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Responses of Serum Chemokines to Dramatic Changes of Air Pollution Levels, A Panel Study

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Abstract

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Author's contributions: Dr. Li analyzed data and drafted the manuscript; Dr. Bonner helped the study design and interpreted the data; Dr. Browne helped with laboratory design, quality control and results interpretation; Dr. Deng oversaw the field work; Dr. Tian helped with model building and data analysis; Dr. Zhang contributed to the data analysis; Mrs. Swanson helped with data management and initial analysis; Dr. Rittenhouse-Olson was involved in the original study design and manuscript revision; Ms. Farhat helped with the interpretation of the data; Dr. Mu oversaw the entire study.

Declaration of interest: We disclose that no conflict interest is involved in the submitted work. We declare that the work has not been published previously and it is not under consideration for publication elsewhere.

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Consent for publication: No individual's information will be published in this manuscript

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Background—Despite the *in vitro* and *in vivo* evidence, studies are limited in evaluating whether chemokines are potential inflammatory mediators in response to air pollution exposure in humans.

Methods—We conducted a panel study coinciding with the Beijing Olympics, when temporary air pollution controls were implemented. We measured a suite of serum chemokines among healthy adults before, during and after the Olympics, respectively. Linear mixed-effect models were used to evaluate changes in chemokine levels over the three time periods.

Results—In response to the 50% drop in air pollution levels during the games, levels of RANTES, MCP-2, and TARC decreased by 25.8%, 20.9% and 35.3% respectively (P<0.001) from pre-Olympics, and then increased by 45.8%, 34.9% and 61.5% respectively (P<0.001) after the games when air pollution levels went up again. Similar patterns were observed in subgroup analyses by sex, age, smoking and body mass index. GRO-α and IL-8 decreased significantly during the games (22.5% and 30.4%), and increased non-significantly after the games. Eotaxin-1 only increased significantly from during- to post-games.

Conclusions—The strongest associations with air pollution levels were observed among RANTES, TARC and MCP-2. Those chemokines may play important roles in the air pollution induced inflammatory pathway.

Keywords

Air Pollution; Chemokines; Panel Study; Inflammation; Biological Mechanism

1. INTRODUCTION

Air pollution imparts a tremendous burden to the global public health and accounts for approximately 800,000 deaths annually.(Brook, 2008) Substantial epidemiological evidence has linked ambient air pollution with respiratory diseases, cardiovascular diseases and several types of cancers.(Bonner et al., 2005; Brook et al., 2010; Cohen, 2003; Raaschou-Nielsen and Reynolds, 2006) However, the underlying pathophysiological mechanisms and pathways, especially at the cellular and molecular levels, are not adequately understood.

Chemokines are a large family of structurally related chemo-attractant cytokines with a pivotal role in orchestrating inflammation and directing activation and migration of specific leukocytes.(Taub and Oppenheim, 1993) Chemokines are also active in modulating apoptosis, angiogenesis, and cell proliferation.(Rollins, 1997) Alterations in chemokine expression are associated with initiation and maintenance of a variety of acute and chronic respiratory diseases, coronary heart disease, atherosclerosis, and cancer initiation and progression.(Balkwill, 2012; Canoui-Poitrine et al., 2011; Sabroe et al., 2002) In vitro and in vivo studies suggest that pro-inflammatory chemokines can be induced by air pollution exposure.(He et al., 2010; Inoue et al., 2005; Kang et al., 2010; Ovrevik et al., 2009). Furthermore, organic matter extracted from air pollution has been found to induce caspase activation and DNA fragmentation in human leukocytes (Cimino et al., 2014). However, very few epidemiological studies have been conducted to evaluate whether chemokines are potential inflammatory mediators in response to air pollution exposure in humans (Pope et al., 2016).

Beijing is one of the most polluted cities in China. The annual average particulate air pollutants with less than or equal to 10 um aerodynamic diameter (PM_{10}) levels in the urban areas of Beijing were between 100 and 150 μg/m (Class-III standard), which are two to three fold higher than the World Health Organization Air Quality Guidelines 2005 (2007; WHO, 2005). Temporary air pollution control measures were implemented during the Beijing Olympics, which included banning high polluting vehicles, restricting automobile use on alternate days, and temporarily ceasing or reducing the operation of high polluting facilities. These temporary interventions led to a substantial decline in air pollution levels, followed by a return to the pre-Olympic levels. Taking advantage of this "natural experiment", we collected blood samples from a group of adult Beijing residents at three time points: before, during and after the Beijing Olympics, to assess changes in serum concentrations of chemokines in relation to the bi-directional changes of air pollution levels over the Beijing Olympics. Although there are several published articles based on this particular "natural experiment", there is no publication so far that has studied serum chemokines (Huang et al., 2012a; Kipen et al., 2010; Rich et al., 2012).

2. MATERIALS AND METHODS

2.1 Study population

Beijing Olympic and Paralympic Games were held between August 8, 2008 and September 17, 2008. Prior to implementing the temporary air quality control measures, 201 residents living in one community in Haidian district of Beijing were recruited. Eligible participants were healthy adults aged 20 to 65 years old, Han nationality and with no previous medical history of cancers, serious immunological diseases, chronic respiratory diseases, cardiovascular diseases or diabetes. The study participants were scheduled to have three visits to the community health center in the before (July 26–27, 2008), during (September 6–7, 13, 2008) and after (November 19, 2008) Beijing Olympic periods respectively, to coincide with changes in air pollution levels. During each visit, participants were asked to complete an interview-based questionnaire on basic demographics and lifestyle habits, and their fasting blood samples were collected in each morning of the scheduled visits. Total of 180 participants completed three interviews. Details regarding participant selection and study design were described elsewhere.(Mu et al., 2014) In the current analysis, study population was limited to 104 subjects whose blood samples were collected at each of the three visits and who have sufficient volume of serum for the chemokine assay. The subset of 104 subjects included in this study was not different by basic characteristics (e.g., age, gender, smoking status) from the original 201 subjects recruited. The current study was approved by the institutional review boards of the State University of New York at Buffalo and Peking University Health Science Center. Written inform consent was obtained from all study participants.

2.2 Laboratory analysis of serum chemokines

The collected blood samples were immediately transferred to laboratory for processing. Serum and blood clots were separated by centrifugation and stored at −80°C. Chemokines in serum samples were analyzed using the Q-Plex™ Human Chemokine ELISA-based chemiluminescent assay (Quansys Biosciences, Logan, UT). The assay allows concurrent

measurement of eight chemokines including CXCL-1 (GRO-α), CXCL-8 (IL-8), CXCL-10 (IP- 10), CCL-2 (MCP-1), CCL-5 (RANTES), CCL-8 (MCP-2), CCL-11 (Eotaxin-1) and CCL-17 (TARC) (Li et al., 2014). All the serum samples were measured in triplicate and all samples from a single individual were contained within the same plate. The intra-assay coefficients of variation (CVs) using the triplicate samples were all less than 10%. In addition, external quality control samples collected from healthy volunteers in the US were repeated in all the plates to assess the intra-assay and inter-assay repeatability. The intra-assay CVs using the external samples were all less than 15%, except for GRO-α; the inter-assay CVs were less than 20%, except for GRO-α and IL-8. The higher variations for GRO-α and IL-8 assays using the external quality control samples might relate to their significantly lower expression levels in the external quality control samples compared to the samples from the study population.

2.3 Air pollution monitoring

PM levels were continuously monitored in the period starting 20 days prior to the start of Beijing Olympics (August 8, 2008) until the end of November 2008 in the community where the study participants were recruited. A particle mass monitor (Met One® 531 AEROCET Particulate Profiler, Met One Instruments, Inc. Grant Pass, Oregon) was placed in an open space in the center of the Beihang community of the Haidan District (GPS coordinates: 39°59’19.1”N 116°20’38.2”E), which is a relatively small and closed community with an area of 0.27 km^2 (Farhat et al., 2018). The PM monitor was placed 1.5 meters above the ground. We measured particles with an aerodynamic diameter below 1 μm (PM_1), 2.5 μm ($PM_{2.5}$), 7 μm (PM_7), 10 μm (PM_{10}), and total suspended particles (TSP), along with temperature and relative humidity.

2.4 Statistical analysis

To describe the basic characteristics of the study participants, we calculated means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. We calculated medians and inter-quartile ranges (IQR) for all the chemokines.

Linear mixed effects regression models were used to compare serum concentrations of chemokines across the three time periods to account for the repeated measurements of chemokines within the same individual. Time period was included in the linear mixed models as a categorical variable with “during Olympics” as reference group. A random intercept for study subject was included in this model to account for within-individual correlation. We log-transformed chemokines with right-skewed distributions, including IL-8, IP-10, Eotaxin-1 and TARC, to achieve normal distributions required by this model. To reduce the possible impact due to the large intra-assay variability of GRO-α, we conducted a sensitivity analysis to categorize all the GRO-α measurements into tertiles. We used generalized estimating equation model to examine changes of GRO-α distribution across different tertiles over the three time periods. We assumed the correlation structure between repeated measurements was “unstructured”, i.e. no special structure would be imposed and the correlation structure was completely determined by the data. In the mixed-effects models, we controlled for age, sex, smoking status, body mass index (BMI) and their interactions with time period.

We also conducted stratified analyses by age groups (≤40, 40–50, and >50 years), sex, smoking status and BMI categories to explore potential effect measure modifications. We initially categorized BMI into underweight (<18.5 kg/m^2), normal (18.5–24 kg/m^2), overweight (24–28 kg/m^2) and obesity (>28 kg/m^2), based on the cutoffs recommended for the Chinese population (Zhou, 2002). We decided to combine the underweight and normal weight categories, due to the small sample size of the underweight group.

All statistical analyses were performed using the SAS software package version 9.3 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided and were considered statistically significant at $P < 0.05$.

3. RESULTS

Table 1 shows the characteristics of 104 participants (50 males and 54 females) included in this study. Average age of the participants was 48.3 years. About 60.6% of study participants were underweight or normal weight, 28.9% were overweight and 10.6% were obese. Smokers constituted about 35.6% of the population and about 32.7% were alcohol drinkers. Medians and IQRs of measured chemokines are also summarized in Table 1. The temporary air quality control measures during the Beijing Olympics resulted in approximately 50–60% decline in levels of different air pollutants compared to the pre-Olympic period. As expected, PM levels returned similar to the pre-Olympic levels after the temporary control measures ceased. Average $PM_{2.5}$ levels in the before, during and after Beijing Olympic periods were 83.2 μg/m^3, 32.7 μg/m^3 and 45.7 μg/m^3, respectively. Average PM_{10} levels in the before, during and after Beijing Olympic periods were 127.8 μg/m^3, 55.9 μg/m^3 and 139.8 μg/m^3, respectively.

Mean concentrations (95% CIs) of chemokines in the before, during and after Beijing Olympic periods in the overall study population are presented in Table 2. Serum concentrations of chemokines RANTES, MCP-2, and TARC decreased by 25.8% (95% CI: 18.2%, 33.5%), 20.9% (95% CI: 14.9%, 26.9%) and 35.3% (95% CI: 26.1%, 43.4%) respectively (P<0.001) from the before to the during-Olympic period and then increased by 45.8% (95% CI: 28.2%, 63.5%), 34.9% (95% CI: 18.5%, 51.4%) and 61.5% (95% CI: 38.5%, 88.5%) respectively (P<0.001) after the pollution control measures ceased. These “U-shape” relationships persisted in the stratified analyses by sex (Figure 1), smoking status (Figure 1), age groups (not shown) and BMI categories (not shown).

For IL-8, Eotaxin-1 and GRO-α, each of them showed suggestive evidence of “U- shape” relationships across the three periods, although some of the changes over time were not statistically significant (Table 2). In the semi-quantitative analyses for GRO-α, study participants were more likely to be categorized in the highest tertile of GRO-α in the pre-Olympic period (36.9%) and post-Olympic period (34.0%), compared to the during-Olympic period (28.7%); while they were less likely to be categorized in the lowest tertile in the pre-Olympic period (30.1%) and post-Olympic period (33.0%), compared to the during-Olympic period (38.6%). Contrary to our prior hypothesis, there was evidence of continuous increase in MCP-1 concentrations in the serum samples collected in before, during and after Beijing Olympic periods. No significant changes of serum IP-10 concentrations were observed

across the periods (Table 2), similar null associations were found in the subgroup analyses (not shown). No effect modifications by sex, age, smoking status and BMI were observed for any chemokines (not shown).

4. DISCUSSION

This panel study observed that serum concentrations of RANTES, MCP-2, and TARC decreased significantly in response to the drastic drop of air pollution level during the Olympic period and then increased significantly when the air pollution levels went up again after the games. Positive associations with air pollution levels, although not always statistically significant, were found for chemokine IL-8, Eotaxin-1 and GRO-α.

Chemokines are important inflammatory mediators with a key role in mediating recruitment and activation of leukocytes and modulating angiogenesis, apoptosis, and cell proliferation. (Rollins, 1997; Taub and Oppenheim, 1993) *In vitro* studies using different human cell lines provided preliminary evidence that air pollution exposure might increase production of different chemokines (Kang et al., 2010; Ovrevik et al., 2009). Several animal studies confirmed this possible association.(He et al., 2010; Inoue et al., 2005)

Human evidence regarding the effects of air pollution on chemokines is limited, except for the first identified chemokine, IL-8. The positive association between air pollution exposure and IL-8 observed in the current study is consistent with previous exposure controlled studies (Salvi et al., 2000; Stenfors et al., 2004) and longitudinal field studies (Chen et al., 2012; Steerenberg et al., 2001) conducted among healthy individuals, although many of those studies examined IL-8 expression in respiratory track instead of systemic circulation (Moller et al., 2014). For the other chemokines, human evidence is limited and inconsistent. A longitudinal field study conducted among healthy, non-smoking, young adults observed that elevated $PM_{2.5}$ levels were accompanied by suppressed circulating levels of RANTES and GRO-α, and increased levels of IP-10 and MCP-1 (Pope et al., 2016). One cross-sectional field study found children living in more polluted areas had higher RANTES in sera (Ando et al., 2001). An experimental controlled chamber study showed that diesel exhaust enhanced GRO-α protein expression in bronchial epithelium among healthy nonsmokers (Salvi et al., 2000). While another chamber exposure controlled study found levels of RANTES and Eotaxin-1 in sputum did not change after diesel exhaust exposure in asthmatic individuals (Riedl et al., 2012). Moreover, the current study examined a larger number of chemokines and observed positive associations between air pollution exposure and serum concentrations of MCP-2 and TARC. Chemokines are capable of activating several intra-cellular signaling pathways and altering multiple physiological functions, which may further affect disease risk.

RANTES, MCP-2, GRO-α, IL-8, and MCP-1 have been related to the pathogenesis of chronic obstructive pulmonary disease (COPD), cardiovascular diseases and cancer.(Cai et al., 2009; Lebrecht et al., 2001; Niwa et al., 2001; Xia and Frangogiannis, 2007) GRO-α, IL-8, and MCP-1 attract and activate neutrophils and monocytes to release proteases, which further cause elastin degradation and emphysema in COPD.(Hardaker et al., 2004; Koelink et al., 2012) MCP-1 and MCP-2 are important chemotactic proteins in recruiting monocytes

from blood into early atherosclerotic lesions.(Charo and Taubman, 2004; Sasayama et al., 2000) Eotaxin-1, RANTES, TARC and MCP-2 are chemokines that affect the major effector cells in pathogenesis of allergic diseases, including eosinophils, Th2 and basophils.(Gerard and Rollins, 2001) Eotaxin-1 and RANTES are chemoattractants for eosinophils.(Fulkerson et al., 2006) TARC may stimulate eosinophilic inflammation through Th2 cells.(Xiao et al., 2003) MCP-1, MCP-2 and RANTES are capable of activating basophils and increasing allergic inflammation.(Kaplan, 2001)

Previous reports have observed similar trends for other blood soluble mediators. Changes in air pollution levels during the Beijing Olympics were associated with changes in biomarkers of inflammation and thrombosis and measures of cardiovascular physiology including fibrinogen, C-reactive protein [CRP], white blood cell [WBC] count, platelet activation markers P-selectin [sCD62P] and soluble CD40 ligand [sCD40L] as well as the adhesive endothelial glycoprotein von Willebrand factor. These factors tended to improve from the pre-Olympic periods to during the Olympics but tended to return to pre-Olympic levels after the Olympics when air pollution levels increased again. (Rich et al., 2012; Zhang et al., 2013). These findings may implicate that the biomarker changes across the Olympic periods were acute inflammatory and prothrombotic responses to changes in air pollution. Based on these studies and our findings, there is evidence to support policies that can be put in place to control sources of air pollution from a public health perspective.

The possible explanation for the greater rebound is PM_{10} in our current study may be due to the sources of emission. Wang et al. (2010) reported that fugitive dust was the largest PM_{10} emission source, which contributed 79% of total PM_{10} emissions in Beijing. Construction sites and industrial sources contributed 35% and 34%, respectively, to PM_{10} emission reductions (Wang et al., 2010). Furthermore, there are factors other than source controls, such as weather and wind conditions, that are important in determining day-to-day variation. Wang et al. (2009) determined that source control measures were in fact less effective in reducing $PM_{2.5}$ concentrations than $>PM_{2.5}$ and $PM_{2.5–10}$ concentrations (Wang et al., 2009). It is hypothesized that while ultrafine particles make up a small fraction of total PM_{10} mass, they can still have substantial health effects by crossing the blood barrier of the lung and entering the bloodstream leading to systemic inflammatory responses (Polichetti et al., 2009). Other pollutant levels were also regularly monitored and were reported in previous studies. Huang et al. (2012b) reported a reduction of 27.6% in black carbon, 50% reduction in sulfur dioxide, 20% reduction in nitrogen dioxide, 10% reduction on ozone when comparing levels during Olympics with the pre-Olympics period.

The current study has several notable strengths. First, in this study, each participant served as his or her own control in this panel study, thereby reducing confounding. Second, this bi-directional “before-during-after” design has the advantage of being less affected by time-variant confounding factors, since it is less likely that time-variant confounding factors rose and fell in parallel with air pollutants and thereby account for any observed association. Therefore, results from this “before-during-after” design may provide a stronger support to a causal inference than “before-after” comparison design. (Huang et al., 2012a; Rich et al., 2012) Third, the substantial change of ambient air pollution levels within a relatively short period of time may help to detect modest changes of physiological endpoints, which might

remain otherwise undetected in the studies with relatively low peak level of air pollution and/or small changes of air pollution levels over the study period. (Li et al., 2012)

Despite the aforementioned advantages, this study was subject to certain limitations. First, the study did not have personal level air pollution estimates. The monitored air pollution levels in the local community may not represent the actual individual exposure levels given individual's travel to other areas and the possible impact of indoor air pollution. However, these errors are more likely to be non-differential over the three time periods, which tends to attenuate the associations towards null. Second, the ambient air contains a mixture of different gaseous and particulate pollutants and multi-collinearity might exist among the pollutants. In the current study, the measured particulate air pollutants presented similar patterns of change over the course of the study period; therefore, it might be hard to attribute the observed associations to any single particular air pollutant. In addition, small particles such as PM2.5 did not return completely to the previous level after the games. This might affect how we should interpret the comparison between after vs during, especially for those chemokines where we did not observe the significant changes after the Olympics. Third, only one single measurement of chemokines was made on each participant in each time period, therefore it is possible that the potential intra-individual variability of the selected biomarkers within each time period was not captured. However standardized timed collection of blood at each visit may minimize the potential intra-individual variation, because several inflammatory cytokines and chemokines exhibit significant circadian oscillation with a 2-fold peak-to-trough ratio over 24-h day cycle.(Hayashi et al., 2007; Keller et al., 2009) Having one blood collection for each participant during each time period makes it impossible for us to control for the possible confounding effects from ambient temperature, humidity, and other individual behaviors changes in the three-time comparison analysis.

5. CONCLUSION

This panel study is a comprehensive examination of the associations between short-term changes in ambient air pollution levels and serum chemokines. Our findings suggest that chemokines may be mediators in the inflammatory pathway through which air pollution increases risks of different human diseases.

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Declarations:

Ethnics approval: The current study was approved by the institutional review boards of the State University of New York at Buffalo *(SPM1080708E)* and Pekin g University Health Science Center *(IRB00001052–08057)*.

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Abbreviations

PM	Particulate matter

COPD	chronic obstructive pulmonary disease
IQR	inter-quartile ranges
BMI	body mass index
95% CI	95% confidence interval
CV	coefficients of variation

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Clinical significance

The study provide the evidence that exposure to high air pollution level might result in the changes in chemokines. The chemokines play critical roles in initiation and progression of various diseases including cardiovascular disease, cancer and allergic disease. The finding contribute to better understanding of the molecular mechanisms that linking environmental exposure with clinical diseases.

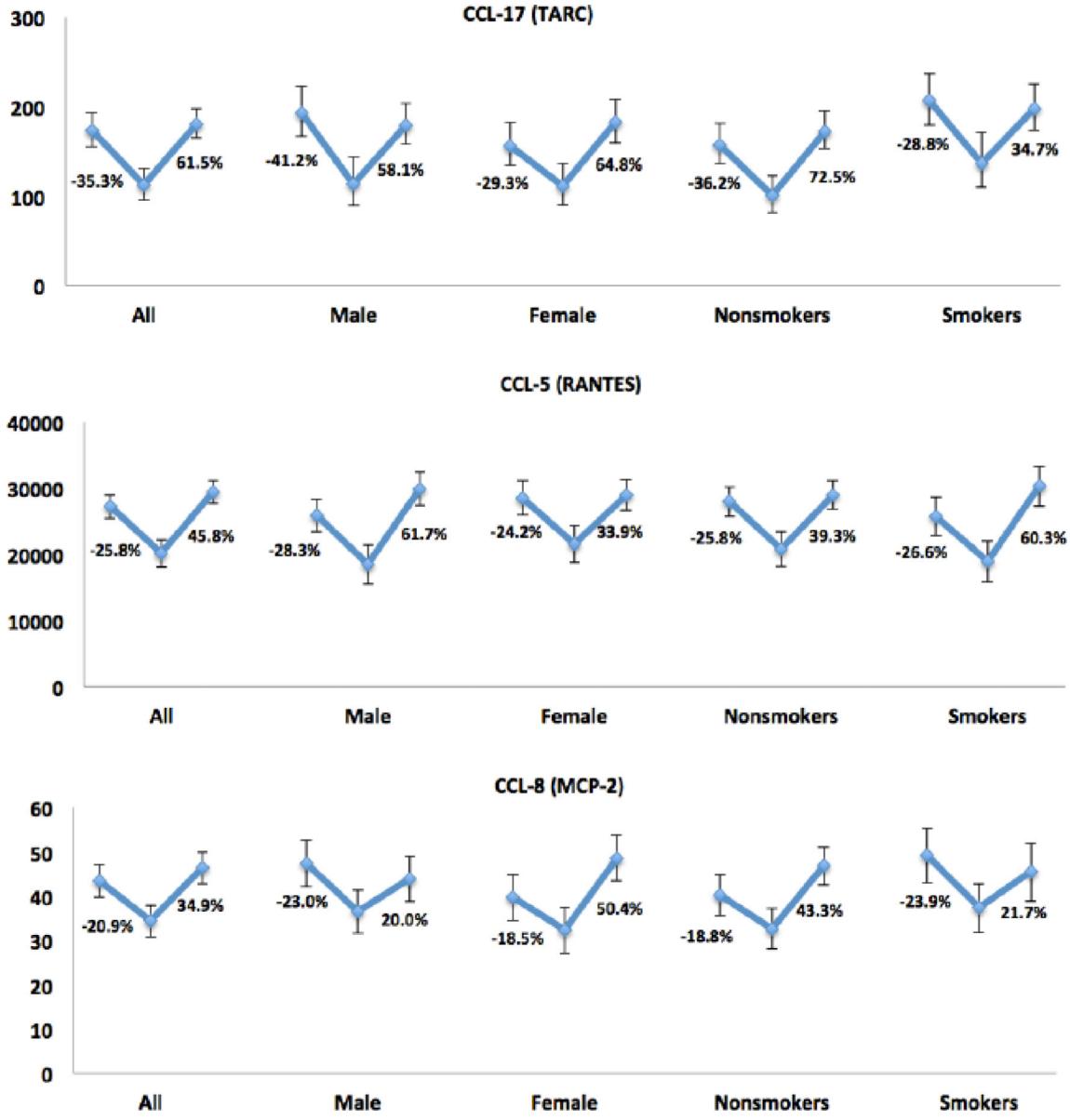

Figure 1. Change of Selected Chemokines (A) CCL-17 (TARC) (B) CCL-5 (RANTES) (C) CCL-8 (MCP-2) in Overall Population and in Subgroups by Sex and Smoking Status across the Beijing Olympics

Units of all chemokines presented in this table are pg/ml. Error bars indicated 95% confidence intervals.

Table 1

Basic Characteristics of Study Participants

Variables	Distribution
	Mean (SD)
Age (years)	48.3 (9.1)
BMI (kg/m^2)	23.7 (3.4)
	N (%)
Sex	
Male	50 (48.1)
Female	54 (51.9)
Age groups	
≤ 40	16 (15.4)
40–50	36 (34.6)
> 50	52 (50.0)
BMI categories	
Underweight and normal (<24 kg/m^2)	63 (60.6)
Overweight (24–28 kg/m^2)	30 (28.9)
Obesity (≥28 kg/m^2)	11 (10.6)
Smoking status	
Smokers	37 (35.6)
Non-smokers	67 (64.4)
Alcohol drinking	
Drinkers	34 (32.7)
Non-drinkers	70 (67.3)
	Median (IQR)
GRO-α (pg/ml)	47.20 (25.35, 86.98)
IL-8 (pg/ml)	40.01 (19.63, 92.89)
IP-10 (pg/ml)	75.61 (58.40, 103.89)
MCP-1 (pg/ml)	121.75 (90.56, 163.27)
RANTES (pg/ml)	25779 (18895.61, 32212.47)
MCP-2 (pg/ml)	38.45 (27.42, 53.90)
Eotaxin-1 (pg/ml)	146.02 (109.26, 192.29)
TARC (pg/ml)	169.02 (108.40, 243.05)

Table 2

Change of Serum Chemokines Concentrations across the Beijing Olympics

		Before Olympics	During Olympics	After Olympics
GRO-α	Mean (95% CI)	52.83 (44.33, 62.97)	41.45 (34.58, 49.68)	50.51 (42.81, 59.60)
	Percent change across period (95% CI)	**−22.53 (−34.31, −8.64)**		23.71 (−3.57, 58.71)
	Adjusted P-value[1]	**0.0020**		0.0837
IL-8	Mean (95% CI)	53.11 (43.33, 65.09)	36.72 (28.54, 47.23)	42.39 (34.77, 51.69)
	Percent change across period (95% CI)	**−30.41 (−48.54, −5.89)**		14.71 (−13.15, 51.48)
	Adjusted P-value[1]	**0.0184**		0.3159
IP-10	Mean (95% CI)	79.92 (72.72, 87.82)	80.38 (73.00, 88.51)	80.27 (72.63, 88.72)
	Percent change across period (95% CI)	0.58 (−7.27, 9.11)		−0.14 (−13.18, 14.87)
	Adjusted P-value[1]	0.8851		0.9843
MCP-1	Mean (95% CI)	121.00 (109.90, 132.10)	130.28 (119.71, 140.84)	144.72 (133.60, 155.84)
	Percent change across period (95% CI)	**7.67 (0.77, 14.57)**		11.08 (−0.31, 22.48)
	Adjusted P-value[1]	**0.0228**		**0.0380**
RANTES	Mean (95% CI)	27202 (25437, 28966)	20113 (18099, 22126)	29424 (27710, 31137)
	Percent change across period (95% CI)	**−25.84 (−33.46, −18.22)**		**45.84 (28.16, 63.51)**
	Adjusted P-value[1]	**<0.001**		**<0.001**
MCP-2	Mean (95% CI)	43.39 (39.68, 47.10)	34.33 (30.82, 37.84)	46.33 (42.76, 49.90)
	Percent change across period (95% CI)	**−20.88 (−26.90, −14.86)**		**34.92 (18.50, 51.35)**
	Adjusted P-value[1]	**<0.001**		**<0.001**
Eotaxin-1	Mean (95% CI)	138.61 (125.87, 152.64)	132.27 (119.80, 146.04)	153.87 (140.21, 168.86)
	Percent change across period (95% CI)	−5.31 (−11.70, 1.54)		**16.37 (1.91, 32.88)**
	Adjusted P-value[1]	0.1334		**0.0166**
TARC	Mean (95% CI)	172.94 (155.41, 192.43)	111.89 (95.94, 130.50)	180.80 (165.08, 198.01)
	Percent change across period (95% CI)	**−35.30 (−43.39, −26.05)**		**61.53 (38.46, 88.46)**
	Adjusted P-value[1]	**<0.001**		**<0.001**

1. Adjusted for age, sex, smoking status, BMI categories and their interaction terms with time-points.

2. IL-8, IP-10, Eotaxin-1 and TARC were log transformed.

3. Units of all chemokines presented in this table are pg/ml