller magnitude (0.6 cm shorter than the screened,  $P = .08$ ). In girls, the screened experienced a somewhat later (12.5 years vs 11.7 years,  $P = .12$ ) and smaller PHV (7.3 cm vs 7.9 cm,  $P = .33$ ) than the controls. Menarche

**TABLE 1** Characteristics of Study Population

|                                     | All Patients | By CF Phenotype |            |             | Patients With PI        |             |
|-------------------------------------|--------------|-----------------|------------|-------------|-------------------------|-------------|
|                                     |              | MI              | PI         | PS          | Screen                  | Control     |
| <i>N</i> (%)                        | 106          | 24 (23)         | 64 (60)    | 18 (17)     | 35 (55)                 | 29 (45)     |
| Boys, <i>N</i> (%)                  | 64 (60)      | 14 (58)         | 41 (64)    | 9 (50)      | 22 (63)                 | 19 (66)     |
| Age at diagnosis, mo                |              |                 |            |             |                         |             |
| Mean ± SD                           |              |                 | 9.3 ± 17.9 | 31.9 ± 29.7 | 3.6 ± 10.9 <sup>a</sup> | 15.9 ± 21.8 |
| Median                              |              |                 | 2.1        | 31.2        | 1.6 <sup>a</sup>        | 5.7         |
| Range                               |              |                 | 0.8–75.7   | 0.6–85.3    | 0.8–64.5                | 1.3–75.7    |
| Genotype, <i>N</i> (%) <sup>b</sup> |              |                 |            |             |                         |             |
| F508/F508                           | 52 (51)      | 10 (45)         | 42 (68)    | 0 (0)       | 21 (64)                 | 21 (72)     |
| F508/other                          | 42 (41)      | 9 (41)          | 19 (31)    | 14 (78)     | 12 (36)                 | 7 (24)      |
| Other/other                         | 8 (8)        | 3 (14)          | 1 (2)      | 4 (22)      | 0 (0)                   | 1 (3)       |
| Parental heights <sup>c</sup>       |              |                 |            |             |                         |             |
| Maternal, %tile                     | 61 ± 31      | 44 ± 35         | 65 ± 29    | 72 ± 32     | 64 ± 29                 | 61 ± 28     |
| Paternal, %tile <sup>b</sup>        | 61 ± 28      | 53 ± 31         | 69 ± 27    | 40 ± 22     | 74 ± 26                 | 55 ± 27     |
| Average, %tile                      | 61 ± 22      | 48 ± 22         | 67 ± 20    | 56 ± 23     | 69 ± 20                 | 64 ± 21     |

One boy with MI and F508del/F508del did not have apparent PHV and was excluded. %tile, percentile.

<sup>a</sup> These values are significantly different between the screen and control group,  $P < .05$ .

<sup>b</sup> Significantly different among 3 phenotype groups: MI, PI and PS.

<sup>c</sup> The number of children with parental heights available is 22 in MI, 58 in PI (33 in the screen and 25 in the control group), and 13 in PS.

**TABLE 2** Prepubertal Height, PHV, and Adult Height by Phenotype

|   | All Patients | By Phenotype         |              |             |
|---|--------------|----------------------|--------------|-------------|
|   |              | MI                   | PI           | PS          |
| Overall patients  | 106          | 24                   | 64           | 18          |
| Prepubertal growth at age 7 y   |              |                      |              |             |
| Height percentile   | 35 ± 29      | 21 ± 28*             | 38 ± 30**    | 50 ± 26**   |
| Adjusted height percentile  | 28 ± 27      | 22 ± 25*             | 28 ± 26***   | 44 ± 29**   |
| BMI percentile  | 56 ± 26      | 44 ± 26*             | 58 ± 23***   | 67 ± 32**   |
| PHV categories, <i>N</i> (%)  |              |                      |              |             |
| Normal  | 87 (82)      | 17 (71)              | 53 (81)      | 17 (94)     |
| Late  | 8 (8)        | 2 (8)                | 6 (9)        | 0 (0)       |
| Impaired  | 11 (12)      | 5 (21)               | 5 (8)        | 1 (6)       |
| Nutritional status at age 18 y  |              |                      |              |             |
| Unadjusted height, percentile   | 38 ± 30      | 20 ± 29*             | 41 ± 29**    | 56 ± 28**   |
| Adjusted height, percentile <sup>a</sup>  | 25 ± 23      | 19 ± 21*             | 24 ± 21*     | 48 ± 29**   |
| BMI percentile  | 39 ± 30      | 25 ± 25*             | 41 ± 28***   | 60 ± 36**   |
| Unadjusted percentile < average parental height percentile, <i>n</i> (%) <sup>a</sup> | 73 (78)      | 20 (91) <sup>b</sup> | 47 (81)      | 6 (46)      |
| Pubertal PHV, boys  |              |                      |              |             |
| <i>N</i>  | 64           | 14                   | 41           | 9           |
| Age at take-off, y  | 11.3 ± 0.9   | 11.6 ± 1.1           | 11.3 ± 0.9   | 11.1 ± 0.7  |
| HV at take-off, cm/y  | 4.2 ± 0.9    | 3.7 ± 1.0*           | 4.3 ± 0.9*** | 4.7 ± 0.9** |
| Age at PHV, y   | 13.6 ± 1.2   | 13.8 ± 1.6           | 13.6 ± 1.2   | 13.2 ± 0.9  |
| PHV magnitude, cm/y   | 9.1 ± 1.3    | 8.4 ± 1.6*           | 9.2 ± 1.2*** | 9.6 ± 1.2** |
| Pubertal PHV, girls   |              |                      |              |             |
| <i>N</i>  | 42           | 10                   | 23           | 9           |
| Age at take-off, y  | 9.6 ± 1.2    | 9.8 ± 1.3            | 9.7 ± 1.3    | 9.1 ± 1.0   |
| HV at take-off, cm/y  | 4.8 ± 0.9    | 4.5 ± 1.0*           | 4.7 ± 0.9*   | 5.4 ± 0.5** |
| Age at PHV, y   | 12.0 ± 1.2   | 12.3 ± 1.3           | 12.2 ± 1.2   | 11.5 ± 1.1  |
| PHV magnitude, cm/y   | 7.6 ± 1.5    | 7.2 ± 1.7            | 7.6 ± 1.4    | 8.3 ± 1.6   |
| Age at menarche, y  | 13.3 ± 1.7   | 13.7 ± 1.3           | 13.1 ± 1.8   | 13.4 ± 1.9  |

Values with asterisks are significantly different,  $P < .05$ .

<sup>a</sup> The number of children with parental heights available is 22 in MI, 58 in PI (33 in the screen and 25 in the control group), and 13 in PS.

<sup>b</sup> Significantly different among phenotype groups by Fisher's exact test.

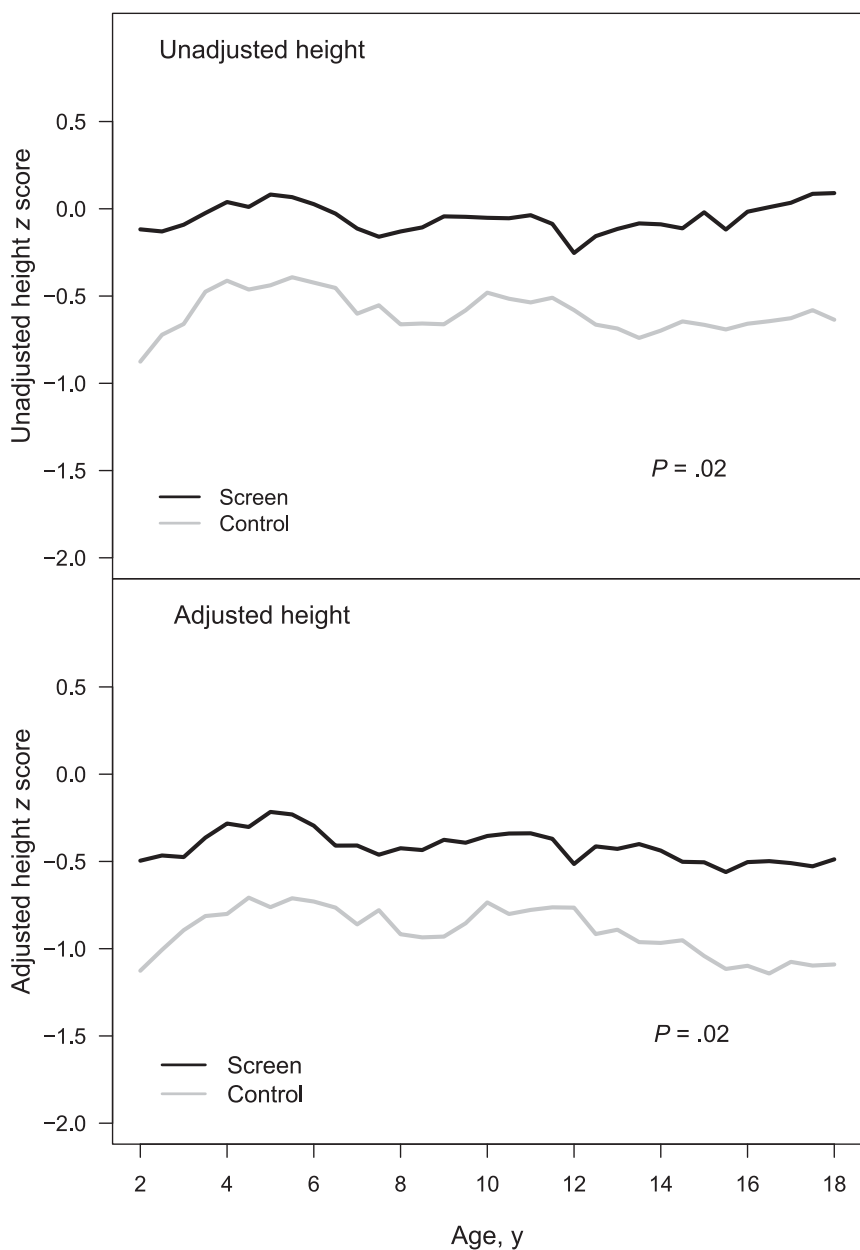
also occurred later in the screened girls (13.6 years versus 12.2 years,  $P = .10$ ). Nevertheless, the sample

size is rather small ( $n = 13$  for the screened versus  $n = 10$  for the control girls). Five out of these 64

children (8%, compared with 5% in Tanner reference) had impaired PHV, and the distribution did not differ significantly between the screened and controls,  $P = .65$ .

### Comparisons of Height Status Between the Screened and Controls in PI

Boys and girls were combined for this analysis due to small sample size. From age 2 to 18 years, the screened was significantly taller than the controls by an average of ~15 percentile (49th vs 34th,  $P = .02$ ), or by ~10 percentile after adjusting for genetic potential for height (28th vs 19th,  $P = .02$ ; Fig 1). No gender difference was observed. Height status did not change significantly before and after puberty in both the screened and controls. Prepubertal height percentile at age 7 years was similar to that at age 18 years in the screened (unadjusted height: 47th vs 50th,  $P = .71$ ; adjusted height: 35th vs 32nd,  $P = .67$ ) as well as in the controls (unadjusted: height 27th vs 29th,  $P = .83$ ; adjusted height: 20th vs 15th,  $P = .43$ ; Table 3). The screened children had better adult height compared with the controls (50th vs 29th percentile,  $P = .02$ ), even after adjusting for genetic potential (32nd vs 15th percentile,  $P = .006$ ). More screened



**FIGURE 1** Comparisons of height status 2 to 18 years between the screened and the control group in children with PI. The screened group was taller than the control:  $P = .02$  for unadjusted height and  $P = .02$  for adjusted height.

children reached midparental height percentile at age 18 years than the controls, 30% vs 4%,  $P = .02$ .

### Factors Associated With Adult Height in PI

Results from multiple regression models (Table 4) show that NBS was associated with better adult height, both unadjusted and adjusted for genetic potential ( $P < .05$ ).

Prepubertal height status at age 7 years and parental heights were also strong predictors ( $P < .001$ ). PHV was not associated with adult height.

### DISCUSSION

With more than 20 years of data generated from the Wisconsin RCT project, finally we were able to examine long-term growth benefits

of CF NBS through adolescence. Our analyses demonstrate that early linear growth advantages of NBS persist through puberty and lead to better adult height. However, the screened children did not seem to gain more height during puberty over the controls. Specifically, in children with PI, the subgroup most likely to benefit from NBS, PHV and pubertal height gain were similar between the screened and the controls. Nevertheless, the screened children were significantly taller before, during, and after puberty than the controls, even after adjusted for genetic potential for height. Both the screened and controls had declined height status at CF diagnosis.<sup>10</sup> The screened children were more likely to recover compared with controls, who also experienced catch-up growth, but never reached the same level as the screened did.<sup>8,10</sup> All children in RCT received standard care by protocol after CF diagnosis.<sup>10</sup> Thus, differences in the attained height (15th percentile) between the screened and controls must be primarily attributed to early diagnosis through CF NBS.

The RCT screened children were diagnosed at a median age of 6.9 weeks, compared with 22.0 weeks in the controls.<sup>10</sup> The 4-month gap seems trivial but results in different growth status in early infancy, the most rapid growth period in life. Healthy infants on average gain more than 15 cm on recumbent length and 4 kg on weight in the first 6 months of life.<sup>29</sup> This is also an extremely critical period for postnatal bone development, because the skeletal system goes through important adaptations to extrauterine environment.<sup>30</sup> The physical bone mineral density of long bones decreases by ~30% in the first few months of life due to faster increase of the marrow cavity size relative to the cross-sectional area of the bone cortex, followed by a rapid increase until 2 years of age and a

slower increase thereafter.<sup>31</sup> Adverse events (ie, malnutrition and/or disease condition) that interfere with postnatal skeletal adaptations may lead to lifelong health consequences.

The concept that early postnatal or even intrauterine growth exerts long-term effects on the structure and function of particular organs and tissues is well established.<sup>32,33</sup> The mechanism is believed to be the programming of a range of metabolic and endocrine systems caused by environmental stimuli during critical/sensitive periods of early development, which leads to persisting changes in structure and function. Poor nutrition and growth during early life have been linked to a number of adverse health outcomes in adulthood, including decreased adult bone mass.<sup>34,35</sup> The RCT screened children had better nutrition and growth status than the control in early childhood,<sup>10</sup> which could have long-lasting influence on growth and explain long-term benefit of CF NBS.

Compared with our previous study using CFFPR data,<sup>5</sup> PHV was further improved in RCT cohort born in 1985–1994. For example, the CFFPR study revealed PHV of 8.4 cm/year at age 14.0 years, 0.7 cm lower and 0.4 years later than RCT boys. A consistent trend was observed in girls (ie, 0.6 cm lower and 0.1 year later; 7.0 cm/year at age 12.1 years) than the RCT cohort. One-quarter of children in the CFFPR study experienced impaired PHV compared with 10% in the RCT cohort. The adult height was also found to be ~10 percentile shorter in the CFFPR study, even after adjusted for genetic potential. Half of the children in RCT were diagnosed through NBS compared with 3% in the CFFPR study. Therefore, NBS is likely to be 1 of the major contributing factors for the improvement. Nevertheless, sample size for the comparisons is small, especially for female subjects. Future studies are needed to reexamine all the findings. However, the potential clinical

**TABLE 3** Comparisons of PHV and Height Status Between the Screen and Control Group in PI

|   | Screen     | Control    | <i>P</i> |
|---|------------|------------|----------|
| Boys, <i>N</i>  | 22         | 19         |          |
| Age at puberty take-off, y  | 11.2 ± 0.9 | 11.4 ± 0.8 | .35      |
| HV at puberty take-off, cm/y  | 4.4 ± 1.1  | 4.1 ± 0.5  | .27      |
| Age at PHV, y   | 13.5 ± 1.0 | 13.6 ± 1.4 | .67      |
| PHV magnitude, cm/y   | 9.5 ± 1.3  | 8.9 ± 1.0  | .08      |
| Height gain, take-off to 18 y, cm   | 32.7 ± 4.9 | 31.6 ± 4.4 | .46      |
| Unadjusted height 7 y, percentile   | 47 ± 30    | 31 ± 32    | .24      |
| Adjusted height 7 y, percentile <sup>a</sup>  | 33 ± 27    | 23 ± 29    | .35      |
| BMI 7 y, percentile   | 61 ± 21    | 62 ± 27    | .96      |
| Unadjusted height 18 y, percentile  | 51 ± 29    | 32 ± 29    | .11      |
| Adjusted height 18 y, percentile <sup>a</sup>   | 27 ± 20    | 16 ± 15    | .11      |
| BMI 7 y, percentile   | 36 ± 27    | 38 ± 33    | .88      |
| Girls, <i>N</i>   | 13         | 10         |          |
| Age at puberty take-off, y  | 10.1 ± 1.2 | 9.1 ± 1.2  | .07      |
| HV at puberty take-off, cm/y  | 4.5 ± 0.9  | 5.0 ± 0.9  | .16      |
| Age at PHV, y   | 12.5 ± 1.3 | 11.7 ± 0.9 | .12      |
| PHV magnitude, cm/y   | 7.3 ± 1.3  | 7.9 ± 1.5  | .33      |
| Age at menarche, y  | 13.6 ± 1.8 | 12.2 ± 1.7 | .10      |
| Height gain, take-off to 18 y, cm   | 25.6 ± 6.6 | 27.0 ± 6.8 | .66      |
| Unadjusted height 7 y, percentile   | 47 ± 32    | 21 ± 16    | .06      |
| Adjusted height 7 y, percentile <sup>a</sup>  | 37 ± 27    | 14 ± 21    | .03      |
| BMI 7 y, percentile   | 52 ± 21    | 47 ± 12    | .68      |
| Unadjusted height 18 y, percentile  | 49 ± 32    | 23 ± 14    | .07      |
| Adjusted height 18 y, percentile <sup>a</sup>   | 41 ± 25    | 13 ± 10    | .08      |
| BMI 18 y, percentile  | 46 ± 23    | 53 ± 29    | .61      |
| Overall patients, <i>N</i>  | 35         | 29         |          |
| PHV categories, <i>N</i> (%)  |            |            | .70      |
| Normal  | 29 (83)    | 24 (83)    | —        |
| Late  | 4 (11)     | 2 (7)      | —        |
| Impaired  | 2 (6)      | 3 (10)     | —        |
| Prepubertal growth at age 7 y   |            |            |          |
| Unadjusted height percentile  | 47 ± 30    | 27 ± 27    | .05      |
| Adjusted height percentile  | 35 ± 27    | 20 ± 25    | .05      |
| BMI percentile  | 58 ± 21    | 57 ± 26    | .91      |
| Nutritional status at age 18 y  |            |            |          |
| Unadjusted height, percentile   | 50 ± 29    | 29 ± 26    | .03      |
| Adjusted height, percentile <sup>a</sup>  | 32 ± 22    | 15 ± 14    | .003     |
| BMI, percentile   | 39 ± 26    | 42 ± 31    | .76      |
| Unadjusted percentile < average parental height percentile, <i>n</i> (%) <sup>a</sup> | 23 (70)    | 24 (96)    | .02      |

<sup>a</sup> The number of children with parental heights available is 33 in the screen group, and 25 in the control group.

**TABLE 4** Factors Associated With Adult Height at Age 18 y in PI

| Multiple Regression Models | Unadjusted Height Z Score |          | Adjusted Height Z Score |          |
|----------------------------|---------------------------|----------|-------------------------|----------|
|                            | Coefficient               | <i>P</i> | Coefficient             | <i>P</i> |
| NBS                        |                           |          |                         |          |
| Screen versus control      | .35                       | .02      | .34                     | .04      |
| Gender                     |                           |          |                         |          |
| Boys versus girls          | -.044                     | .79      | -.43                    | .02      |
| Prepubertal growth         |                           |          |                         |          |
| Height z score at age 7    | .51                       | <.001    | .33                     | <.001    |
| BMI z score at age 7       | .091                      | .41      | .28                     | .01      |
| PHV                        |                           |          |                         |          |
| Normal versus late         | -.11                      | .66      | -.16                    | .57      |
| Normal versus impaired     | .52                       | .02      | .36                     | .15      |
| Late versus impaired       | .63                       | .05      | .52                     | .14      |
| Midparental height z score | .45                       | <.001    | —                       | —        |

significance of NBS is obvious with regard to growth and lung disease.<sup>9</sup>

Attained height in screened children, though close to 50th percentile, still did not reach the genetic potential, but up to 30th percentile because their parents were taller than the average. Parental height data in the Wisconsin RCT project were self-reported and likely to be subjective and overestimated.<sup>36</sup> Nevertheless, no difference was observed between the screened and controls. The reported values were also comparable to the CFFPR study (61st vs 59th percentile).<sup>5</sup> Another important point to mention is that not all the screened children were diagnosed before age 1 month in the RCT cohort. The age of diagnosis varied from 3.6 to 15.9 weeks. A recent study also observed big variations in age at CF diagnosis, as well as the first CF center visit in children born after 2010 (unpublished data). With improved NBS technologies and protocol, our hope is to ensure that every child with CF is diagnosed and treated earlier, ideally within 2 to 4 weeks of birth.

With regard to factors influencing pubertal linear growth and adult height, findings in the Wisconsin RCT are consistent with our previous CFFPR study.<sup>5</sup> MI seemed associated with the worst pubertal growth and adult height stature, whereas PS was more likely to achieve normal linear growth. In patients with PI, height at age 7 years and parental heights appeared to be strong predictors of adult height. More importantly, NBS was still a significant determinant of adult height after accounting for these 2 factors, indicating its independent and long-lasting beneficial effect. PHV, on the other hand, was not

associated with adjusted adult height. It is noted that some patients with CF continue to grow after their 18th birthday. Therefore, height obtained at age 18 years may not be the final adult height. Nevertheless, we found that height percentiles after age 18 years hardly changed in 53 subjects in RCT who had height measurements beyond age 20 years (38th, 39th, 36th, and 39th percentile at age 18, 19, 20, and 21 years, respectively). This observation indicates that height percentile at age 18 years can be used as a proxy for adult height percentile.

The key point and take-home message from our study is to get patients with CF diagnosed and treated as early as possible. In the recent national birth cohort born 2009–2013 with majority diagnosed through NBS, height status at ages 2 to 4 years (~43th percentile)<sup>28</sup> is similar to that in the RCT screened group, despite improved CF care in the last 2 decades. This observation further indicates the pivotal role of early diagnosis of CF through NBS.

## CONCLUSIONS

The Wisconsin RCT project demonstrated that early diagnosis of CF within weeks of birth provides great opportunity to prevent detrimental nutrition and growth faltering in early infancy; in conjunction with appropriate nutritional therapy, such early growth benefits of NBS sustain long-term through puberty and lead to better adult height.

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## ABBREVIATIONS

CDC: Centers for Disease Control and Prevention  
CF: cystic fibrosis  
CFFPR: CF Foundation Patient Registry  
HV: height velocity  
MI: meconium ileus  
NBS: newborn screening  
PHV: peak height velocity  
PI: pancreatic insufficiency  
PS: pancreatic sufficiency  
RCT: Wisconsin Randomized Clinical Trial of Neonatal Screening for Cystic Fibrosis

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