Published in final edited form as:
Inhal Toxicol. 2010 February ; 22(3): . doi:10.3109/08958370903207274.

Impact of Ambient Air Pollution on the Differential White Blood Cell Count in Patients with Chronic Pulmonary Disease

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Abstract

Epidemiologic studies report associations between particulate air pollution and increased mortality from pulmonary diseases.To examine whether the exposure to ambient gaseous and particulate air pollution leads to an alteration of the differential white blood cell count in patients with chronic pulmonary diseases like chronic bronchitis, chronic obstructive pulmonary disease, and asthma.

A prospective panel study was conducted in Erfurt, Eastern Germany, with 12 repeated differential white blood cell counts in 38 males with chronic pulmonary diseases. Hourly particulate and gaseous air pollutants and meteorological data were acquired. Mixed models with a random intercept adjusting for trend, meteorology, weekday, and other risk variables were used.

In this explorative analysis we found an immediate decrease of polymorphonuclear leukocytes in response to an increase of most gaseous and particulate pollutants. Lymphocytes increased within 24 hours in association with all gaseous pollutants but showed no effect in regard to particulate air pollution. Monocytes showed an increase associated with ultrafine particles, and nitrogen monoxide. The effect had two peaks in time, one 0-23 hours before blood withdrawal and a second one with a time lag of 48-71 hours.

The increase of particulate and gaseous air pollution was associated with multiple changes in the differential white blood cell count in patients with chronic pulmonary diseases.

Keywords

air pollution; C-reactive protein; PM10; differential white blood cell count; ultrafine particles

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All authors declare that they have no competing financial interests in regard to the manuscript.

Introduction

The importance of ambient particulate air pollution for respiratory (Sint et al. 2008) and cardiovascular (Brook et al. 2004) disease burden in various populations has been shown in numerous epidemiological studies. Though the biological mechanisms responsible for the connection between particulate air pollution and effects on different organ systems are still incompletely understood, evidence is growing that there is a local pulmonary inflammatory state due to particulate matter which spreads on a systemic level.(van Eeden et al.2001) An accumulation of band and polymorphonuclear leukocytes (PMN) as first line inflammatory cells could activate oxidative stress response which may lead to an activation of transcription factors like the nuclear factor-kappa B (NF-κB), possibly initiating a cascade of gene expressions.(MacNee et al. 2000) As a result, the inflammatory process could reach a systemic influence and thus explain the extrapulmonary effects of air pollution.(Fujii et al. 2002; van Eeden et al.2002)

Aside from particulate matter with aerodynamic diameter < 10 μm (PM_{10}), also ultrafine particles (UFP) with a size range between 0.01-0.1 μm are supposed to be able to exert a local and systemic inflammatory influence capable of causing exacerbations of lung disease and increased blood coagulability explaining increased cardiovascular events in susceptible individuals.(Utell et al. 2000) The translocation of inhaled ultrafine particles into the systemic circulation suggested by Nemmar et al. (Nemmar et al.2002) may support this assumption.

We hypothesized that effects of particulate and gaseous air pollutants are reflected in changes of white blood cells. As people with chronic cardiopulmonary disease, influenza, or asthma are most susceptible to react to short-term acutely elevated exposures (Pope, III et al. 2006), a panel of patients with chronic pulmonary diseases was selected for the study.

Methods

Study population

A prospective panel study was conducted between October 15th 2001 and May 6th 2002 in Erfurt, a city of 200,000 inhabitants in Eastern Germany. Male participants with impaired lung function and/or chronic pulmonary disease diagnosed by a physician were enlisted to participate in 12 subsequent clinical examinations. The following exclusion criteria were applied: intake of anti-coagulants with exception of acetylsalicylic acid, wearing a cardiac pacemaker, recent (less than three months ago) myocardial infarction or bypass-surgery/ coronary angioplasty, diabetes mellitus type 1, pneumoconiosis (silicosis or asbestosis), hospitalization more than three times in the previous year because of COPD, continuing oxygen therapy and antibiotics more than four times during six months or the winter half-year prior to the study (the first five exclusion criteria pertain to a different analysis of the same study. (Hildebrandt et al. 2008)) All participants signed a written consent and the study protocol was approved by the Ethics Commission of the Bavarian Chamber of Physicians (“Bayerische Landesaerztekammer”). Data on health status, pulmonary and cardiac symptoms, medication, and smoking history were obtained at baseline and during follow-up visits. The patients had clinical examinations and blood withdrawals every other week at the same time and at the same day of the week over a period of six months.

White blood cell count analysis

All blood specimens were analyzed by an Abbott Cell-Dyn 1800 cell counter, an automated differential leukocyte counter. In addition, platelets were counted. The following white blood cells were distinguished: lymphocytes, monocytes, and eosinophils/basophils and neutrophilic granulocytes. A synonym for the latter is polymorphonuclear leukocytes

(PMNs). After being released from the bone marrow they will circulate in the peripheral blood for 6-10 hours before entering organ tissue for phagocytosis. Precursor cells of PMNs - so called band cells - can generally be detected in the peripheral blood only during times of particular stimulation. Monocytes replenish resident macrophages and dendritic cells. In response to inflammation signals, monocytes will leave the circulating blood within 1-2 days to the interstitial tissues where they differentiate to organ-specific macrophages to elicit an immune response. An increase in lymphocytes is usually a sign of a viral infection.

The different types of leukocytes reflect their different functions in the immune response which corresponds to different time lags in relation to exposure.

Air pollution monitoring

Hourly ambient air pollutants were measured at a fixed monitoring station in the vicinity of the city center of Erfurt representing urban background levels. All study participants lived within a radius of 3.5 kilometers from the monitoring station. Continuous UFP counts and accumulation mode particles (ACP, 0.1-1.0 μm) were measured with a mobile aerosol spectrometer. PM_{10} were collected by tapered element oscillating microbalance method (TEOM 1400a, Thermo Fisher Scientific Inc., USA). Elemental (EC) and organic carbon (OC) were determined from an ambient carbon monitor (ACPM 5400, Thermo Fisher Scientific Inc., USA). Data on meteorological and gaseous variables sulfur dioxide (SO_2), nitrogen dioxide (NO_2), nitrogen monoxide (NO) and carbon monoxide (CO) were obtained from existing networks. Ozone was also available but not analyzed here, as previous studies have shown that the effects of ozone are limited to the higher concentrations during the spring/summer period. (Zanobetti et al.2008)

We used moving averages of ambient concentrations of air pollutants and meteorological variables to characterize the exposures by calculating the individual 0-23 hours average exposure (split into: 0 – 5, 6 -11, 12 – 17, and 18 – 23 hours) for each person immediately preceding the blood withdrawal up to two days (24 – 47, 48 – 71 hours before blood withdrawal). Missing values for UFP and PM_{10} were imputed by a generalized additive regression model. The squared multiple correlations (R-square) were 0.93 for the UFP regression model and 0.79 for PM_{10}. Two missing values for air temperature and relative humidity were replaced based on parallel measurements of other devices.

Statistical analyses

The longitudinal data were analyzed with SAS statistical package (version 9.1; SAS Institute Inc., Cary, NC, USA) using additive mixed models with random patient intercepts. To model the correlation between repeated measures in each patient we assumed a compound symmetry structure for the covariance matrix, because the half-lives of the markers were shorter than the intervals between visits.

In a first step, a confounder selection without air pollutants was conducted for every blood parameter, separately. The confounder model consisted of long-term time trend and a variable for lag of air temperature, relative humidity and barometric pressure. Possible lags for meteorological variables were defined as individual 0 – 23, 24 – 47, 48 – 71, 72 – 95, and 96 – 119 hours before the blood withdrawal. The confounders were included linearly or smooth as penalized splines (P-splines) to allow for a non-parametric relationship. The lag which minimized Akaike Information Criterion (AIC) was selected. Trend and the best lag for air temperature and relative humidity were forced into the confounder model, while barometric pressure was selected only, if it improved the model fit. If a confounder was included as a P-Spline, it was checked whether a polynomial (linear, quadratic or cubic) led to a smaller AIC. Two variables with questionnaire information indicating an airway

infection or the intake of antibiotics two weeks before the blood withdrawal were forced into the model in order to account for an inflammation that was not the result of elevated air pollution. In addition, the intake of corticosteroids with its impact on the differential white blood cell count was taken into account. Weekday was included as a confounder if it improved AIC.

After assessing the confounder model, single air pollution lags were added and their effects were estimated linearly. The effects are presented as percent change of arithmetic mean per interquartile range (IQR: difference between the third and first quartile) increase in air pollutant together with 95% confidence intervals (CI). The air pollution effects on both the proportion and the absolute numbers of the specific white blood cells were calculated.

Several dichotomous interaction variables were added to the model in order to estimate the air pollution effects of the corresponding subgroups. The analyzed interaction terms were: smoking status (current smoker vs. ex/never-smoker) and suffering from asthma or hay fever (yes vs. no). Instead of adjusting for the intake of corticosteroids it was also included as an interaction variable. Additionally, air pollutants were also estimated smoothly as P-Splines in order to check the assumed linearity of the effects.

CO and NO_2 are closely linked with UFP as well as EC and OC with ACP (Cyrys et al. 2003). In order to identify the influential air pollutant several multi-pollutant models were calculated. The models included UFP and CO or NO_2, or ACP and EC or OC. As a sensitivity analysis air pollution effects were calculated without adjusting for meteorological variables.

Results

Patient characteristics

The data of 38 of 42 male persons could be included in the analyses: three persons were excluded as they had only one single measurement, and one additional patient was excluded because of cancer diagnosed after the study had started. 438 of the targeted 456 visits took place (96.1%). 10 times (2.2%) the blood withdrawal failed for technical reasons. 47 blood samples were excluded because of fever the week before the withdrawal or a diagnosed airway infection at the day of the visit. In total 381 observations were available for analysis.

The age ranged from 35 to 78 years and the body mass index varied between 20 and 36 kg/m^2 (Table 1). Lung function tests were done for all patients. The majority of patients suffered from chronic bronchitis and/or asthma with normal pulmonary function tests measured as forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratios higher than 70%. 14 patients suffered from chronic obstructive pulmonary disease (COPD) with impaired lung function: two patients had a mild form, further seven a moderate ($50\% \leq FEV_1/FEV_1$ predicted $< 80\%$) and another five a severe degree of the disease ($30\% \leq FEV_1/FEV_1$ predicted $< 50\%$). Information regarding other diseases, smoking habits and drug therapy is also presented in Table 1.

Table 2 shows the summary statistics of daily concentrations (24 h-averages) of air pollutants and meteorological variables for the whole study period in Erfurt, including imputed values. Temperature, number concentrations of UFP and PM_{10} for the study period are presented in Figure 1. The average 24 h PM_{10} values over the time period was 17.9 $\mu g/m^3$ with only one measurement of PM_{10} exceeding the EU ambient air quality standard of 50 $\mu g/m^3$. In Table 3 the correlations between particulate and gaseous pollutants are noted. As expected, the correlations were highest between EC and OC, ACP and PM_{10}, as well as

between ACP and EC or OC. The correlations of UFP with ACP and PM_{10} were considerably weaker.

Association between air pollution and white blood cell count

Table 4 gives an overview of the distribution of the total and differential white blood count as well as number of platelets and CRP-level. Table 5 shows the estimated percent change of the mean outcome parameter PMN, band cells, platelets, and monocytes (measured in absolute cell numbers) per increase in IQR for particulate air pollution concentrations (UFP, ACP, PM_{10}, EC, and OC) in different time lags within 23 hours. Figure 2 shows the results for gaseous pollutants and figure 3 for particulate pollutants covering also the longer lag periods 24-47h and 48-71h.

We found a decrease of PMN and platelets within the first 24 hours associated with all particulate air pollution parameters, but most pronounced for ACP. In absolute numbers the mean decrease of PMN is equivalent up to 276 cells per μl and the increase of band cells up to 39 cells per μl. An immediate increase (0-5 hours) in band cells was seen for PM_{10}, ACP, EC/OC, but not for UFP (table 5). The drop of PMN during the first 24 hours was more pronounced in current smokers than in ex- or non-smokers and in patients taking corticosteroids compared to those without such medication (data not shown). Effects tended to be stronger for the younger age group (<60 years) compared to the older age group especially for band cells.

Monocytes showed an increase associated with UFP, and NO. The effect had two peaks in time, one 0-23 hours before blood withdrawal and a more pronounced second one with a time lag of 48-71 hours (figures 2-3). The 26% increase related to UFP corresponds to 67 monocytes/μl in absolute numbers.

Lymphocytes increased within 24 hours in association with CO and NO coming back to normal thereafter, but showed no effect in regard to particulate air pollution (figure 3). Eosinophils showed no response to either gaseous or particulate air pollution (data not shown).

The inclusion of air pollutants as smooth terms showed that the effects on the blood markers were linear. After adjusting for a second air pollutant the influential air pollutant of the single-pollutant model remained significant or both air pollutants showed no effect. Excluding the meteorological variables led to smaller and weaker air pollution effects.

Discussion

In an explorative analysis we looked for percent changes in various outcome parameters of the differential white blood cell count in association with particulate and gaseous air pollutants. Most changes in the white blood cell count (with the exception of monocytes) were observed for exposures that occurred within 24 hours before blood withdrawal.

The decrease of circulating PMN we have found in association with particulate and gaseous air pollution has been reported before by Ghio et al. (Ghio et al.2003). The authors exposed twenty healthy young volunteers to either filtered air (n = 5) or concentrated ambient pollution (n = 15) with a mean PM mass of 120.5 +/− 14.0 $\mu g/m^3$. Regression analysis verified significant linear relationships between particle mass the individual was exposed to and decrements in the total WBC count 24 h later. No differential WBC was analysed, but one can assume that the effect was due to a decrement in PMN which contribute about 60% of cells to the total WBC.

The increase in band cells suggests a possible stimulation of the human bone marrow by acute particulate exposure. Tan et al. (Tan et al. 2000) reported an association between an acute air pollution episode due to the Southeast Asian Smoke-haze in 1997 and the development of elevated band cells expressed as a percentage of total PMN in healthy military recruits with maximal coherences with PM_{10} on lags 0 and 1. Immature PMNs harvested from the bone marrow have a lower deformability and reduced motility and are less phagocytic compared to mature cells in the peripheral blood. These maturity-related abnormalities of younger PMNs may lead to a preferential sequestration in the microvessels of the lung and may also cause damage of adjacent endothelium if these trapped PMNs are activated by circulating inflammatory mediators (van Eeden et al. 1999). It may be assumed that the immaturity of those young PMNs will compromise their ability to eradicate bacterial infections of the lung so that particulate matter can be seen as an immunosuppressive factor to undermine normal pulmonary antimicrobial defense mechanisms. That effect would support epidemiological findings of increased pneumonia-related deaths with ambient PM-exposed elderly and therefore more susceptible individuals (Zelikoff et al. 2003).

A significant drop of platelets associated with the exposure to ACP has been reported before in a panel of patients with coronary artery disease in Erfurt (Ruckerl et al.2007b). The authors describe a decrease with the exposure to UFP as well, which was not observed in the present study. As potential mechanisms were discussed: (1) an increase of von Willebrand's factor that promotes the coagulation of platelets and that has been associated with high exposures to ACP, UFP and PM_{10} (Ruckerl et al.2007a); (2) or an early consumption coagulopathy secondary to a change in the adhesive properties of erythrocytes (Seaton et al. 1999).

Ambient particles deposited in the lung may lead to an acute phase response by cytokine production of alveolar macrophages.(van Eeden et al. 2001) Acute response cytokines such as interleukin (IL-)1β, tumor necrosis factor (TNF)-α released by alveolar macrophages may amplify the production of further pro-inflammatory mediators like IL-6, IL-8, and granulocyte-macrophage colony stimulating factor.(Ishii et al. 2004; Romano et al. 1997). The observed strong and 48 - 71 hours delayed effect of increased monocytes in response to NO_2 UFP might reflect the bone marrow's attempt to replace monocytes that had migrated from the bloodstream in order to differentiate into resident macrophages or dendritic cells with the function to protect tissues from foreign substances.

Strength and limitations

Our longitudinal study with multiple observations per subject had the advantage of an almost complete follow-up in all 38 male participants over half a year with each subject being his own control. Using a differential white blood count allowed to keep the effects of air pollution on various blood parameters apart. Patients with a chronic pulmonary disease might have reacted particularly sensitive to the effects of air pollution episodes and will not be representative for women and the more healthy general population.

Since the number of leukocytes differs from person to person the confounder model included random intercepts for each participant and thus indirectly adjusted for the inter-person differences and medication use of the participants. By testing multiple blood cell counts and a set of air pollutants, the possibility that some effects might have occurred only by chance cannot be excluded, but the results were fairly consistent for correlated particulate (PM_{10}, ACP, OC/EC) and gaseous (NO, NO_2, CO) pollutants. The lag patterns are in agreement with physiological mechanisms.

Misclassification of air pollution exposure is another potential source of bias especially in time-series studies.(Zeger et al. 2000) Factors such as wind direction, climatic conditions

and distances from sources affect personal exposure patterns to pollutants. But any exposure misclassification would be expected to be non differential and bias the estimates towards the null.

Conclusion

The increase of particulate air pollution was associated with an immediate decrease of polymorphonuclear leukocytes in patients with chronic pulmonary disease. Monocytes showed an increase associated with UFP, EC, and ACP as well as CO and NO. The effect had two peaks in time, one 12-17 hours before blood withdrawal and a more pronounced second one with a time lag of 48-71 hours.

Acknowledgments

The study was funded through the US Environmental Protection Agency STAR center grant R-827354. The Focus-Network of Aerosols and Health, Helmholtz Zentrum (HMGU), Germany coordinates all HMGU research on health effects and the characteristics of aerosols at the Institutes of Ecological Chemistry, Epidemiology, Inhalation Biology, Radiation Protection, and Toxicology at HGMU.

Abbreviations list

ACP	Number concentration of accumulation mode particles (0.1 to 1.0 μm in aerodynamic diameter)
AIC	Akaike information criterion
CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
EC	Elemental carbon
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GAM	Generalized additive models
IL	Interleukin
IQR	Interquartile range
NFκB	Nuclear factor κB
NO	Nitrogen monoxide
NO_2	Nitrogen dioxide
OC	Organic carbon
PM_{10}	Particulate matter less than 10 μm in aerodynamic diameter
PMN	Polymorphonuclear leukocytes
SD	Standard deviation
SO_2	Sulfur dioxide
UFP	Number concentration of ultrafine particles (0.01 to 0.1 μm)
WBC	White blood cell count

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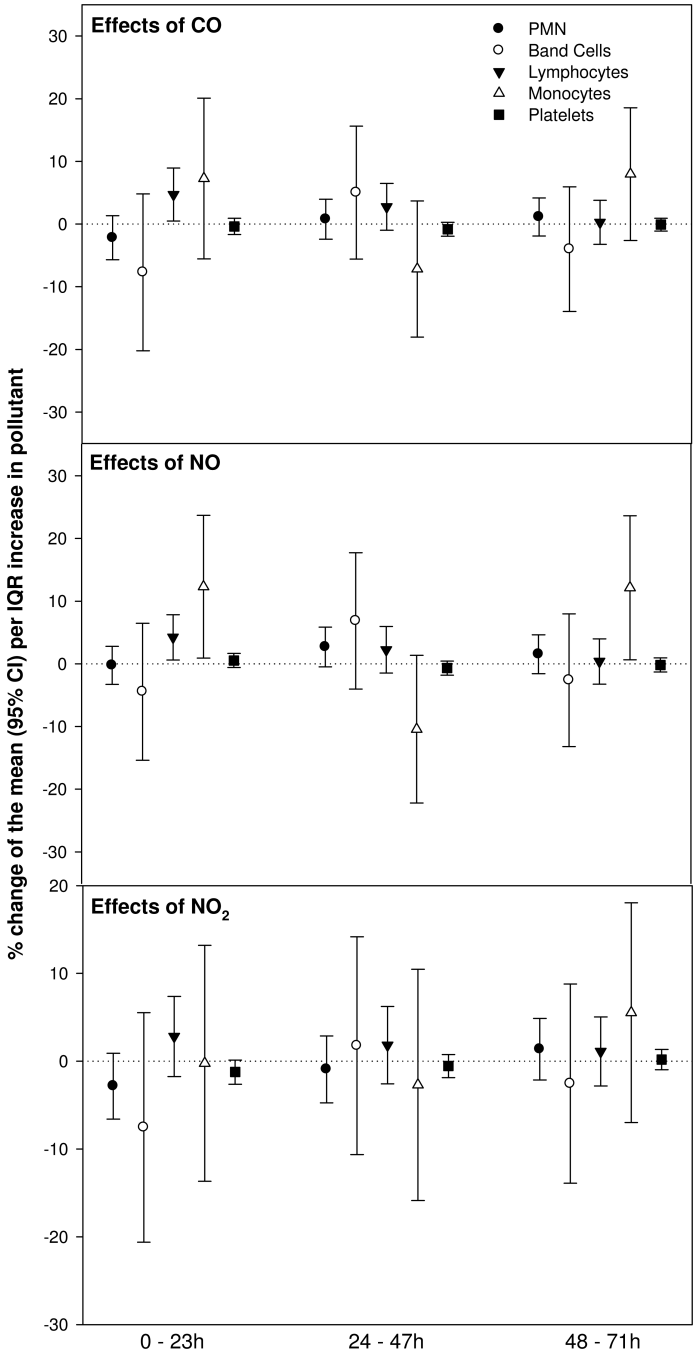

Figure 1.
Effects of gaseous air pollutants on the differential white blood cell count in absolute numbers and platelets in relation to various time lags.

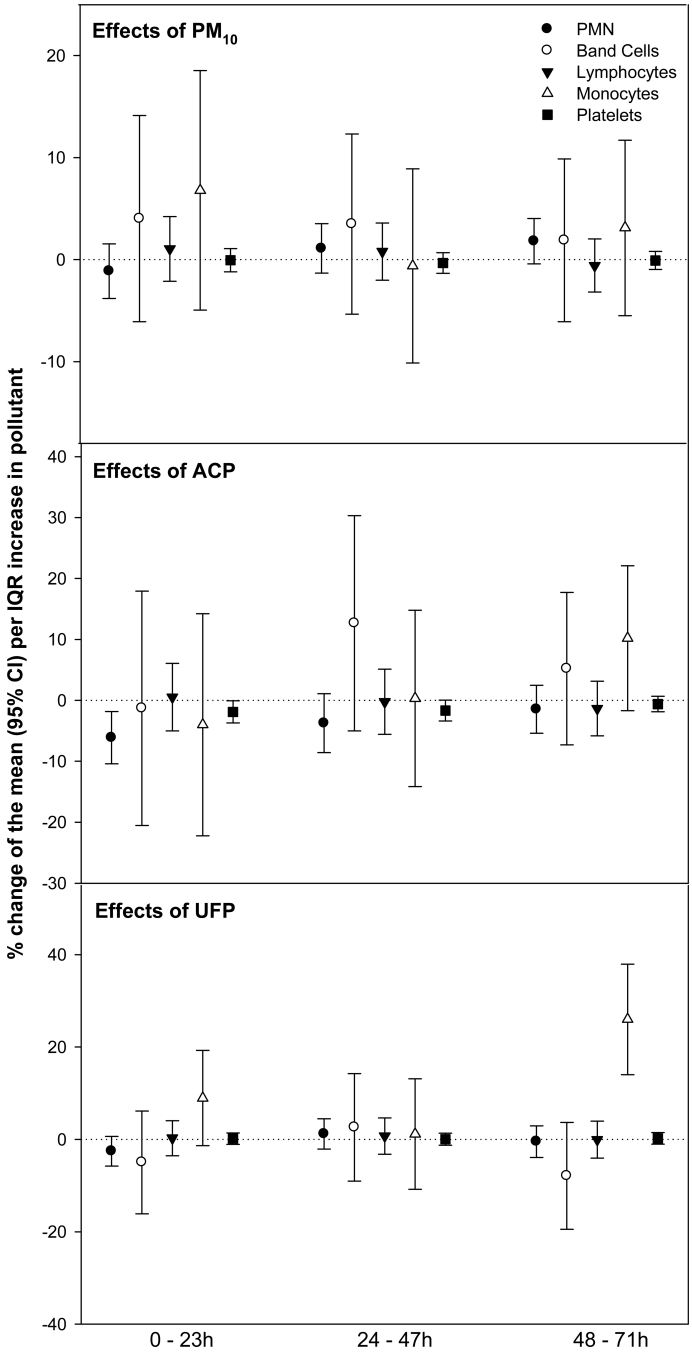

Figure 2.
Effects of particulate air pollutant on the differential white blood cell count in absolute numbers and platelets in relation to various time lags.