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Low-level ozone has both respiratory & systemic effects in African-American adolescents with asthma despite asthma controller therapy

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Capsule Summary:

In a cohort of African American adolescents with persistent asthma on guidelines-based daily controller therapies, short–term elevation of low ozone levels below the National Ambient Air Quality Standard of 70 ppb were associated with lung function decrements and elevated lipid levels.

Keywords

Ozone; adolescent; asthma; controller therapies; African-American; spirometry; lipids; pollution

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To the Editor:

Short-term exposure to ambient air ozone has long been recognized to have adverse respiratory effects, leading the Environmental Protection Agency (EPA) to lower the 8-hour National Ambient Air Quality Standard (NAAQS) to 70 parts per billion (ppb) in 2015 (1). Although short-term ozone exposure has been shown to affect respiratory outcomes, recent murine and human studies in adults have also suggested that ozone has systemic effects, including altered low-density lipoproteins (LDL)(2).

Minorities often live in low-income, urban housing in areas with increased exposure to both indoor and outdoor pollution, increasing their risk for pollutant-induced disease. In this report, we examined the respiratory and systemic response of African-American adolescents with persistent asthma, a high-risk group for pollutant-related asthma morbidity (3), to changes in ambient air ozone at levels below the NAAQS.

Twenty-three African-American teens, ages 12–17, with persistent asthma were recruited from the Allergy/Immunology and Pediatric Pulmonary clinics located in Raleigh, NC. Asthma medication use was reviewed and optimized for all patients at the baseline visit, including inhaler with spacer technique. The work described was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), approved by the UNC Institutional Review Board and the EPA Human Protocols Office, and posted on Clinicaltrials.gov (NCT01891630). Written informed consent was obtained from parents and assent obtained from all participants prior to enrollment.

Each participant completed six study visits between August 2013 and October 2014, for a total of 138 person-observation times (Table EI). Visits were spaced a week apart on the same day of the week and time of day (~3 pm) to minimize day-of-week or time-of-day confounding. At each visit spirometry was performed using American Thoracic Society guidelines (4). Blood, drawn at each visit, was sent to a clinical laboratory (LabCorp., Burlington, NC, USA) to obtain non-fasting blood lipids.

Analyses used average daily exposure concentrations for exam day (lag 0) and the 4 preceding days (lags 1–4). Mean 24-hr ozone and particulate matter with a diameter of less than 2.5 micrometers ($PM_{2.5}$) levels were calculated from hourly central monitor data, obtained from a monitoring station located in Raleigh (Wake County, NC). The maximum 8-hr ozone concentration (8-hr max) represents the highest 8-hr average in the relevant 24-hr period. Because the EPA-estimated 8-hr maximum (midnight to midnight) often includes the 3pm hour at which the exam occurred, we used the average daily exposure for analyses and calculated the 8-hr max for the relevant 24-hr (3pm-3pm) period.

We used a linear mixed effects model with a random participant intercept to evaluate the relationship of exposure to each continuous outcome in single pollutant (ozone), and co-pollutant models (ozone+$PM_{2.5}$). Using repeated measures on each subject allowed each person to act as his/her own control in modeling procedures. All models were adjusted for temperature and relative humidity (selected *a priori*) corresponding to the lag of the exposure. As a sensitivity analysis, we further adjusted for season using natural spline with knots at the change of seasons; season was retained in the model if it substantially modified

the effect estimate. Effect estimates are presented as changes in the outcome variable together for an interquartile range (IQR) increase in ambient ozone concentration. We visually assessed normality of model residuals, and used Cook's distance to evaluate potential influential values or subjects. Data were analyzed using R 3.4.0 (5).

All subjects were on daily controller therapy, and most were atopic (Table EI). The average 24-hr ozone concentrations during the study period ranged from 2.0 to 50.6 ppb, with a mean value of 26.8 ppb (Figure E1, Table EII). The 8-hr maximum concentrations ranged from 14.8 to 69.6 ppb, all below the 8-hr NAAQS. $PM_{2.5}$ mass concentrations during this period ranged from 0.8 to 29.6 $\mu g/m^3$ (all below the NAAQS of 35 ug/m^3), with a mean value of 10.9 $\mu g/m^3$. Ozone and $PM_{2.5}$ levels were weakly but significantly correlated (ρ=0.097, p = 0.04, Spearman correlation) during the study period.

Elevations in ambient ozone concentrations were associated with reduced lung function measurements. The strongest effect was observed for ozone concentrations in the 24-hour period preceding clinic visits (lag 0), where there the % predicted FVC was 2.7 points lower (p =0.02) (Figure 1a). This decrement diminished for the preceding 24 to 48-hr period (lag 1) to 1.3 points. For the previous 5-day moving average, a decrease of 2.9 points was seen (p=0.07). For % predicted FEV_1 (Figure 1b), there was a drop of 2.5 points at lag 0 (p=0.07) and a 1.6 point drop at lag 1. The effect estimates were minimally altered in the two-pollutant model, with a drop of 2.5 points in %FVC and 1.4 points in $\%FEV_1$ seen at lag 0 and lag 1, respectively.

Ozone was associated with an increase in total cholesterol levels of 5.56 mg/dL at lag 1, per IQR of ozone (p<0.006) (Figure 2a); further controlling for season, the effect estimate decreased slightly to 5.21 mg/dL (p = 0.014). At the same lag 1, an association with a 3.6 mg/dL increase in LDL (p=0.06) was observed (Figure 2b). No changes in triglycerides or VLDL were observed. In all cases where significant outcomes were found in the single pollutant model, no more than 10% variation was observed in any outcome using the two-pollutant model.

Low-level increases of ambient air ozone concentrations were associated with both adverse respiratory and systemic changes in African American adolescents with persistent asthma despite guidelines-based therapy, the first report of its kind in children. Previous studies in asthmatic children have shown associations between acute exposure to high levels of ozone and decrements in lung function (6, 7). It is hypothesized that use of asthma therapies such as inhaled corticosteroids may modify the adverse effects of air pollution; here, we show that decrements in lung function are observed even at ozone levels within the current NAAQS standard of 70 ppb and with the use of daily asthma controller therapy. Given that 61% of participants were using combined inhaled corticosteroid/long-acting beta agonist therapy, we may be underestimating the association between low-level ozone exposure and diminished lung function due to the long-acting beta agonist effect.

Additionally, we demonstrate that ambient ozone exposure is associated with systemic changes in blood lipids. Though the clinical consequences of these increases in blood lipid

levels are unclear, it has been proposed development of atherosclerotic cardiovascular disease is linked to increased blood lipids in adolescence (8).

The study has several potential limitations. We used central site monitoring to establish ozone concentrations rather than home or school monitoring. Since ozone has a largely homogeneous spatial distribution and participants lived within 30 miles of the monitoring station, it is unlikely to influence the results. We cannot distinguish the isolated effect of environmental allergens on lung function in our primarily atopic cohort as ozone can increase sensitivity to allergens and enhance airway eosinophilia (9). Due to this exploratory study's small size, all findings are susceptible to influential observations, though removing no one observation or individual abolished the findings reported. Although we scheduled participants to return for study visits at the same time of day, ozone effects on blood lipid levels may be affected by dietary intake.

In summary, we show that increases in ambient air ozone at sub-NAAQS levels are associated with pulmonary and systemic changes in African-American adolescents with persistent asthma. Additionally, use of asthma controller therapies did not protect against respiratory effects. This is the first report of systemic changes associated with short-term ozone exposure in adolescents, and will need to be confirmed in larger scale studies involving more diverse groups at high risk of exposure to ambient air pollution.

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Abbreviations:

CI	Confidence Intervals
EPA	Environmental Protection Agency
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume in 1 second
IQR	Interquartile range
LDL	Low-density lipoproteins
NAAQS	National Ambient Air Quality Standards
$PM_{2.5}$	Particulate Matter less than 2.5 microns
PPB	Parts per billion
UNC	University of North Carolina

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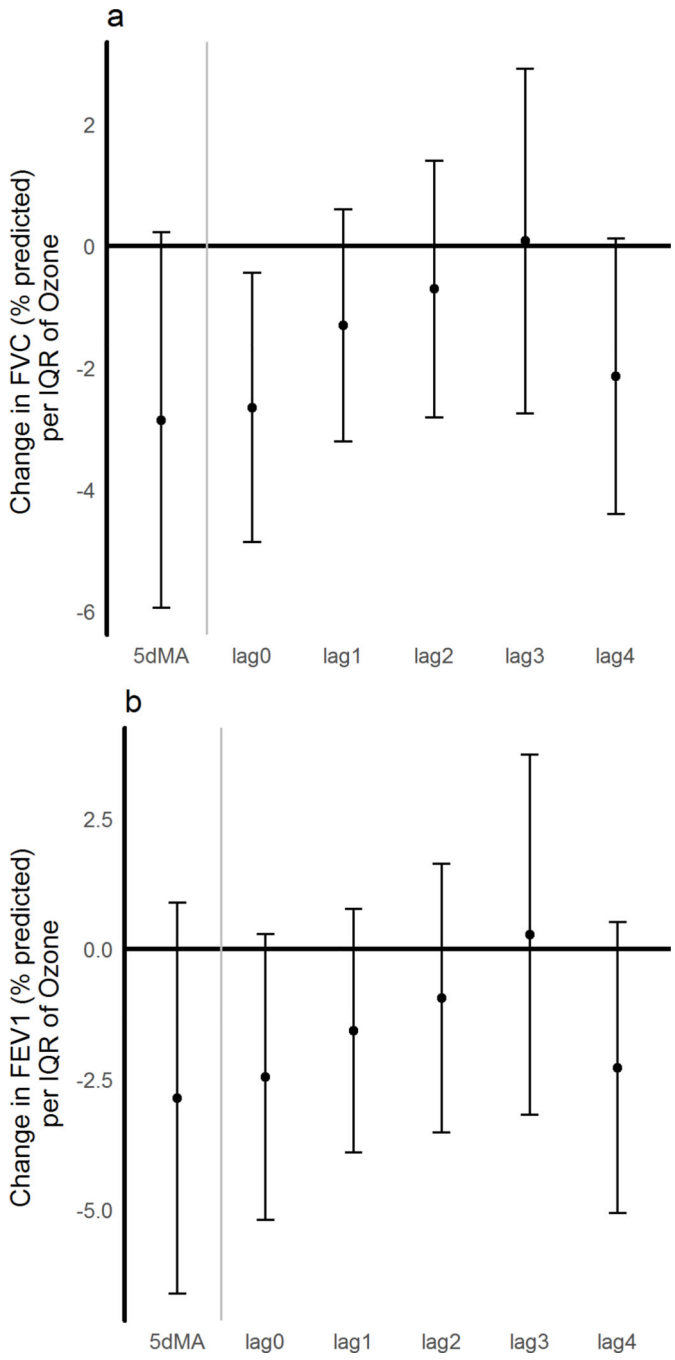

Figure 1: Changes in lung function with ambient ozone concentrations.

A) Change in % predicted FVC; **B**) Change in % predicted FEV_1 under a single pollutant model for ozone. Effect estimates and 95% CI are shown and correspond to changes per IQR of ozone for the day of exam (lag 0) for each of the 4 preceding days (lags 1–4), and for the 5-day moving average (5dMA). All models were adjusted for temperature, and humidity.

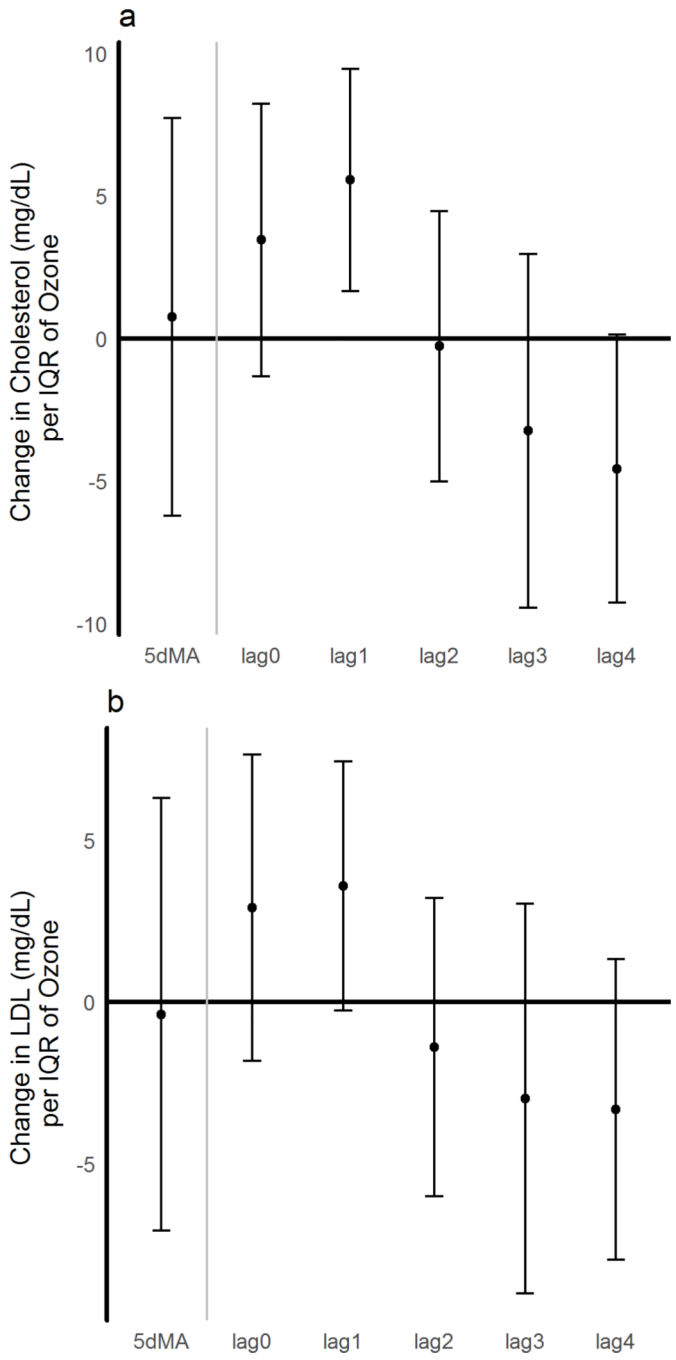

Figure 2. Ozone effects on blood lipids.

A). Changes in total Cholesterol and **B**). LDL (mg/dL). Effect estimates and 95% CI are shown and correspond to changes per IQR of ozone for the day of exam (lag 0) for each of the 4 preceding days (lags 1–4), and for the 5-day moving average (5dMA). A single pollutant model for ozone was used and adjusted for temperature, and humidity.

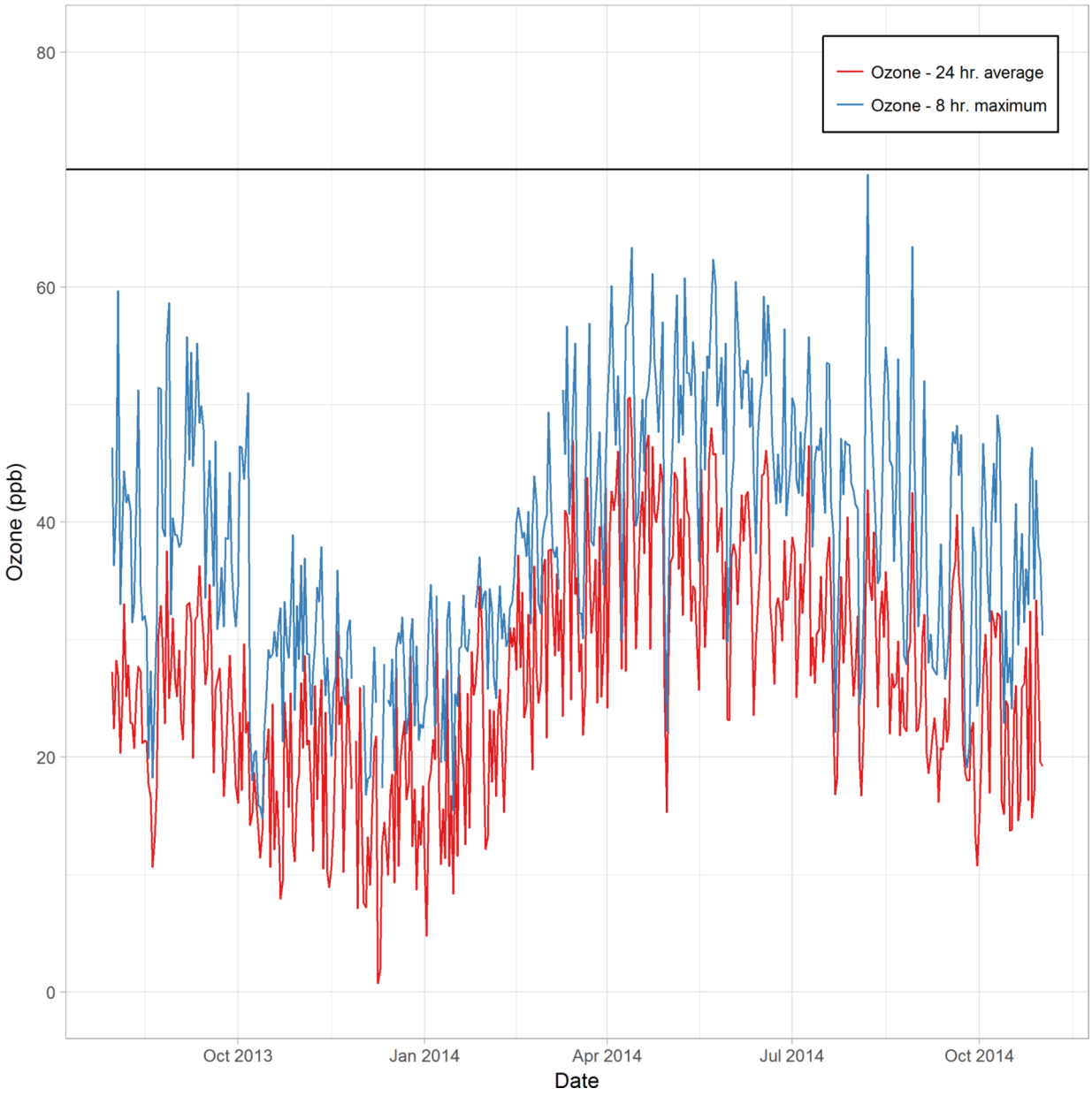

Figure E1: Ambient ozone levels throughout the study period.

Daily ozone (ppb) concentrations 24-hr average (red line) and 8-hr maximum (blue line) from August 2013 to November 2014. Values were calculated from a central monitor. The horizontal line represents the current NAAQS for ground level ozone of 70 ppb.

Table EI.

Study Participants Characteristics

		All Subjects
Total visits		138
Sex		
	Females	8
	Males	15
Age		
	Mean (± SD) years	14.0 (1.9)
	range	12–17
BMI		
	greater than 85%tile for age	48%
	greater than 95%tile for age	26%
Asthma Control		
	Physician diagnosed control at baseline	61%
Exposure to Tobacco Smoke		
	Yes	13%
Family Income		
	Less than 30,000	57%
	31,000 or more	30%
	Undetermined	13%
Highest education of either parent/guardian		
	more than High School diploma	26%
	high school diploma or less	74%
Allergies †		
	Foods (e.g., tree, nuts, peanuts, fruit, shellfish, soy)	35%
	Seasonal or dust	65%
	Drug	35%
	None	17%
IgE (UI/mL)		
	Mean ± SD	501.4 (616.1)
	Range	(7, 1964)
	# missing	7
Asthma Therapy (N) °		
	Step 2 therapy	3
	Step 3 therapy	9
	Step 4 therapy	5
	Step 5 therapy	5
	Step 6 therapy	1

† Because individual patients may have more than one allergy, the sum of percentages does not equal 100%.

° The step of therapy was classified according to the NHLBI guidelines.

Table EII

Average daily pollutant concentrations during study periods (August 2013 -October 2014)

	Mean (SD)	Min	25th percentile	Median	75th percentile	Max	IQR*
Ozone – 24-hr average (ppb)	26.8 (9.5)	2.0	19.9	26.3	33.1	50.6.	16.5
Ozone – 8-hr maximum (ppb)	38.6 (10.8)	14.8	30.3	38.6	46.7	69.6	18.1
PM2.5 (μg/m3)	10.9 (4.7)	0.8	7.6	10.1	10.9	29.6	6.6
Avg. Daily Temperature (°F)	61.4 (15.4)	16.4	48.9	65.3	61.4	85.8	20.3
Relative humidity (%)	67.9 (13.3)	34.0	59.0	69.0	67.9	95	17.0
Barometric pressure (hPa)	1002.2 (5.4)	982.7	998.8	1002	1002.2	1017.9	6.1

*IQR was determined from the lag 0 values on visit days