PRELIMINARY COMMUNICATION

Association Between Changes in Air Pollution Levels During the Beijing Olympics and Biomarkers of Inflammation and Thrombosis in Healthy Young Adults

David Q. Rich, ScD
Howard M. Kipen, MD, MPH
Wei Huang, ScD
Guangfa Wang, MD
Yuedan Wang, PhD
Ping Zhu, MD
Pamela Ohman-Strickland, PhD
Min Hu, PhD
Claire Philipp, MD
Scott R. Diehl, PhD
Shou-En Lu, PhD
Jian Tong, MS
Jicheng Gong, PhD
Duncan Thomas, PhD
Tong Zhu, PhD
Junfeng (Jim) Zhang, PhD

Context Air pollution is a risk factor for cardiovascular diseases (CVD), but the underlying biological mechanisms are not well understood.

Objective To determine whether markers related to CVD pathophysiological pathways (biomarkers for systemic inflammation and thrombosis, heart rate, and blood pressure) are sensitive to changes in air pollution.

Design, Setting, and Participants Using a quasi-experimental opportunity offered by greatly restricted air pollution emissions during the Beijing Olympics, we measured pollutants daily and the outcomes listed below in 125 healthy young adults before, during, and after the 2008 Olympics (June 2-October 30). We used linear mixed-effects models to estimate the improvement in outcome levels during the Olympics and the anticipated reversal of outcome levels after pollution controls ended to determine whether changes in outcome levels were associated with changes in pollutant concentrations.

Main Outcome Measures C-reactive protein (CRP), fibrinogen, von Willebrand factor, soluble CD40 ligand (sCD40L), soluble P-selectin (sCD62P) concentrations; white blood cell count (WBC); heart rate; and blood pressure.

Results Concentrations of particulate and gaseous pollutants decreased substantially (–13% to –60%) from the pre-Olympic period to the during-Olympic period. Using 2-sided tests conducted at the .003 level, we observed statistically significant improvements in sCD62P levels by –34.0% (95% CI, –38.4% to –29.2%; $P<.001$) from a pre-Olympic mean of 6.29 ng/mL to a during-Olympic mean of 4.16 ng/mL and von Willebrand factor by –13.1% (95% CI, –18.6% to –7.5%; $P<.001$) from 106.4% to 92.6%. After adjustments for multiple comparisons, changes in the other outcomes were not statistically significant. In the post-Olympic period when pollutant concentrations increased, most outcomes approximated pre-Olympic levels, but only sCD62P and systolic blood pressure were significantly worsened from the during-Olympic period. The fraction of above-detection-limit values for CRP (percentage ≥0.3 mg/L) was reduced from 55% in the pre-Olympic period to 46% in the during-Olympic period and reduced further to 36% in the post-Olympic period. Interquartile range increases in pollutant concentrations were consistently associated with statistically significant increases in fibrinogen, von Willebrand factor, heart rate, sCD62P, and sCD40L concentrations.

Conclusions Changes in air pollution levels during the Beijing Olympics were associated with acute changes in biomarkers of inflammation and thrombosis and measures of cardiovascular physiology in healthy young persons. These findings are of uncertain clinical significance.

JAMA. 2012;307(19):2068-2078 www.jama.com

Air pollution is a risk factor for cardiovascular diseases (CVD), but the mechanisms by which air pollution leads to CVD is not well understood.[1-3] Hypothesized mechanisms with associated biomarkers include systemic inflammation (fibrinogen, C-reactive protein [CRP], white blood cell [WBC] count) and thrombosis or endothelial dysfunction (platelet activation markers P-selectin [sCD62P] and soluble CD40 ligand [sCD40L] as well as the adhesive endothelial glycoprotein von Willebrand factor). In addition, air pollution may adversely affect

For editorial comment see p 2100.

Author Affiliations are listed at the end of this article.
Corresponding Authors: Junfeng (Jim) Zhang, PhD, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 2001 N Soto St, Room 225Q, Los Angeles, CA 90089 (junfengz@usc.edu) and Tong Zhu, PhD, College of Environmental Sciences and Engineering, Peking University, Beijing, 100871, China (tzhu@pku.edu.cn).

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

measures of cardiovascular physiology such as heart rate and blood pressure.

Pollution-associated elevations in these biomarkers, observed in both young persons[4-6] and older individuals with coronary artery disease or diabetes,[7-9] have not always agreed in terms of the direction, magnitude, and timing of response, or the specific pollutants with which they are most strongly associated. This inconsistency may be partially due to the inherent limitations of panel study designs that assessed biomarker changes in relation to natural day-to-day variations in ambient concentrations of air pollutants (eg, residual confounding, differences in population characteristics, differences in particulate matter [PM] composition and pollutant mixture). In contrast, governmental pollution control interventions can result in large pollution changes and hence provide real-world quasi-experimental conditions, facilitating more controlled examination of pollution-mediated health effects. However, previous studies capitalizing on such opportunities have not assessed mechanistic biomarkers, limiting outcomes to morbidity, mortality, or both.[10-15]

As a condition for hosting the 2008 Olympic Games, the Chinese government agreed to temporarily and substantially improve air quality in Beijing for the Olympics and subsequent Paralympics. This provided a unique opportunity to use a quasi-experimental design in which exposures and biomarkers were measured at baseline (pre-Olympics), following a change in pollution (during-Olympics), and then repeated after an expected return to baseline (post-Olympics). We hypothesized that levels of inflammatory and thrombotic biomarkers as well as heart rate and blood pressure would decrease from the pre-Olympic to the during-Olympic period, followed by increases in these biomarkers from the during-Olympic to the post-Olympic period. Furthermore, across the entire period, we hypothesized that changes in biomarker levels would be correlated with changes in concentrations of specific pollutants.

METHODS

Pollution Control Measures

A series of aggressive pollution control measures were implemented from July 20 to September 17, 2008, encompassing the entire Olympic Games (August 8-24) through the end of the Paralympic Games (September 6-17), mainly limiting operation of industrial and commercial combustion facilities in Beijing and use of alternate-day driving to remove approximately one-half of the cars (≈1.5 million cars) from Beijing roads each day.[16] After the Paralympics, these pollution control actions were relaxed.

Study Design and Participants

At a central Beijing hospital, we used advertisements on hospital bulletin boards and word of mouth to screen 137 potential participants from a pool of medical residents, enrolling 128 into the study. Nine individuals either refused to participate or did not meet the inclusion criteria that participants had to be never-smokers and free of cardiorespiratory, liver, kidney, neurologic, and other chronic diseases. Participants all worked at the hospital, with 92% residing in dormitories within 5 km from the hospital. The remaining 8% lived in off-campus apartments within 9 km of the hospital. The dormitories had no cooking facilities, eliminating a major source of indoor air pollution. The participants spent, on average, approximately 70% of their time in environments other than in hospital work places, mainly in their residences that were not air conditioned. The air conditioned buildings in the hospital were not air tight and had windows that were often open during hours of the day with cooler outdoor temperatures. We used a panel study design in which each participant was asked to complete 6 clinical visits, separated by at least 1 week, with 2 in each of the pre-Olympic (June 2-July 20), during-Olympic (July 21-September 24), and post-Olympic (September 25-October 31) periods. Our period definition followed the schedule of the pollution control measures described elsewhere.[16]

Among the enrolled participants, 119 completed all 6 visits, and 6 participants completed 5 visits. Three participants who had only 1 or 2 visits were dropped from the analysis. The remaining 125 participants (744 person-visits) were used in all data analyses. Of the 63 male participants, the mean (SD) age was 24.2 (2.1) years and body mass index, calculated as weight in kilograms divided by height in meters squared, was 22.5 (2.9). Of the 62 female participants, the mean (SD) age was 24.1 (1.5) years and BMI was 20.6 (2.4). This study was approved by the University of Medicine and Dentistry of New Jersey institutional review board and the joint Ethics Committee of the Peking University Health Sciences Center and the Peking University First Hospital. All participants provided written informed consent before participating in the study.

Outcome Measurements

Each participant came to the clinic at the same time of the morning on a weekday for all clinic visits. Participants were fasting on each test day to reduce extraneous effects on platelet activation. They had not taken any medications and had no symptoms of respiratory infection or allergies for at least 7 days prior to each visit. To avoid potential effects from sleep pattern changes and nonroutine activities, no visits were made following a night shift or travel event. At each visit, we performed electrocardiographic measurements in the supine position to assess heart rate, measured blood pressure (both systolic and diastolic) manually using a sphygmomanometer following a 5-minute rest period, and drew blood without a tourniquet into heparinized or citrated tubes.[17]

Concentrations of sCD62P and sCD40L in the plasma were measured using a commercially available enzyme-linked immunosorbent assay ([ELISA] Rapidbio).[18] The detection limit for both

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

sCD62P and sCD40L was 1 ng/mL. Blood cell counts were measured using standard automated clinical methods in the hospital. Plasma fibrinogen concentrations were analyzed, within 4 hours of venous blood collection, using an automated ACL9000 analyzer. The detection limit for fibrinogen was 0.28 g/L. Concentrations of von Willebrand factor protein in the plasma were measured using a commercially available ELISA kit (Hushang Biotech) and reported as the percentage of the von Willebrand factor concentration in a standard species-specific plasma pool. C-reactive protein (CRP) concentrations were measured in EDTA (anticoagulant)–treated plasma using a clinical immunonephelometric assay with an automated nephelometer. The detection limit for CRP was 0.3 mg/L (to convert CRP from mg/L to nmol/L, multiply by 9.524).

Air Pollution and Weather Measurements

We measured 24-hour concentrations of fine particles (particulate matter ≤ 2.5 μm in aerodynamic diameter [$PM_{2.5}$]) and 3 constituents: elemental carbon, organic carbon, and sulfate. Teflon filters were used to determine $PM_{2.5}$ concentrations gravimetrically and then for sulfate by ion chromatography. Elemental carbon and organic carbon were collected on heat-treated quartz fiber filters and measured using the NIOSH Method 5040 in a commercial laboratory. We also measured gaseous pollutants (sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone) using monitors that were calibrated and maintained following the manufacturer's protocols (Ecotech Ltd). We measured ambient temperature and relative humidity at the same site. All the samplers and monitors were collocated on the rooftop of a 7-story building in the center of the same hospital campus.

Statistical Analyses

We calculated descriptive statistics for each pollutant by period. We log-transformed concentrations of sCD62P and sCD40L because both had right skewed distributions. We estimated the change in each biomarker from the before to during the Olympic period and from the during to after the Olympic period using the biomarkers as the dependent and period as the independent variable in mixed-linear models with normally distributed errors. Using the Akaike information criterion (AIC), we compared alternatives for modeling the correlation between errors within participant. Across biomarkers, this criterion consistently chose the model with equicorrelated errors. Thus, we included a single random intercept for participant, inducing equicorrelation between all observations within participant. We adjusted for temperature and relative humidity in the 24 hours before biomarker measurement (ie, if blood pressure was measured at 10 AM on June 20, 2008, then the mean relative humidity from 10 AM on June 19, 2008, to 9 AM on June 20, 2008, was included in the model) using natural splines with degrees of freedom (≤3) chosen to minimize the AIC. We also accounted for additional seasonal differences by including cumulative averages of temperature and relative humidity of up to 7 prior 24-hour periods using natural splines if these terms resulted in lower AICs. Residuals were checked for normality. To control the family-wise type I error rate at a .05 level, a Bonferroni correction was applied. With 16 between-period comparisons (8 biomarkers by 2 between-period changes), each individual 2-sided test was considered statistically significant relative to a .003 significance level.

In exploratory analyses, we estimated the change in biomarker concentration associated with each interquartile range (IQR) increase in pollutant concentration using the mixed-linear models described above. We included indicator variables for sex, day of the week, mean temperature, and relative humidity in the previous 24 hours, and if indicated by a reduced AIC value, the cumulative average of up to 7 days of temperature, relative humidity, or both. We then used this model to estimate the change in biomarker concentration associated with each IQR increase in pollutant concentrations in the 24 hours before the clinic visit (lag day 0), as well as the 6 previous 24-hour periods (lags 1-6). We report the mean percentage change, along with its 95% confidence interval, in the biomarker associated with each IQR pollutant increase. Statistical analyses were performed using the R Programming Language (Version 2.12.2; *R* Development Core Team) with the gls procedure (nlme package) to examine the pollutant time series and the lme procedure (nlme package) for evaluating changes in the biomarkers.

RESULTS

Pollutant concentrations are summarized in TABLE 1. We observed reductions in the mean concentration of sulfur dioxide (–60%), carbon monoxide (–48%), nitrogen dioxide (–43%), elemental carbon (–36%), $PM_{2.5}$ (–27%), organic carbon (–22%), and sulfate (–13%) from the pre-Olympic to the during-Olympic period. In contrast, ozone concentrations increased (24%). Pollutant concentrations generally increased substantially from the during- to post-Olympic period for all the pollutants (21% to 197%) except ozone (–61%) and sulfate (–47%). Throughout the study period, several pairs of pollutants were highly correlated ($r > 0.7$) ($PM_{2.5}$ and sulfate; elemental carbon and organic carbon; elemental carbon and nitrogen dioxide; organic carbon and nitrogen dioxide; organic carbon and sulfur dioxide; $PM_{2.5}$ and sulfur dioxide). Ozone was negatively correlated with nitrogen dioxide, elemental carbon, organic carbon, and carbon dioxide but was weakly correlated with sulfur dioxide, $PM_{2.5}$ and sulfate (TABLE 2).

Period-specific means, 95% confidence intervals, between-period changes, and *P* values testing whether these changes were statistically significantly different from 0 are shown in TABLE 3 for each biomarker. As hypothesized, we observed statistically significant decreases in sCD62P and von Willebrand factor and nonstatistically significant decreases in sCD40L, heart

 ©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

rate, and systolic and diastolic blood pressure from the before- to the during-Olympic period. The fraction of above-detection-limit values for CRP (≥0.3 mg/L) was also reduced from 55% during the pre-Olympic period to 46% in the during-Olympic period. As hypothesized, we observed increases in sCD62P, sCD40L, heart rate, fibrinogen, systolic blood pressure, and WBC count from the during- to the post-Olympic period, but only the increase in sCD62P was statistically significant after correcting for multiple comparisons. In contrast, the fraction of above-detection-limit CRP values was the lowest (36%) in the post-Olympic period.

We observed statistically significant increases in sCD62P associated with interquartile range (IQR) increases in all pollutants but ozone with the largest increases per pollutant, ranging from 5.7% or 0.055 ng/mL (95% CI, 0.030-0.081 ng/mL) to 19.1% or 0.18 ng/mL (95% CI, 0.14-0.21 ng/mL) at 24 to 95 hours (lags, 1 to 3) prior to the clinic visit. In contrast, we observed a 12% decrease or –0.13 ng/mL (95% CI, –0.18, to –0.076 ng/mL) in sCD62P associated with each IQR increase in ozone concentration in the previous 24 hours (FIGURE 1). In comparison, sCD40L increases were smaller, ranging from 2.9% or 0.029 ng/mL (95% CI, 0.0037-0.054 ng/mL) to 7.4% or 0.071 ng/mL (95% CI, 0.035-0.11 ng/mL), but still statistically significantly associated with IQR increases in $PM_{2.5}$, sulfate, elemental carbon, and sulfur dioxide concentrations (at lags, 3-5).

We observed statistically significant 4.80% (95% CI, 2.78%-6.83%) to 7.51% (95% CI, 5.20%-9.83%) increases in von Willebrand factor associated with IQR increases in most pollutants at various lag periods, with the largest effects associated with $PM_{2.5}$, sulfate, nitrogen dioxide, and elemental carbon in the previous 96 to 143 hours (lags 3-4) before the clinic visit, sulfur dioxide in the previous 24 to 71 hours (lag days, 2-3), and carbon monoxide in the previous 24 hours (lag 0; FIGURE 2). In contrast, we observed a statistically significant decrease in von Willebrand factor (–17.5%; 95% CI, –21.7% to –13.2%) associated with each IQR increase in ozone in the previous 24 hours.

For heart rate , we observed statistically significant 1.1% or 1.01/min (95% CI, 1.00-1.02/min) to 2.2% or

Table 1. Distributions of 24-Hour Mean Concentrations of Pollutants, Temperature, and Relative Humidity

Pollutant and Period[a]	No. of 24-h Periods	Mean (SD) [Range]	Median (IQR)
$PM_{2.5}$, μg/m^3			
Entire study	100	85.2 (51.9) [14.6-268.2]	80.6 (76.8)
Before	35	100.9 (38.8) [24.4-219.1]	95.8 (39.3)
During	33	69.4 (42.9) [14.6-171.4]	59.2 (66.5)
After	32	84.2 (67.2) [15.0-268.2]	60.4 (105.3)
Sulfate, μg/m^3			
Entire study	92	21.8 (17.0) [1.0-73.9]	20.7 (28.0)
Before	35	28.4 (12.8) [5.4-65.0]	29.6 (16.9)
During	28	23.2 (19.4) [2.0-73.9]	20.7 (32.0)
After	29	12.4 (15.2) [1.0-47.8]	4.8 (15.9)
Elemental carbon, μg/m^3			
Entire study	94	2.3 (1.3) [0.6-6.7]	2.1 (1.4)
Before	35	2.2 (0.7) [0.6-4.3]	2.2 (0.7)
During	28	1.4 (0.6) [0.6-3.1]	1.3 (0.6)
After	31	3.3 (1.6) [1.0-6.7]	3.3 (2.3)
Organic carbon, μg/m^3			
Entire study	94	10.2 (6.6) [1.1-43.3]	8.2 (5.1)
Before	35	8.8 (3.3) [1.1-21.9]	8.2 (2.2)
During	28	6.9 (2.7) [2.7-14.0]	6.5 (2.8)
After	31	14.8 (9.1) [3.0-43.3]	14.5 (12.5)
Sulfur dioxide, ppb			
Entire study	91	6.1 (4.0) [0.9-21.0]	4.9 (5.4)
Before	35	7.6 (4.5) [2.0-21.0]	5.8 (6.9)
During	24	3.1 (1.6) [0.9-7.7]	3.0 (2.7)
After	32	6.6 (3.6) [0.9-14.9]	6.2 (5.0)
Carbon monoxide, ppm			
Entire study	100	0.91 (0.50) [0.10-2.67]	0.82 (0.65)
Before	35	1.25 (0.41) [0.71-2.46]	1.17 (0.32)
During	33	0.63 (0.22) [0.31-1.29]	0.58 (0.26)
After	32	0.82 (0.59) [0.10-2.67]	0.74 (0.85)
Nitrogen dioxide, ppb			
Entire study	100	27.0 (15.3) [9.5-80.7]	24.7 (18.7)
Before	35	26.0 (5.1) [15.8-41.2]	25.3 (5.4)
During	33	13.9 (4.6) [9.8-30.0]	13.0 (2.5)
After	32	41.4 (17.2) [9.5-80.7]	38.9 (23.9)
Ozone, ppb			
Entire study	100	29.1 (17.0) [3.5-69.1]	25.1 (25.4)
Before	35	31.8 (16.4) [5.3-64.3]	34.1 (23.5)
During	33	39.5 (16.0) [10.0-69.1]	38.4 (17.3)
After	32	15.3 (6.5) [3.5-33.5]	14.8 (6.1)
Temperature, °C			
Entire study	99	23.3 (5.5) [9.0-32.2]	24.1 (8.1)
Before	34	25.1 (3.0) [18.5-32.2]	24.4 (3.9)
During	33	27.7 (2.5) [21.8-31.4]	28.0 (3.4)
After	32	16.8 (3.5) [9.0-22.5]	17.1 (5.2)
Relative humidity, %			
Entire study	99	60.1 (15.1) [16.3-86.7]	61.5 (19.9)
Before	34	66.6 (12.1) [41.5-86.7]	66.3 (19.2)
During	33	64.8 (10.0) [41.1-85.6]	65.2 (10.4)
After	32	48.6 (16.0) [16.3-74.3]	49.3 (24.6)

Abbreviations: IQR, interquartile range; $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter.
[a] Before the Olympics represents June 2, 2008, to July 6, 2008; during, July 28, 2008, to August 29, 2008; and after September 29, 2008, to October 30, 2008.

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

1.02/min (95% CI, 1.00-1.04/min) increases associated with IQR increases in $PM_{2.5}$, sulfate, and sulfur dioxide concentrations lagged 24 to 47 hours (lag 1), and with elemental carbon lagged 72 to 95 hours (lag, 3; FIGURE 3). For fibrinogen, we observed statistically significant increases associated with increases in $PM_{2.5}$, elemental carbon, organic carbon, sulfur dioxide, and nitrogen dioxide concentrations at multiple lag times and observed similarly sized nonstatistically significant increases associated with IQR increases in sulfate and carbon monoxide also at multiple lag times (Figure 2). The largest fibrinogen changes, ranging from 0.8% or 0.019 g/L (95% CI, 0.006-0.038 g/L) to 1.9% or 0.049 g/L (95% CI, 0.010-0.088 g/L) were associated with IQR pollutant increases lagged by 48 to 71 hours (lag 2) and 72 to 95 hours (lag 3).

We observed both statistically significant increases and decreases, without a consistent pattern, in systolic blood pressure associated with multiple pollutants. We did not observe significant increases or decreases in diastolic blood pressure with any pollutant at any lag period (FIGURE 4). In contrast and contrary to the hypothesis, the pollutant-WBC count association (Figure 3) appeared to have a generally decreasing trend with increasing lag periods. We observed 1.5% or 76/μL (95% CI, –120/μL to –30/μL) to 3.4% or –170/μL (95% CI, –310/μL to –30/μL) decreases in WBC associated with IQR increases in organic carbon, sulfur dioxide, carbon monoxide, and nitrogen dioxide, lagged 96 to 143 hours (lags 4 to 6).

COMMENT

During the unprecedented pollution intervention for the Beijing Olympics, we observed moderate to large concentration decreases in all measured air pollutants except ozone, a secondary pollutant of photochemical smog. In the post-Olympic period after the relaxation of the pollution control measures, all pollutants except the 2 secondary pollutants (ozone and sulfate) increased from their during-Olympic levels. Some reached or exceeded their pre-Olympic levels. Similar findings on these pollution changes during and after the Olympics have been reported previously.[16,19]

Concomitantly, we observed statistically significant biomarker reductions in von Willebrand factor and sCD62P, confirming the importance of

Table 2. Spearman Correlation Coefficients for Air Pollutants, Ambient Temperature, and Relative Humidity, Measured on a 24-Hour Basis

Pollutants	$PM_{2.5}$ Mass	Sulfate	Elemental Carbon	Organic Carbon	Sulfur Dioxide	Carbon Monoxide	Nitrogen Dioxide	Ozone	Temperature	Relative Humidity
No. of 24-h periods	100	92	94	94	91	100	100	100	99	99
$PM_{2.5}$ mass	1									
Sulfate	0.90[b]	1								
Elemental carbon	0.67[b]	0.40[b]	1							
Organic carbon	0.69[b]	0.44[b]	0.92[b]	1						
Sulfur dioxide	0.74[b]	0.63[b]	0.71[b]	0.72[b]	1					
Carbon monoxide	0.69[b]	0.57[b]	0.58[b]	0.55[b]	0.58[b]	1				
Nitrogen dioxide	0.42[b]	0.12	0.80[b]	0.75[b]	0.64[b]	0.53[b]	1			
Ozone	0.12	0.35[b]	–0.30[a]	–0.22[a]	0.02	–0.13	–0.58[b]	1		
Temperature	0.18	0.47[b]	–0.27[b]	–0.16	–0.07	0.03	–0.59[b]	0.72[b]	1	
Relative humidity	0.33[b]	0.50[b]	–0.14	–0.11	–0.06	0.33[b]	–0.11	–0.12	0.19	1

Abbreviation: $PM_{2.5}$, particulate matter ≤2.5 μm in aerodynamic diameter.
[a] $P<.05$.
[b] $P<.01$.

Table 3. Biomarker Concentrations by Period and Between-Period Change in Participant-Specific Biomarker Concentrations, Adjusted for Temperature and Relative Humidity

	Olympic Period, Mean (95% CI)			Between-Period Percentage Change			
Biomarker, Units	Before	During	After	Before to During, Mean (95% CI), %	*P* Value[b]	During to After, Mean (95% CI), %	*P* Value[b]
sCD62P, ng/mL[a]	6.29 (5.97 to 6.63)[a]	4.16 (3.86 to 4.48)[a]	5.36 (5.10 to 6.05)[a]	–34.0 (–38.4 to –29.2)	<.001	33.7 (17.7 to 51.8)	<.001
sCD40L, ng/mL[a]	1.86 (1.79 to 1.94)[a]	1.76 (1.66 to 1.86)[a]	1.92 (1.77 to 2.07)[a]	–5.7 (–10.5 to –0.7)	.03	9.1 (–3.7 to 23.5)	.17
von Willebrand factor, %	106.4 (98.5 to 114.4)	92.6 (82.6 to 102.5)	79.5 (66.9 to 92.1)	–13.1 (–18.6 to –7.5)	<.001	–14.2 (–29.9 to 1.6)	.19
Heart rate/min	66.5 (65.0 to 68.1)	65.4 (63.8 to 67.0)	66.1 (64.2 to 68.1)	–1.7 (–3.4 to –0.1)	.04	1.1 (–2.5 to 4.9)	.54
Fibrinogen, mg/dL	250 (242 to 258)	250 (240 to 259)	261 (249 to 273)	0.1 (–2.5 to 2.2)	.90	4.3 (–1.7 to 10.2)	.21
Blood pressure, mm hg							
Systolic	102.5 (99.9 to 105.2)	100.9 (97.4 to 104.4)	110.5 (105.9 to 115.0)	–1.8 (–3.9 to 0.4)	.10	10.7 (2.8 to 18.6)	.01
Diastolic	60.2 (57.9 to 62.6)	60.1 (57.0 to 63.1)	60.1 (56.2 to 64.0)	–0.3 (–3.0 to 2.5)	.86	0.1 (–9.7 to 9.9)	.99
White blood cell count, μL	5290 (5050 to 5540)	5400 (5100 to 5700)	5210 (4890 to 5530)	2.2 (–2.3 to 6.6)	.34	–3.9 (–11.5 to 3.6)	.44

Abbreviations: sCD40L, soluble CD40 ligand; soluble P-selectin sCD62P
[a] Biomarker was log-transformed. Geometric means and its 95% confidence interval.
[b] Significance is established if *P* value <.003, the individual significance level needed to maintain a family-wise Type I error rate of 0.05.

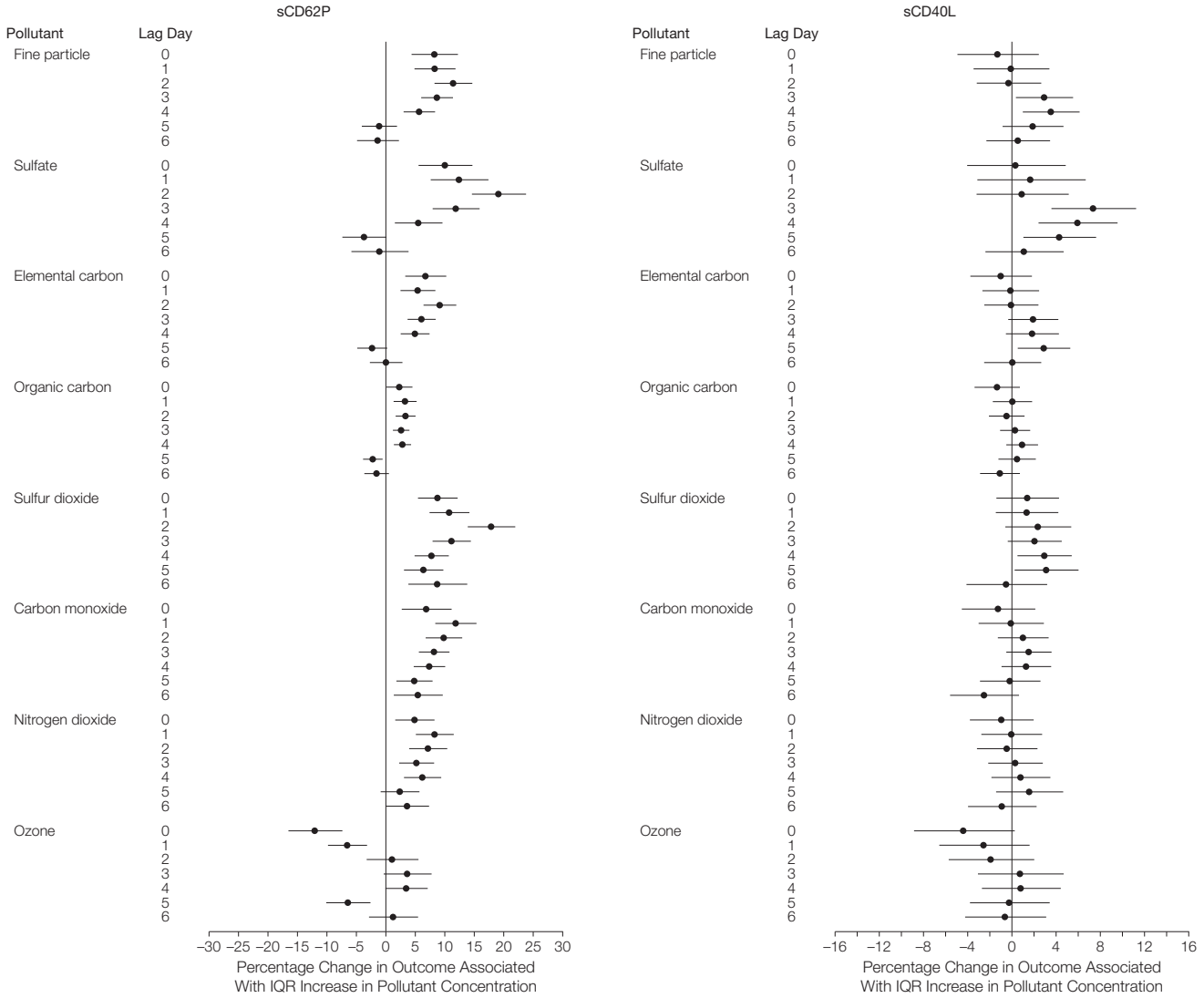
©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

the thrombosis–endothelial dysfunction mechanism, with sCD62P also demonstrating significant increases in the post-Olympic period. Two of these measures (sCD62P and systolic blood pressure) increased significantly from the during-Olympic to the post-Olympic period. Consistent with previous findings, diastolic blood pressure was less sensitive to air pollution changes.[20] Among the inflammation pathway biomarkers, the fraction of CRP above the detection limit (0.3 mg/L) decreased from the pre-Olympic to the during-Olympic period but decreased further in the post-Olympic period.

There have been other national or regional air pollution reductions resulting from a governmental policy, national political realignment, industrial facility employee strike, or large scale sporting event.[10,11,13,15,21] Each has been associated with a beneficial public health effect, including reductions in cardiorespiratory mortality rates,[11,15] bronchitis prevalence,[12] childhood hospital admissions for respiratory disease,[22] reduced preterm deliveries,[13] and childhood asthma admissions.[23] A few health studies have also been conducted using the Beijing Olympic air quality intervention opportunity to assess changes in pulmonary inflammation in children and heart rate variability in taxi drivers.[24,25] However, none of these studies has investigated the mechanistic pathways underlying cardiovascular benefits brought by the interventions.

Figure 1. Percentage Changes in sCD62P and sCD40L Associated With Each IQR Change in Pollutant Concentration



Data markers represent the percentage change (error bars are 95% confidence intervals) associated with each interquartile range (IQR) increase in pollutant concentration, by 24-hour lag period. Zero lag represents 0 to 23 hours; lag 1, 24 to 47 hours; lag 2, 48 to 71 hours; lag 3, 72 to 95 hours; lag 4, 96 to 119 hours; lag 5, 120 to 143 hours; and lag 6, 144 to 167 hours before a clinic visit. sCD62P indicates soluble P-selectin; sCD40L, soluble CD40 ligand.

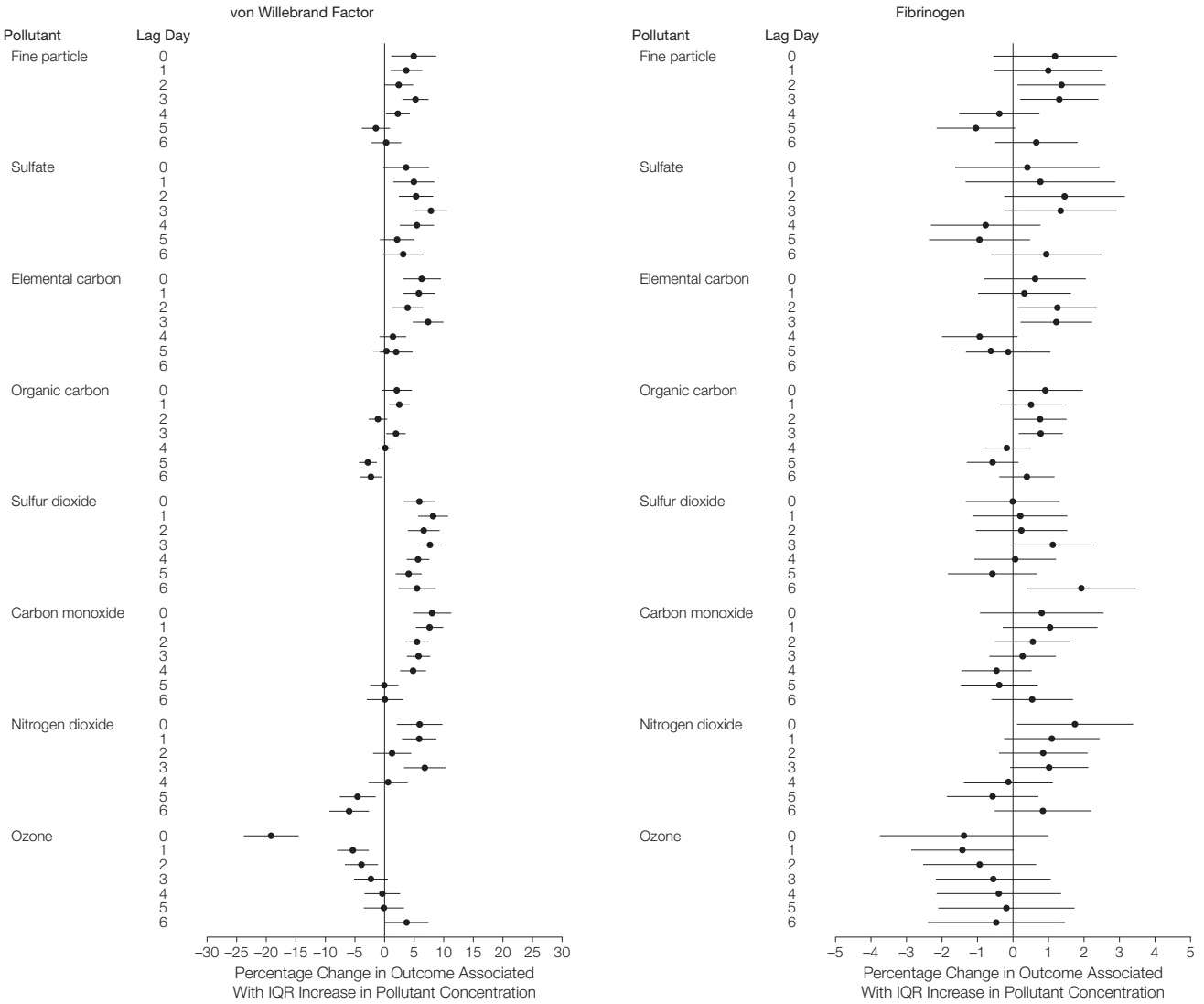
©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

The findings from our quasi-experimental design may reflect the effects of air pollution as a whole mixture rather than as the action of one or more specific pollutants. It has been of great interest, both from a scientific standpoint and from a regulatory perspective as to what specific components of the air pollution mixture (eg, gases vs particulate matter) and what specific constituents of particulate matter are more toxic than others.[26,27] We attempted to address this question through our pollutant-biomarker association analysis. However, correlations among pollutants, due in part to the simultaneous shutdown of multiple pollutant sources during the Olympics and subsequent relaxation of pollution controls, made it difficult to differentiate effects of individual pollutants or pollutant sources. The seemingly beneficial effects of ozone on several biomarkers is likely due to its negative correlations with nitrogen dioxide and other pollutants, as was similarly observed in previous studies.[28,29]

Some of the lag-day patterns shown in the Figures are intriguing. The changes in von Willebrand factor and sCD62P associated with pollutant concentration increases in the previous 24 hours are consistent with their roles in the rapid thrombotic response, while the slower response for fibrinogen more than 2 to 3 days is consistent with its role as an acute phase protein.[30-33] For most biomarkers, there was a gradual increase in effect estimates in the early lag periods (lags 0-2), followed by a gradual decrease in effect estimates to

Figure 2. Percentage Changes in von Willebrand Factor and Fibrinogen Associated With Each IQR Change in Pollutant Concentration



See Figure 1 legend for definitions.

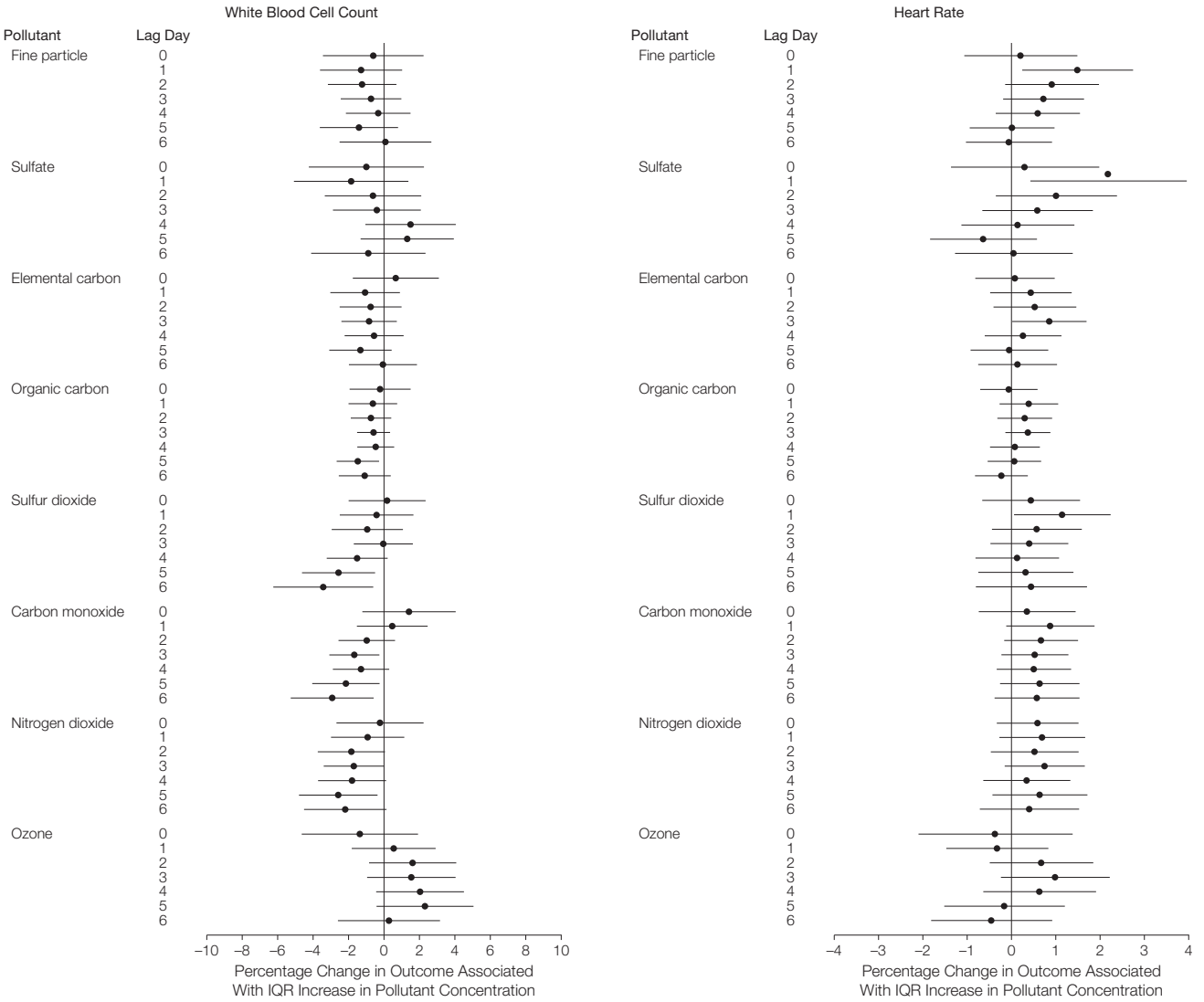
©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

often negative effects (ie, increased pollutant concentration associated with decreased biomarker levels) in later lag periods. These negative ("protective") effects could be due to compensatory mechanisms responding to the increases in the biomarker triggered by pollution at early lags. Overall, the pollutant-biomarker associations provide further mechanistic support that the biomarker changes across the Olympic periods were acute inflammatory and prothrombotic responses to changes in air pollution.

Each biomarker or outcome used in our study has been related to cardiovascular morbidity or mortality in clinical studies, but only blood pressure and CRP are in clinical use for risk stratification at the present time. For both of these, risk is typically expressed in strata or tiers based on a cutoff value rather than in the mean comparisons and percentage increases that we present herein. Fibrinogen, von Willebrand factor, heart rate, sCD62P, WBC count, and sCD40L all have been used in observational epidemiology studies in which increased biomarker levels were associated with 1 or more acute or chronic cardiovascular events or mortality.[34-39] Changes in cardiovascular physiology parameters (eg, blood pressure) and inflammation contribute to the instability of preexisting atherosclerotic plaques. Furthermore, thrombosis, dependent on platelet activation, is responsible for arterial obstruction on the surface of such a ruptured plaque. At the present time, however, quantitative implications of these biomarker changes for cardiovas-

Figure 3. Percentage Changes in White Blood Cell Count and Heart Rate Associated With Each IQR Change in Pollutant Concentration



See Figure 1 legend for definitions.

©2012 American Medical Association. All rights reserved.

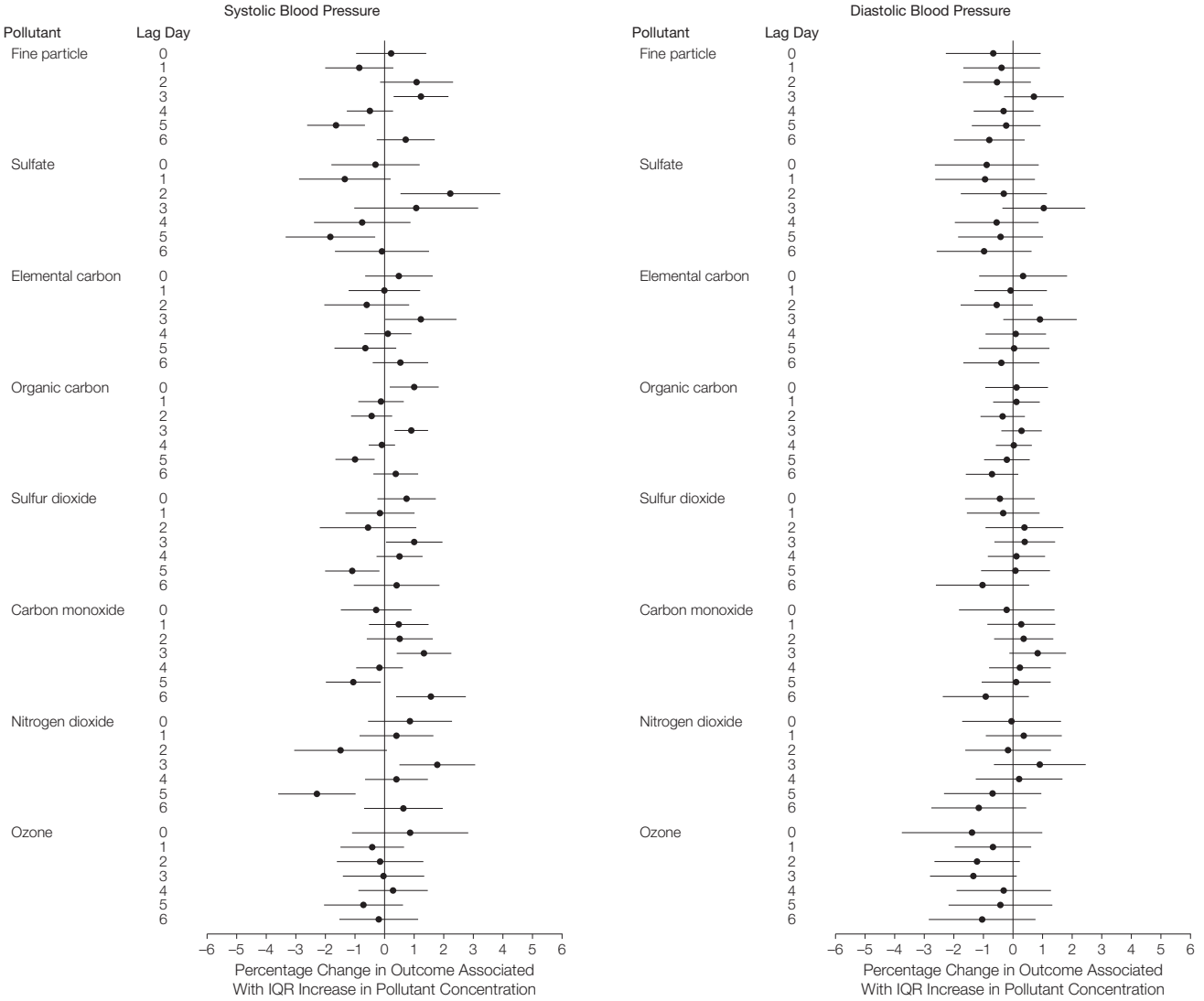
Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

cular risk assessment cannot be estimated due to the lack of data directly linking biomarker changes with mortality or morbidity rates.

Each biomarker used in our study has also previously been associated with acute air pollution changes in field observational or laboratory studies, although there is substantial heterogeneity, even disagreement, between individual studies. For example, we found increases in fibrinogen concentration associated with increased $PM_{2.5}$ concentration in the previous few days, which is in agreement with prior field studies[4,9] and laboratory studies,[5,40] but in disagreement with another field study.[41] Increases in von Willebrand factor have been associated with exposure to road traffic particles.[30,42,43] Systolic blood pressure—and, to a lesser extent, diastolic blood pressure—has been documented to increase with pollutant exposure.[20] Increased heart rate has also been previously associated with increases in air pollution levels.[44] All of these are consistent with our findings. Likewise, positive associations between sCD62P (our most sensitive biomarker) or sCD40L and particulate matter have been reported in previous studies.[6,7,45] These platelet activation marker associations with pollutant changes in the previous 24 hours provide an explanation for previously reported triggering of myocardial infarction by ambient particulate matter.[46-51]

Epidemiological associations of air pollution as a risk factor for acute cardiopulmonary events (eg, stroke, myocardial infarction) and chronic mor-

Figure 4. Percentage Changes in Systolic and Diastolic Blood Pressure Associated With Each IQR Change in Pollutant Concentration



See Figure 1 legend for definitions.

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

bidity (eg, deep vein thrombosis, atherosclerotic cardiovascular disease) are largely driven by the elderly and those with cardiorespiratory diseases.[2,52,53] However, we observed biomarker changes linking air pollution with disease pathways in the young and healthy. This may be particularly important because chronic effects of hypertension and hyperlipidemias that begin in youth convey CVD risk at older ages.[54]

Although this study has several strengths—including a relatively large sample size with excellent participation, a large range of pollutant concentrations across the study period and the prospective measurement of pollution and end points at the same site—there are several limitations that should be noted when interpreting our results. First, we did not measure pollutant concentrations at locations other than the hospital grounds, thereby possibly missing important exposures. Second, we did not measure each participant's personal exposure to each pollutant and instead used pollutant concentrations measured at this hospital monitor as proxies for his/her pollutant exposure during the study. However, these should both result only in nondifferential exposure error and underestimates of pollutant mediated biomarker changes. Third, there may be potential temporal confounding by changes in season and in participant activity patterns over the course of the 6 clinical visits. To address potential confounding by season, we performed sensitivity analysis using only the pre-Olympic and during-Olympic data because these periods were both in the summer; however, the post-Olympic period was in early autumn (see temperature values in Table 1). We found little difference between the results from the main analysis (with 3 periods included) and those from the sensitivity analysis (2 periods only; eFigure available at http://www.jama.com). Concerning activity pattern changes, we collected diary data on participant activities for the 24 hours prior to each of the 6 clinic visits. Noticeable between-period differences were only observed for walking or biking duration (0.96 h/d before, 0.69 h/d during, and 0.65 h/d after the Olympic period) and time spent outdoors (1.65 h/d before, 1.26 h/d during, and 1.22 h/d after the Olympic period). However, the direction of these differences is such that they would tend to enhance the personal exposure to outdoor pollution in the pre-Olympic period, thereby enhancing the pre-Olympic vs during-Olympic comparison. Neither of these 2 parameters differed between the during- and post-Olympic periods.

During the Beijing Olympics, changes in air pollution were associated with acute changes in biomarkers of systemic inflammation and thrombosis as well as measures of cardiovascular physiology in healthy young persons. Although these findings are of uncertain clinical significance, this study provides quasi-experimental, mechanistic data to support the argument that air pollution may be a global risk factor for CVD.[2]

Author Affiliations: Department of Community and Preventive Medicine, School of Medicine and Dentistry, University of Rochester, Rochester, New York (Dr Rich), Environmental and Occupational Health Sciences Institute (Drs Kipen, Ohman-Strickland, Lu, and Zhang), Departments of Environmental and Occupational Medicine (Dr Kipen) and Medicine (Dr Phillipp), Robert Wood Johnson Medical School; Departments of Biostatistics (Dr Ohman-Strickland) and Environmental Health (Ms Tong and Drs Gong and Zhang), School of Public Health, Piscataway; and Center for Pharmacogenomics and Complex Disease, School of Dentistry, Newark (Dr Diehl), University of Medicine and Dentistry of New Jersey; State Key Laboratory of Environmental Simulation and Pollution Control, College of Environmental Sciences and Engineering and Center for Environment and Health (Drs Huang, Hu, and T. Zhu), Departments of Pulmonary Medicine (Dr G. Wang) and Hematology (Dr P. Zhu), First Hospital, and Department of Immunology, Health Sciences Center (Dr Y. Wang), Peking University, Beijing, China; and Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles (Drs Gong, Thomas, and Zhang).

Author Contributions: Drs Zhang and Zhu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Drs Rich, Kipen, and Huang contributed equally and are co-first authors of this article.
Study concept and design: Zhang, Kipen, Zhu, G. Wang, Y. Wang, Zhu, Ohman-Strickland, Lu, Hu, Thomas.
Acquisition of data: Wei, G. Wang, Y. Wang, P. Zhu, Gong, Hu, Zhang, Kipen, Rich.
Analysis and interpretation of data: Zhang, Kipen, Rich, Ohman-Strickland, Lu, Thomas, Diehl, Tong, Gong, Huang, Philipp.
Drafting of the manuscript: Rich, Kipen, Zhang, Ohman-Strickland.
Critical revision of the manuscript for important intellectual content: Rich, Kipen, Zhang, Ohman-Strickland, Thomas, Gong.
Statistical analysis: Ohman-Strickland, Lu, Tong, Gong.
Obtained funding: Zhang T. Zhu.
Administrative, technical or material support: Zhang, Zhu, G. Wang, Zhu, Y. Wang, Rich, Kipen, Huang, Hu, Tong, Gong.
Study supervision: Zhang, Kipen, G. Wang, Huang, Hu, T. Zhu, Rich.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Funding/Support: This study was jointly funded by grants 1R01ES015864, P30ES005022, and 5P30ES007048 from the National Institute of Environmental Health Sciences, 4760-RPFA05-3 from the Health Effects Institute, OITC-G08026056 from the Beijing Environment Protection Bureau, and HB200504-6, HB200504-2 from the Beijing Council of Science and Technology.
Role of the Sponsors: None of the funding agencies had a role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Online-Only Material: An eFigure is available at http://www.jama.com.
Additional Contributions: We are indebted to the study participants for their commitment to the study and to the students and staff members at Peking University and Peking University First Hospital for their assistance with sample and data collection.

REFERENCES

1. Brook RD, Rajagopalan S, Pope CA III, et al; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121(21):2331-2378.
2. Mateen FJ, Brook RD. Air pollution as an emerging global risk factor for stroke. *JAMA*. 2011;305(12):1240-1241.
3. Mustafic H, Jabre P, Caussin C, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. *JAMA*. 2012;307(7):713-721.
4. Chuang KJ, Chan CC, Su TC, Lee CT, Tang CS. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med*. 2007;176(4):370-376.
5. Ghio AJ, Kim C, Devlin RB. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med*. 2000;162(3 pt 1):981-988.
6. Lucking AJ, Lundback M, Mills NL, et al. Diesel exhaust inhalation increases thrombus formation in man. *Eur Heart J*. 2008;29(24):3043-3051.
7. Delfino RJ, Staimer N, Tjoa T, et al. Circulating biomarkers of inflammation, antioxidant activity, and platelet activation are associated with primary combustion aerosols in subjects with coronary artery disease. *Environ Health Perspect*. 2008;116(7):898-906.
8. Jacobs L, Emmerechts J, Mathieu C, et al. Air pollution related prothrombotic changes in persons with diabetes. *Environ Health Perspect*. 2010;118(2):191-196.
9. Peters A, Döring A, Wichmann HE, Koenig W. Increased plasma viscosity during an air pollution episode: a link to mortality? *Lancet*. 1997;349(9065):1582-1587.

©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016

10. Clancy L, Goodman P, Sinclair H, Dockery DW. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *Lancet*. 2002; 360(9341):1210-1214.
11. Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, Anderson HR. Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *Lancet*. 2002; 360(9346):1646-1652.
12. Heinrich J, Hoelscher B, Wichmann HE. Decline of ambient air pollution and respiratory symptoms in children. *Am J Respir Crit Care Med*. 2000;161 (6):1930-1936.
13. Parker JD, Mendola P, Woodruff TJ. Preterm birth after the Utah Valley Steel Mill closure: a natural experiment. *Epidemiology*. 2008;19(6):820-823.
14. Peel JL, Klein M, Flanders WD, Mulholland JA, Tolbert PE; HEI Health Review Committee. Impact of improved air quality during the 1996 Summer Olympic Games in Atlanta on multiple cardiovascular and respiratory outcomes. *Res Rep Health Eff Inst*. 2010; (148):3-23.
15. Pope CA III, Rodermund DL, Gee MM. Mortality effects of a copper smelter strike and reduced ambient sulfate particulate matter air pollution. *Environ Health Perspect*. 2007;115(5):679-683.
16. Wang M, Zhu T, Zheng J, et al. Use of a mobile laboratory to evaluate changes in on-road air pollutants during the Beijing 2008 Summer Olympics. *Atmos Chem Phys*. 2009;9(21):8247-8263.
17. Kipen H, Rich D, Huang W, et al. Measurement of inflammation and oxidative stress following drastic changes in air pollution during the Beijing Olympics: a panel study approach. *Ann N Y Acad Sci*. 2010; 1203:160-167.
18. Heeschen C, Dimmeler S, Hamm CW, et al; CAPTURE Study Investigators. Soluble CD40 ligand in acute coronary syndromes. *N Engl J Med*. 2003;348 (12):1104-1111.
19. Wang T, Nie W, Gao J, et al. Air quality during the 2008 Beijing Olympics: secondary pollutants and regional impact. *Atmos Chem Phys*. 2010;10(16): 7603-7615.
20. Brook RD. You are what you breathe: evidence linking air pollution and blood pressure. *Curr Hypertens Rep*. 2005;7(6):427-434.
21. Lee JT, Son JY, Cho YS. Benefits of mitigated ambient air quality due to transportation control on childhood asthma hospitalization during the 2002 summer Asian games in Busan, Korea. *J Air Waste Manag Assoc*. 2007;57(8):968-973.
22. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am J Public Health*. 1989;79(5):623-628.
23. Lee SL, Wong WH, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. *Clin Exp Allergy*. 2006;36 (9):1138-1146.
24. Lin W, Huang W, Zhu T, et al. Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. *Environ Health Perspect*. 2011;119(10):1507-1512.
25. Wu S, Deng F, Niu J, Huang Q, Liu Y, Guo X. Association of heart rate variability in taxi drivers with marked changes in particulate air pollution in Beijing in 2008. *Environ Health Perspect*. 2010;118(1): 87-91. doi:10.1289/ehp.0900818.
26. Delfino RJ, Staimer N, Tjoa T, et al. Air pollution exposures and circulating biomarkers of effect in a susceptible population: clues to potential causal component mixtures and mechanisms. *Environ Health Perspect*. 2009;117(8):1232-1238.
27. *Air Quality Criteria for Particulate Matter*. Vol 2. Research Triangle Park, NC: US Environmental Protection Agency; October 2004. EPA 600 P-99 002bF.
28. Anderson HR, Ponce de Leon A, Bland JM, Bower JS, Emberlin J, Strachan DP. Air pollution, pollens, and daily admissions for asthma in London 1987-92. *Thorax*. 1998;53(10):842-848.
29. Hajat S, Haines A, Goubet SA, Atkinson RW, Anderson HR. Association of air pollution with daily GP consultations for asthma and other lower respiratory conditions in London. *Thorax*. 1999;54(7): 597-605.
30. Riediker M, Cascio WE, Griggs TR, et al. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med*. 2004;169(8):934-940.
31. Andreotti F, Burzotta F, Maseri A. Fibrinogen as a marker of inflammation: a clinical view. *Blood Coagul Fibrinolysis*. 1999;10(suppl 1):S3-S4.
32. Hilt B, Qvenild T, Holme J, Svendsen K, Ulvestad B. Increase in interleukin-6 and fibrinogen after exposure to dust in tunnel construction workers. *Occup Environ Med*. 2002;59(1):9-12.
33. Kappelmayer J, Nagy B Jr, Miszti-Blasius K, Hevessy Z, Setiadi H. The emerging value of P-selectin as a disease marker. *Clin Chem Lab Med*. 2004;42(5): 475-486.
34. Blann AD, Nadar SK, Lip GY. The adhesion molecule P-selectin and cardiovascular disease. *Eur Heart J*. 2003;24(24):2166-2179.
35. Choudhury A, Chung I, Panja N, Patel J, Lip GY. Soluble CD40 ligand, platelet surface CD40 ligand, and total platelet CD40 ligand in atrial fibrillation: relationship to soluble P-selectin, stroke risk factors, and risk factor intervention. *Chest*. 2008;134(3):574-581.
36. Conway DS, Pearce LA, Chin BS, Hart RG, Lip GY. Prognostic value of plasma von Willebrand factor and soluble P-selectin as indices of endothelial damage and platelet activation in 994 patients with nonvalvular atrial fibrillation. *Circulation*. 2003;107 (25):3141-3145.
37. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998;279 (18):1477-1482.
38. Fox K, Borer JS, Camm AJ, et al; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50(9):823-830.
39. Heeringa J, Conway DS, van der Kuip DA, et al. A longitudinal population-based study of prothrombotic factors in elderly subjects with atrial fibrillation: the Rotterdam Study 1990-1999. *J Thromb Haemost*. 2006;4(9):1944-1949.
40. Ghio AJ, Hall A, Bassett MA, Cascio WE, Devlin RB. Exposure to concentrated ambient air particles alters hematologic indices in humans. *Inhal Toxicol*. 2003;15(14):1465-1478.
41. Seaton A, Soutar A, Crawford V, et al. Particulate air pollution and the blood. *Thorax*. 1999; 54(11):1027-1032.
42. Riediker M. Cardiovascular effects of fine particulate matter components in highway patrol officers. *Inhal Toxicol*. 2007;19(suppl 1):99-105.
43. Liao D, Heiss G, Chinchilli VM, et al. Association of criteria pollutants with plasma hemostatic /inflammatory markers: a population-based study. *J Expo Anal Environ Epidemiol*. 2005;15(4):319-328.
44. Simkhovich BZ, Kleinman MT, Kloner RA. Air pollution and cardiovascular injury epidemiology, toxicology, and mechanisms. *J Am Coll Cardiol*. 2008; 52(9):719-726.
45. Rückerl R, Phipps RP, Schneider A, et al. Ultrafine particles and platelet activation in patients with coronary heart disease—results from a prospective panel study. *Part Fibre Toxicol*. 2007;4:1.
46. Zanobetti A, Schwartz J. The effect of particulate air pollution on emergency admissions for myocardial infarction: a multicity case-crossover analysis. *Environ Health Perspect*. 2005;113(8):978-982.
47. Peters A, Dockery DW, Muller JE, Mittleman MA. Increased particulate air pollution and the triggering of myocardial infarction. *Circulation*. 2001;103 (23):2810-2815.
48. Peters A, von Klot S, Heier M, et al; Cooperative Health Research in the Region of Augsburg Study Group. Exposure to traffic and the onset of myocardial infarction. *N Engl J Med*. 2004;351(17):1721-1730.
49. Rich DQ, Kipen HM, Zhang J, Kamat L, Wilson AC, Kostis JB. Triggering of transmural infarctions, but not nontransmural infarctions, by ambient fine particles. *Environ Health Perspect*. 2010;118(9): 1229-1234.
50. Pope CA III, Muhlestein JB, May HT, Renlund DG, Anderson JL, Horne BD. Ischemic heart disease events triggered by short-term exposure to fine particulate air pollution. *Circulation*. 2006;114(23):2443-2448.
51. D'Ippoliti D, Forastiere F, Ancona C, et al. Air pollution and myocardial infarction in Rome: a case-crossover analysis. *Epidemiology*. 2003;14(5):528-535.
52. Baccarelli A, Martinelli I, Zanobetti A, et al. Exposure to particulate air pollution and risk of deep vein thrombosis. *Arch Intern Med*. 2008;168(9):920-927.
53. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007; 356(5):447-458.
54. Feinstein JA, Quivers ES. Pediatric preventive cardiology: healthy habits now, healthy hearts later. *Curr Opin Cardiol*. 1997;12(1):70-77.

 ©2012 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 02/07/2016