IMPORTANCE Few studies have investigated the association of long-term ambient ozone exposures with respiratory morbidity among individuals with a heavy smoking history.

OBJECTIVE To investigate the association of historical ozone exposure with risk of chronic obstructive pulmonary disease (COPD), computed tomography (CT) scan measures of respiratory disease, patient-reported outcomes, disease severity, and exacerbations in smokers with or at risk for COPD.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cross-sectional study, conducted from November 1, 2010, to July 31, 2018, obtained data from the Air Pollution Study, an ancillary study of SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study). Data analyzed were from participants enrolled at 7 (New York City, New York; Baltimore, Maryland; Los Angeles, California; Ann Arbor, Michigan; San Francisco, California; Salt Lake City, Utah; and Winston-Salem, North Carolina) of the 12 SPIROMICS clinical sites. Included participants had historical ozone exposure data (n = 1874), were either current or former smokers (≥20 pack-years), were with or without COPD, and were aged 40 to 80 years at baseline. Healthy persons with a smoking history of 1 or more pack-years were excluded from the present analysis.

EXPOSURES The 10-year mean historical ambient ozone concentration at participants’ residences estimated by cohort-specific spatiotemporal modeling.

MAIN OUTCOMES AND MEASURES Spirometry-confirmed COPD, chronic bronchitis diagnosis, CT scan measures (emphysema, air trapping, and airway wall thickness), 6-minute walk test, modified Medical Research Council (mMRC) Dyspnea Scale, COPD Assessment Test (CAT), St. George’s Respiratory Questionnaire (SGRQ), postbronchodilator forced expiratory volume in the first second of expiration (FEV1) % predicted, and self-report of exacerbations in the 12 months before SPIROMICS enrollment, adjusted for demographics, smoking, and job exposure.

RESULTS A total of 1874 SPIROMICS participants were analyzed (mean [SD] age, 64.5 [8.8] years; 1479 [78.9%] white; and 1013 [54.1%] male). In adjusted analysis, a 5-ppb (parts per billion) increase in ozone concentration was associated with a greater percentage of emphysema (β = 0.94; 95% CI, 0.25-1.64; P = .007) and percentage of air trapping (β = 1.60; 95% CI, 0.16-3.04; P = .03); worse scores for the mMRC Dyspnea Scale (β = 0.10; 95% CI, 0.03-0.17; P = .008), CAT (β = 0.65; 95% CI, 0.05-1.26; P = .04), and SGRQ (β = 1.47; 95% CI, 0.11-2.93; P = .048); lower FEV1,% predicted value (β = −2.50; 95% CI, −4.42 to −0.59; P = .01); and higher odds of any exacerbation (odds ratio [OR], 1.37; 95% CI, 1.12-1.66; P = .002) and severe exacerbation (OR, 1.37; 95% CI, 1.07-1.76; P = .01). No association was found between historical ozone exposure and chronic bronchitis, COPD, airway wall thickness, or 6-minute walk test result.

CONCLUSIONS AND RELEVANCE This study found that long-term historical ozone exposure was associated with reduced lung function, greater emphysema and air trapping on CT scan, worse patient-reported outcomes, and increased respiratory exacerbations for individuals with a history of heavy smoking. The association between ozone exposure and adverse respiratory outcomes suggests the need for continued reevaluation of ambient pollution standards that are designed to protect the most vulnerable members of the US population.


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Tropospheric, or ground-level, ozone is generated mainly in and downwind of large urban areas by chemical reactions between multiple pollutants in the presence of sunlight. Exposure to ambient concentrations of tropospheric ozone is regulated by the US Environmental Protection Agency Clean Air Act, and data from controlled human exposure studies and observational cohort studies support a causal relationship between ozone exposure and adverse health effects in humans. Short-term ozone exposure (which varies from hours to weeks) is associated with adverse respiratory outcomes, including acute changes in lung function, and increases in asthma symptoms and respiratory-related emergency department (ED) visits. Less is known about the respiratory sequelae of long-term ozone exposure (which varies from months to years). Although previous studies suggest that long-term ozone exposure is associated with increased respiratory-related mortality, few studies have focused on the implications of ozone exposure for those with a heavy smoking burden who may be at high risk for developing chronic lung disease. Furthermore, little is known about the association of ozone exposure with respiratory morbidity in individuals with chronic obstructive pulmonary disease (COPD), despite the knowledge that exposure to particles and gases can cause COPD. A recent scientific assessment by the Environmental Protection Agency acknowledges the scarcity of epidemiologic studies into the association between long-term ozone exposure and COPD-related health outcomes.

The goal of this cross-sectional study was to investigate the association between 10-year historical ozone exposure and the respiratory health of current and former smokers with or without airways obstruction. These individuals were enrolled in the Subpopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS), an ongoing multicenter prospective cohort study that aims to identify new COPD subgroups and intermediate markers of disease progression. We hypothesized that exposure to higher concentrations of 10-year historical ozone, estimated with fine-scale spatiotemporal modeling, was associated with increased risk of respiratory disease, worse respiratory-related morbidity, and higher exacerbation risk.

Methods

Study Population

The current cross-sectional study, conducted from November 1, 2010, to July 31, 2018, is an analysis of data collected at the SPIROMICS enrollment visit as part of the SPIROMICS Air Pollution Study (SPIROMICS AIR), an ancillary study that included 2382 participants enrolled at 7 (New York City, New York; Baltimore, Maryland; Los Angeles, California; Ann Arbor, Michigan; San Francisco, California; Salt Lake City, Utah; and Winston-Salem, North Carolina) of the 12 SPIROMICS clinical sites. A total of 1874 SPIROMICS AIR participants (648 smokers without airways obstruction and 1226 smokers with COPD) had available 10-year historical ozone exposure data. SPIROMICS was approved by the institutional review board at each of the 12 clinical centers throughout the United States. All study participants provided written informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Participants in SPIROMICS AIR were 40 to 80 years of age at baseline and were current or former smokers (≥20 pack-years) with or without evidence of obstructive lung disease. Healthy persons with a smoking history of 1 or more pack-years were not included in the present analysis. Spirometry was performed before and after the administration of a bronchodilator. Current and former smokers were categorized as having either no spirometric evidence of airflow obstruction or having COPD (postbronchodilator forced expiratory volume in the first second of expiration/forced vital capacity [FEV1/FVC] < 70%).

Ambient Ozone Exposure Assessment

Residential address at baseline and over the previous 10 years was obtained and geocoded with a geographic information system (ArcGIS 10.3; ESRI). Two-week mean outdoor concentrations of ozone outside each participant’s home were predicted using spatiotemporal modeling methods. Models incorporated cohort-focused monitoring conducted by SPIROMICS AIR; pollutant concentrations previously measured by the MESA (Multi-Ethnic Study of Atherosclerosis and Air Pollution) Air Study in Baltimore, New York City, Los Angeles, and Winston-Salem; monitoring by the New York City Community Air Study; and regulatory agencies in all SPIROMICS AIR communities. The 2-week mean concentration predictions were calculated to obtain a long-term historical ozone concentration for the 10 years prior to the baseline visit that was specific to the residential history reported. Ozone estimates were unavailable for 239 individuals with at least 1 address outside the geographic areas covered by the prediction models and for 269 individuals whose addresses could not be geocoded accurately.

Participant Characterization

Trained staff at the clinical sites collected demographic and clinical data. Smoking history was defined as lifetime cumulative pack-years and as a binary indication (yes or no) of smok-
ing within the past month. Occupational exposure to vapors, gas, dust, or fumes (VGDF) at the longest-held job was ascertained by interview.20-22 Educational attainment was defined as high school or less or more than high school, and personal income was categorized by yearly income of less than $15 000, $15 000 to $34 999, $35 000 to $49 999, $50 000 to $74 999, or more than $75 000. Neighborhood median household income was obtained using 2010 federal census data at the tract level.23 Participants reported the usual number of hours spent outside per day per season; mean seasonal values were calculated to obtain a yearly estimate.

Respiratory Outcomes
Respiratory-specific quality of life was ascertained using the St. George's Respiratory Questionnaire (SGRQ),24 and health status was identified with the COPD Assessment Test (CAT).25 Dyspnea was assessed with the modified Medical Research Council (mMRC) Dyspnea Scale,26 and functional exercise capacity was evaluated with the 6-minute walk test (6MWTT).27 Chronic bronchitis was defined by a positive response to either the classic or alternative SGRQ definition.28 Exacerbations were based on report of antibiotic and/or steroid use, unscheduled physician visits, ED visits and hospitalizations for COPD, and frequency of these instances over the past year. Severe exacerbations were defined as events requiring an ED visit or hospitalization.

Participants underwent whole-lung multidetector helical computed tomography (CT) scans.29 Percentage of emphysema was defined as percent of total voxels in the field less than −950 HU (Hounsfield units) at total lung capacity, and percentage of air trapping was defined as percent of total voxels in the field less than −856 HU at residual volume. PI10 (the square root of the wall area of a theoretical airway with a lumen perimeter of 10 mm) was used as a measure of airway wall thickness.30

Statistical Analysis
From May 1, 2018, to September 1, 2019, we performed multivariable regression analyses to examine the association between 10-year historical ozone exposure concentration and outcomes assessed at the enrollment visit. A minimally adjusted model accounted for age, race/ethnicity (white vs non-white), sex, and study site, and a moderately adjusted model added personal and neighborhood income. Fully adjusted models accounted for body mass index, current smoking status, smoking pack-years, VGDF exposure, and educational status in addition to the covariates included in the moderately adjusted model.

For continuous outcomes, including CT metrics and disease severity outcomes (ie, respiratory symptoms, lung function, and functional status), we used least-squares regression modeling to estimate the change in the predicted level of outcomes for a 5-ppb (parts per billion) increase in 10-year historical ozone concentration. For dichotomous outcomes, including COPD diagnosis, chronic bronchitis diagnosis, and exacerbations (event of reporting any exacerbation in the past 12 months), we used logistic regression models to estimate the odds ratio (OR) of the event for a 5-ppb increase in 10-year historical ozone concentration. We conducted standard regression analyses, including checking linearity assumption using a fractional polynomial model approach as well as evaluating residual distribution for normality and heteroscedasticity as appropriate (eFigure 1 in the Supplement). In addition, we used the fractional polynomial approach to explore the functional shape of the exposure-response associations.31

Sensitivity analyses included the addition of 10-year historical concentration of particulates with a diameter of 2.5 μm (PM2.5) or less to the fully adjusted model, 1- and 5-year mean ambient ozone concentration as the main exposure variable, and modeled ozone concentration limited to the warm season (April-September) as the exposure. In separate analyses, to explore effect modification given a priori hypotheses, we ran fully adjusted 2-way interaction models, examining the interaction between COPD status, smoking pack-years, current smoking status, sex, and time spent outdoors with ozone exposure. For the COPD effect modification analysis, COPD was not included as an outcome.

All analyses were performed with StataMP software, version 15.1 (StataCorp LLC). The threshold of statistical significance for the main associations and interaction terms was a 2-sided P < .05.

Results
This cross-sectional study analyzed 1874 participants, with a mean (SD) age of 64.5 (8.8) years and among whom 1479 (78.9%) were white and 1013 (54.1%) were male. More than a third of participants (n = 688 [36.7%]) reported current smoking, and the mean (SD) pack-years reported were 49.8 (28.9). Mean (SD) postbronchodilator FEV1 was 74.7% (25.8%) predicted, and 1226 participants (65.4%) had a COPD diagnosis. Almost half of participants (904 [48.6%]) reported VGDF exposure. Over the course of the year, the median (interquartile range [IQR]) time spent outdoors was 3.3 (2.0-5.5) hours per day (Table 1).

The median (IQR) of the 10-year mean of modeled 2-week ozone concentrations was 25.1 (21.8-28.1) ppb. Ozone concentrations varied by site of enrollment (P < .001), ranging from a median (IQR) of 16.3 (14.0-19.0) ppb in New York City to 29.1 (27.2-33.0) ppb in Salt Lake City (Figure 1). Compared with individuals without available ozone data, participants with estimated ozone concentrations were older (mean age, 62.2 years vs 64.5 years; P < .001), were less likely to be current smokers (45.8% [n = 230] vs 37.3% [n = 688]; P < .001), were less likely to be in the lowest income category of less than $15 000 (24.8% vs 15.4%; P < .001), and tended to have higher neighborhood mean income ($57 000 vs $61 000; P = .003). No differences were observed in race/ethnicity, sex, smoking pack-years, VGDF exposure, COPD status, time spent outdoors, or body mass index in those with or without available ozone data. For the outcomes of percentage of emphysema, FEV1% predicted, and 6MWTT, the fractional polynomial models suggested that the association between historical ozone exposure and outcome may be other than linear (eFigure 2 in the Supplement). For all outcomes, results of the minimally and moderately adjusted model are included in eTable 1 in the Supplement.
Association of Ozone Exposure With Respiratory Morbidity

Original Investigation Research

In the fully adjusted model, a 5-ppb increase in historical ozone exposure concentration was associated with a 0.94 (95% CI, 0.25-1.64; P = .007) increase in percentage of emphysema and a 1.60 (95% CI, 0.16-3.04; P = .03) increase in percentage of air trapping (Figure 2A). No association was observed between ozone exposure and chronic bronchitis (OR, 1.14; 95% CI, 0.96-1.35; P = .14), COPD (OR, 1.16; 95% CI, 0.97-1.40; P = .10), or Ph10 effect estimate, 0.0001; 95% CI, −0.005 to 0.006; P = .87) (Table 2).

When accounting for confounders in the fully adjusted model, higher concentration of 10-year ozone exposure was associated with worse quality of life, functional status, and dyspnea. Specifically, a 5-ppb increase in ozone was associated with a 1.47-point increase in SGRQ score (95% CI, 0.01-2.93; P = .048), a 0.65-point increase in CAT score (95% CI, 0.05-1.26; P = .04), and a 0.10-point increase in mMRC Dyspnea Scale score (95% CI, 0.03-0.17; P = .008) (Figure 2B). Greater 10-year ozone exposure concentration was associated with a −2.50% lower FEV1, % predicted value (95% CI, −4.42 to −0.59; P = .01) (Figure 2C). No association was observed between historical ozone exposure and 6MWT result (Table 2).

Table 2. Baseline Participant Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64.5 (8.8)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1013 (54.1)</td>
</tr>
<tr>
<td>White race/ethnicity</td>
<td>1479 (78.9)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>28.0 (5.3)</td>
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<tr>
<td>Pack-years, mean (SD)</td>
<td>49.8 (28.9)</td>
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<td>Current smoker</td>
<td>688 (36.7)</td>
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<tr>
<td>10-y mean of 2-wk ozone concentration, median (IQR), ppb</td>
<td>25.1 (6.3)</td>
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<tr>
<td>10-y mean of PM2.5 concentration, median (IQR), µg/m³</td>
<td>11.2 (3.6)</td>
</tr>
<tr>
<td>Time spent outdoors annually, median (IQR), h/d</td>
<td>3.3 (3.5)</td>
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<tr>
<td>Exposure to VGDF at longest job</td>
<td>904 (48.6)</td>
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<td>Census tract median household income, in thousands, mean (SD)</td>
<td>59 (28)</td>
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<tr>
<td>Income, US $</td>
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<td>&lt;15 000</td>
<td>342 (18.2)</td>
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<tr>
<td>15 000-34 999</td>
<td>250 (13.3)</td>
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<tr>
<td>35 000-74 999</td>
<td>308 (16.4)</td>
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<tr>
<td>≥75 000</td>
<td>330 (17.6)</td>
</tr>
<tr>
<td>Declined to answer</td>
<td>356 (19.0)</td>
</tr>
<tr>
<td>High school education or lower</td>
<td>679 (36.3)</td>
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<tr>
<td>COPD diagnosis</td>
<td>1226 (65.4)</td>
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<tr>
<td>Chronic bronchitis</td>
<td>802 (42.9)</td>
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<tr>
<td>Postbronchodilator FEV1, % predicted, mean (SD)</td>
<td>74.7 (25.8)</td>
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<tr>
<td>6MWT distance, mean (SD), m</td>
<td>401.3 (106.9)</td>
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<tr>
<td>mMRC Dyspnea Scale score, mean (SD)</td>
<td>1.01 (0.97)</td>
</tr>
<tr>
<td>CAT score, mean (SD)</td>
<td>13.4 (8.0)</td>
</tr>
<tr>
<td>SGRQ score, mean (SD)</td>
<td>31.3 (19.8)</td>
</tr>
<tr>
<td>Prevalence of total exacerbations in the 12 mo before baseline visit</td>
<td>419 (22.4)</td>
</tr>
<tr>
<td>Prevalence of severe exacerbations in the 12 mo before baseline visit</td>
<td>195 (10.4)</td>
</tr>
</tbody>
</table>

Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second of expiration; IQR, interquartile range; mMRC, modified Medical Research Council Dyspnea Scale; ppb, parts per billion; PM2.5, particulate matter with an aerodynamic diameter of 2.5 microns or less; SGRQ, St. George Respiratory Questionnaire; VGDF, vapors, gas, dust, or fumes.

* Data presented as number (percentage) unless otherwise specified.

Effect Modification by Time Spent Outdoors, Smoking, Sex, and COPD Status

The association between historical ozone exposure and CAT score was modified by the amount of time spent outdoors such that adverse ozone association with CAT score was significantly amplified for participants who spent more (vs less) than the median time outdoors. For example, a 5-ppb increase in historical ozone exposure concentration was associated with a 1.22-point increase (95% CI, 0.49-1.94; P = .001) in CAT score for those who spent more than the median time outdoors; no associated increase was found among participants who spent less time outdoors (Figure 2D).

The boxes indicate the interquartile range (IQR), the lower hinge (bottom of box), the 25th percentile value, the center line, the median concentration, and the upper hinge (top of box), the 75th percentile value. The upper whisker represents the maximum observation that falls within the upper limit (75th percentile + 1.5 × IQR); the lower whisker, the minimum observation that falls within the lower limit (25th percentile − 1.5 × IQR). The circles represent outlier values.

AA indicates Ann Arbor, Michigan; Bal, Baltimore, Maryland; LA, Los Angeles, California; NYC, New York City, New York; ppb, parts per billion; SF, San Francisco, California; SLC, Salt Lake City, Utah; WS, Winston-Salem, North Carolina.

Figure 1. Distribution of 10-Year Historical Ozone Concentration by Study Site

The circles represent outlier values.
less than the median time outdoors (β = 0.42; 95% CI, −0.29 to 1.13; P = .25; P for interaction = 0.03). Similarly, evidence of effect modification was observed by time spent outdoors for the outcome of SGRQ score (above median time: β = 2.97 [95% CI, 1.24-4.69; P = .001]; below median time: β = 0.89 [95% CI, −0.83 to 2.61; P = .31; P for interaction = 0.02]). No
Further evidence of effect modification was found by time spent outdoors and other outcomes, not for smoking pack-years, sex, or COPD case status for any of the measured outcomes. Evidence of effect modification was found by smoking status only for the outcome of mMRC Dyspnea Scale score. Specifically, a 5-ppb increase in historical ozone exposure concentration was associated with a 0.17-point increase (95% CI, 0.08-0.26; P < .001) in mMRC Dyspnea Scale score in current smokers; no associated increase was observed in former smokers (β = 0.07; 95% CI, −0.01 to 0.15; P = .11; P for interaction = 0.02) (Figure 3).

**Sensitivity Analyses**

Inclusion of both ozone and PM$_{2.5}$ concentration in the same model introduced a modest collinearity issue (correlation when accounting for study site = −0.71), resulting in an increase in the variability of effect estimates for ozone concentration. However, in general, the associations between ozone and COPD outcomes were consistent in models including PM$_{2.5}$. Specifically, when including PM$_{2.5}$ in the model, the association between ozone and air trapping, emphysema, mMRC, and lung function remained statistically significant. Although the association with emphysema remained in the same direction, a statistically significant association was no longer observed between ozone and SGRQ, CAT, or exacerbations (eTable 2 and Figure 3 in the Supplement). When considering alternate mean times of ozone exposure, the association between historical ozone exposure and outcomes was similar when using 1- and 5-year historical ozone concentrations (eTable 3 in the Supplement). Similarly, the association between historical ozone exposure and outcomes did not meaningfully vary when ozone predictions were limited to the warm season (eTable 4 in the Supplement).

**Discussion**

This cross-sectional study of a multicenter cohort of heavy smokers with or at risk for COPD demonstrated an adverse association of historical ozone exposure with COPD and emphysema risk as well as with several markers of respiratory morbidity, including patient-reported outcomes and exacerbations. We found that exposure to a higher concentration of 10-year historical ozone was associated with lower lung function, as well as with more emphysema and air trapping on CT scan, even after accounting for smoking history. These findings support the role of ambient ozone exposure in COPD morbidity, the fourth leading cause of death in the United States and which is often attributed to tobacco exposure in developed countries. Ten-year cumulative ozone exposure was also associated with greater symptom burden, worse quality of life and functional status, and more frequent exacerbations among SPIROMICS participants with or without COPD. These results take into account additional occupational and environmental exposures, smoking history, and individual and neighborhood socioeconomic factors. Thus, they highlight the association of long-term ozone exposure with individual-level health outcomes in smokers with or without COPD.

These results are in line with findings of a general population study of 5780 individuals that demonstrated a long-term association between higher ozone concentration and increased emphysema and a study of 300 individuals with α1-antitrypsin deficiency that showed an association between higher concentration of 1-year ozone exposure and emphysema severity. The magnitude of the association between long-term ozone exposure and percentage of emphysema was similar to that seen with several other inhalational exposures, such as occupational exposures in the longest held job. In addition, we found that those with higher concentration of historical ozone exposure had significantly lower FEV$_1$% predicted value, supporting previous studies that demonstrated an association between ozone exposure and decreased lung function in respiratory diseases, including both asthma and COPD. Furthermore, although the data in the present study support the existing literature describing the association between long-term ozone exposure and respiratory outcomes in asthma, this study fills a substantial knowledge gap by demonstrating that exposure to higher concentrations of long-term ambient ozone may also be a factor in...
increased respiratory symptoms and burden in adults at risk for chronic lung disease owing to smoking and among those with COPD, which is a leading driver of hospitalizations in the United States.37

The effect sizes found in this analysis translate to meaningful health outcomes that have important implications for assessing the burden of disease in COPD. Specifically, ozone was associated with worse quality of life (as measured by SGRQ) and health status (as measured by CAT) such that living in areas with a 15–ppb higher concentration of historical 10-year ozone was associated with decrements of 4.0 points in SGRQ and 2.0 points in CAT that met the minimal clinically important difference. In addition, long-term ozone exposure was associated with worse dyspnea (according to the mMRC Dyspnea Scale), which, along with CAT score and exacerbation frequency, is a particularly important measure of disease severity and is currently used in the COPD Global Initiative for Chronic Obstructive Lung Disease guidelines to assess symptoms and risk of exacerbations.38 This assessment, along with the degree of airflow limitation based on FEV1% predicted value, provides a composite of disease severity and guides medical management. A 5–ppb increase in 10-year mean ozone concentration was associated with an increase in the odds of total and severe exacerbations (OR, 1.37 for both) in the 12 months before the baseline visit. According to data from the Centers for Disease Control and Prevention,39 approximately 7 million COPD-related ED visits occurred in 2015. A 5–ppb reduction in 10-year historical ozone concentration could potentially decrease ED visits by 27% to 5.1 million, resulting in an impressive reduction in the existing burden of health care resources spent on COPD.40

Indoor concentrations of ozone are substantially lower than outdoor levels41; thus, it is not surprising that the association of ozone exposure with COPD-related health status (CAT score) and quality of life (SGRQ score) tended to be greater in individuals who spent more time outdoors. Future research is warranted to address whether public health messaging concerning poor air quality may influence activity patterns and health outcomes in populations with COPD. Such health alerts on high-outdoor-pollution days should take into consideration the known adverse health implications of poor indoor air quality for COPD outcomes independent of outdoor air quality.42

The present study highlighted that ozone exposure had adverse implications for COPD risk and respiratory morbidity despite heavy smoking exposure (at least 20 pack-years) among all study participants. No effect modification of ozone by cumulative smoking history was found, such that the adverse outcomes of ozone were consistent across pack-years of exposure, suggesting that the association of ozone exposure may be independent of smoking intensity. Current smokers were more susceptible to the implications of ozone exposure only for the outcome of mMRC Dyspnea Scale; for most outcomes, ozone exposure was associated with increased morbidity regardless of smoking status. In addition, the adverse implications of ozone for respiratory outcomes were persistent despite adjustments for multiple confounders, including job exposures, which have been linked with poor outcomes in the SPIROMICS population.34,43 Furthermore, these results remained largely consistent with consideration of historical exposure to PM2.5, a pollutant that has been implicated in both the development and worsening of COPD.44–46 The modest collinearity found between ozone and PM2.5 increases the uncertainty in the estimates of ozone outcomes. However, the general consistency in the patterns of associations between both models suggests an independent association between ozone and respiratory outcomes that is robust to the inclusion of additional pollutants. These results are among the first to highlight the distinct association of ozone with important disease outcomes in COPD.

Epidemiologic and controlled chamber studies showed adverse health outcomes after exposure to relatively low concentrations of ozone,47 and the present study provides additional evidence of adverse outcomes associated with ozone throughout the observed concentration range, suggesting the absence of a safe threshold of exposure concentration. The 2015 US National Ambient Air Quality Standards (NAAQS) limited the maximum 8-hour mean concentration to 70 ppb, and no current long-term ozone standard exists.1 Although the mean time used in the current study did not allow for direct comparison with the NAAQS limit, 8-hour peaks are correlated with long-term mean concentrations,17 and more than a third of the US population lives in areas that exceed the current short-term ozone exposure limit.48 Since 2000, ozone concentrations have decreased the least as compared with other criteria air pollutants under NAAQS (ie, 16% decrease from 2000 to 2018, compared with a 39% decrease in PM2.5 concentration over the same period).49 The relative flattening of ozone reduction demonstrates that the US population has been exposed to relatively fixed concentrations of ozone over the past several decades. Results of this study support recent epidemiologic evidence that associated these long-term exposures, in addition to adverse short-term exposures, with health outcomes.8,9,50 We believe that further consideration of adopting the long-term ozone standard of the NAAQS is a public health necessity.

Limitations and Strengths

This study has some limitations. We were unable to establish outdoor behavior patterns over time, and participant report of outdoor activity at the baseline visit may differ from reports in previous years. In addition, generalizability beyond the study sites with available spatiotemporal ozone data may be limited. The potential nonlinear association between ozone and percentage of emphysema, FEV1,5% predicted, and 6MWT results is intriguing, and the underlying structure of these associations deserves further investigation. In addition, SPIROMICS comprises volunteer participants and thus is not a population-based study, which may introduce self-selection bias.

This study also has several strengths. Previous studies often relied on pollution data gathered from local and national regulatory agencies, which limited the studies’ ability to capture participants’ actual exposure near their home, as local meteorological conditions, emissions, and geographic features can influence ozone levels, resulting in a large amount of spatial variability in ozone concentration.1 The pollution prediction
models we used included additional fine-scale spatial information not available from existing public data sets. In addition, the extensive clinical phenotyping of SPIROMICS participants allowed us to examine the association of ozone exposure with several respiratory-specific outcomes in a vulnerable population of current and former heavy smokers.

Conclusions

This cross-sectional study found that long-term exposure to ozone was associated with worse outcomes in smokers with or at risk for COPD. Specifically, long-term ozone exposure was associated with lower lung function and a greater percentage of emphysema and air trapping on CT scan. Furthermore, the significant clinical association of ozone exposure with several measures of respiratory morbidity, including worse patient-reported outcomes, functional status, and higher exacerbation risk, provides additional evidence that long-term ozone exposure has a substantial association with a range of respiratory outcomes. We believe these findings support continued reexamination of ambient pollution standards that are designed to protect the health of the most vulnerable members of the US population.
interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Shining New Light on Long-term Ozone Harms

Vijay S. Limaye, PhD; Kim Knowlton, DrPH

An important new study published by Paulin et al1 in this issue of JAMA Internal Medicine investigates the outcomes of long-term exposures to outdoor ground-level ozone air pollution in people with a history of heavy smoking. Using a comprehensive set of metrics to assess lung function, the research team identified associations between long-term ozone exposures and increased respiratory disease severity, disease symptoms, and lung disease exacerbations in a cross-sectional analysis.

Ozone air pollution (also known as smog, and typically a concern during hot summer months) can travel hundreds of miles, triggering health problems for populations far downwind of the locations of pollution formation. This research area is important because there are relatively few epidemiologic studies analyzing the health outcomes of ozone exposures on adult populations, especially over long time horizons of months to years. Studies like the one by Paulin et al1 are especially relevant, given the millions of individuals who currently or formerly smoked heavily and at least 16 million people with chronic obstructive pulmonary disease (COPD) in the US population. As noted by the study authors,1 COPD is currently the fourth leading cause of death in the United States.

The adverse respiratory health outcomes identified in this study1 were found to be potentially independent of smoking intensity or exposures to air pollution on the job, underscoring the health risks that ozone air pollution poses to tens of millions of individuals who currently smoke or formerly smoked. The observed health outcomes largely persisted even after adjustment for exposure to fine particulate matter (PM2.5), another fossil fuel-generated air pollutant that causes even more damaging health problems than ozone. Risk estimates for lung disease exacerbations were particularly high and demonstrate harmful repercussions of ozone exposures, even for relatively small increases of 5 parts per billion in ozone pollution.

Importantly, the authors1 identified adverse health outcomes from long-term ozone exposures at levels that are less than half of the current US federal regulatory limits. Those limits, called National Ambient Air Quality Standards, are required by the Clean Air Act, regulated by the US Environmental Protection Agency, and revised in accordance with the best available scientific evidence. The median ozone level observed in this study1 was 25.1 parts per billion (per the study’s...