

## NUTRITIONAL BENEFITS OF NEONATAL SCREENING FOR CYSTIC FIBROSIS

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**ABSTRACT**

**Background** Many patients with cystic fibrosis are malnourished at the time of diagnosis. Whether newborn screening and early treatment may prevent the development of a nutritional deficiency is not known.

**Methods** We compared the nutritional status of patients with cystic fibrosis identified by neonatal screening or by standard diagnostic methods. A total of 650,341 newborn infants were screened by measuring immunoreactive trypsinogen on dried blood spots (from April 1985 through June 1991) or by combining the trypsinogen test with DNA analysis (from July 1991 through June 1994). Of 325,171 infants assigned to an early-diagnosis group, cystic fibrosis was diagnosed in 74 infants, including 5 with negative screening tests. Excluding infants with meconium ileus, we evaluated nutritional status for up to 10 years by anthropometric and biochemical methods in 56 of the infants who received an early diagnosis and in 40 of the infants in whom the diagnosis was made by standard methods (the control group). Pancreatic insufficiency was managed with nutritional interventions that included high-calorie diets, pancreatic-enzyme therapy, and fat-soluble vitamin supplements.

**Results** The diagnosis of cystic fibrosis was confirmed by a positive sweat test at a younger age in the early-diagnosis group than in the control group (mean age, 12 vs. 72 weeks). At the time of diagnosis, the early-diagnosis group had significantly higher height and weight percentiles and a higher head-circumference percentile (52nd, vs. 32nd in the control group;  $P=0.003$ ). The early-diagnosis group also had significantly higher anthropometric indexes during the follow-up period, especially the children with pancreatic insufficiency and those who were homozygous for the  $\Delta F508$  mutation.

**Conclusions** Neonatal screening provides the opportunity to prevent malnutrition in infants with cystic fibrosis. (N Engl J Med 1997;337:963-9.)

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**C**YSTIC fibrosis, one of the most common life-threatening autosomal recessive disorders, can be difficult to diagnose, and its recognition is therefore often delayed. In 1995, the mean age at the time of diagnosis was 2.9 years in the United States.<sup>1</sup> At the time of diagnosis, many patients are malnourished or have chronic lung disease,<sup>2,3</sup> and some have hypoproteinemia with edema (acute kwashiorkor), vitamin E deficiency with hemolytic anemia, or severe hyponatremia, hypochloremia, and dehydration.<sup>4,6</sup> In fact, a recent analysis of data from the National Cystic Fibrosis Foundation Registry showed that 44 percent of the patients who received a diagnosis of cystic fibrosis in 1993 had malnutrition severe enough to cause either wasting of body mass or stunting of growth.<sup>7</sup>

The potential nutritional advantages of early diagnosis led Shwachman et al.<sup>8</sup> to recommend neonatal screening for cystic fibrosis in 1970. Screening based on meconium analysis was unsuccessful, but the detection of low values of trypsinogen in dried blood specimens obtained in routine screening programs for metabolic disorders proved effective for this purpose.<sup>9</sup> Subsequent studies confirmed the usefulness of trypsinogen testing,<sup>10</sup> and its efficacy has been improved with a two-step approach in which the trypsinogen assay is followed by an analysis of DNA for mutations in the gene for the cystic fibrosis transmembrane regulator.<sup>11</sup> Before routine neonatal screening for cystic fibrosis can be recommended, however, the efficacy of early diagnosis must be established by demonstrating that the benefits outweigh the potential risks and justify the costs of screening.<sup>12</sup> In 1985, a comprehensive evaluation of neonatal screening for cystic fibrosis was implemented in Wisconsin to determine the optimal screening strategy and to assess the benefits, risks, and costs of screening. A description of the screening tests,<sup>13</sup> their costs,<sup>14</sup> and the potential risks of screening<sup>15</sup> have been reported elsewhere. To investigate the potential benefits of screening, we have chosen nutri-

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tional factors and pulmonary disease as outcome measures. The analysis of pulmonary outcomes will continue until 1999. We report here on the nutritional benefits of neonatal screening for cystic fibrosis.

## METHODS

### Study Design

The design of the study has been described in detail elsewhere.<sup>16</sup> To summarize, we performed a randomized investigation of neonatal screening for cystic fibrosis in two concurrent groups of infants followed prospectively with the use of the same protocol. Sequential comparisons were made between a group of infants who received an early diagnosis through neonatal screening and a control group identified by other means. All the infants were screened with the use of trypsinogen testing of blood spots obtained for routine neonatal screening (between April 15, 1985, and June 30, 1991) or trypsinogen testing followed, in the case of abnormal results, by analysis of DNA for the  $\Delta F508$  mutant allele (between July 1, 1991, and June 30, 1994). Only the infants whose blood-specimen numbers ended in an odd digit were recalled for sweat testing if the results of the trypsinogen or trypsinogen-DNA tests were abnormal (the early-diagnosis group). Trypsinogen was measured by a radioimmunoassay with the use of the Sorin method.<sup>10,11</sup> The  $\Delta F508$  mutation was identified with the use of allele-specific oligonucleotides after polyacrylamide-gel electrophoresis of DNA digests amplified by the polymerase chain reaction.<sup>12,13</sup> The children in the control group were identified on the basis of the presence at birth of meconium ileus, which usually leads to a rapid diagnosis; a family history of cystic fibrosis; the development of symptoms or signs of cystic fibrosis, leading to a sweat test before four years of age; or positive results on neonatal trypsinogen or trypsinogen-DNA testing, revealed on unblinding of the data when the children were four years old.<sup>16</sup> We could therefore identify all children with cystic fibrosis by four years of age.

Once a diagnosis of cystic fibrosis was confirmed by a positive sweat test (sweat chloride concentration, 60 mmol per liter or higher), the patient was followed every three months until the age of 10 years. Follow-up assessments included anthropometric and biochemical measurements of nutritional status and evaluation of the clinical severity of disease according to the Shwachman-Kulczycki method.<sup>17</sup> All follow-up assessments were performed at the Madison Cystic Fibrosis Center (University of Wisconsin) or the Milwaukee Cystic Fibrosis Center (Medical College of Wisconsin). All patients were treated according to a protocol that specified interventions for nutritional deficiencies and pulmonary disease.<sup>18</sup> Nutritional therapy for patients with pancreatic insufficiency included high-calorie diets and supplementation with pancreatic enzymes and fat-soluble vitamins.

The study was approved by the human subjects committee at the University of Wisconsin and the research and publications committee and human rights board at Children's Hospital of Wisconsin. The children's parents gave informed consent.

### Nutritional Assessments

The starting point for the nutritional assessments was the date of a positive sweat test at one of the participating centers. At each visit, a research nurse or dietician measured the child's length or height and weight. The child's recumbent length, to the nearest 0.5 cm, was measured with the use of a calibrated wooden board. After two years of age, height was measured with a stadiometer. For infants, weight was determined to within 0.1 kg, with the child placed in the center of a balance-scale platform and wearing minimal clothing and no diaper. Weight-for-age, length-for-age, and weight-for-length percentiles were calculated with the use of growth charts from the National Center for Health Statistics and the EpiInfo software program.<sup>19</sup> In addition, deviations of the an-

thropometric measurements from the growth-chart reference medians were determined by the standardized z-score technique.

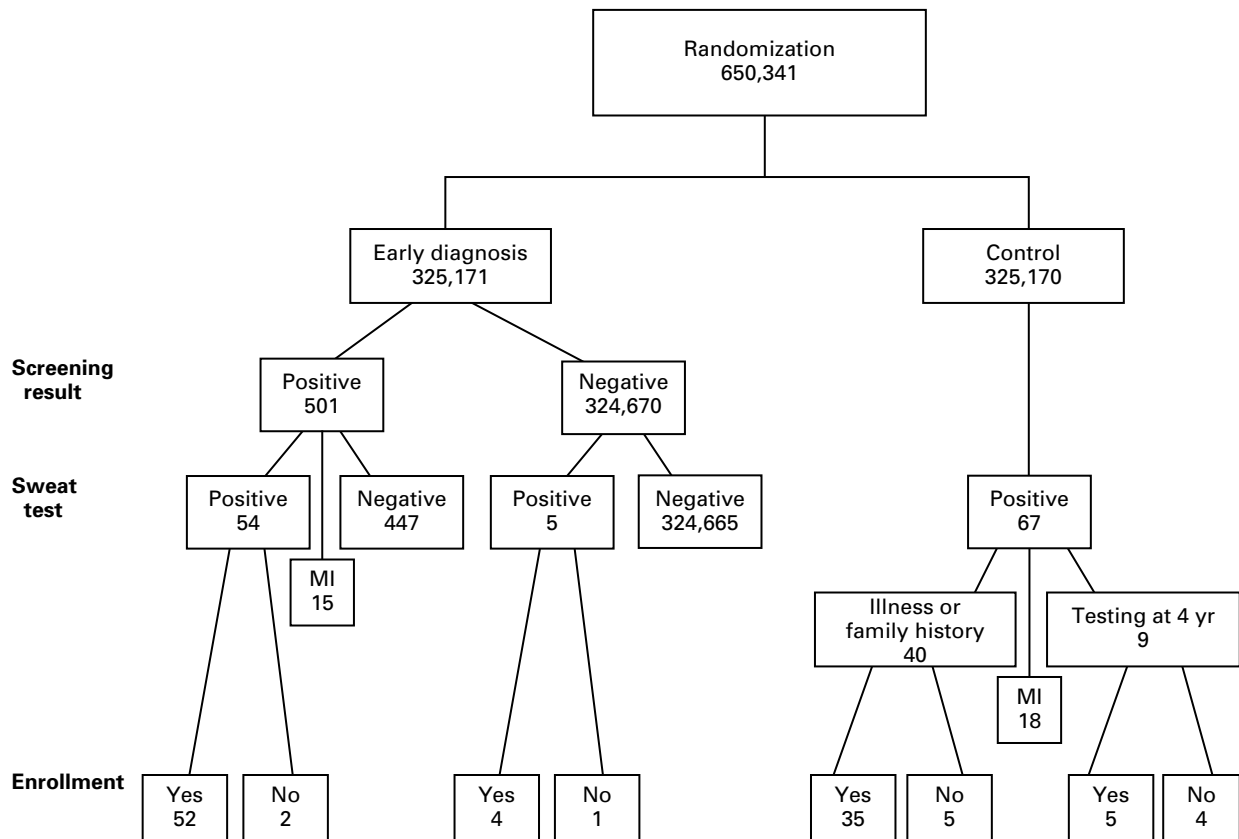
Blood was obtained every six months for measurement of plasma vitamins A and E by high-performance liquid chromatography.<sup>20</sup> At a mean age of four years, the children were classified according to their pancreatic function on the basis of three-day fat-absorption studies, whenever possible, and a new classification method developed with the use of our fat-absorption data and information from previous studies.<sup>21-23</sup> With the new method, pancreatic function was classified according to the plasma concentrations of vitamin E (normal value for  $\alpha$ -tocopherol,  $\geq 500$   $\mu\text{g}$  per deciliter [11.5  $\mu\text{mol}$  per liter]; normal value for  $\beta$ -tocopherol or  $\gamma$ -tocopherol,  $\geq 180$   $\mu\text{g}$  per deciliter [4.1  $\mu\text{mol}$  per liter]) and vitamin A (normal value,  $\geq 20$   $\mu\text{g}$  per deciliter [0.7  $\mu\text{mol}$  per liter]) and the blood trypsinogen concentration. If at least two of the three values were normal or unchanged, the patient was classified as having probable pancreatic sufficiency; otherwise, the patient was classified as having probable pancreatic insufficiency. This method was validated with the use of data from the patients who underwent fat-absorption studies; 91 percent accuracy was achieved with the three blood tests.

### Statistical Analysis

We used the method of Wei et al.<sup>24</sup> to assess the effect of screening, with adjustments for stratification variables and multiple interim analyses.<sup>25</sup> We performed a repeated-measures analysis using generalized-estimating-equation methods with a working assumption of independence among observations<sup>26,27</sup> to assess the differences in anthropometric indexes between the early-diagnosis group and the control group. The analyses were adjusted for age, sex, center, genotype, pancreatic status, and age at diagnosis. Interaction terms for sex and other covariates were also included in the regression models to determine whether the differences between the groups were due to sex. Because there was a 5 percent difference in birth weight between the two groups, we reassessed the overall differences in nutritional outcomes between the groups by adding the birth-weight percentile as a covariate in the repeated-measures analyses. The validity of these models was assessed by examining normal quantile-quantile plots of residuals as well as plots of residuals versus fitted values.<sup>28</sup> Other statistical methods included the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables (both used as two-sided tests).

## RESULTS

Between April 15, 1985, and June 30, 1994, a total of 650,341 infants were screened for cystic fibrosis during the first 28 days of life. Screening during the neonatal period led to the diagnosis of cystic fibrosis in 54 infants. Fifteen infants in the early-diagnosis group had meconium ileus, and 5 other infants had false negative screening tests and were identified because of either a family history (2 infants) or symptoms of cystic fibrosis (3 infants). The control group included 67 infants or children, 18 of whom had meconium ileus and 9 of whom had positive results on sweat testing performed at the age of four years because of a positive neonatal screening test. Because the presence of meconium ileus led to an early diagnosis routinely in both groups and in view of the fundamental principle<sup>29</sup> that screening involves the use of a test to identify people who are still asymptomatic,<sup>30</sup> our nutritional study was focused on patients who had cystic fibrosis without meconium ileus. All reported results refer to the patients without



**Figure 1.** Identification and Enrollment of Patients with Cystic Fibrosis.

Patients were assigned to the early-diagnosis group if the identification number for the neonatal blood specimen ended in an odd digit and to the standard-diagnosis (control) group if it ended in an even digit. Screening was performed with the trypsinogen test (87 percent sensitivity, 100 percent specificity) or the trypsinogen test combined with DNA analysis (100 percent sensitivity, 100 percent specificity).<sup>13</sup> Of the five patients with false negative trypsinogen tests in the early-diagnosis group, two were identified because of a family history, and three because of symptoms of cystic fibrosis. The patients in the control group were identified on the basis of a family history of cystic fibrosis or symptoms or signs of the disease (usually malabsorption or respiratory disease), meconium ileus (MI) leading to a sweat test, or the unblinding of neonatal data when the child reached four years of age. The diagnosis of cystic fibrosis required a sweat chloride concentration of 60 mmol per liter or higher. Patients with meconium ileus were excluded from the analysis.

meconium ileus. Fifty-six patients assigned to the early-diagnosis group and 40 assigned to the control group were enrolled in the study (Fig. 1).

The demographic and genetic characteristics of the two groups of patients without meconium ileus are shown in Table 1. There was a significant difference in the age at diagnosis, with a mean of 12 weeks in the early-diagnosis group as compared with 72 weeks in the control group ( $P=0.001$ ). The age at the time of diagnosis in the control group did not differ significantly from that of the 35 consecutive children with cystic fibrosis diagnosed at the Madison Cystic Fibrosis Center before the screening trial (mean, 73 weeks; median, 36 weeks). There were no significant differences in sex or center distribution between the two groups; however, more patients in

the early-diagnosis group had the  $\Delta F508$  mutation. The two groups also differed with regard to pancreatic functional status, but the overall frequency of pancreatic insufficiency (83 percent) was similar to that reported in other studies of young children with cystic fibrosis.<sup>21,31,32</sup>

At the time of diagnosis, the length or height, weight, and head-circumference percentiles in the early-diagnosis group were significantly higher than those in the control group (Table 1). The mean growth-and-nutrition component of the Shwachman-Kulczycki score and the total score were also significantly higher in the early-diagnosis group. Plasma vitamin E concentrations were low in 71 percent of the early-diagnosis group and 57 percent of the control group ( $P=0.25$ ), and plasma vitamin A

**TABLE 1. DEMOGRAPHIC, NUTRITIONAL, AND CLINICAL CHARACTERISTICS AT THE TIME OF DIAGNOSIS OF CYSTIC FIBROSIS IN PATIENTS WITHOUT MECONIUM ILEUS.\***

CHARACTERISTIC	EARLY-DIAGNOSIS GROUP (N=56)	CONTROL GROUP (N=40)	P VALUE
Age at diagnosis — wk			<0.001
Mean	12±37	72±106	
Median (range)	7 (4–281)	23 (3–372)	
Sex — no. (%)			0.68
Male	35 (62)	23 (58)	
Female	21 (38)	17 (42)	
Genotype — no. (%)†			0.001
ΔF508/ΔF508	32 (58)	19 (50)	
ΔF508/other	23 (42)	11 (29)	
Other/other	0	8 (21)	
Pancreatic status — no. (%)‡			0.04
Sufficiency (probable or established)	5 (10)	10 (28)	
Insufficiency (probable or established)	46 (90)	26 (72)	
Length or height			
Percentile	44±28	25±27	<0.001
z Score	-0.2±1	-1.2±1.1	<0.001
Weight			
Percentile	36±28	22±26	0.008
z Score	-0.5±1.1	-1.2±1.1	0.008
Head circumference — percentile	52±28	32±24	0.003
Shwachman–Kulczycki score§			
Activity	24±2	24±2	0.94
Physical examination	23±4	22±4	0.37
Growth and nutrition	22±4	20±5	0.02
Chest film	23±3	22±4	0.20
Total	91±10	88±10	0.05
Mean (±SE) age-adjusted score¶	92±1	87±2	0.006
Plasma vitamin A — μg/dl	28±16	35±20	0.06
Plasma vitamin E — μg/dl	471±375	534±476	0.48

\*Data were not available for all patients. The numbers of patients with missing data were as follows: genotype, 1 in the early-diagnosis group and 2 in the control group; pancreatic status, 5 in the early-diagnosis group and 4 in the control group; length or height and weight, 2 in the early-diagnosis group; head circumference, 10 in the early-diagnosis group and 11 in the control group; Shwachman–Kulczycki score, 4 in the early-diagnosis group and 2 in the control group; and plasma vitamins A and E, 1 in the early-diagnosis group and 5 in the control group. Except where otherwise noted, plus–minus values are means ±SD.

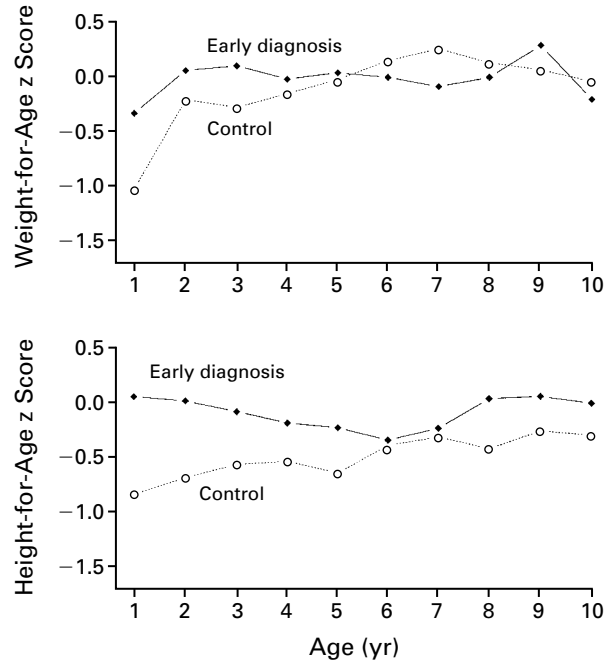
†ΔF508 is the most common mutation of the cystic fibrosis transmembrane conductance regulator (a 3-bp deletion at codon 508). Other denotes mutations other than ΔF508.

‡Pancreatic status was determined with the use of three-day fat-absorption studies (in 79 percent of the children) or a new classification method based on the plasma concentrations of vitamins E and A and the blood immunoreactive trypsinogen concentration<sup>22</sup> during the interval from the neonatal period to the age of four years.

§The Shwachman–Kulczycki score was calculated as recommended,<sup>17</sup> with the use of the component and total (summation) methods at diagnosis and during each follow-up visit. At each visit, a clinical investigator calculated the scores for the four components and combined them into a total score. The maximal score for each component is 25 points, indicating normal status. Points were deducted for disease indicators (decreased activity, symptoms, signs, abnormal growth measures, or abnormalities on the chest film). A score of 100 indicates perfect health.

¶Since some measures may be age-dependent and the mean ages of the two groups at the time of diagnosis were significantly different, the mean values were recalculated for each group after adjustment for age at the time of diagnosis. The age-adjusted means for the two groups were compared with the use of rank-transformed data and an analysis of covariance.

||To convert values for vitamin A and vitamin E to micromoles per liter, multiply by 0.035 and 0.023, respectively.

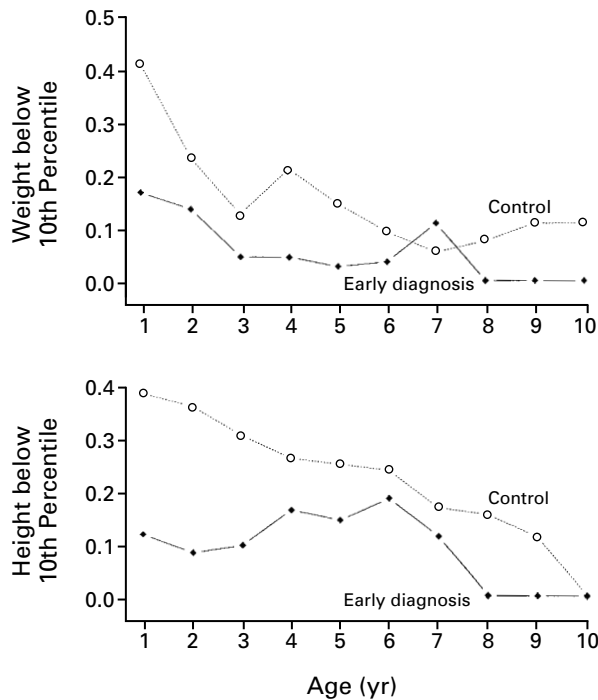


**Figure 2.** Anthropometric Indexes in Relation to Age in the Early-Diagnosis and Control Groups, Standardized According to z Scores.

There were 294 observations each for weight and height in the early-diagnosis group and 187 each in the control group; the number of observations ranged from 4 (at 10 years) to 52 (at 1 year) in the early-diagnosis group and from 9 (at 10 years) to 26 (at 1 year) in the control group. Overall, during the 10-year study period, there were significant differences between the two groups in the z scores for both weight ( $P=0.04$ ) and height ( $P=0.02$ ), by repeated-measures analyses. There were also significant differences in the z score for weight at one year ( $P=0.005$ ) and height at one year ( $P=0.002$ ) and two years ( $P=0.01$ ).

(retinol) concentrations were low ( $<20 \mu\text{g}$  per deciliter [ $0.7 \mu\text{mol}$  per liter]) in 36 percent and 29 percent, respectively ( $P=0.49$ ); the mean values for vitamins A and E in the two groups were similar. The differences in growth indexes at the time of diagnosis were of such magnitude that we obtained data on birth weight retrospectively and found that the mean ( $\pm\text{SD}$ ) weight was higher in the early-diagnosis group than in the control group ( $3.37 \pm 0.37 \text{ kg}$  [ $59 \pm 26$  percentile] vs.  $3.19 \pm 0.57 \text{ kg}$  [ $45 \pm 32$  percentile]) ( $P=0.03$ ).

Overall, during the 10-year follow-up period, the weight and height were higher in the early-diagnosis group than in the control group. Specifically, the early-diagnosis group had significantly higher weight-for-age ( $P=0.04$ ) and height-for-age ( $P=0.02$ ) percentiles (data not shown) and higher z scores for weight ( $P=0.04$ ) and height ( $P=0.02$ ) than the control group (Fig. 2). After adjustment for the differ-



**Figure 3.** Proportions of Patients in the Early-Diagnosis and Control Groups Whose Weight or Height Were below the 10th Percentile at the Annual Assessment.

Both weight and height percentiles were significantly higher in the early-diagnosis group than in the control group. The numbers of observations are given in the legend for Figure 2.

ence in birth weight, the children in the early-diagnosis group were still heavier and taller than those in the control group, but the only differences between the groups that remained significant during follow-up were the height-for-age percentile ( $P=0.04$ ) and the z score ( $P=0.02$ ). When height or weight below the 10th percentile was used as an index of severe malnutrition,<sup>7</sup> the outcome was also significantly better in the early-diagnosis group. The odds ratio for the risk of a weight below the 10th percentile in the control group, as compared with the early-diagnosis group, was 3.1 (95 percent confidence interval, 1.3 to 7.2), and the corresponding odds ratio for height was 3.5 (95 percent confidence interval, 1.3 to 9.7). Neonatal screening reduced the risk of a height below the 10th percentile throughout the first 10 years of life, with no overlap in values between the two groups (Fig. 3).

There were no significant differences in weight and height percentiles according to the sex of the patients, but there was significant variation associated with pancreatic function and genotype (Table 2). Among the patients with pancreatic sufficiency, there were no significant differences in weight or height at

the time of diagnosis or at one year, but among those with pancreatic insufficiency, the patients in the early-diagnosis group were heavier and taller than those in the control group until the age of five years. Among the patients who were homozygous for the  $\Delta F508$  mutation, those in the early-diagnosis group were at significantly higher weight and height percentiles than those in the control group at the time of diagnosis and at one year (Table 2).

### DISCUSSION

Multiple factors influence the nutritional status of patients with cystic fibrosis, including pancreatic function, genotype, diet, eating behavior, nutritional supplements, severity of lung disease, and possibly age at the time of diagnosis.<sup>7,32-35</sup> We evaluated the role of age at the time of diagnosis by studying the nutritional status of patients with cystic fibrosis who were enrolled in our neonatal screening study. We found that the patients in whom cystic fibrosis was detected by screening were heavier and longer and had a larger head circumference than those in whom the disorder was diagnosed on the basis of a family history, illness, or testing at four years because of high blood trypsinogen concentrations at birth. Although the greater weight of children in the early-diagnosis group may be attributable in part to the 5 percent higher birth weight in this group, the nearly twofold higher mean weight percentile and consistently higher length or height percentile in the early-diagnosis group are clinically important findings. The differences associated with screening were especially marked in the subgroups of patients with cystic fibrosis who had pancreatic insufficiency or the  $\Delta F508/\Delta F508$  genotype. Such patients are known to have the most severe disease.<sup>31,35</sup> Thus, we conclude that age at the time of diagnosis is an important factor in the nutritional status of patients with cystic fibrosis and associated pancreatic insufficiency.

Questions have arisen about whether our neonatal screening study resulted in an earlier diagnosis of cystic fibrosis by standard methods in Wisconsin during the study period. The mean age at the time of diagnosis in the members of the control group, who were identified between 1985 and 1994, was almost identical to that of children in whom the diagnosis was made before the study (72 and 73 weeks, respectively). In addition, the age at the time of diagnosis in the control group did not differ significantly from that of patients in the National Cystic Fibrosis Foundation Registry.<sup>7</sup> Furthermore, our control (standard-diagnosis) group resembles the registry group in terms of height and weight.<sup>7</sup> Thus, our control group is representative of the U.S. population of patients with cystic fibrosis.

Our longitudinal assessments showed that the early-diagnosis group had significantly higher height

**TABLE 2.** WEIGHT AND HEIGHT PERCENTILES ACCORDING TO PANCREATIC STATUS AND GENOTYPE.\*

VARIABLE	EARLY-DIAGNOSIS GROUP				CONTROL GROUP			
	NO.	WEIGHT	HEIGHT	P VALUE	NO.	WEIGHT	HEIGHT	P VALUE
	STUDIED	percentile			STUDIED	percentile		
Pancreatic status								
Sufficiency (probable or established)								
At diagnosis	5	56±40	67±28	0.30	10	38±31	39±21	0.13
At 1 year	5	69±21	64±20	0.18	4	35±27	63±41	0.54
Insufficiency (probable or established)								
At diagnosis	45	33±27	43±27	<0.001	26	13±15	17±24	<0.001
At 1 year	43	37±27	51±31	0.07	21	25±27	26±24	0.002
Genotype								
$\Delta F508/\Delta F508$								
At diagnosis	31	31±27	40±26	0.02	19	15±16	19±27	0.005
At 1 year	32	37±27	49±32	0.02	16	20±24	23±22	0.007
$\Delta F508$ /other								
At diagnosis	23	42±32	50±30	0.08	11	22±30	24±29	0.02
At 1 year	20	45±27	55±24	0.26	6	30±34	35±39	0.29

\*Plus-minus values are means  $\pm$ SD.

and weight percentiles and z scores not only at the time of diagnosis but also during the 10-year follow-up period. The differences, however, diminished with time, and the convergence of the values for the two groups by five to six years of age probably reflects the effects of nutritional therapy, because nearly all patients identified clinically through symptoms and signs received the diagnosis by four years of age and were given aggressive treatment, as were those recalled at the age of four years because of a positive screening test. Nevertheless, there was no overlap or crossover in values for height throughout the trial. Consequently, the nutritional-status component of this investigation should be regarded as demonstrating a positive effect of both neonatal screening and nutritional therapy. We conclude that a delayed diagnosis of cystic fibrosis increases the risk of malnutrition in childhood. We also conclude that early initiation of comprehensive nutritional therapy prevents malnutrition in children with pancreatic insufficiency. The essential components of nutritional management are a high-calorie diet and supplementation with pancreatic enzymes and fat-soluble vitamins.<sup>20,21,35</sup>

The characteristics of screening tests for cystic fibrosis have been studied thoroughly.<sup>11,13,36,37</sup> Neonatal screening with the trypsinogen test and DNA analysis is preferable, in our judgment, to screening with the trypsinogen test alone.<sup>13,37</sup> The advantages of the combined method include higher sensitivity, a higher positive predictive value, fewer false positive tests, a more rapid diagnosis with no need for re-

peated testing, and the identification of heterozygous carriers, which permits genetic counseling.<sup>13</sup> In addition, the cost per patient identified is no greater with the combined method.<sup>14</sup> In 1992, the estimated cost of diagnosis was \$11,377 per patient with the standard sweat test, \$7,613 with the trypsinogen test, and \$7,403 with the combined trypsinogen-DNA method. In 1995, when we implemented combined testing as a statewide service, the cost was \$10,150 per patient identified. In fact, the laboratory costs for trypsinogen-DNA testing for cystic fibrosis are similar to the costs of tests for phenylketonuria, and the positive predictive value of trypsinogen-DNA testing is higher.<sup>11,37</sup> Our economic analyses suggest that cost will not be the determining factor in deciding how to perform neonatal screening for cystic fibrosis. Rather, the question should be based on an analysis of the relation between benefits and risks. With regard to the risks, in nearly 10 years of investigating neonatal screening for cystic fibrosis, we have not identified any long-term adverse effects. With regard to the benefits, data from uncontrolled studies suggest that patients identified through neonatal screening subsequently have less severe lung disease than those identified by other means,<sup>36,38</sup> but more compelling evidence of the long-term pulmonary benefits is required. On the basis of our data, it is clear that early diagnosis through neonatal screening has nutritional benefits, as evidenced by better growth. Neonatal screening for cystic fibrosis provides an important opportunity to prevent malnutrition in many patients.

Supported by grants from the National Institutes of Health (DK 34108 and RR03186) and the Cystic Fibrosis Foundation (A001 5-01).

APPENDIX

In addition to the authors, the following investigators participated in the Wisconsin Cystic Fibrosis Neonatal Screening Study Group: University of Wisconsin, Madison, Medical School, Madison — C. Green, M. Palta, M.J. Rock, A. Tluczek, M. Block, L.A. Davis, L. Feenan, L.J. Wei, and B.S. Wilfond; Medical College of Wisconsin, Milwaukee — H. Colby, W. Gershan, C. McCarthy, L. Rusakow, and M.E. Freeman; and Wisconsin State Laboratory of Hygiene, Madison — G. Hoffman, D.J. Hassemer, and R.H. Laessig.

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