HEALTH EFFECTS INSTITUTE

STATEMENT

Synopsis of Research Report 192, Part 2

Prior Air Pollutant Exposures and Cardiorespiratory Effects of Ozone

INTRODUCTION

Ozone exposure has been associated with adverse health effects in children and adults at current ambient concentrations. Its effects on the respiratory system are well established and include worsening of asthma symptoms (acute effects), increases in deaths and hospital admissions for respiratory illnesses such as chronic obstructive pulmonary disease and asthma (acute and chronic effects), reduced lung growth, and higher risk of developing asthma (chronic effects). Some recent studies have reported that short-term exposure to ozone is associated with adverse cardiovascular outcomes, including an increased risk of cardiovascular mortality.

Ozone is an oxidant gas that easily reacts with other molecules. After inhalation, ozone reacts with constituents of the lung lining fluid to generate reactive oxygen species that can cause local oxidative stress in the lung and lead to lung irritation. With repeated exposure, oxidative stress may lead to lung injury and chronic lung disease. Ozone may have effects on the cardiovascular and other organ systems through systemic inflammation, oxidative stress, or changes in activity of the autonomic nervous system, which could lead to changes in heart rhythm, endothelial dysfunction, constriction of arteries, and blood clotting.

APPROACH

In 2010, HEI funded the Multicenter Ozone Study in oldEr Subjects (MOSES), conducted at three clinical centers in California, North Carolina, and New York. From 2012 through 2015, the investigators used a common protocol to expose

What This Study Adds

- The previously published MOSES study (Part 1) found that controlled ozone exposure at concentrations similar to the current U.S. air quality standard was not associated with changes in cardiovascular endpoints in 87 healthy, older adults, but there were moderate adverse effects on lung function and two markers of lung injury and inflammation.
- The MOSES, Part 2 study in the current report presents additional analyses to evaluate whether the MOSES 1 results were influenced by exposure to ambient air pollutants up to 4 days prior to the controlled ozone exposures. It also evaluated whether the prior exposures were associated with changes in baseline levels of biomarkers.
- MOSES 1 provided confirmation of ozone effects on the lung at low concentrations (70 and 120 ppb). MOSES 2 showed that those results were not affected by prior exposure to ambient pollutants. However, ambient concentrations of ozone and other pollutants were associated with differences in baseline levels of several biomarkers.
- The results of the MOSES studies add to the body of evidence of changes in health outcomes associated with air pollutant exposures at the current — relatively low — ambient concentrations in the United States.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Drs. David Q. Rich and Mark W. Frampton of the Pulmonary & Critical Care Department, University of Rochester Medical Center, Rochester, NY, and colleagues. The complete report, *Multicenter Ozone Study in oldEr Subjects (MOSES): Part 2. Effects of Personal and Ambient Concentrations of Ozone and Other Pollutants on Cardiovascular and Pulmonary Function* (© 2020 Health Effects Institute), can be obtained from HEI or our website (see last page).

87 healthy volunteers (ages 55–70 years) to 0, 70, and 120 ppb ozone. Exposures lasted 3 hours, during which the participants exercised on a stationary bicycle, alternating 15 minutes of exercise with 15 minutes of rest. Participants stayed at a hotel the night before testing to minimize variability in exposure to ambient air pollutants and were evaluated the day before, during, and up to 22 hours after exposure.

In the previously published MOSES report (Research Report 192, Part 1), the investigators measured a large suite of endpoints, including changes in autonomic nervous system function, heart rhythm, blood pressure, and pulmonary function, as well as markers of endothelial function, thrombosis, lung injury, and both systemic and lung inflammation. They specified in advance a key group of cardiovascular endpoints as primary; all other endpoints were secondary. Results were analyzed by mixed-effects linear models, adjusting for the three centers and multiple time points, and presented as the difference between pre-exposure and post-exposure values. The statistical significance threshold was set at $P < 0.01$ in light of multiple comparisons.

Because the controlled exposure concentrations were close to ambient ozone concentrations experienced every day, there was considerable interest in evaluating whether ambient exposures to ozone and other pollutants during the days leading up to the clinical visits may have influenced the outcome of the experiments. Therefore, the investigators measured each participant's exposure to ozone and nitrogen dioxide using a personal sampler for 72 hours before the pre-exposure visit. They also collected air quality data for ozone, fine particulate matter, nitrogen dioxide, sulfur dioxide, and carbon monoxide from central monitors closest to each clinical center.

MOSES, Part 2 describes analyses conducted by the team at the University of Rochester, who generally used the same statistical approach as in MOSES 1. They ran the statistical models with inclusion of personal exposure measurements for ozone or nitrogen dioxide, or ambient concentrations of each pollutant at various time lags (from 0 to 96 hours prior) for a total of 37 statistical models per biomarker. They also conducted several sets of sensitivity analyses.

The investigators pursued four specific aims: to investigate (1) whether any changes in biomarkers before and after the controlled ozone exposures were *confounded* by prior exposures to ambient air pollutants; (2) whether there was *effect modification*, that is, whether controlled ozone effects could only be seen when prior ambient exposures were low or, alternatively, when they were high; (3) whether prior pollutant exposures were associated with differences in *baseline values* of the biological markers measured before the start of the controlled ozone exposures; and (4) whether prior pollutant exposures were associated with *changes in biomarkers* before and after controlled ozone exposure.

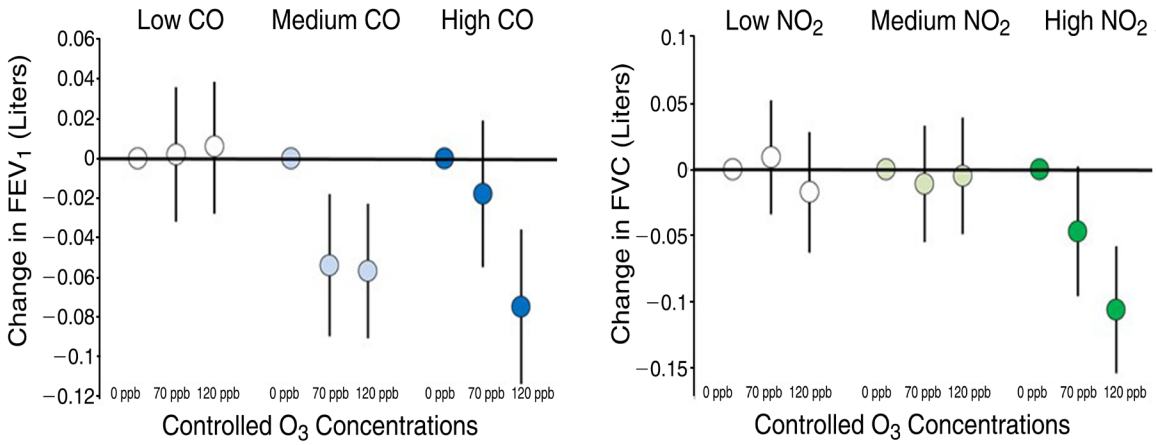
KEY RESULTS

As reported in MOSES 1, there was no evidence that a 3-hour exposure to 70 or 120 ppb ozone with moderate exercise affected cardiovascular endpoints in these healthy older adults. However, short-term exposures at these low ozone concentrations did produce pulmonary effects. In MOSES 2, the investigators found no evidence of confounding by prior exposures to ozone or other air pollutants. They also found no evidence of effect modification when the results were analyzed by tertile of ambient pollutant concentrations, except for changes in lung function. Specifically, changes in forced expiratory volume in one second and in forced vital capacity were observed when carbon monoxide and ambient or personal nitrogen dioxide concentrations were in the medium and highest tertiles (Statement Figure). Although there was some variation in the level of statistical significance across these comparisons, the pattern of changes appeared to be coherent. The investigators hypothesized that prior exposures to these pollutants may have sensitized or primed the airways to respond to the controlled ozone exposures.

The investigators reported possible associations between ambient ozone exposure and baseline heart rate variability in the frequency domain. There were also possible associations between ambient concentrations of fine particulate matter, carbon monoxide, and nitrogen dioxide and baseline C-reactive protein levels or lung function measures. On the other hand, possible associations of ambient ozone with high-frequency-power heart rate variability were independent of ambient concentrations of fine particulate matter, carbon monoxide, and nitrogen dioxide.

REVIEW PANEL'S EVALUATION

In its independent review of the study, the MOSES Review Panel, specially convened by the HEI Review Committee, commended the investigators for a well-designed and well-executed follow-on study to MOSES 1. In addition to evaluating possible confounding of MOSES 1 results, they evaluated various other research questions to understand



Statement Figure. Influence of ambient concentrations during preceding days on changes in lung function after controlled ozone exposure. Ambient pollutant concentrations up to 72 hours prior to ozone exposure were divided into tertiles. Left panel: forced expiratory volume in one second and ambient carbon monoxide. Right panel: forced vital capacity and ambient nitrogen dioxide.

how daily ambient pollutant exposures may have affected baseline levels of biomarkers and whether the pollutants interacted with each other. The Panel commended the investigators for conducting a large number of informative statistical analyses in MOSES 2 and agreed with the report's main conclusion that the MOSES 1 results were not confounded by the participants' prior exposures to air pollutants.

The Panel made additional observations on the results and their interpretation. By using an interaction term in MOSES 2, the analysis no longer compared outcomes within each person, because each visit to the clinic may have been preceded by a different ambient pollutant concentration. Thus, the strength of the original crossover design in MOSES 1 no longer applied. The Panel also expressed some concern about multiple testing (37 statistical analyses per biomarker) potentially yielding false positive associations.

The Panel thought the analyses of prior ambient pollutant exposures on baseline levels of the cardiovascular biomarkers (Aim 3) were interesting and the results were consistent with current knowledge. However, the Panel found the analyses for Aim 4 difficult to interpret. The fact that the direction of effects for frequency-domain heart rate variability was inconsistent decreased confidence in the interpretation that prior exposure to ambient ozone may have affected heart rate variability.

CONCLUSIONS

The Multicenter Ozone Study in oldEr Subjects was a large, well-conducted study in 87 healthy adults (55–70 years old). MOSES 1 showed the following important results: (1) there was no convincing evidence that a 3-hour exposure to near ambient concentrations of 70 or 120 ppb ozone with moderate exercise resulted in statistically significant changes in cardiovascular endpoints in these healthy older adults; (2) short-term exposures at these relatively low ozone concentrations did lead to pulmonary effects, consistent with previous studies, which were conducted primarily in younger adults; and (3) no susceptible subgroups could be identified in which ozone elicited cardiovascular effects that were not evident in the group as a whole. MOSES 2 showed that these results were not affected by the participants' immediate prior exposures to ambient air pollutants, providing confidence in the results. The MOSES Review Panel agreed with the main findings of the study and that the results support the conclusion that adverse lung effects can be observed at ozone concentrations resembling the current 8-hour U.S. National Ambient Air Quality Standard (NAAQS) of 70 ppb.

It remains possible that ozone may lead to cardiovascular effects in more susceptible individuals, following longer exposures, or in the presence of common ambient air pollutants. MOSES 2 presented evidence that ambient air pollution exposure may be associated with changes in baseline levels of some cardiovascular and pulmonary biomarkers measured before the clinical visits. These results add to the body of evidence of changes in health outcomes associated with air pollutant exposures at the current — relatively low — ambient concentrations in the United States.

CONTENTS

HEALTH EFFECTS INSTITUTE

75 Federal Street, Suite 1400
Boston, MA 02110, USA
+1-617-488-2300 phone
+1-617-488-2335 fax
www.healtheffects.org