Environment International 119 (2018) 264–273

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Short- and long-term exposure to ambient air pollution and circulating biomarkers of inflammation in non-smokers: A hospital-based cohort study in South Korea

Hyewon Lee[a,b,1], Woojae Myung[a,1], Byeong-Ho Jeong[c], Hong Choi[d,e], Byung Woo Jhun[c,*,2], Ho Kim[b,f,**,2]

[a] Department of Neuropsychiatry, Seoul National University Bundang Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do 13619, South Korea
[b] Institute of Health and Environment, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, South Korea
[c] Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul 06351, South Korea
[d] Center for Health Promotion, Samsung Medical Center, Gangnam-gu, Seoul 06351, South Korea
[e] Department of Psychiatry, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnam-gu, Seoul 06351, South Korea
[f] Department of Public Health Sciences, Graduate School of Public Health, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, South Korea

ARTICLE INFO

Handling Editor: Xavier Querol

Keywords:
Ambient air pollution
C-Reactive protein
Ferritin
Fibrinogen
Inflammation
White blood cell count

ABSTRACT

Despite increasing epidemiological evidence of an association between air pollution and adverse health outcomes, the detailed mechanisms underlying the adverse effects of air pollution on medical conditions remain unclear. We evaluated the effects of short- and long-term exposure to ambient air pollution on key inflammatory markers in non-smoking subjects. Serum fibrinogen, C-reactive protein, ferritin, and white blood cell counts were repeatedly measured 3 times in 6589 subjects at the Samsung Medical Center (Seoul, South Korea) between 2010 and 2016. Both short- (≤8-day averages) and long-term (annual averages) exposure measures of 6 air pollutants (particles < 2.5 μm, particles < 10 μm, nitrogen dioxide, sulfur dioxide, ozone, and carbon monoxide) were estimated for each subject based on available residential addresses. Linear mixed-effects models were used to relate interquartile range increases in pollutant concentrations to inflammatory marker levels. Short-term exposure to air pollution was associated with increased fibrinogen and ferritin levels. Long-term exposure to air pollution was associated with increased fibrinogen levels and white blood cell counts. The largest short- and long-term associations were observed for ferritin in response to nitrogen dioxide exposure (1.4%, 95% confidence interval [CI] 0.3–2.5) and fibrinogen exposed to particles < 2.5 μm (3.4%, 95% CI 3.0–3.8), respectively. Significantly higher associations were observed among subjects with elevated levels of inflammatory markers (upper 25th percentile), including C-reactive protein, and those with cardiac infarction, chronic obstructive pulmonary disease, cerebral infarction, or diabetes. We found clear associations between short- and long-term exposure to air pollution and inflammatory markers, especially among vulnerable subgroups. Our findings provide evidence in support of the hypothesis that air pollution increases systemic inflammation, particularly among susceptible subgroups.

1. Introduction

Ambient air pollution has been associated with numerous adverse health outcomes, including cardiopulmonary disease, exacerbation of neurological or autoimmune disease, and all-cause mortality (Brook et al., 2004; Cai et al., 2017; Dockery et al., 1993; Garshick, 2014; Lee et al., 2017). Short-term exposure to particulate matter (PM) or ozone (O_3) has been associated with an increased risk of hospital admission

Abbreviations: BMI, body mass index; CI, confidence interval; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; NO_2, nitrogen dioxide; NO_x, nitrogen oxide; O_3, ozone; PM, particulate matter; $PM_{2.5}$, particles < 2.5 μm; PM_{10}, particles < 10 μm; SO_2, sulfur dioxide; WBC, white blood cell

* Correspondence to: B.W. Jhun, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Irwon-ro 81, Gangnam-gu, Seoul 06351, South Korea.
** Correspondence to: H. Kim, Graduate School of Public Health, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, South Korea.
E-mail addresses: byungwoo.jhun@gmail.com (B.W. Jhun), hokim@snu.ac.kr (H. Kim).
[1] These individuals contributed equally to this article as co-first authors.
[2] These individuals contributed equally to this article as co-corresponding authors.

https://doi.org/10.1016/j.envint.2018.06.041
Received 18 March 2018; Received in revised form 2 June 2018; Accepted 30 June 2018

and mortality from cardiopulmonary disease (Bell et al., 2004; Dominici et al., 2006). In addition, increased exposure to nitrogen oxide (NO_x) has been associated with reduced pulmonary function (Adam et al., 2015; Bell et al., 2004; Pope III et al., 2002). These findings suggest that air pollution can trigger or exacerbate factors associated with potential pathophysiological mechanisms.

Despite increasing epidemiological evidence, the detailed mechanisms underlying the adverse effects of air pollution on medical conditions remain unclear. It has been postulated that oxidative stress from inhaled pollutants leads to cytokine-mediated inflammation or a hypercoagulable state, increasing the risk of disease exacerbation (Chen and Schwartz, 2008; Hajat et al., 2015; Hoffmann et al., 2009; Li et al., 2017). To confirm this, studies have investigated whether specific inflammatory markers are associated with exposure to air pollution (Chuang et al., 2007; Dubowsky et al., 2006; Hajat et al., 2015; Ruckerl et al., 2007). However, the majority of studies have focused only on short-term exposure, and studies of biomarker responses have been inconsistent. Moreover, there are insufficient data on whether inflammatory responses to air pollution exposure differ according to the underlying disease.

Therefore, we investigated the effects of short- and long-term exposure to urban ambient air pollution, including particles $< 2.5\,\mu m$ ($PM_{2.5}$), particles $< 10\,\mu m$ (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), O_3, and carbon monoxide (CO), on key inflammatory markers (serum fibrinogen, C-reactive protein [CRP], ferritin, and white blood cell [WBC] counts) in non-smoking subjects. We also evaluated whether these associations were modified by underlying medical conditions.

2. Material and methods

2.1. Study population

The study population was retrospectively derived from a cohort of 84,914 subjects who underwent comprehensive health check-ups at the Samsung Medical Center (Seoul, South Korea) between 2010 and 2016. The inclusion criteria were as follows: non-smokers or ex-smokers, > 3 hospital visits, residents of one of the 25 districts of Seoul, South Korea (during the study period), and available data on district-level residential addresses for assigning exposure estimates. These criteria resulted in 6589 participants. Comprehensive health check-ups included a blood draw, laboratory examination, anthropometric examination, and questionnaire by specialists. We evaluated the data from the first to third visit, although the number of visits varied according to the participant (≤ 7 visits; $n = 100$). The year of the first visit (2010 [$n = 1447$] to 2014 [$n = 189$]) and the interval between the first and third visits (2 [$n = 3101$] to 6 [$n = 164$] years) also varied by participant. Thus, 19,767 samples from the 6589 participants were analyzed. The study was approved by the Institutional Review Board of our hospital. Informed consent was waived due to the retrospective nature of the study.

2.2. Inflammatory markers

Serum fibrinogen, CRP, and WBC counts were selected as the target inflammatory markers associated with air pollution. Serum ferritin, which has been reported to be associated with disease (Fumeron et al., 2006; Salonen et al., 1992), was also examined. These markers were measured in peripheral blood at each visit. Serum fibrinogen was measured using a clotting assay with STA-Fibrinogen and STA-Owren-Koller Buffer (Stago STA-R Evolution). Serum CRP was measured using a particle-enhanced immunoturbidimetric assay for human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies (Hitachi 7600; Tokyo, Japan). WBC counts were measured using laser optical flow cytometry (Sysmex XE-2100/XN-9000). Serum ferritin was measured using a chemiluminescent immunoassay with 5 ReadyPack® primary reagent packs: ADVIA Centaur™ Ferritin Lite Reagent and Solid Phase (Siemens ADVIA Centaur XP).

2.3. Assessment of exposure to air pollution

Because information on the subjects' addresses was only provided up to district-level for privacy, exposure measurements were based on district-level residential addresses. Seoul is the largest city and the capital city of Korea. It comprises 25 districts ranging from 10 to 47 km^2 (mean 24 km^2); each district has a centrally located regular monitoring site to measure hourly concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, and CO, which is operated by the Seoul Research Institute of Public Health and Environment. Concentrations were measured by beta-ray absorption ($PM_{2.5}$ and PM_{10}), chemiluminescence (NO_2), ultraviolet fluorescence (SO_2), ultraviolet photometry (O_3), and nondispersive infrared photometry (CO).

We calculated daily representative district-specific concentrations: 24-hour mean values were calculated for $PM_{2.5}$, PM_{10}, NO_2, and SO_2, and maximum 8-hour mean values were constructed for O_3 and CO according to the World Health Organization Air quality guidelines (2006). These daily concentrations were further used for the construction of short- (on the day of blood draw [lag0] and moving average of the day and the previous 1- [lag0–1], 2- [lag0–2], 3-, 4-, 6-, and 8-day periods) and long-term exposure measures (moving average during the previous 365 days before the day of blood draw at each visit).

2.4. Covariates

Individual-level covariates, such as age, sex, body mass index (BMI), and morbidity (state of disease), were obtained from the comprehensive health check-ups. District-level contextual covariates (*e.g.*, the proportion of green space) were obtained from the Korean Statistical Information Service (2010) Census (http://kosis.kr/eng/). Ambient temperature and relative humidity data were provided by the Korea Meteorological Administration.

2.5. Statistical analysis

Before regression analysis, all markers were log-transformed to better approximate normality. Extreme outliers (> 4 standard deviations from the mean) were excluded. Linear mixed-effects regression models were used to examine the association between exposure to air pollution and inflammatory markers, accounting for correlation between multiple measurements from the same participants. In the main model, each log-transformed inflammatory marker was the response variable with a random effect for each participant and with fixed linear effects for air pollution measures and other covariates. Air pollutants were entered separately into single-pollutant models. The following covariates were selected *a priori* and kept in the model after a variance inflation factor test: sex, age, BMI, smoking status (never/former), alcohol consumption (yes/no), hypertension, diabetes, dyslipidemia, cerebral infarction, cardiac infarction, thyroid disorders, cancer, statin use, visit number (first/s/third), visit year, season, 2-day moving average of temperature and relative humidity on the same day and 1 day prior to blood draw, and district-level contextual variables (economic environment satisfaction [10-point Likert scale] and the proportions of green space, medical personnel, the married among the population aged > 15 years, and the highly educated [college level or above]).

We examined potential effect modification by sex, age (< 65 or ≥ 65 years), asthma, cardiac infarction, cerebral infarction, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, statin use, season, and inflammatory marker levels (low, lower 75th percentile; high, upper 25th percentile) using interaction terms for each modifier and measures of exposure to air pollution. This reflected changes in the participants' status at each visit. As inflammatory marker