the study period. Nonetheless, taken together, these two studies provide compelling evidence that CT scan scores are good predictors of future lung dysfunction. It would have been interesting to know if higher baseline CT scores were predictive of an accelerated rate of FEV_1 decline from baseline to follow-up spirometry using longitudinal modeling; however, this study may not have been powered to evaluate this highly variable outcome. It is important to realize that further studies will be needed to determine whether or not specific findings in chest radiographs or CT scans will be able to directly predict outcomes in a given patient.

Overall this study is novel in its confirmation for the CF community that CT scans and plain chest radiographs have a role in predicting future lung disease and may be useful in identifying children at risk for worse pulmonary outcomes. The optimal timing of scored radiography to predict outcomes is unknown. The average age at baseline chest radiograph and CT scan was 11.5 years in Sanders' observation, and generally the radiography scores, both on CT scan and on chest radiograph, showed mild structural lung disease. Earlier imaging might allow earlier intervention for children at risk (2), but could be too early to pick up the magnitude of structural change seen in this study. More research is needed and the Cystic Fibrosis Foundation's registry (1) could be an important tool for correlating radiology with future lung dysfunction in a large cohort. CFF guidelines currently recommend obtaining yearly chest radiographs (14, 15). However, these radiographs need to be scored by trained radiologists using standardized scoring systems (5, 13) to be of greatest use in epidemiologic analyses. If standardized scores were reported with yearly CF patient data to the registry in a more consistent manner, then comprehensive longitudinal analyses could be accomplished.

Chest CT scans may have a role the routine monitoring of children with CF; however, radiation exposure must be minimized, particularly if repeated scans are to be obtained over the life span. More importantly, it appears that plain chest radiographs with rigorously applied scoring systems may be as effective in predicting lung disease progression and would accomplish this goal with less radiation exposure and at lower cost.

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Psychological Stress: A Social Pollutant That May Enhance Environmental Risk

Evidence suggests an etiologic role for both physical toxins (1) and social determinants (2, 3) in the evolution and trajectory of children's lung function growth and development. Traffic-related air pollution is a global public health problem (4), and children may be most vulnerable (5). The adverse effects of air pollution on respiratory development in children have been extensively documented (6). In parallel, a growing body of literature suggests that psychological factors influence the programming of neuroendocrine, autonomic, and immune inflammatory processes implicated in respiratory development, suggesting they too play a role in lung development, although studies in humans remain scarce (2, 7).

Whereas traditional research has focused on the main effects of social and physical environmental factors, evolving research underscores the importance of interactions among these factors (8). Although a number of theoretical models have been put forth to explain how social conditions "get into the body" to

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impact health, the psychosocial stress model has been increasingly adopted. Psychological stress is conceptualized as a social pollutant that, when "breathed" into the body, disrupts biological systems overlapping with those altered by physical pollutants and toxicants (e.g., immune and nonimmune inflammatory processes). It is thus plausible that biologically compromised systems related to earlier life stress may be more vulnerable to subsequent environmental toxins and vice versa.

In general, stress may result in long-lasting physiological effects that influence disease risk (9). Under stress, physiological systems may operate at higher or lower levels than in normal homeostatic conditions. Disturbed regulation of stress systems (e.g., hypothalamic-pituitary-adrenal [HPA] axis, autonomic nervous system) may modulate immune function leading to increased airway inflammation, remodeling, and altered airway reactivity. Air pollution exposures have also been linked to disruption of neuroimmune responses (10) and autonomic reactivity, even in young healthy subjects (11). Moreover, air pollutants may generate oxidative species activating pathways similar to psychological stressors (9, 12). Consequent aberrant or excessive proinflammatory immune responses as well as oxidant-induced changes and sympathovagal imbalance, are determinants of lung structure–function changes during development.

Data presented by Islam and coworkers (13) in this issue of the *Journal* (pp. 822) builds on growing literature demonstrating interactive effects between psychosocial stress and ambient air pollution on respiratory morbidity (14–16). These data are first to suggest a synergistic relationship between stress and subsequent ambient air pollution effects on childhood lung function (13).

However, when interpreting the findings it is important to understand the stress measure being used. Stress has been conceptualized in a number of different ways with noted advantages and disadvantages as recently summarized (17). Islam and colleagues (13) used the Perceived Stress Scale (PSS), a brief self-report questionnaire that measures one's subjective perception of how stressful they find their life to be over the preceding month. This conceptualization taps into the individual's appraisal of whether the events they encounter are threatening, taxing, or potentially overwhelming to their existing coping resources. The measure may be tapping into the extent of the environmental demands the child's caregiver was under at the time the questionnaire was administered, stable individual differences in how caregivers in the study evaluate events in the world, or their ability to cope for example. The authors used a one-time PSS measure at enrollment. This then was used as an index of chronic stress to predict lung function in relation to air pollution exposures assessed approximately 6 years later when children were on average 11.2 years of age. This assumes that perceived stress is stable over time in these caregivers, an assumption that may not hold true, particularly if the environment is not stable (i.e., the stressors and life events they experience are likely dynamic) or their approach to stress appraisal changes depending on the challenges being faced. Thus a single assessment using the PSS may reflect more contemporaneous stress rather than chronic, ongoing experiences. Studies that incorporate repeated assessments of stress appraisal over time or more comprehensive measurements of life events and chronic stressors that these families may be experiencing over time will address this more definitively. Stressors may be experienced across a number of life domains and social structures (e.g., household, work, community), and knowing more about the sources of stress leading to adverse effects will better inform intervention and prevention strategies (18). As the authors point out, more direct assessment of stress experienced by the children when age appropriate, rather than their caregivers, will be important. Additional prospective studies examining stress effects on lung function and enhanced environmental vulnerability are needed. Incorporation of biomarkers to assess underlying mechanisms that may be operating in the additive and/or synergistic effects of stress and air pollution on lung function is also needed.

Another area of particular interest in children's environmental health is the search for mechanisms responsible for disparities across economic and ethnic groups. There are well-documented negative correlations between lung function measures and socioeconomic status (SES) (3). Lower SES during childhood has been associated with lower maximally attained lung function in young adulthood, as well as a more accelerated lung function decline (19). Populations living in more impoverished urban neighborhoods are disproportionately exposed to air pollutants and may also be more likely to experience stress (20, 21). The authors noted a number of social and economic correlates of the PSS scores in this cohort (e.g., caregiver education level, household income, health insurance status, and ethnicity-related factors, such as language). Analysis suggested that the interaction between baseline PSS in these caregivers and ambient pollution measures on lung function were not explained by insurance status. It was not clear whether similar adjustments were made for other SES indicators to determine residual confounding by SES. One can argue that psychological stress should be considered as a mediator of the relationships among SES, air pollution exposure, and lung function outcomes, and thus should not be controlled for at all. Rather, alternative statistical approaches (e.g., structural equation modeling) could be implemented to formally test mediation. Smoking can also be considered as a mediator of stress-health effects. Thus, another question that arises is whether the enhancing effect due to stress reported here may, at least in part, be due to environmental tobacco smoke exposure related to caregiver stress in the home. Such pathways should be explored more directly in future research.

Because social stress and other environmental toxins (e.g., air pollutants) are often concurrent and may influence common physiological pathways, understanding the potential synergistic effects and how they may be operating across sociodemographic factors promises to more completely inform respiratory disease risk in children. We need to better understand how the physical and psychological demands of living in a disadvantaged environment may potentiate an individual's susceptibility to environmental exposures across these domains. Conducting this work in childhood and adolescence is critical, given that these early effects may persist into adult life, magnifying the public health impact.

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Semi–Long-Term Mortality Effects of Ozone

Ozone's short-term effects on (reversible) pulmonary function decrements have been well established through controlled laboratory human studies, and they generally support the results from observational panel studies of ozone effects on lung functions (1). There have been many time-series (i.e., short-term) mortality studies in the past decade that reported associations between ambient ozone and mortality. These mortality effects results emerged often as a "by-product" of research whose main focus was the mortality effects of ambient particulate matter (PM), as the researchers attempted to evaluate confounding by other gaseous pollutants. While meta-analyses (2–4) and an international multi-city analysis (5) found generally consistent short-term mortality risk estimates, these time-series studies also presented some unanswered questions, including the long-term implications of the short-tem mortality effects (i.e., the time scale of life-shortening). Time-series study design does not allow examination of the associations longer than a few weeks (and researchers generally do not look for lagged associations beyond a few days) because the model ascribes such temporal variations to unmeasured confounding embedded in seasonal and temporal trends. Most of the cohort studies of long-term mortality effects of air pollution to date also focused on PM. Only one study by Jerrett and coworkers specifically examined the long-term mortality effects of ozone using the American Cancer Society (ACS) cohort (6). However, the result from the analysis by Jerrett and colleagues was nuanced in that the observed association between ozone and cardiovascular mortality became null once the model adjusted for fine particles ($PM_{2.5}$), while the association between ozone and respiratory mortality was robust to the adjustment for $PM_{2.5}$ or using alternative models (6).

The study by Zanobetti and Schwartz in this issue of the *Journal* (pp. 836) adds one more piece of information to the puzzle of ozone mortality effects. They report associations between "long-term" ozone exposures and survival of Medicare participants in 105 major U.S. cities who have been hospitalized during the study years 1985–2006 for four underlying causes that were hypothesized to be major risk factors for ozone mortality effects: chronic obstructive pulmonary disease, diabetes, congestive heart failure, and myocardial infarction. The analysis finds significant associations between annual summer-average levels of ozone and deaths in the corresponding years for all of these four groups when combined across the cities, with estimated hazard ratios ranging from 1.06 to 1.08 per 5 ppb increase in summer average of daily maximum 8-hour ozone.

The study design used by Zanobetti and Schwartz is novel, but because the method has not been used in databases other than the authors' own studies of $PM_{2.5}$ (8, 9), and because the time scale of exposure and outcomes are different from that commonly used in most air pollution cohort studies, interpretation of the result requires some caution. The authors call the subject in the four hospitalization categories "cohorts," but they are not "cohorts" in the usual sense as used in prospective cohort studies such as the ACS study, because subjects were not recruited for their individual characteristics and followed but instead "chosen" in the administrative database based on specific chronic conditions for which they were hospitalized. Individual risk factors commonly collected in cohort studies such as smoking history or body mass index are not available in this analysis, but these individual risk factors are not confounders (but may be effect modifiers) in this analysis because the survival analysis is conducted within each city over time, with year-to-year variation in summer average ozone as the exposure variable. This is in contrast to common air pollution