

## REVIEW ARTICLE

Jeffrey M. Drazen, Editor, M.D.

# Early-Life Origins of Chronic Obstructive Pulmonary Disease

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**I**N THE UNITED STATES, MORE PEOPLE DIE FROM CHRONIC OBSTRUCTIVE pulmonary disease (COPD) than from any other condition except cancer and cardiovascular illnesses.<sup>1</sup> There is currently no curative therapy for COPD, and treatment is mostly palliative. Given the degree of airway or parenchymal damage (or both) in most advanced cases of the disease, a strategy aimed at reversing the condition once it is established is fraught with challenging obstacles. Thus, the approach with the highest likelihood of success is one that addresses the predisposing factors of this condition. By far the most common cause of COPD is smoking (and exposure to biomass smoke in poor countries<sup>2</sup>), and smoking cessation continues to be the potentially most successful prevention strategy.

Until recently, the prevailing idea was that during development (i.e., from birth to approximately 25 years of age), all people — those destined to have no lung disease and those destined to have COPD — reached the same plateau for lung function as measured by the forced expiratory volume in 1 second (FEV<sub>1</sub>). What determined whether COPD developed was the rate of subsequent decline in the FEV<sub>1</sub> level. Was this rate at the physiologic level (approximately 25 ml per year) and thus not associated with lung disease, or was it much faster owing to the continuous and progressive noxious effects of cigarette or biomass smoke on small airways and surrounding parenchyma,<sup>3</sup> leading to COPD (Fig. 1)? This “classic” form of COPD is indeed a very frequent clinical presentation of the disease<sup>4</sup>; it is associated with chronic bronchitis, emphysema, or a combination thereof and is characterized by neutrophilic and CD8-mediated inflammation. The complex biologic mechanisms of this form of COPD have been studied extensively.<sup>5</sup>

Emerging evidence, however, has radically challenged the concept of a single natural history for COPD, indicating that the spectrum of patients presenting with chronic respiratory symptoms and irreversible airway obstruction (as assessed by an abnormally low FEV<sub>1</sub>) is much more heterogeneous than previously thought. Results from longitudinal cohort studies have shown that in a considerable proportion of patients with COPD the decline in the FEV<sub>1</sub> was not steeper than that in healthy adults.<sup>6</sup> It has also been shown that some people with COPD who do not show excessive lung-function decline reach a lower FEV<sub>1</sub> level early in adult life than those with future rapid decline and normal populations<sup>7</sup> (Fig. 1). These findings thus identify an entirely different pathway leading to the diagnosis of COPD from the rapid-decline form, one in which smoking can certainly play a role, especially in the clinical expression of the disease, but in which the central derangement is already present early in adult life. What emerges is a fundamentally new concept of COPD, in which the factors that determine the maximal (or “plateau”) FEV<sub>1</sub> level attained during the third decade of life become major elements in the pathogenesis of the disease.

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In this review, three major questions are addressed. First, what causes certain persons to enter into adult life with a diminished FEV<sub>1</sub> level? Second, which diverse biologic mechanisms are involved in determining this lower plateau? Third, could early-life events influence the rate of FEV<sub>1</sub> decline that is observed in classic COPD?

#### THE ROLE OF GENETICS IN LUNG FUNCTION, STARTING AT BIRTH

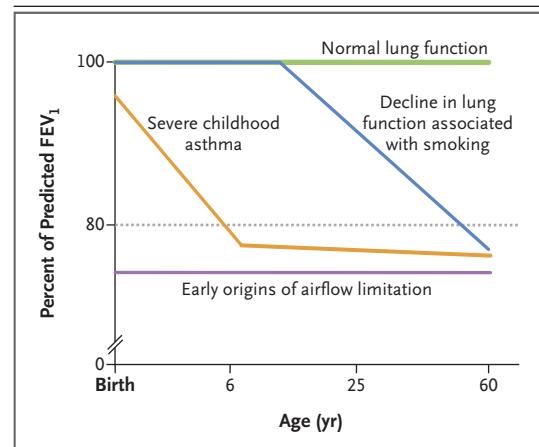
It is now well established that trajectories of lung function during childhood are already at least partially established at birth. Levels of maximal expiratory flow that are measured shortly after birth with the use of a chest-compression technique are significantly correlated with the ratio of FEV<sub>1</sub> to forced vital capacity (FVC) into adult life.<sup>8</sup> Infants in the lowest quartile of maximal expiratory flow at birth as measured by this technique had FEV<sub>1</sub>:FVC ratios in early adult life that were significantly lower than those of infants in the highest quartile (0.82 vs. 0.88, *P*=0.001 for trend) (Fig. 2). These results thus point to genetic and prenatal influences as major contributing factors in the level reached at the plateau of lung function.

Lung function, as measured by the FEV<sub>1</sub> or FVC, has a large heritable component. Studies that use pedigree data and those that are based on single-nucleotide polymorphism (SNP) data have reached similar conclusions: genetic factors explain 50% of the phenotypic variance for the FEV<sub>1</sub> and up to two thirds of that for the FEV<sub>1</sub>:FVC ratio.<sup>9</sup> Although there are several genomewide association studies assessing the role of SNPs as determinants of FEV<sub>1</sub>, most of such studies enrolled adults and included smokers, thus making it difficult to identify bona fide genetic determinants of baseline FEV<sub>1</sub>, as opposed to genes influencing the decline in the FEV<sub>1</sub> associated with smoking.

Nevertheless, the largest published genomewide association study, involving almost 100,000 white participants, suggested that 26 loci and more than 100 variants could collectively explain 7.5% of the additive polygenic variance for the FEV<sub>1</sub>:FVC ratio and 3.4% of the variance for the FEV<sub>1</sub> values, independent of smoking.<sup>10</sup> Some of the SNPs that were identified were present in genes with potentially plausible roles in lung

growth and development, including genes involved in the structure of cilia, elastin-associated microfibrils, and retinoic acid receptor beta, an important factor in lung growth.<sup>11</sup>

The only study that spanned the whole age spectrum from infancy to adulthood showed an association between lung function and a variant in the gene encoding vascular endothelial growth factor, also a critical growth factor for airway development,<sup>12</sup> which was not captured in the larger genomewide association study.<sup>13</sup> Of interest was the discovery that there are genetic variants associated with the FEV<sub>1</sub> that are also associated with myocardial infarction, cancer, and height. These and other studies that combined



**Figure 1. Three Major Lung-Function Pathways That Lead to Stage 2 Chronic Obstructive Pulmonary Disease (COPD).**

Stage 2 COPD is defined as a forced expiratory volume in 1 second (FEV<sub>1</sub>) that is less than 80% of the predicted value plus a ratio of FEV<sub>1</sub> to forced vital capacity (FVC) of less than 0.70. The green line represents a normal lung-function trajectory. The blue line (classic COPD) represents a decline in lung function associated with cigarette smoking or chronic exposure to biomass smoke; illnesses due to respiratory syncytial virus and parental smoking may increase susceptibility to these exposures. The orange line represents the three-phase lung-function trajectory associated with severe childhood asthma. Lung function is lower than normal at birth, shows a major decline during the preschool years, and may continue to decline at a slower pace thereafter. Lower respiratory tract illnesses (especially pneumonia before 3 years of age) and air pollution may similarly alter lung-function growth. The purple line represents the early origins of airflow limitation. Genetic and prenatal factors influence lung function at birth, and deficits persist into adult life.

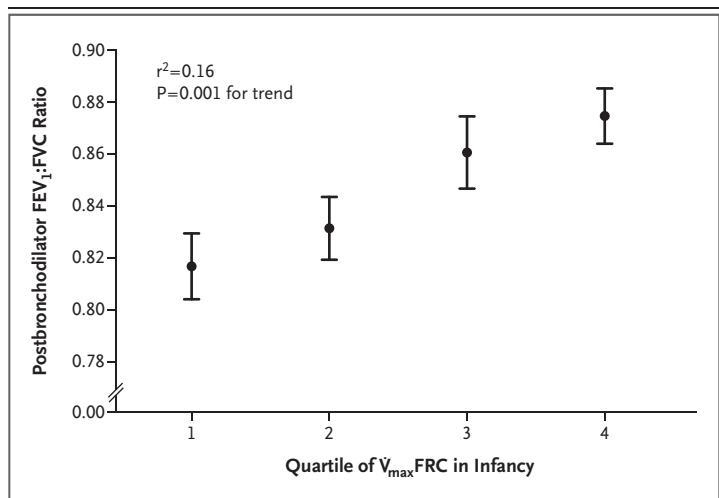
genetic with gene-expression analyses<sup>14</sup> suggest that the FEV<sub>1</sub> level is controlled by a very large number of biologic pathways, most of which remain to be identified, with genetic variation in each pathway having small effects on phenotypic expression.

#### PRENATAL INFLUENCES

Exposure to noxious stimuli in utero may have long-term effects on lung health and influence the maximally attained FEV<sub>1</sub> level. The most widely studied among such exposures is maternal smoking, which has been consistently found to be associated with small but significant reductions of approximately 1.5% in the FEV<sub>1</sub> and 5% in the maximal expiratory flow in older children and young adults.<sup>15</sup> In animal models, exposure of the fetus to nicotine showed similar effects to those observed in fetuses whose mothers were exposed to cigarette smoke.<sup>16,17</sup> Specifically, prenatal nicotine exposure led to a decreased maximal expiratory flow by stimulating epithelial-cell growth and lung branching, resulting in longer and more torturous airways, which led to greater resistance to airflow.<sup>18</sup> If most of the effects of maternal smoking during pregnancy are caused by nicotine, e-cigarettes are likely to be as harmful to the fetal lung as standard cigarettes.

Approximately 10% of all births in the United States occur prematurely (i.e., before 37 weeks of gestation), and preterm birth has been shown to have profound effects on long-term lung function. This is especially true for the 0.3% of all newborns who are born very prematurely (before 27 weeks of gestation)<sup>19</sup> and who require oxygen supplementation for more than 28 days after birth, the standard definition of bronchopulmonary dysplasia. A recent meta-analysis<sup>20</sup> of studies involving children and young adults born prematurely concluded that major deficits in the FEV<sub>1</sub> level among those who had bronchopulmonary dysplasia occurred in 16.2% of those requiring oxygen for more than 28 days and in 18.9% of those requiring oxygen for more than 36 weeks. These results identify bronchopulmonary dysplasia as a major risk factor for major deficits in maximally attained FEV<sub>1</sub> in early adult life.

The results of a recent clinical trial strongly suggest that a potentially critical biologic mech-



**Figure 2. Relationship between the Quartile of Lung Function in Early Life and the FEV<sub>1</sub>:FVC Ratio at 26 to 32 Years of Age.**

Maximal flows at functional residual capacity ( $V_{\max}FRC$ ) were measured shortly after birth in 67 infants and were adjusted for infant length and sex; spirometry was performed in the same participants in adult life. An estimated 16% of the variance in the FEV<sub>1</sub>:FVC ratio was explained by the level of lung function in infancy. I bars indicate standard errors. Data are from the Tucson Children's Respiratory Study (unpublished data).

anism for persistent airway obstruction in bronchopulmonary dysplasia is airway inflammation resulting from mechanical ventilation and oxygen therapy. Very-low-birth-weight children with severe respiratory distress syndrome who were given budesonide, an inhaled glucocorticoid, together with surfactant intratracheally had a significantly lower incidence of bronchopulmonary dysplasia or death than those receiving surfactant only (55 of 131 children [42.0%] vs. 89 of 134 [66.4%],  $P < 0.001$ ). They also had a lower concentration of inflammatory mediators in tracheal fluids.<sup>21</sup>

Although the most severe consequences are observed in newborns with bronchopulmonary dysplasia, premature infants without the disorder also have FEV<sub>1</sub> levels later in life that are 7.2% lower than those of children born at term.<sup>20</sup> Small deficits in adult FEV<sub>1</sub> have also been reported in children with intrauterine growth retardation.<sup>22</sup>

In chronically undernourished populations, maternal micronutrient deficiency may also affect maximally attained FEV<sub>1</sub> and FVC in the offspring. Nepalese children of women whose diet had been supplemented with vitamin A before, during, and after pregnancy had higher levels of

FEV<sub>1</sub> and FVC at 9 to 13 years of age than those whose mothers received placebo.<sup>23</sup>

#### RESPIRATORY ILLNESSES IN EARLY LIFE

Several longitudinal studies have shown that children who have lower respiratory tract illnesses in early life are at increased risk for subsequent chronic respiratory symptoms and FEV<sub>1</sub> deficits, which often persist into adult life.<sup>24</sup> The largest deficits have been observed in adults who had radiologically ascertained pneumonia before 3 years of age, who had an FEV<sub>1</sub>:FVC ratio that was significantly lower than those with no early-life respiratory illnesses (0.76 vs. 0.80,  $P < 0.001$ ), whereas those with lower respiratory tract illnesses but no pneumonia had less severe impairment in the FEV<sub>1</sub>:FVC ratio.<sup>25</sup> Both in developed<sup>26,27</sup> and developing<sup>28</sup> countries, the most frequent agents currently associated with pneumonia in early life are viruses, especially respiratory syncytial virus.

From the available data, it is impossible to determine whether the association between pneumonia and impaired lung function is due to airway damage caused by the etiologic agent triggering the episode of pneumonia or to preexisting deficits in lung function in young children in whom pneumonia develops. However, some young children with pneumonia that is caused by adenovirus serotypes 3, 7, and 21 have severe long-term sequelae, including bronchiolitis obliterans and bronchiectasis,<sup>29</sup> and others have moderate subsequent deficits in the FEV<sub>1</sub> level.<sup>30</sup> It is thus plausible to surmise that the deficits in the FEV<sub>1</sub> observed in adults with a history of early childhood pneumonia may be due in part to abnormalities present before the episode occurred but also, as has been shown for adenoviral pneumonia, to airway damage caused by the episode itself.

#### AIR POLLUTION

There is now convincing evidence that exposure to airborne contaminants is associated with reduced growth in lung function during adolescence and lower maximally attained FEV<sub>1</sub> levels. In a comprehensive study in the Los Angeles area,<sup>31</sup> mean deficits in the growth of FEV<sub>1</sub> between 10 and 18 years of age for participants living in the most polluted communities, as

compared with those living in the least polluted communities, within the area were 105.8 ml for acid vapor ( $P = 0.004$ ), 101.4 ml for nitrogen dioxide ( $P = 0.005$ ), 87.9 ml for elemental carbon ( $P = 0.007$ ), and 79.7 ml for particulate matter with an aerodynamic diameter of less than 2.5  $\mu\text{m}$  (PM<sub>2.5</sub>) ( $P = 0.04$ ). As a result, the percentage of 18-year-old participants with an attained FEV<sub>1</sub> below 80% of the predicted value was much higher in the most polluted zones than in the least polluted zones; for PM<sub>2.5</sub>, for example, these values were 7.9% and 1.6%, respectively ( $P = 0.002$ ). Maternal exposure to pollutants during pregnancy may also affect the FEV<sub>1</sub> level in the offspring.<sup>32</sup>

It is notable that decreases in PM<sub>2.5</sub> and nitrogen dioxide contamination in California were associated with significant improvements in the FEV<sub>1</sub> in a 13-year follow-up.<sup>33</sup> As a result, the percentage of children with an FEV<sub>1</sub> below 80% of the predicted value at 15 years of age declined significantly, from 7.9% to 3.6%, as the air quality improved ( $P = 0.001$ ).

#### CHILDHOOD ASTHMA

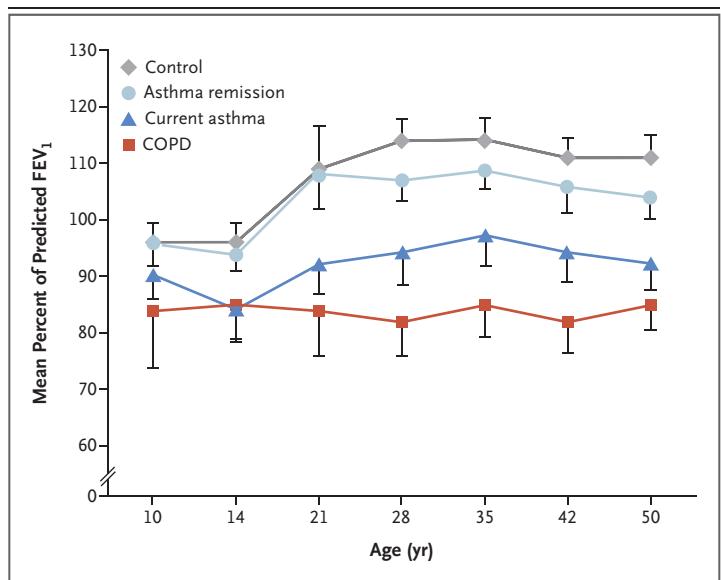
Children with persistent asthma have been consistently shown to reach a lower FEV<sub>1</sub> plateau during the third decade of life than children without asthma.<sup>34</sup> Only a fraction of children with asthma go on to have fixed airflow limitation, but among those who do, three phases have been described<sup>35</sup> (Fig. 1). First, children with persistent asthma have a slightly but significantly lower maximal expiratory flow and respiratory-system compliance assessed shortly after birth than do those without asthma,<sup>36</sup> which suggests that factors impairing lung growth in utero confer a predisposition for the subsequent development of asthma. Second, longitudinal studies have shown that by the time they reach the early school years, children with subsequent persistent asthma already have a large percentage of the deficits in FEV<sub>1</sub> that they will show during the plateau phase of lung function.<sup>37</sup> Approximately 40% of the deficits in the maximal expiratory flow that were observed at 6 to 7 years of age in children with asthma were present at birth, whereas 60% of the deficits developed during the preschool years.<sup>38</sup> Taken together, these findings identify the period between birth and 6 years of age as critical for the development of airflow

limitation in children with persistent asthma. Third, further declines in FEV<sub>1</sub> occur during the school years<sup>39</sup> and in adult life<sup>40</sup> as part of the natural history of asthma, but these declines seem to be a much smaller fraction of the total impairment than those observed in early life.

As a result of these deficits in FEV<sub>1</sub> growth associated with childhood asthma, by the third decade of life approximately 17% of all patients with mild or moderate asthma reach stage 1 COPD, as established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (i.e., postbronchodilator FEV<sub>1</sub>:FVC ratio <0.70 and FEV<sub>1</sub> ≥80% of the predicted value), whereas 5% reach stage 2 COPD (<0.70 and <80%, respectively).<sup>41</sup> Moreover, among a group of patients in whom severe asthma had been diagnosed by the age of 10 years, 44% had stage 1 COPD at 50 years of age,<sup>42</sup> a rate that was independent of smoking. Most of the reduction in lung function that was observed in patients with COPD at 50 years of age and a history of severe childhood asthma was already established in the childhood years (Fig. 3).

The mechanisms by which asthma causes nonreversible airflow limitation, especially during early childhood, are not well understood. Airway biopsy samples obtained from infants with recurrent wheezing show no evidence of airway remodeling, as assessed by the presence of a thickened reticular basement membrane in medium-size bronchi,<sup>43</sup> which is characteristic of school-age children with persistent asthma. However, incipient thickening can be observed in preschool children with wheezing<sup>44</sup> at approximately the age at which the largest deficits in airway growth are observed in children with subsequent persistent asthma.

For years, airway remodeling was attributed to chronic airway inflammation, but randomized trials did not show a better prognosis in children receiving long-term treatment with daily inhaled glucocorticoids than in those treated with placebo.<sup>45,46</sup> Sputum cells obtained from children with acute exacerbations of asthma and evidence of persistent airway obstruction have a lower expression of genes encoding proteins involved in the regulation of interferon type I responses and of genes involved in type 1 helper T cell (Th1)-like and cytotoxic responses than do those obtained from children with asthma and no evidence of persistent airway obstruction.<sup>47</sup> In



**Figure 3. Percent of Predicted FEV<sub>1</sub> in Participants Followed between the Ages of 10 and 50 in the Melbourne Asthma Study.**

Participants were classified at 50 years of age as follows: no asthma (control), current asthma, childhood asthma with remission in adult life, and stage 1 COPD, defined as an FEV<sub>1</sub> of 80% or more of the predicted value and an FEV<sub>1</sub>:FVC ratio of less than 0.70. Among participants with COPD, airway obstruction that justified a definition of COPD was already present at 10 years of age. Adapted with permission from Tai et al.<sup>42</sup>

vitro studies of epithelial cells from patients with asthma have shown abnormal airway repair after injury.<sup>48</sup> It is reasonable to surmise that these alterations may induce remodeling processes that lead to narrowed airways.

Bronchial hyperresponsiveness, which can be present as early as 6 years of age, is a hallmark of childhood asthma that persists into adult life,<sup>49</sup> and its corollary, recurrent airway smooth-muscle contraction, may increase compressive mechanical stress and activate airway repair and remodeling mechanisms independent of airway inflammation.<sup>50</sup> It is tempting to speculate that such processes may have stronger effects on airway structure during early childhood, a period of normally active lung and airway remodeling.

#### ACTIVE SMOKING DURING ADOLESCENCE

Active smoking during adolescence is associated with significant reductions in the FEV<sub>1</sub> level and the FEV<sub>1</sub>:FVC ratio,<sup>51</sup> decreases that could have major effects on maximally attained lung func-

tion. Fortunately, a major public health success in the United States has been the dramatic reduction in the prevalence of active smoking among adolescents: whereas 18% of 10th graders reported regular daily smoking in 1996, only 3% did in 2014.<sup>52</sup> These trends coincided with major restrictions in tobacco advertisement and the allocation of funds from legal settlements between the federal government and tobacco companies to antitobacco campaigns.

Unfortunately, consumption of e-cigarettes has become increasingly more common among adolescents. The percentage who reported use of e-cigarettes in the past 30 days increased from 1.5% in 2010 to 17.2% in 2014.<sup>53</sup> This is a matter of great concern, because adolescents who try e-cigarettes are more likely to start smoking than those who do not.<sup>52</sup> If these trends persist, some of the gains made in the past 20 years in preventing adolescent smoking could be lost.

#### EARLY-LIFE EVENTS AND THE RATE OF LUNG-FUNCTION DECLINE

The above discussion focuses on the potential for early-life events to influence the maximally attained FEV<sub>1</sub> during the third decade of life. There is increasing evidence from longitudinal studies, however, that childhood events and exposures can accelerate the rate of decline in the FEV<sub>1</sub> level and induce early expression of chronic respiratory symptoms in both smokers and nonsmokers. Prenatal and postnatal parental smoking increases susceptibility to the ill effects of active smoking in adult life, with smokers who were exposed to parental smoking having greater deficits in FEV<sub>1</sub> than those whose parents did not smoke.<sup>54</sup> Smokers who had lower respiratory illnesses due to respiratory syncytial virus before 3 years of age are more likely to receive a diagnosis of asthma in the third decade of life than smokers without such an early-life history.<sup>55</sup> Women who as young girls lived through the so-called Dutch famine, a circumscribed episode of severe human starvation that occurred between October 1944 and May 1945 in the Netherlands, were more likely to be hospitalized for COPD before 60 years of age than their age peers who were not exposed to famine.<sup>56</sup> These

effects were particularly noticeable among active smokers, suggesting that postnatal malnutrition may increase susceptibility to the deleterious effects of smoking.

Evidence from less reliable retrospective studies also suggests that childhood adversity may increase the risk of COPD. As compared with smokers without a history of pneumonia, smokers who recalled having had pneumonia during childhood were 40% more likely to have COPD, and they had an FEV<sub>1</sub>:FVC ratio that was significantly lower (0.63 vs. 0.67,  $P < 0.001$ ).<sup>57</sup> In a European study, participants who recalled having “childhood disadvantage factors” (i.e., parental or childhood asthma, childhood respiratory infections, or maternal smoking) showed a steeper FEV<sub>1</sub> decline in adult life than those without such factors.<sup>58</sup>

#### CONCLUSIONS

There has been a major change in our understanding of the natural history and risk factors for COPD, a frequent cause of illness and death. Although smoking is still a major culprit, genetic, environmental, and developmental factors that are associated with diverse biologic mechanisms and that exert their effects during the growing years can both diminish the maximally attained FEV<sub>1</sub> and accelerate FEV<sub>1</sub> decline in adult life, thus increasing the risk of COPD. Prevention of prematurity, and especially of bronchopulmonary dysplasia, is a major public health priority that is made more urgent by its potential role in the pathogenesis of COPD. Promising advances in the development of vaccines against respiratory syncytial virus<sup>59</sup> and of prevention strategies for childhood asthma<sup>60</sup> could markedly decrease the risk of COPD. Efforts to decrease exposure to air contaminants during pregnancy and childhood and to preserve and expand the striking reduction in adolescent smoking during the past 20 years could also decrease the incidence of COPD.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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