Lung Function in Very Low Birth Weight Adults

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abstract

BACKGROUND AND OBJECTIVES: Lung function attained in young adulthood is 1 of the strongest predictors of obstructive airways disease in later life. Adults born preterm at very low birth weight (VLBW; <1500 g) who have experienced bronchopulmonary dysplasia (BPD) have reduced lung function. We studied the association of lung function in young adulthood with preterm birth at VLBW and with BPD and other prenatal and neonatal conditions.

METHODS: We performed spirometry for 160 VLBW subjects (29 with BPD according to Northway criteria) aged 18 to 27 years and 162 term control subjects group-matched for gender, age, and birth hospital. Lung function was expressed as z scores according to the Global Lung Function Initiative standards.

RESULTS: Forced expiratory volume in 1 second z score was 1.41 units (95% confidence interval [CI]: 0.89 to 1.94) lower in BPD-VLBW subjects and 0.39 units (95% CI: 0.08 to 0.69) in non-BPD VLBW subjects compared with control subjects. Corresponding differences for forced expiratory volume in 1 second/forced vital capacity were 1.52 (95% CI: 0.99 to 2.05) and 0.51 (95% CI: 0.21 to 0.81), respectively. Maternal smoking in pregnancy predicted poorer airflow in all groups; this finding was strongest in the BPD-VLBW group. Lung function was unrelated to fetal or postnatal growth or to neonatal respiratory distress syndrome.

CONCLUSIONS: Young adults born at VLBW have reduced airflow. The outcome is stronger in those who have a history of BPD but is present among those with no such history. This finding suggests an increased risk of later obstructive airways disease in adults born at VLBW.

WHAT'S KNOWN ON THIS SUBJECT: Children born preterm at very low birth weight have reduced lung function. Reduced lung function may extend to adult life, but to what extent this outcome is attributable to bronchopulmonary dysplasia and other prenatal and neonatal conditions is not known.

WHAT THIS STUDY ADDS: Young adults born preterm at very low birth weight had impaired airflow. This finding suggests an increased risk of later obstructive airways disease and was observed also among those with no bronchopulmonary dysplasia, regardless of other prenatal and neonatal complications.
In childhood, very low birth weight (VLBW) survivors have, on average, poorer lung function, particularly those with a history of bronchopulmonary dysplasia (BPD) but possibly also those without such a history.1–4 Lung function in adults who were born as small preterm infants has not been extensively studied, even though this factor is, in addition to smoking, 1 of the strongest predictors of obstructive airways disease in later life.5 Much of the existing evidence focuses on adults with a history of BPD, who do have more pulmonary symptoms and respiratory function abnormalities (including obstructed airflow) than those born at term.2,6–12 Whether this outcome applies to adults born preterm at VLBW who have no history of BPD is less conclusive. Most studies may not include a sufficient number of subjects to distinguish between those with a history of BPD and those without.13–16 Moreover, there are many other prenatal and neonatal conditions that could predispose VLBW infants to or protect them from later respiratory disease.17,18 The long-term effects of these conditions could provide valuable insights regarding those mechanisms that link them with airway obstruction in later life.

The aim of the present study was to assess lung function in young adults born at VLBW, with or without a history of BPD. We also focused on other prenatal and neonatal factors that may predispose subjects to or protect them from adverse pulmonary consequences in adult life.

METHODS
Study Population
The subjects were derived from the Helsinki Study of Very Low Birth Weight Adults.19 The original VLBW cohort consisted of 335 consecutive VLBW infants born between 1978 and 1985 who were discharged alive from the NICU of Helsinki University Central Hospital, the only tertiary neonatal center serving the province of Uusimaa, Finland. For each VLBW subject, we chose as a control subject the next infant of the same gender who was born at term (gestational age: ≥37 weeks) and was not small for gestational age (birth weight SD score: −2.0 or higher20) at the same hospital. For the present study, 255 VLBW subjects and 314 control subjects who were living in greater Helsinki were invited to participate; of those, 166 (65.1%) and 172 (54.8%) accepted, respectively, and 160 VLBW subjects and 162 control subjects had lung function data available. The nonparticipants were unbiased except that those who had been diagnosed with cerebral palsy by 15 months of age were less likely to participate; a detailed nonparticipation analysis has been published elsewhere.19

Prenatal and neonatal data were extracted from medical records. SD scores for weight, length, and head circumference at birth were based on Finnish standards,20 and the ponderal index was calculated as weight/length/3. Preeclampsia was defined by using standard criteria,21 and chorioamnionitis was diagnosed by a clinician on the basis of maternal fever, leukocytosis, and elevated C-reactive protein levels. BPD, based on the Northway criteria (respiratory distress, supplemental oxygen, and characteristic radiographic findings at 1 month of postnatal age),22 and respiratory distress syndrome (RDS), based on classic (clinical and radiograph) criteria,23,24 had both been diagnosed by 1 neonatologist (A.-L.J.). Ten infants had been exposed to antenatal glucocorticoids and 1 infant to postnatal glucocorticoids, and 7 had received human surfactant (4 prophylactically at birth and 3 as rescue therapy for RDS symptoms) in a randomized trial. In addition, 12 infants had participated in another randomized trial and been exposed to either antenatal glucocorticoids or placebo; this information was no longer available.

Clinical Measurements and Data Collection
The study protocol was approved by an ethics committee at the Helsinki University Central Hospital. Each participant signed an informed consent form. The participants were instructed not to use bronchodilators in the morning of the clinical visit and not to smoke during the visit before they had completed the lung function test.19 Medical history, use of medication, current smoking, physical activity, and parental educational attainment were assessed with questionnaires.19,25,26

Respiratory function was measured with spirometry testing (Medikro Windows, Spiro2000 version 1.3; Medikro, Kuopio, Finland). The device was calibrated daily before measurements. Six VLBW subjects and 10 control subjects could not complete spirometry for various reasons. The graphs were inspected visually, and the measurement was repeated until 3 reproducible, technically acceptable spirometry curves were obtained. The largest value of each spirometry parameter was reported. The parameters measured were forced vital capacity (FVC) and the following parameters reflecting airflow: forced expiratory volume in 1 second (FEV1), the FEV1/FVC ratio, forced expiratory flow when 75% of FVC has been exhaled and when 50% of FVC have been exhaled (FEF50%), forced expiratory flow at 25% to 75%, and peak expiratory flow. Spirometry was completed with the subject seated, wearing nose clips, and holding mouthpieces tightly between the lips and teeth. The lung volumes and flows were standardized to barometric pressure at sea level and body temperature. As main outcomes, these findings were expressed as z scores for gender, age, and height (all subjects were of Finnish ancestry, and standards for white subjects were thus used) based on the Global Lung Function Initiative guidelines. To allow comparison with previous studies, descriptive data were also described...
as percent predicted based on Finnish reference values. If the spirometry results suggested airflow obstruction according to Finnish guidelines (FVC <80% of predicted value, FEV₁ <90%, FEV₁/FVC ratio <88%, peak expiratory flow <75%, or FEF50% <63%), which are based on the American Thoracic Society/European Respiratory Society standards, it was repeated 10 to 15 minutes after inhaling 200 µg of salbutamol from a metered-dose inhaler through a spacer. The bronchodilation test was considered to indicate reversible airways obstruction if FEV₁ or FVC increased ≥12% or FVC increased ≥200 mL from baseline.

**Statistical Analysis**

Data were analyzed with PASW Statistics 18.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Student’s t test was used to compare the differences of continuous variables between groups, and Pearson’s χ² test was used for categorical variables. Multiple linear and logistic regression analyses were used to adjust for the potential confounders and other covariates. All P values are 2-sided.

**RESULTS**

**Characteristics of the VLBW and Control Subjects**

The characteristics of the subjects are shown in Table 1. Because differences in respiratory function between the VLBW and control groups were similar among women and men (P values for interaction gender*VLBW were not statistically significant), we report the results for both genders pooled.

**Respiratory Function in the VLBW and Control Groups**

Lung function in all VLBW subjects versus lung function in control subjects was compared. Table 2 displays these measurements expressed in absolute units, in z scores according to Global Lung Function Initiative standards, and in percent predicted according to Finnish standards. VLBW adults had lower absolute FVC, reflecting lung volume, which was due to their smaller body size and was therefore not observed in z scores. By contrast, all variables reflecting airflow (FEV₁, FEV₁/FVC, forced expiratory flow at 75% of FVC, FEF50%, and forced expiratory flow at 25% to 75% of FVC) were lower in VLBW adults also when expressed as z scores or percent predicted values.

Further adjustments for age, gender, current height, BMI, parental education, maternal smoking during pregnancy, the subject’s current daily smoking, obstructive airways disease, atopy, and frequency of leisure time conditioning activity had little effect on the difference in the variables reflecting airflow (Table 3). Relationships between these covariates and outcomes are shown in Supplemental Table 4. To assess whether these differences could be attributed to manifest asthma, a secondary analysis was conducted excluding the subjects with ≥1 sign of obstructive airways disease (discussed in the paragraph entitled “Obstructive Airways Disease and Atopic Predisposition”). The results remained unchanged.

The results were similar when the 19 subjects with neurosensory impairments were excluded, as in previous publications.

**Bronchopulmonary Dysplasia**

Of all VLBW subjects, 29 (18.1%) had a history of BPD (“BPD-VLBW”). They had lower gestational age at birth than VLBW subjects with no such history (Table 1). As adults, they were, on average, 3.1 cm shorter and were less likely to smoke. Figure 1 and Supplemental Table 5 show that variables reflecting airflow were lower in BPD-VLBW subjects than in those with no such history. This difference remained statistically significant after adjusting for gestational age and birth weight SD score. Figure 1 and Supplemental Table 5 also show that VLBW subjects with no history of BPD have lower airflow variables than control subjects.

Alternative criteria to define BPD were also used. Forty-nine subjects (30.6%) fulfilled the less strict criterion of supplemental oxygen at 28 days. The use of this definition attenuated the difference between the BPD-VLBW adults and the remaining VLBW adults (Supplemental Table 5). The criterion of supplemental oxygen at 36 postmenstrual weeks (moderate or severe BPD) was fulfilled by 13 subjects (8.1%). The use of this definition also seemed to attenuate the difference with the remaining VLBW adults, although the small numbers resulted in wide confidence intervals.

**Other Prenatal and Neonatal Factors Among the VLBW Group**

The 52 VLBW subjects born small for gestational age had respiratory function similar to the VLBW subjects born appropriate for gestational age (P values ≥ .6). Birth weight SD scores and gestational age as continuous variables were unrelated to respiratory function, whether entered separately or simultaneously in the regression model; there was also no interaction between these variables. The result was the same when the birth weight SD score was substituted with length or head circumference SD score or the Ponderal Index.

There were no differences in lung function between the 32 (20%) VLBW adults who had been exposed to maternal preeclampsia and the 128 who had not been exposed, between those 12 (7.5%) who had neonatal sepsis and those 145 who did not, or between those 77 (48.1%) who had neonatal RDS and the 81 who did not. The 14 (8.8%) VLBW adults who had been exposed to maternal chorioamnionitis had a 0.59 units (−0.17 to 1.34 [adjusted for variables in model 3 in Table 3]) higher z score of FEV₁/FVC ratio than the VLBW adults not exposed. The 27 VLBW adults born from multiple births had
a 0.65 units (0.14 to 1.16) lower FVC z score than singleton VLBW adults but similar airflow variables.

To assess the effects of growth between birth and term among VLBW subjects, the associations of weights at 36 and 40 weeks of postmenstrual age with respiratory function were analyzed. Neither the weight SD scores at 36 or 40 weeks nor their differences from birth were associated with respiratory function. Obstructive Airways Disease and Atopic Predisposition

Fifty-seven VLBW subjects and 30 control subjects (P = .0005) received short-acting salbutamol because their spirometry suggested airflow obstruction according to standard criteria.27,28 For 20 VLBW subjects (12.5%) and 8 control subjects (4.9%), spirometry repeated after inhaling salbutamol indicated reversible airflow obstruction (adjusted odds ratio [aOR; odds ratio adjusted as in model 3 of Table 3]):
 standards to allow comparison with previous studies. VLBW was defined as <1500 g. One or more signs of obstructive airways disease: reversible obstruction in bronchodilator challenge test, asthma previously diagnosed by a physician or inhaled glucocorticoid treatment. No missing values. FEF75%, forced expiratory flow at 75% of FVC; FEF75–78%, forced expiratory flow at 75% to 78% of FVC; FEF peak expiratory flow. *P value for the difference with term <.05. †P value for the difference with term <.001.

According to Finnish current care guidelines.30

### TABLE 2 Lung Function Test Results (Absolute and % of Predicted) in Study Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BPD-VLBW (n = 29)</th>
<th>Non-BPD-VLBW (n = 131)</th>
<th>All VLBW (n = 160)</th>
<th>Term Control (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (l)</td>
<td>3.96 ± 0.87†</td>
<td>4.30 ± 1.02‡</td>
<td>4.24 ± 1.00‡</td>
<td>4.57 ± 1.01</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>3.26 ± 0.82‡</td>
<td>3.77 ± 0.81‡</td>
<td>3.67 ± 0.83§</td>
<td>4.10 ± 0.83</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>82.23 ± 9.82‡</td>
<td>88.34 ± 8.13‡</td>
<td>87.23 ± 8.75†</td>
<td>90.23 ± 6.83</td>
</tr>
<tr>
<td>FEF75%, L/s</td>
<td>65.9 ± 29.3‡</td>
<td>92.1 ± 33.1*</td>
<td>87.3 ± 33.9†</td>
<td>101.5 ± 31.3</td>
</tr>
<tr>
<td>FEF25–75%, L/s</td>
<td>3.40 ± 1.42</td>
<td>4.33 ± 1.29‡</td>
<td>4.16 ± 1.36§</td>
<td>4.85 ± 1.26</td>
</tr>
<tr>
<td>FEF50%, L/s</td>
<td>3.82 ± 1.63‡</td>
<td>4.82 ± 1.46‡</td>
<td>4.64 ± 1.54‡</td>
<td>5.41 ± 1.44</td>
</tr>
<tr>
<td>PEF, L/s</td>
<td>7.60 ± 2.20§</td>
<td>8.54 ± 2.00‡</td>
<td>8.37 ± 2.07‡</td>
<td>9.18 ± 2.00</td>
</tr>
<tr>
<td>% of predicted values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>−0.64 ± 0.10</td>
<td>−0.30 ± 1.28</td>
<td>−0.37 ± 1.22</td>
<td>−0.34 ± 1.12</td>
</tr>
<tr>
<td>FEV1</td>
<td>−1.01 ± 1.23‡</td>
<td>−0.09 ± 1.35</td>
<td>−0.25 ± 1.37*</td>
<td>0.10 ± 1.18</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>−0.57 ± 1.38‡</td>
<td>0.42 ± 1.29*</td>
<td>0.24 ± 1.35‡</td>
<td>0.77 ± 1.12</td>
</tr>
<tr>
<td>FEF75%</td>
<td>−0.49 ± 1.20‡</td>
<td>0.47 ± 1.11</td>
<td>0.29 ± 1.18‡</td>
<td>0.68 ± 0.97</td>
</tr>
<tr>
<td>FEF25–75%</td>
<td>−1.02 ± 1.45‡</td>
<td>−0.01 ± 1.26*</td>
<td>−0.19 ± 1.35‡</td>
<td>0.33 ± 1.10</td>
</tr>
<tr>
<td>Obstructive airways disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed bronchodilation test</td>
<td>18 (62.1)*</td>
<td>39 (29.8)*</td>
<td>57 (35.6)†</td>
<td>30 (18.5)</td>
</tr>
<tr>
<td>Positive bronchodilation test*</td>
<td>4 (13.8)</td>
<td>16 (12.2)*</td>
<td>20 (12.5)*</td>
<td>8 (4.9)</td>
</tr>
<tr>
<td>Self-reported asthma, as diagnosed by a physician</td>
<td>7 (25.9)*</td>
<td>19 (14.6)</td>
<td>26 (16.6)</td>
<td>17 (10.5)</td>
</tr>
<tr>
<td>Current use of inhaled glucocorticoids</td>
<td>2 (6.9)</td>
<td>4 (3.1)</td>
<td>6 (3.8)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>One or more signs of obstructive airways disease</td>
<td>11 (37.9)†</td>
<td>32 (24.4)*</td>
<td>43 (26.9)*</td>
<td>24 (14.8)</td>
</tr>
<tr>
<td>Obstructive airways disease with atopy</td>
<td>5 (17.2)</td>
<td>14 (10.7)</td>
<td>19 (11.9)</td>
<td>17 (10.5)</td>
</tr>
<tr>
<td>Obstructive airways disease and no atopy</td>
<td>6 (20.7)†</td>
<td>18 (13.7)†</td>
<td>24 (15.0)†</td>
<td>7 (4.3)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n (%). The z scores are based on Global Lung Function Initiative standards.36 Values are also presented as percent predicted by Finnish standards27,28,30 to allow comparison with previous studies. VLBW was defined as <1500 g. One or more signs of obstructive airways disease: reversible obstruction in bronchodilator challenge test, asthma previously diagnosed by a physician or inhaled glucocorticoid treatment. No missing values. FEF75%, forced expiratory flow at 75% of FVC; FEF25–75%, forced expiratory flow at 25% to 75% of FVC; FEF peak expiratory flow. *P value for the difference with term <.05. †P value for the difference with term <.001.

As previously reported,72 72 VLBW subjects and 93 control subjects had atopic predisposition as defined by skin-prick positivity to at least 1 of the tested common allergens (crude odds ratio: 0.61 [95% CI: 0.39 to 0.94]). When comparisons of respiratory function were adjusted for the presence of signs suggesting obstructive airways disease and atopic predisposition, the results remained similar (model 4, Table 3).

### DISCUSSION

Our main finding was that young adults born at VLBW had, on average, reduced airflow compared with their peers born at term. The finding was stronger in those with a history of BPD but was also present in the majority of VLBW adults with no such...
history. The difference was not explained by their smaller body size, family socioeconomic status, smoking, or maternal smoking during pregnancy. Another key finding was that there were few additional risk factors other than BPD and maternal smoking during pregnancy.

Other than the study in 26 VLBW survivor adolescents by Northway et al, only a few studies have assessed spirometry in adults born very preterm. No reduction in airflow was found among 35 VLBW subjects and 48 control subjects in a study in London, England. By contrast, a study comparing 42 VLBW young adults from the Dutch POPS (Project on Preterm and Small for Gestational Age Infants) cohort with 48 control subjects and another study in Trondheim, Norway, with 37 VLBW subjects and 63 control participants, found a lower percent predicted FEV₁ of 14% and 13%, respectively. The reason for the difference between these 3 studies is not clear. All had a similar proportion of VLBW subjects with a history of BPD (~20%); this size did not allow for statistically meaningful comparisons regarding BPD. Another study included 83 subjects (63 with BPD), born at a birth weight <1000 g or before 28 weeks of gestation, who exhibited reducing airflow with increasing severity of the early neonatal respiratory history.

The largest studies published before the present study include 1 in Victoria, Australia, with 147 VLBW survivors (33 with BPD) and 37 normal birth weight control subjects, studied at age 19 years and a partly overlapping group reassessed at 26 years. Another large study was published from Belfast, Northern Ireland, with 96 small preterm survivors (56 with BPD) and 55 control subjects. Consistent with our findings and those previously reported in children, these studies showed reduced airflow also in VLBW adults without BPD, although this outcome was strongest in the BPD-VLBW groups. Our results extend these findings by demonstrating that the effects of VLBW birth per se and BPD seem to override the effects of most other clinical conditions, including intrauterine growth restriction, growth restriction during postnatal care, and neonatal RDS, which had very little additional value in predicting lung function in young adult life.

We also found that maternal smoking during pregnancy predicted reduced airflow of the offspring.
finding was strongest among VLBW subjects with a history of BPD. No data were available to distinguish the effects of maternal smoking from exposure to parental smoking after birth. Regardless of whether the critical smoking exposure is prenatal or postnatal, the finding reinforces previous suggestions of the joint harmful effects of smoking exposure and lung injury.35 Paradoxically, asthma in childhood or early adult life36 up to 31 years of age37 is predicted by high birth weight. This outcome is more likely to reflect atopic asthma, which is more common in children and young adults.38 Low birth weight, by contrast, is associated with late adulthood outcomes such as death from chronic obstructive airways disease39 and higher rates of asthma medication use40 and premorbid outcomes, including impaired airflow.41 These birth weight studies are paralleled by studies linking preterm birth with manifest disease, including hospital-treated obstructive airways disease among older adult women42 and “asthma” in children and young adults.43–45 The use of the term “asthma” for obstructive airways disease in those born preterm has been criticized, and the effect of standard asthma treatment in these subjects is uncertain.46 Importantly, most of these studies included all infants born before 37 weeks of gestation, suggesting that our findings of obstructed airflow in the VLBW group (comprising the smallest 0.9%–1.5% of all newborns) are relevant to all people born preterm.47 Together with smoking, lung function in early adulthood is 1 of the strongest predictors of chronic obstructive pulmonary disease.5 It also predicts cardiovascular mortality.48 To prevent chronic obstructive pulmonary disease, abstinence from smoking is obviously important. Moreover, adults born at VLBW undertake less physical activity49 and have a less healthy diet50 than their peers born at term. Promotion of physical activity and a healthy diet have other benefits, including prevention of cardiovascular disease.

A major strength of the present study was its sufficient size and detailed perinatal and neonatal data, which allowed us to assess the effects of potential confounders and clinical conditions that underlie or follow preterm birth at VLBW. In terms of its limitations, our study may not be representative of all VLBW infants in the original cohort. However, a previous detailed nonparticipant analysis19 raised little concern over participation bias. To assess reversible airflow obstruction, we performed bronchodilator testing according to Finnish clinical guidelines, which warrant testing only in subjects whose baseline spirometry indicates airflow obstruction. These selection criteria may miss some subjects who would have experienced improved airflow after bronchodilator use, and the frequency of reversible airflow obstruction thus represents a minimum estimate. We did not have data on lung function in childhood, which precludes discussion on whether alterations in lung function tend to improve, deteriorate, or remain similar over time.2,14,33,51–53 Our subjects represent treatment during a presurfactant period, and only a few received antenatal or postnatal glucocorticoids. The study is thus directly relevant to VLBW survivors born in the 1970s or 1980s (who are now in their 30s and 40s) who total ∼500 000 people in the United States only.54,55

CONCLUSIONS

Young adults born at VLBW have reduced airflow compared with their peers born at term. The reduction is stronger among those with a history of BPD but is also present among those without. Of the many potential prenatal and postnatal risk factors assessed, only maternal smoking in pregnancy predicted reduced airflow. It may be particularly harmful for VLBW subjects who develop BPD. Our results offer a strong example of programming of respiratory function early in life. They also underscore the importance of following up the VLBW cohorts to assess whether the reduced airflow translates into increased rates of chronic obstructive pulmonary disease later in life.

ABBREVIATIONS

aOR: adjusted odds ratio
BPD: bronchopulmonary dysplasia
CI: confidence interval
FEF50%: forced expiratory flow when 50% of forced vital capacity has been exhaled
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
RDS: respiratory distress syndrome
VLBW: very low birth weight

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.
FUNDING: Supported by grants from the Academy of Finland, the Emil Aaltonen Foundation, the Finnish Foundation for Pediatrics Research, the Finnish Special Governmental Subsidiary for Health Sciences (EVO), the Jalmari and Rauha Ahokas Foundation, the Juho Vainio Foundation, Medical Societies of Finland (Duodecim and Finnsa Lékarefalskapet), the Novo Nordisk Foundation, the Paiviikki and Sakari Sohlberg Foundation, the Signe and Ane Gyllenberg Foundation, the Sigrid Jusélius Foundation, and the Yrjö Jahnsson Foundation.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.


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Pediatrics originally published online September 7, 2015;

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Pediatrics originally published online September 7, 2015;

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