Multicenter Ozone Study in oldEr Subjects (MOSES): Part 2

Impacts of Personal and Ambient Concentrations of Ozone and Other Pollutants on Cardiovascular and Pulmonary Function

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Abstract

BACKGROUND. The Multi-center Ozone Study of Elderly Subjects (MOSES) was a multi-center study evaluating whether short-term controlled exposure of older, healthy individuals to low levels of ozone induced acute changes in cardiovascular biomarkers. In MOSES Part 1 (*Arjomandi M, et al. AJRCCM Dec. 12, 2017*), ozone exposure caused concentration-related reductions in lung function with evidence for airway inflammation and injury, without convincing evidence for effects on cardiovascular function. However, pollutant exposures before the study may have independently impacted the study biomarkers, and/or modified biomarker responses to controlled ozone exposures.

STUDY DESIGN. In MOSES Part 2, we used a longitudinal panel study design, cardiopulmonary biomarker data from Part 1, and passively collected personal exposure samples (PES) of ozone and NO_2, and ambient air pollution and weather measurements in the 96 hours before the pre-exposure visit. Using mixed effects linear regression, we evaluated whether PES concentrations and ambient pollutant concentrations in the previous 96 hours were: associated with pre- to post-exposure biomarker changes, independent of the controlled ozone exposures (Aim 1); modified biomarker responses to the MOSES controlled ozone exposures (Aim 2); and associated with changes in biomarkers measured at the pre-exposure visit (Aim 3).

RESULTS. As hypothesized for Aim 3, increased ambient ozone concentrations were associated with decreased pre-exposure heart rate variability (HRV). For example, High Frequency (HF) HRV decreased in association with increased ambient ozone concentrations in the previous 96 hours (-0.460 ln of ms^2; 95% CI, -0.743, to -0.177 for each 10.35 ppb increase in ozone; p=0.002). However, these increases in ambient ozone were also associated with increases in HF and LF from pre- to post-exposure (Aim 1), likely reflecting a 'recovery' of HRV during the MOSES ozone exposure sessions. Similar patterns were observed for FEV_1 and FVC and increased ambient $PM_{2.5}$, CO, and NO_2 in the previous 96 hours. However, increased pollutant concentrations were not associated with adverse changes in other cardiopulmonary biomarkers. In Aim 2, effects of MOSES controlled ozone exposures on FEV_1 and FVC (but not other biomarkers) were modified by ambient NO_2 and CO, and PES NO_2, with reductions in FEV_1 and FVC observed only when these concentrations were "High" in the 72 hours before the pre-exposure visit.

CONCLUSIONS: Increased ambient ozone concentrations were associated with reduced HRV, with "recovery" during exposure visits. Increased ambient $PM_{2.5}$, NO_2, and CO (markers of traffic pollution), were associated with reduced pulmonary function, independent of the MOSES controlled ozone exposures. Pulmonary responses to the controlled ozone exposures were modified by ambient NO_2 and CO concentrations and PES NO_2 concentrations. Adverse changes in FEV_1 occurred only when ambient and PES pollutant levels were high.

Arjomandi M, et al. Respiratory responses to ozone exposure: the multicenter ozone study in older subjects (MOSES). In press: Am J Respir Crit Care Med.

MOSES Part 1: Study Design

Subjects: ≥55 and ≤70 years of age; nonsmoking (tobacco or marijuana) healthy males & females of all ethnic backgrounds.
Number of subjects to be studied in each center: n=30 (target)
Exposure: Subjects will be exposed for 3 hours to:
purified ambient air at 22° C and 40% relative humidity
purified ambient air with 70 ppb (low) ozone,
purified ambient air with 120 ppb (high) ozone
Number of visits per subject: 11 (see timeline and visits below)
Screening visit. During this visit the subject completed a series of questionnaires including medical history and underwent a physical exam
Training visit. During this visit the subject exercised on a treadmill or a stationary bicycle to determine the appropriate exercise load sufficient to achieve the pre-set V_E
Exposure visits. Each exposure session was spread over 3 days

Health Endpoints

The majority of the endpoints were measured on the day before the exposure, within 4 hours post-exposure, and 22 hours post-exposure. FMD was not measured 22 hours post-exposure, while sputum was obtained only 22 hours post-exposure.
Cardiac function. Measured by ECG (24 hour Holter with 12-lead recording averaged over last 5 min of a 15-min period pre-exposure, and 10 min, 3 hours and 24 hours post-exposure (all supine)
- Heart rate and HRV parameters in both the time domain (SDNN, and RMSSD) and the frequency domain (LF, HF, and LF/HF).
- Repolarization (QTc, T-wave amplitude, and ST-segment)

Oxidative stress and systemic inflammation
- C-reactive protein (CRP), 8-isoprostane, nitrotyrosine, & interleukin-6 (IL-6)
- Differential blood cell counts.

Endothelial and vascular function
- Blood pressure (SBP and DBP).
- MaxFMD, brachial artery diameter (BAD), and velocity time integral (VTI)
- Endothelin-1 (ET-1) and P-selectin

Prothrombotic markers: von Willebrand factor (vWF), tissue factor associated with microparticles (MP-TFA), platelet activation, fibrinogen
Lung injury markers: CC16
Airway inflammation markers (in sputum samples): Differential white cell counts, total protein, IL-6, IL-8, TNF-α, and CD40 ligand.
Lung function (spirometry): FEV_1, FVC, and FEV_{25-75}.
Genetic susceptibility to ozone : GSTM1 null genotype

Part 1: Results and Conclusions

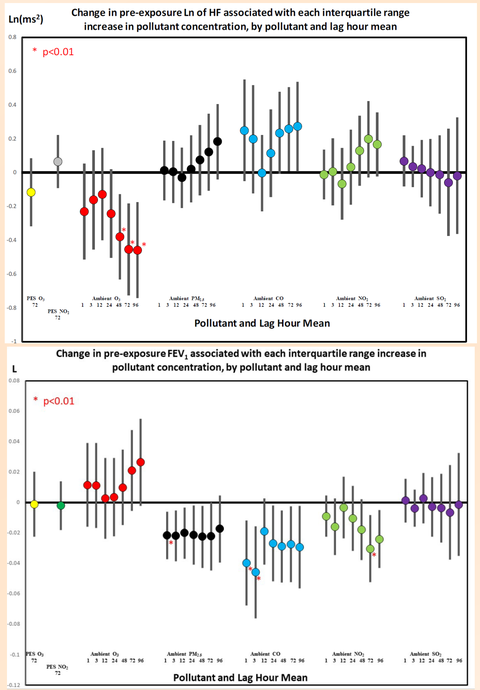
In Part 1 of this multicenter clinical study of older healthy subjects, ozone exposure caused concentration-related limitations in lung function and evidence for airway inflammation and injury. However, there was no evidence for acute effects of ozone on cardiovascular function or systemic inflammation.

MOSES Part 2: Specific Aims

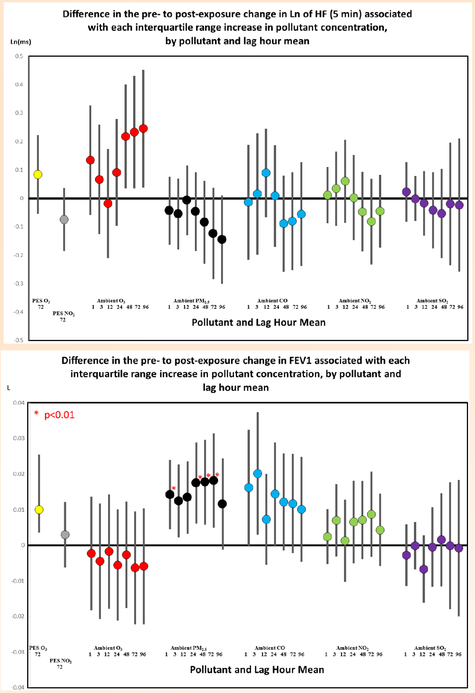
Using MOSES biomarker and subject data, personal measurements of O_3 and NO_2 in the 72 hours before the pre-exposure visit, and hourly ambient concentrations of multiple pollutants (including O_3) in the 96 hours before the pre-exposure visit, measured at ambient air quality monitoring sites near each of the 3 clinical centers.
Aim 1. Determine whether increased personal O_3 and NO_2 concentrations in the previous 72 hours, and increased ambient O_3 and other ambient pollutant concentrations in the previous 96 hours are associated with biomarker changes from pre- to post-exposure, independent of the controlled ozone exposures.
Aim 2. Explore whether increased personal O_3 and NO_2 concentrations in the previous 72 hours, and increased ambient O_3 and other pollutant concentrations in the previous 96 hours modified biomarker responses to the controlled ozone exposures.
Aim 3. Explore whether increased personal O_3 and NO_2 concentrations in the previous 72 hours, and increased ambient O_3 and other pollutant concentrations in the previous 96 hours are associated with changes in biomarkers measured at the pre-exposure visit.

Part 2: Results

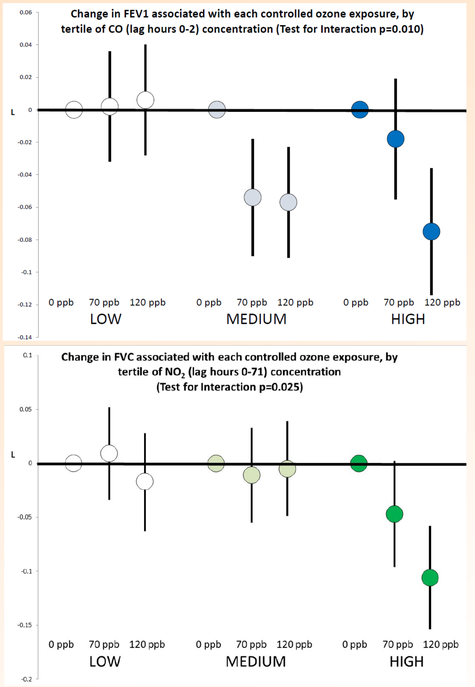
Aim 3



Aim 1



Aim 2



Part 2: Conclusions

Aims 3 and 1: *HRV*: Increased ambient O_3 concentrations had adverse effects on pre-exposure HRV levels, with reductions in HF, LF, RMSSD and SDNN (Aim 3). The O_3 associations with HF were independent of $PM_{2.5}$, CO, and NO_2 in two-pollutant models. The HRV increases from pre- to post-exposure associated with the same increased O_3 concentrations in Aim 1 likely reflect a "recovery" of HRV during the exposure sessions. *Pulmonary Function*: For Aim 3, increases in ambient concentrations of $PM_{2.5}$, CO, and NO_2 in the 96 hours before the pre-exposure visit were significantly associated with decrements in FEV_1, and perhaps FVC. For Aim 1, the same increases in ambient $PM_{2.5}$ were associated with increases in FEV_1 over the subsequent hours of the exposure sessions. This suggests a "recovery" from the effects of these pollutants during the time in the exposure chamber and laboratory. *Other outcomes*: There were no clear patterns of response for other outcome groups.

Aim 2: *Pulmonary Function*: Effects of the 120 ppb and 70 ppb controlled ozone exposures on markers of pulmonary function (FEV_1 and FVC) appeared to be modified by concentrations of ambient NO_2, CO, and PES NO_2 in the 72 hours before the pre-exposure visit, but not by PES O_3, or ambient O_3, $PM_{2.5}$, or SO_2. Reductions in FEV_1 and FVC, in exposure-response patterns, were generally observed in the High tertile (with no change in these markers in the Low tertile (i.e. consistent with Hypothesis #2). Further, the same pollutants showed the same effect modification patterns for both FEV_1 and FVC. *Other outcomes*: There were no clear patterns of effect modification of other outcome groups by any pollutant.