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## Original Contribution

# Association Between Changes in Exposure to Air Pollution and Biomarkers of Oxidative Stress in Children Before and During the Beijing Olympics

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It is not known whether exposure to air pollutants causes systemic oxidative stress in children. We investigated the association between exposure to air pollution and biomarkers of oxidative stress in relation to a governmental air quality intervention implemented during the 2008 Beijing Olympic Games. We studied 36 schoolchildren during 5 time periods before and during the Olympic Games in Beijing (June 2007–September 2008). The oxidative stress biomarkers 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and malondialdehyde were measured in urine samples collected daily during each period. Generalized estimating equations were used to examine the relationship between repeated biomarker measurements and ambient air pollutant levels. During the Olympic intervention period, substantial reductions in air pollution (−19% to −72%), urinary 8-oxodG concentrations (−37.4%; 95% confidence interval: −53.5, −15.7), and urinary malondialdehyde concentrations (−25.3%; 95% confidence interval: −34.3, −15.1) were found. Malondialdehyde and 8-oxodG were significantly associated with concentrations of black carbon, fine particulate matter with an aerodynamic with diameter less than 2.5 μm, sulfur dioxide, nitrogen dioxide, and carbon monoxide. Biomarker changes per each interquartile-range increase in pollutants were largest at lag 0 or lag 1. In a 2-pollutant model, the most robust associations were for black carbon. These findings suggest that exposure to black carbon leads to systemic oxidative stress in children.

air pollution; black carbon; children; 8-oxo-7,8-dihydro-2′-deoxyguanosine; intervention; malondialdehyde; oxidative stress; particulate matter

Abbreviations: 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; PM, particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic with diameter less than 2.5 μm.

Particulate matter (PM) has a substantial impact on the development of cardiovascular and pulmonary diseases. Oxidative stress is thought to be a key factor underlying the development of disease, possibly because reactive oxygen species modify DNA and lipids (1). A growing body of evidence has shown a strong association between increased exposure to PM and an increase in levels of oxidized DNA and lipids (2). However, the association of a decrease in PM levels with health has been evaluated in relatively few studies; thus, the current evidence for a relationship between PM exposure and oxidative stress–induced damage is insufficient to allow inference of a causal relationship. Furthermore, the results of the few studies in which the relationship between PM exposure and oxidative stress in children was investigated have been inconsistent (3–5). Thus, critical gaps exist in our knowledge of the biological mechanisms underlying the potential effects of PM in the pediatric population.

In a series of quasi-experimental intervention studies conducted before, during, and after the air pollution control period instituted for the 2008 Beijing Olympics, researchers investigated the associations of biomarkers of oxidative stress, inflammation, and thrombosis with improvements in air quality (6–9). These studies increased the understanding of the causal link between air pollution and detrimental health effects and provided direct evidence showing that reducing exposure to air pollution can improve human health (10). In the

present study, we show the results of an intervention study of the relationship between short-term exposure to pollution and oxidative stress in children as measured using the urinary biomarkers 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) and malondialdehyde. They have become pivotal biomarkers for the assessment of oxidative stress in recent years and have been associated with the development of cancer, Alzheimer's disease, diabetes mellitus, and atherosclerosis (1, 2, 11). We analyzed the associations of a reduction in fine particulate matter with an aerodynamic with diameter less than 2.5 μm ($PM_{2.5}$) and other air pollution components with urinary levels of 8-oxodG and malondialdehyde to explore the link between oxidative stress and exposure to pollutants.

## METHODS

### Study design

China took unprecedented actions to control air pollution during the 2008 Olympic and Paralympic Games (12). In 2007, before the pollution-control period, we recruited 38 fourth-grade schoolchildren (average age, 10.6 years) from an elementary school that was located 650 m away from an air pollution–monitoring station. Details of the study design have been published previously (9). To obtain a wide range of air pollutant concentrations, we collected samples over 5 time periods between 2007 and 2008; 4 were before the Olympics (June 11–22, 2007; September 10–20, 2007; December 10–21, 2007; and June 16–27, 2008) and 1 was during the Olympics (September 1–12, 2008). During each period, urine samples and daily diaries of the children's activities over the past 24 hours were collected from each subject Monday through Friday during the school lunch break. The data analysis included information from the 36 children who participated in all 5 periods (Web Table 1, available at http://aje.oxfordjournals.org/). The study protocol was approved by the Ethics Committee of Peking University, and written informed consent was provided by a parent of each child.

### Sample collection and analysis

Spot urine samples were collected by trained field technicians daily during the study periods. A detailed description of the analyses of 8-oxodG, malondialdehyde, and creatinine is provided in Web Appendix 1. The final data set consisted of 1,363 creatinine-corrected 8-oxodG measurements and 1,311 creatinine-corrected malondialdehyde measurements from 36 children taken over a 15-month period.

### Air pollution exposure

Air pollutant concentrations were measured continuously at the air pollution–monitoring station located southwest of the elementary school. Hourly averaged concentrations of black carbon, $PM_{2.5}$, sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone, as well as meteorological parameters,

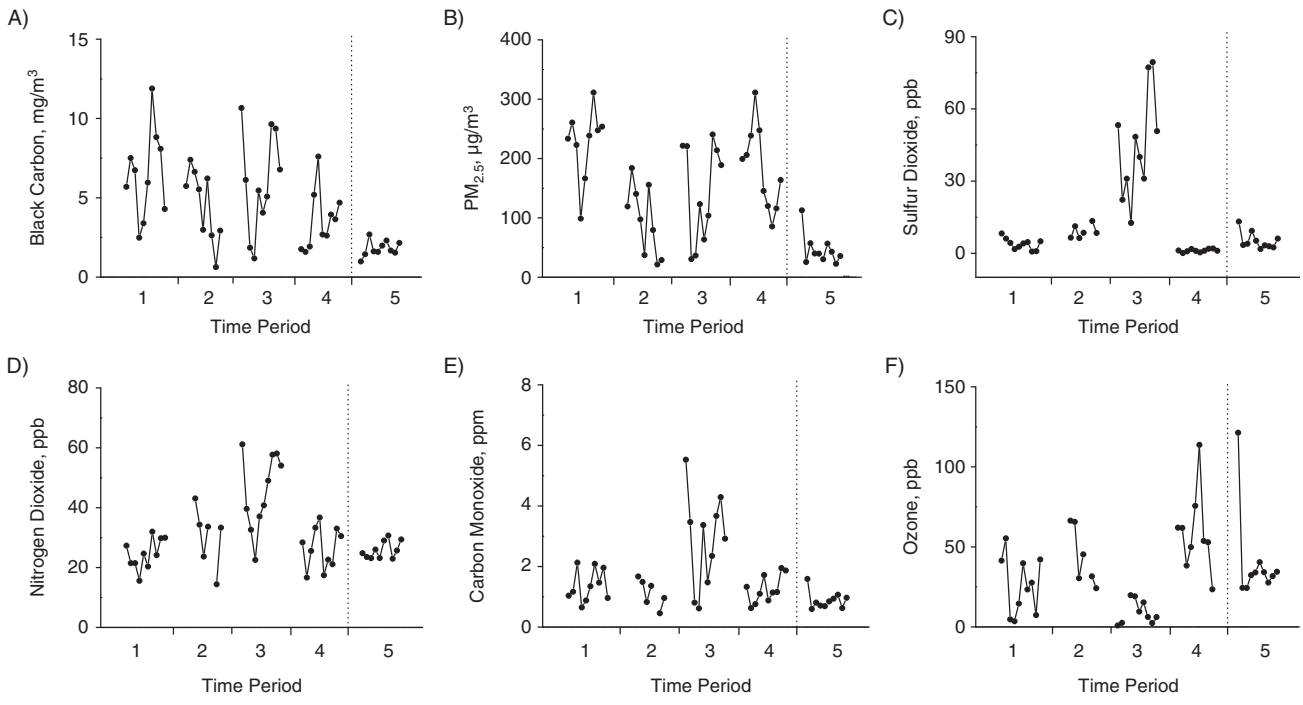


**Figure 1.** Time series of air pollutant levels over the 5 time periods before and during the 2008 Beijing Olympic Games, Beijing, China, 2007–2008. A) Black carbon, B) particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), C) sulfur dioxide, D) nitrogen dioxide, E) carbon monoxide, and F) ozone. Time period 1 was June 11–22, 2007; time period 2 was September 10–20, 2007; time period 3 was December 10–21, 2007; time period 4 was June 16–27, 2008; and time period 5 was September 1–12, 2008. The dashed vertical line separates measurements taken before the Beijing Olympic Games air pollution intervention from those taken during the intervention.

**Table 1.** Distribution and Period Comparison of Urinary Creatinine-Corrected 8-Oxo-7,8-Dihydro-2′-Deoxyguanosine and Malondialdehyde Concentrations, Beijing, China, 2007–2008

| Biomarker and Period[a] | Geometric Mean | 95% CI | Between-Period % Change[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Average of Periods 1–4 to Period 5 | | Period 2–Period 5 | | Period 4–Period 5 | |
| | | | % | 95% CI | % | 95% CI | % | 95% CI |
| 8-oxodG, ng/mg creatinine | | | −37.4 | −53.5, −15.7 | −54.9 | −68.4, −35.5 | −13.2 | −40.0, 25.6 |
| 1 | 2.56 | 2.22, 2.95 | | | | | | |
| 2 | 3.02 | 2.67, 3.42 | | | | | | |
| 3 | 2.45 | 2.14, 2.80 | | | | | | |
| 4 | 1.53 | 1.35, 1.74 | | | | | | |
| 5 | 1.43 | 1.23, 1.67 | | | | | | |
| 1–4 | 2.30 | 2.14, 2.46 | | | | | | |
| *P* value[c] | | | | 0.002 | | <0.0001 | | 0.453 |
| Malondialdehyde, mmol/mol creatinine | | | −25.3 | −34.3, −15.1 | −28.9 | −40.2, −15.5 | −21.5 | −34.1, −6.6 |
| 1 | 0.114 | 0.105, 0.124 | | | | | | |
| 2 | 0.105 | 0.098, 0.114 | | | | | | |
| 3 | 0.114 | 0.106, 0.123 | | | | | | |
| 4 | 0.099 | 0.092, 0.107 | | | | | | |
| 5 | 0.083 | 0.077, 0.091 | | | | | | |
| 1–4 | 0.108 | 0.104, 0.112 | | | | | | |
| *P* value[c] | | | | <0.0001 | | <0.0001 | | 0.006 |

Abbreviations: CI, confidence interval; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine.
[a] Period 1 was June 11–22, 2007; period 2 was September 10–20, 2007; period 3 was December 10–21, 2007; period 4 was June 16–27, 2008; and period 5 was September 1–12, 2008.
[b] Adjusted for daily temperature, humidity, and body mass index.
[c] *P* value for the comparison between subgroups, by *Z* test.

were measured concurrently (Web Table 2). Data obtained from this station are representative of air pollutant exposures in the Beijing urban area (Web Appendix 2).

### Statistical analysis

Full model specifications are provided in Web Appendix 3. Briefly, we compared the levels of air pollution, 8-oxodG, and malondialdehyde before (periods 1–4) and during (period 5) the Olympic Games. Additionally, we compared repeated measurements of urinary biomarkers and daily ambient air pollutant levels using generalized estimating equations (13). Lagged associations up to a maximum of 5 days (lag 0–lag 5) were compared using 3 methods: single-lag, polynomial distributed lag, and unconstrained distributed lag models. In the unconstrained distributed lag models, we distinguished between immediate (lag 0–1 days), delayed (lag 2–5 days), and prolonged (lag 0–5 days) association patterns. All associations are presented per each interquartile-range increase in pollutant concentrations.

The exposure-response relationship, between-pollutant confounding, and potential modifications by sex and asthma status of the associations between air pollution and urinary biomarkers were investigated. All of the models were adjusted for season, day of the week, temperature, relative humidity, body mass index, asthma status, sex, and exposure to environmental tobacco smoke in the home. All reported *P* values are 2-tailed. All calculations were performed using STATA, version 10 (StataCorp LP, College Station, Texas).

## RESULTS

We found considerable variation in daily levels of air pollutants during the 5 study periods. Compared with the average concentrations of the pollutants in periods 1–4, concentrations of black carbon, $PM_{2.5}$, and sulfur dioxide were significantly lower in period 5 (−65%, −72%, and −66%, respectively) (Figure 1A, 1B, and 1E), whereas the changes of nitrogen dioxide (−19%) and carbon monoxide (−48%) were not significant (Figure 1C and 1D). The concentrations of the pollutants were positively correlated with each other (Web Table 3) with the exception of ozone, which was negatively correlated with nitrogen dioxide and sulfur dioxide.

The mean concentrations of 8-oxodG and malondialdehyde for each study period are shown in Table 1. The intraclass correlation coefficient in the same subject over a period of 15 months was 0.33 (95% confidence interval: 0.29, 0.38) for 8-oxodG concentration and 0.16 (95% confidence

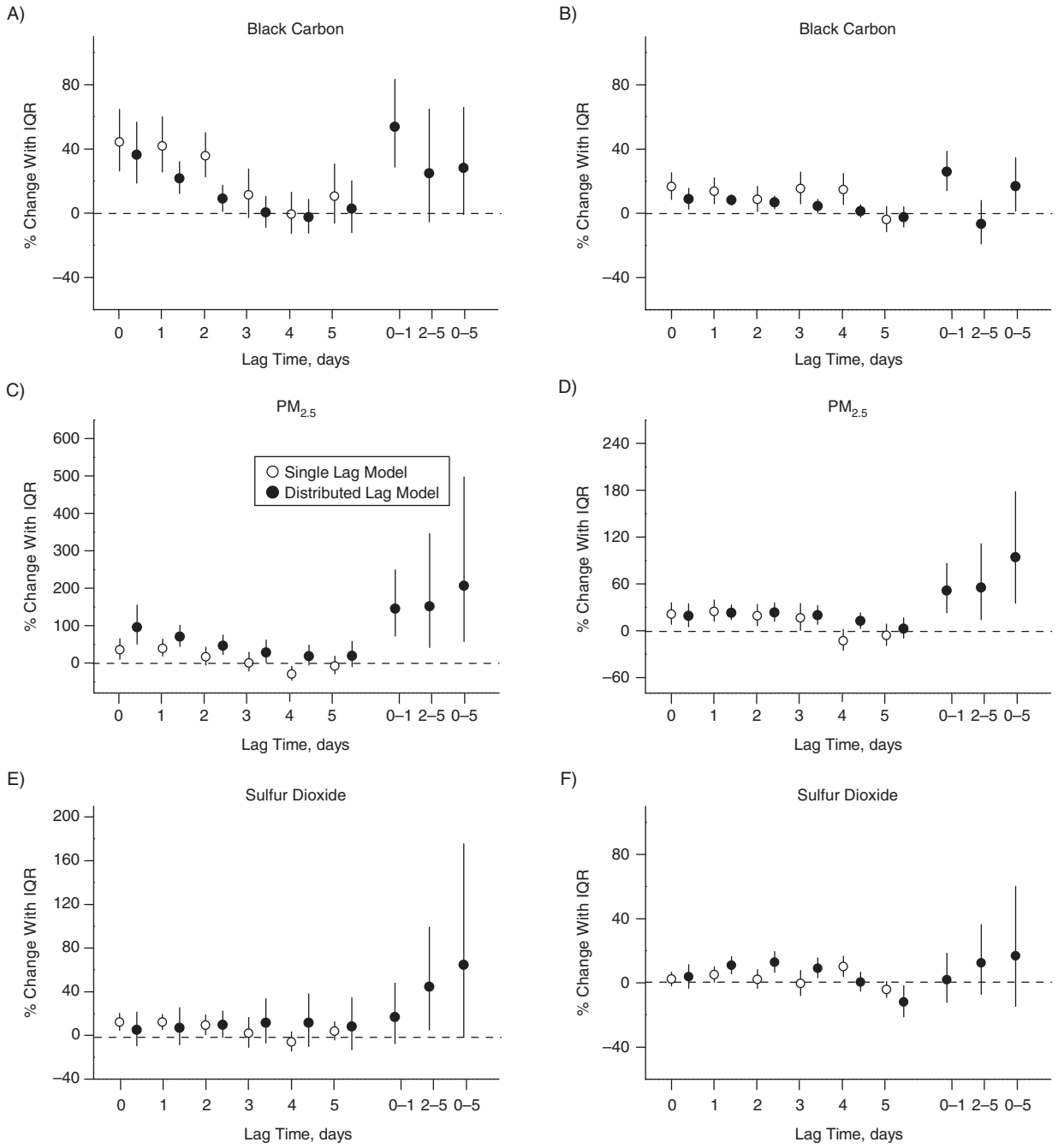


**Figure 2 continues**

interval: 0.13, 0.21) for malondialdehyde concentration. Levels of 8-oxodG and malondialdehyde were significantly lower in period 5 than in the 4 preceding periods (average of periods 1–4 vs. period 5). We compared periods in the same month of different years (period 2 vs. period 5) and in different months of the same year (period 4 vs. period 5). The results indicated that changes in biomarker concentrations during the intervention were not attributable to seasonal changes or long-term trends (Table 1).

The results of the single-lag and polynomial distributed lag models were not significantly different (Figure 2). Biomarker changes per each interquartile-range increase in pollutant concentrations were largest at lag 0 or lag 1. The lag structure suggested immediate associations of black carbon, $PM_{2.5}$, and carbon monoxide with oxidative stress from lag 0 to 1 and a prolonged association of $PM_{2.5}$ with oxidative stress up to lag 5. The results for sulfur dioxide and nitrogen dioxide were less precise, with the strongest associations for lag 0 or lag 1.

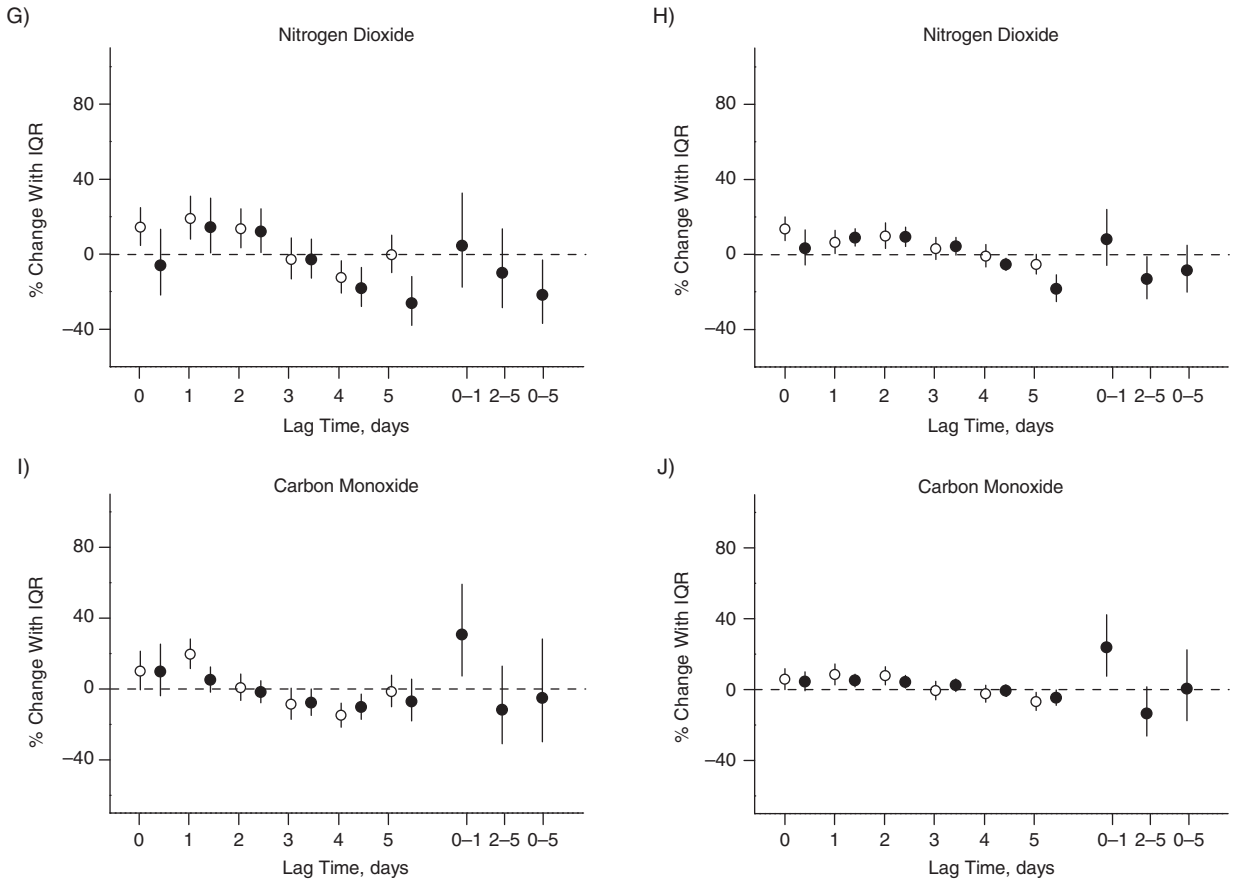


**Figure 2.** Changes in urinary biomarkers per interquartile-range (IQR) increase in air pollution concentrations over different exposure lag times, Beijing, China, 2007–2008. A, C, E, G, and I show data for 8-oxo-7,8-dihydro-2′-deoxyguanosine; B, D, F, H, and J show data for malondialdehyde. The IQR concentrations were as follows: for black carbon, 4.23 μg/m$^3$; for particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), 171.4 μg/m$^3$; for sulfur dioxide, 10.8 ppb; for nitrogen dioxide, 10.5 ppb; and for carbon monoxide, 1.04 ppm. The black circles indicate single-lag models in which each lag term of pollutant concentration was added to the model 1 at a time; the white circles indicate a third-degree polynomial and constraints for 8-oxo-7,8-dihydro-2′-deoxyguanosine and a second-degree polynomial for malondialdehyde from lag 0–5, as well as an unconstrained distributed model for cumulative lags 0–1, 2–5, and 0–5. All estimates were adjusted for season, day of the week, temperature, relative humidity, body mass index, asthma status, sex, and exposure to environmental tobacco smoke in the home.

The associations between the air pollutant concentrations and biomarkers were not altered by sex or asthma status (Web Tables 4 and 5).

We determined the difference in the association between the levels of oxidative stress and each category of exposure relative to the lowest exposure category (Table 2). The results suggest a strong exposure-response relationship between level of 8-oxodG and increasing exposure to black carbon and sulfur dioxide. We did not observe an exposure-response relationship between 8-oxodG and the other pollutants; however, all point estimates (with the exception of that for nitrogen dioxide) for the upper 3 categories were higher compared with the lowest category. Moreover, we found a clear exposure-response relationship between malondialdehyde levels and concentrations of black carbon, $PM_{2.5}$, and sulfur dioxide.

In the 2-pollutant model, black carbon in combination with either $PM_{2.5}$, nitrogen dioxide, sulfur dioxide, or carbon monoxide was the strongest predictor of an increase in 8-oxodG concentration (Figure 3A). Malondialdehyde had a robust association with black carbon and $PM_{2.5}$; estimates of association for black carbon decreased 33% after adjustment for $PM_{2.5}$, whereas adjustment for black carbon reduced the association with $PM_{2.5}$ by almost 55% (Figure 3B). Overall, black carbon was more strongly associated with the biomarkers for oxidative stress than were the other air pollutants.

## DISCUSSION

Our results show that oxidative stress and subsequent DNA damage and lipid peroxidation were reduced in children when the ambient air pollution levels were lower during the 2008 Beijing Olympic Games. The most robust associations were between the biomarkers and black carbon levels.

The strengths of our study include the repeated-measurements design, a wide range of air pollutant exposures, and an air pollution intervention. The citywide air pollution intervention

**Table 2.** Associations of 8-Oxo-7,8-Dihydro-2′-Deoxyguanosine and Malondialdehyde Concentrations With Ambient Air Pollutant Levels During the Whole Study Period, Beijing, China, 2007–2008

| Pollutant Percentile[a] | 8-oxodG | | | Malondialdehyde | | |
|---|---|---|---|---|---|---|
| | Geometric Mean Ratio[b] | 95% CI | *P* Value | Geometric Mean Ratio[b] | 95% CI | *P* Value |
| Black carbon | | | | | | |
| <30th (<2.3 μg/m$^3$) | 1.00 | Referent | | 1.00 | Referent | |
| 30th–60th (2.3–5.2 μg/m$^3$) | 1.55 | 1.28, 1.87 | <0.0001 | 1.16 | 1.03, 1.31 | 0.013 |
| 60th–90th (5.2–8.8 μg/m$^3$) | 1.76 | 1.41, 2.21 | <0.0001 | 1.27 | 1.12, 1.42 | <0.0001 |
| >90th (>8.8 μg/m$^3$) | 2.25 | 1.70, 2.99 | <0.0001 | 1.35 | 1.12, 1.62 | 0.001 |
| $PM_{2.5}$ | | | | | | |
| <30th (<61.8 μg/m$^3$) | 1.00 | Referent | | 1.00 | Referent | |
| 30th–60th (61.8–165.0 μg/m$^3$) | 1.52 | 1.19, 1.93 | 0.001 | 1.17 | 1.03, 1.33 | 0.014 |
| 60th–90th (165.0–248.2 μg/m$^3$) | 1.34 | 1.02, 1.76 | 0.035 | 1.19 | 1.02, 1.39 | 0.025 |
| >90th (>248.2 μg/m$^3$) | 2.42 | 1.71, 3.44 | <0.0001 | 1.33 | 1.08, 1.65 | 0.007 |
| Sulfur dioxide | | | | | | |
| <30th (<2.1 ppb) | 1.00 | Referent | | 1.00 | Referent | |
| 30th–60th (2.1–6.4 ppb) | 1.26 | 0.93, 1.70 | 0.142 | 1.21 | 1.05, 1.40 | 0.010 |
| 60th–90th (6.4–49.1 ppb) | 1.66 | 1.15, 2.41 | 0.007 | 1.40 | 1.15, 1.69 | 0.001 |
| >90th (>49.1 ppb) | 2.31 | 1.54, 3.46 | <0.0001 | 1.40 | 1.08, 1.83 | 0.012 |
| Nitrogen dioxide | | | | | | |
| <30th (<23.6 ppb) | 1.00 | Referent | | 1.00 | Referent | |
| 30th–60th (23.6–30.5 ppb) | 0.89 | 0.75, 1.06 | 0.181 | 1.07 | 0.96, 1.20 | 0.208 |
| 60th–90th (30.5–50.6 ppb) | 1.19 | 1.01, 1.39 | 0.033 | 1.26 | 1.13, 1.40 | <0.0001 |
| >90th (>50.6 ppb) | 1.79 | 1.30, 2.46 | <0.0001 | 1.37 | 1.09, 1.71 | 0.006 |
| Carbon monoxide | | | | | | |
| <30th (<0.9 ppm) | 1.00 | Referent | | 1.00 | Referent | |
| 30th–60th (0.9–1.4 ppm) | 1.33 | 1.10, 1.61 | 0.004 | 1.18 | 1.06, 1.31 | 0.002 |
| 60th–90th (1.4–3.4 ppm) | 1.30 | 1.08, 1.58 | 0.006 | 1.19 | 1.07, 1.32 | 0.001 |
| >90th (>3.4 ppm) | 1.45 | 1.06, 1.98 | 0.018 | 1.08 | 0.89, 1.31 | 0.428 |

Abbreviations: CI, confidence interval; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; $PM_{2.5}$, particulate matter with aerodynamic diameter less than 2.5 μm.

[a] Less than the 30th percentile indicates low exposure; 30th–60th percentiles indicates moderate exposure; 60th–90th percentiles indicates moderate-high exposure; and greater than the 90th percentile indicates high exposure.

[b] Adjusted for season, day of the week, temperature, relative humidity, body mass index, asthma status, sex, and exposure to environmental tobacco smoke in the home.

provided a natural experiment to explore the biological mechanisms associated with exposure to urban air pollution. When the intervention was introduced, the levels of urinary 8-oxodG and malondialdehyde decreased.

Other factors such as diet, physical activity level, and exposure to environmental tobacco smoke might affect the development of 8-oxodG and malondialdehyde (11, 14), although such factors were unlikely to change over the short time frame of the study periods our analysis. We have no detailed information about whether these factors systematically varied between the periods before and during the Olympics; however, we did ascertain from the daily diaries that the exposure patterns, such as the choice of transportation, school hours, and time spent outdoors, did not differ during the study periods. In previous studies, it was shown that age is not correlated with urinary excretion of 8-oxodG in normal healthy children (15), nor is it a significant predictor of intra-individual variability and longitudinal changes in 8-oxodG levels (16). Thus, of the factors we studied, the decreased concentration of air pollutants was the most likely cause of the reduction in oxidative stress biomarkers observed in the children.

The changes in 8-oxodG and malondialdehyde were associated with a cluster of pollutants, including black carbon, $PM_{2.5}$, sulfur dioxide, nitrogen dioxide, and carbon monoxide. This finding is significant because most previous studies have focused on PM mass (3, 4), whereas our data suggest that other pollutants might also play a critical role in oxidative damage. The analyses of daily lags and daily average concentrations black carbon, $PM_{2.5}$, and carbon monoxide revealed prolonged and more immediate associations of the pollutants with 8-oxodG and malondialdehyde, which is consistent with previous investigations in children (3, 4).

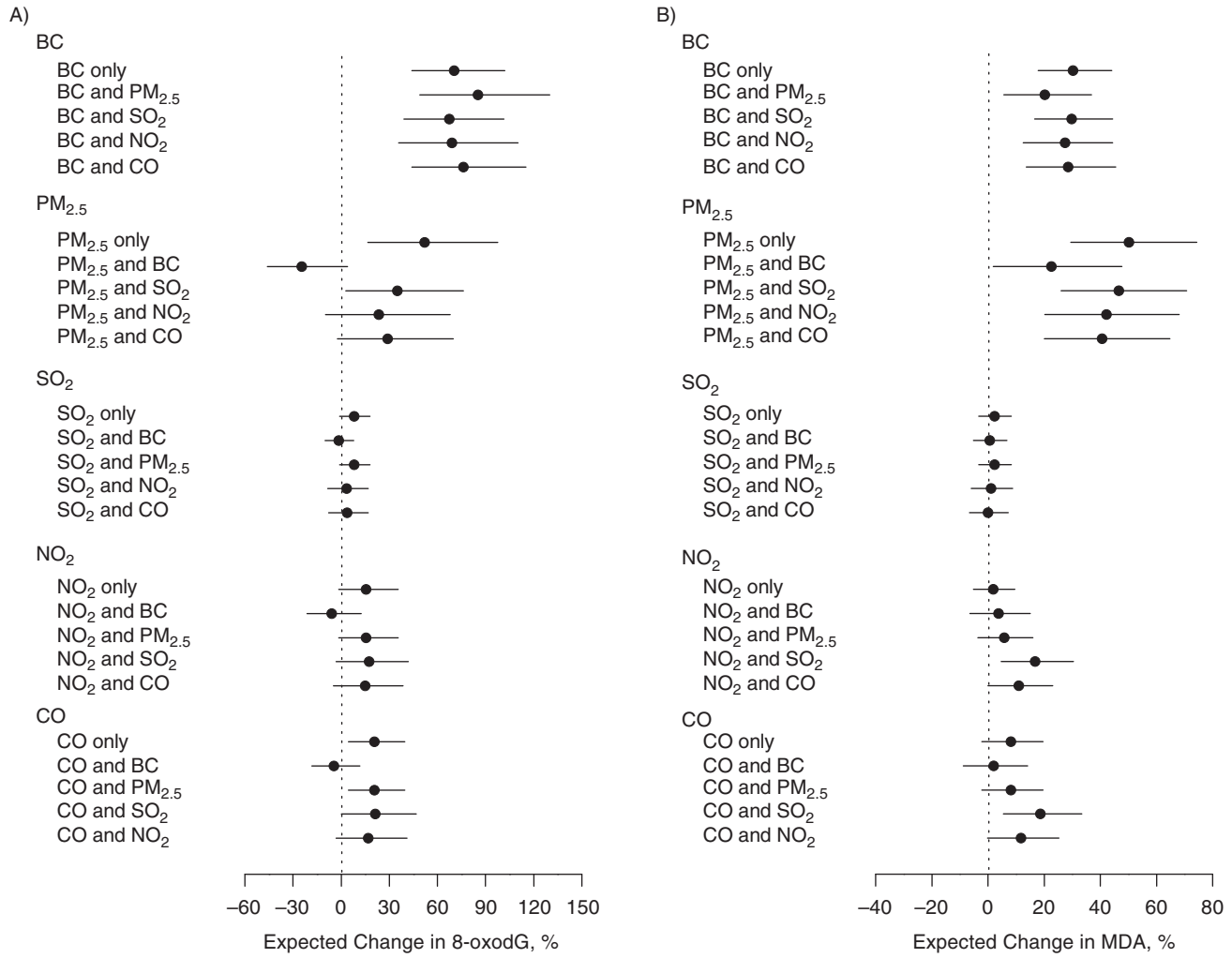


**Figure 3.** Changes in the levels of urinary biomarkers from single-pollutant and 2-pollutant models using 2-day average pollutant exposure, Beijing, China, 2007–2008. A) 8-oxo-7,8-dihydro-2′-deoxyguanosine; B) malondialdehyde (MDA). Change in urinary biomarkers is the percent change of urinary biomarkers per each interquartile-range increase in the pollutant of interest. All estimates were adjusted for season, day of the week, temperature, relative humidity, body mass index, asthma status, sex, and exposure to environmental tobacco smoke in the home. BC, black carbon; CO, carbon monoxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; $SO_2$, sulfur dioxide. Bars, 95% confidence interval.

Although the aggressive emissions controls implemented during the Olympics were effective, it was difficult to determine to what extent each individual pollutant contributed to the health effects. Previous studies of air quality interventions have encountered similar difficulties (7, 17). In our study, however, black carbon was the most likely cause for oxidative stress and subsequent increases in 8-oxodG and malondialdehyde levels. If this were the case, a positive correlation would be expected between exposure to black carbon and disease risk. In fact, in a recent review, Smith et al. (18) reported significant correlations between carbonaceous particles and all-cause and cardiovascular mortality risk. Moreover, in a recent meta-analysis, Janssen et al. (19) found positive correlations between black carbon particles and mortality from and hospital admissions for cardiovascular disease and lung cancer.

To our knowledge, few studies have directly linked air pollution exposure to oxidative stress-induced DNA/lipid damage in children (20, 21). Our findings provide direct, quantitative evidence of an association between exposure to ambient air pollutants, particularly black carbon, and oxidative injury in children. We previously documented a positive association between pollutants and inflammation in the same study (9). Given the findings of the present study, multiple biological mechanisms might underlie the adverse health effects produced by air pollutants. Childhood exposure to respiratory toxicants or carcinogens might increase the risk of developing diseases in adulthood because cell mutations initiated at an early age have a higher probability of fixation in daughter cells and a longer time for progression to malignancy later in life (22).

The present study had several limitations. First, our study lacked postintervention data. We were unable to collect data after the intervention because the children refused further participation because of the pressure of preparing for middle school entrance examinations. An additional limitation that is inherent in the study design was the lack of a control group who were not exposed to the citywide intervention. It was impossible to select controls within the same city because the intervention was citywide, and it was difficult to find another city that matched the air pollutant exposure in Beijing. However, in a panel study with repeated measures, the subjects can act as their own controls. Finally, the exposure measurements were based on data from a continuous air pollution–monitoring station near the elementary school. We were unable to correct for personal exposures.

We conclude that exposure to air pollutants leads to systemic oxidative stress in children. Given the magnitude of the association and the importance of DNA/lipid injury as a risk factor for lung cancer and cardiovascular disease (23, 24), further reductions in concentrations of air pollutants, particularly black carbon, is likely to have a significant health benefit.

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