Vítězslav Jiřík*, Andrea Dalecká, Veronika Vašendová, Jana Janoutová and Vladimír Janout

How serious are health impacts in one of the most polluted regions of Central Europe?

DOI 10.1515/reveh-2016-0031
Received October 21, 2016; accepted October 25, 2016; previously published online December 15, 2016

Abstract

Background: The long-term exposure to pollutants in ambient air is associated with higher mortality and occurrence of respiratory and cardiopulmonary diseases. The longitudinal cross-section study focuses on the associations between long-term exposures to carcinogenic and non-carcinogenic pollutants and the prevalence and incidence of such specific diseases including immunodeficiencies.

Methods: The data on health status from industrial and non-industrial regions were obtained from health documentation for a 5-year period from 2007 to 2011 and represent the whole population living in polluted (1,249,323 inhabitants) and unpolluted (631,387 inhabitants) regions. The data on concentrations of PM_{10}, $PM_{2,5}$, NO_2, SO_2, benzene and benzo[a]pyrene were collected. The concentrations of pollutants were estimated from measured data by using dispersion models. The average population-weighted concentration of pollutants, which is representative for a defined geographic area and time period from 2007 to 2011, was calculated from the obtained data. The logistic regression and the Mantel-Haenszel χ^2 test were used to determine the odds ratios (OR) and p-values for a linear trend. Moreover, the relative risks of mortality and morbidity to specific diseases were calculated according to theoretical dose-response association published by World Health Organization (WHO).

Results: The probability of incidence of chronic obstructive pulmonary disease and bronchial asthma is statistically significantly higher in the population living in the polluted region compared to the population living in the unpolluted region. The association between long-term exposure to pollutants and the prevalence of immunodeficiency with predominantly antibody defects (D80) was confirmed. The strongest association was found for exposures to particulate matter ($PM_{2,5}$). The prevalence of immunodeficiency with predominantly antibody defects was also observed in both regions depending on the age of the population and statistically significant difference was only found in the group of adults (20 and over).

Conclusion: These associations encourage the hypothesis, that the long-term exposure to $PM_{2.5}$ might cause the activation of cellular immune response. Further research is needed to explore the correlative immunoregulatory mechanism linking $PM_{2.5}$ (or other pollutants – SO_2) and immune cells. Nowadays, it is also believed that these associations are important in the increase of incidence of immune inflammatory response which is proven risk factor for cardiovascular disease (atherosclerotic disease, coronary heart disease and sudden cardiac death). Positive association between long-term exposure and prevalence of bronchial asthma and chronic obstructive pulmonary disease might be skewed due to important socio-economic factors (especially smoking).

Keywords: air pollution; health risk; immunodeficiency; particulate matter; respiratory disease.

Introduction

Air pollution is an important environmental risk factor having an unquestionable impact on the health of the population [1, 2]. The Upper Silesian basin is one of the most polluted air regions in Central Europe. Although since the 1990s air pollution is gradually declining, inhabitants of this region are still exposed to excessive concentrations of pollutants [3]. Information about ambient concentrations of air pollutants are captured in extensive measuring stations [3]. The measured pollutants affecting the health of the population include ambient particulate matter of <10 μm and <2.5 μm diameter (PM_{10} and $PM_{2,5}$), sulfur dioxide, nitrogen oxides, benzene, heavy metals and polycyclic aromatic hydrocarbons (primarily benzo[a] pyrene). The source of these substances are traffic, local heat and heavy industry, i.e. coke-ovens (especially in the Moravian-Silesian region) [4].

***Corresponding author: RNDr. Vítězslav Jiřík,** PhD, Institution: Department of Epidemiology and Public Health (Faculty of Medicine), Syllabova 19, Ostrava – Zábřeh, 70103, University of Ostrava, Czech Republic, Phone: +420 553 46 1796, +420 597 09 1796, E-mail: vitezslav.jirik@osu.cz
Andrea Dalecká, Veronika Vašendová, Jana Janoutová and Vladimír Janout: Department of Epidemiology and Public Health, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic

The increase of mortality in all population groups, the increase of specific mortality from cardiopulmonary diseases, respiratory tract cancers in the case of adults and the increase of mortality due to respiratory diseases in the case of children count among the recognized associations between exposures to harmful substances in the air and health indicators [5–7]. Based on the results of the World Health Organization (WHO) up to 3.7 million of premature deaths per year are estimated to be caused by ambient air pollution. Up to 80% of these premature deaths are created by ischemic heart diseases and strokes, 14% are deaths from chronic obstructive pulmonary diseases or acute lower respiratory tract infections, and 6% are caused by lung cancers [8]. Many epidemiological studies have also described an association between levels of PM in the ambient air and reduction of lung function, heightened severity of symptoms in individuals with asthma, chronic obstructive pulmonary disease (COPD), immunodeficiency and ischemic heart disease [9–11].

Epidemiological studies on air pollution and its effect on the immune system are performed rarely, thus this issue requires further examination [12]. Recent researches proved that the immune system is a sensitive toxicological target for environmental chemicals. Moreover, systemic inflammation and immune injuries are closely associated with cardiovascular diseases [13]. There is growing evidence that exposure to immunotoxic pollutants could not only cause immunosuppression, but also an increased expression of aberrant immune responses [14, 15]. Particulate matter can directly affect many effector immune cells, such as lymphocytes, monocytes and macrophages, and cause the immune and inflammatory responses of organism [12]. Similarly, particulate matter pollution may influence allergic [16], immunologic and systemic inflammatory responses [17, 18].

Methods

Population selection

The data on health status from industrial and non-industrial regions were obtained to determine the relationship between air pollution and its adverse effects on health. The data representing polluted regions come from the Czech part of the Upper Silesian basin, which has been the most polluted area in the Czech Republic (Moravian-Silesian Region – MSR) for a long time. In this study, 1,249,323 inhabitants are included. The data representing unpolluted region come from the South Bohemian Region – SBR) which is one of the most industrially unpolluted regions, where 631,387 inhabitants are included. Above mentioned the number of inhabitants are also related to health risk calculations and epidemiologic study. Some of the socio-economic differences could be assumed in both regions, due to the employment, inhabitation and the lifestyle (higher number of smokers in the industrial region).

Air pollution

For the purpose of this research, the data on concentrations of PM_{10}, $PM_{2,5}$, NO_2, SO_2, benzene (BZN) and benzo[a]pyrene, (BaP) were collected in polluted (MSR) and unpolluted (SBR) regions. The data from measuring stations of the Czech Hydrometeorological Institute which is subordinated to the Ministry of Environment of the Czech Republic were provided to identify pollution in determined regions. The concentrations of pollutants were estimated from measured data using dispersion models. In this way it was possible to determine the accurate 5-year (2007–2011) average concentration of pollutants on the territory defined for each km^2. The average population-weighted concentration of pollutants, which is representative for a defined geographic area and time period from 2007 to 2011, was calculated from the obtained data.

Health risks

The probability of the mortality and morbidity of specific diseases was calculated based on the theoretical dose-response association published by the WHO.

Results of overall mortality (among the population older than 30 years), mortality from CD – cerebrovascular disease (including stroke), IHD – ischemic heart disease, COPD and LC – cancer of the trachea, bronchus and lung among the population older than 30 years) are expressed as a relative risk (RR) as follows:

$$RR = \frac{(x+1)^{\beta}}{(x_0+1)^{\beta}}$$

where:

- x is the average population-weighted concentration in polluted region,
- x_0 is average population-weighted concentration in unpolluted region,
- β is the regression coefficient published from the projects HRAPIE, REVIHAAP [19, 20].

The results of PIM – infant mortality, PB – prevalence of bronchitis in children (6–12 years or 6–18 years) and RBI – incidence of chronic bronchitis in adults (18 years +) are expressed as a RR as follows:

$$RR = \frac{(RR_{10}-1)\cdot(x-x_0)}{10}+1$$

where:

- RR_{10} is the relative risk for $(x–x_0)=10$ $\mu g.m^{-3}$ published in the projects HRAPIE and REVIHAAP [19, 20].

US Environmental Protection Agency (EPA) methodology was used for the calculation of the carcinogenic risk. The WHO and the US EPA defined the unit of carcinogenic risk (UCR) for carcinogenic pollutants (benzene and benzo[a]pyrene). UCR expresses generally acceptable health risks associated to lifetime exposure to these pollutants.

The carcinogenic risks are expressed by LICR – lifelong individual cancer risk (LICR) and the annual population cancer risk (APCR) according to the relations below.

$$LICR = LC \cdot UCR$$

where:
- LC is lifetime average concentration,
- UCR is unit of carcinogenic risk

$$APCR = \frac{LICR \cdot P}{AT}$$

where:
- P is number of inhabitants in region,
- AT is average time (70 years), or the average age expectancy.

A longitudinal cross-sectional study

The data on health status from industrial and non-industrial regions were obtained from the National Health Information System (NHIS) for a 5-year period (from 2007 to 2011). The NHIS provides health data and statistics and its main aim is to support epidemiological research. The health data include the entire population in polluted (MSR) and unpolluted (SBR) regions and represents the whole population in defined geographic areas. Data collected in the NHIS contain entries of individuals (information on smoking, occupational exposure, socio-economic status), therefore omitting of other risk factors during the interpretation of the results is not possible.

For the purpose of this study, the association between chronic exposure to pollutants and the morbidity and mortality due to asthma (J45), COPD (J44), immunodeficiency with predominantly antibody defects (D80) common variable immunodeficiency disease (CVID) (D83), cancer of the pleura, bronchi and lungs (C34) and stroke (G46) was verified.

Statistical methods were used for determination of the association between long-term exposure to pollutants and the development of health outcomes (mortality and morbidity for specific diseases). The odds ratio (OR) expresses measure of probability of health effects in exposed population (MSR) compared to unexposed (SBR). The logistic regression and the Mantel-Haenszel χ^2 test were used to determine p-values for the linear trend.

Results

Air pollution

The actual concentrations measured in monitoring stations were modeled and the values were used for a calculation of resulting concentrations of pollutants in ambient air.

The modeled concentrations are representing five population-weighted average concentration of pollutants (from 2007 to 2011) (see Table 1).

Health risks

The probabilities of some health consequences have been calculated as a RR for threshold (non-carcinogenic) effects and individual and population carcinogenic effects for polluted and unpolluted regions.

Table 1: Five-year population-weighted average concentration of pollutants.

Region	PM_{10} (μg/m³)	$PM_{2,5}$ (μg/m³)	NO_2 (μg/m³)	SO_2 (μg/m³)	BZN (μg/m³)	BaP (μg/m³)
Unpolluted	17.23	13.69	11.03	14.07	0.69	0.63
Polluted	36.54	29.19	18.68	39.12	2.75	4.75

Number of inhabitants is 631,387 in unpolluted region; number of inhabitants is 1,249,323 in polluted region.

Table 2: Calculated relative risks (RR) and confidence interval (CImin-CImax) for few health outcomes according to WHO for unpolluted (SBR) and polluted (MSR) regions.

Risks	M-all ($PM_{2.5}$)	CD, IHD, COPD ($PM_{2.5}$)	LC ($PM_{2.5}$)	PIM (PM_{10})	PB (PM_{10})	ICB (PM_{10})
RR	1.0961	1.1182	1.1820	1.0772	1.1545	1.2259
CImin	1.0813	1.0413	1.0636	1.0487	0.9513	1.0973
CImax	1.1420	1.2009	1.3137	1.1879	1.5100	1.5073

M-all, Mortality, all-cause, all ages; RR_{10}=1.0123 per 10 μg/m³; CD, IHD, COPD ($PM_{2,5}$) – mortality; CD, cerebrovascular disease (includes stroke); IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease, where $RR = \frac{(x+1)^{0,15515}}{(x_0+1)^{0,15515}}$ for age 30 + years, x is concentration of $PM_{2.5}$; LC, mortality, trachea, bronchus and lung cancer, where $RR = \frac{(x+1)^{0,23218}}{(x_0+1)^{0,23218}}$ for age 30 + years, x is concentration of $PM_{2.5}$; PIM < 1, postneonatal (age 1–12 months) infant mortality, all-cause for RR_{10} = 1.04 per 10 μg/m³; PB6–12 (6-18), prevalence of bronchitis in children, age 6–12 (or 6–18) years for RR_{10} = 1.08 per 10 μg/m³; ICB > 18, incidence of chronic bronchitis in adults (age 18+ years) for RR_{10} = 1.117 per 10 μg/m³.

The calculation of threshold health risks during the exposure to particulate matter (PM_{10}, $PM_{2.5}$) was identified according to a theoretical association represented by the RR. These associations were published by the WHO and linear and nonlinear association between exposure to pollutants and the development of the adverse health effects are described.

The probability of occurrence of observed health consequences (apart from PB – prevalence of bronchitis in children) in the case of long-term exposure to particulate matter (PM_{10}, $PM_{2.5}$) was significantly higher in populations living in the polluted region compared to the population living in the unpolluted region (see Table 2).

The probability of development of cancer in case of exposure to carcinogenic pollutants (benzene, benzo [a] pyrene) is higher in populations living in the polluted region compared to the population living in the unpolluted region. However, the carcinogenic risks in both observed regions have not exceeded generally acceptable health limits (see Table 3).

Longitudinal cross-section study

The health data obtained from the NHIS provide all the records on the occurrence of the diseases. The diseases, which had to be investigated due to the potential risk to pollutants in the air, were monitored. Moreover, the proven associations from previous studies were demonstrated. For the purpose of this study, the diagnoses anchored in the International Classification of Diseases (ICD) were used.

The differences in the incidence and prevalence of disease in polluted and unpolluted regions were explored. The results might be skewed due to significant socioeconomic factors (especially smoking).

The probability of incidence of chronic obstructive pulmonary disease and bronchial asthma and immunodeficiency with predominantly antibody defects (D80) is statistically significantly higher in the population living in the polluted region compared to the population living in the unpolluted region (see Table 4). The prevalence of immunodeficiency with predominantly antibody defects (D80) was also observed in both regions depending on the age of the population and a statistically significant difference was only found in the group of adults (20 and over). In childhood, there were no statistically significant differences in the prevalence of this disease. The strongest association was found at exposures to particulate matter ($PM_{2.5}$). In addition, the dependence on the age of the population was observed in association between prevalence of the disease bronchial asthma (J45) and air pollution (see Table 4). The association between long-term exposure to all tested pollutants and higher prevalence of disease was statistically confirmed in age of adult and child.

Furthermore, the results indicate that the probability of incidence of chronic obstructive pulmonary disease (J44) and bronchial asthma (J45) is significantly higher in populations living in the polluted region compared to the population living in the unpolluted region (see Table 4). Moreover, the mortality to chronic obstructive pulmonary disease (J44), bronchial asthma (J45), stroke (G46) and trachea, bronchus and lung cancer (C34) was also observed. The results are expressed as a relative risk but no statistically significant differences in mortality of mentioned diseases in populations living in the polluted region compared to the population living in the unpolluted region were proven.

Discussion

Our study observed the association linking long-term exposure to pollutants and the morbidity and mortality of specific diseases between a polluted (MSR) and unpolluted

Table 3: Cancer risks of exposures to benzene (BZN) and benzo(a)pyrene (BaP) for unpolluted (SBR) and polluted (MSR) regions comparing approaches the WHO and US EPA.

Risks		Cancer (BZN)		Cancer (BaP)	
	UCR $(\mu g/m^3)^{-1}$	WHO	US EPA	WHO	US EPA
		6.00E-06	7.80E-06	9.00E-02	1.10E-03
Unpolluted	LICR	4.14E-06	5.38E-06	5.67E-05	6.93E-07
	APCR	0.04	0.05	0.51	0.01
Polluted	LICR	1.65E-05	2.15E-05	4.28E-04	5.23E-06
	APCR	0.29	0.38	7.63	0.09

UCR, unit cancer risk; LICR, lifetime individual cancer risk; APCR, annual population cancer risk.

Table 4: Odds ratios (OR) of prevalence and incidence for unpolluted (SBR) and polluted (MSR) regions and significance of linear trend for dose-response associations.

	J44	J45	D80	D83
Prevalence				
OR	1.954	1.868	1.779	1.149
CI	1.836–2.080	1.760–1.982	1.374–2.304	0.777–1.699
χ^2 (PM_{10})	409.38	425.63	16.53	0.71
p	<0.0001	<0.0001	<0.0001	0.3979
χ^2 ($PM_{2.5}$)	177.44	401.06	61.88	3.92
p	<0.0001	<0.0001	<0.0001	0.04781
χ^2 (NO_2)	522.60	366.78	30.72	5.33
p	<0.0001	<0.0001	<0.0001	0.02098
χ^2 (SO_2)	609.77	172.90	65.40	34.13
p	<0.0001	<0.0001	<0.0001	<0.0001
Incidence				
OR	2.105	1.697	1.526	0.700
CI	1.730–2.563	1.407–2.048	0.856–2.722	0.267–1.839
χ^2 (PM_{10})	64.56	23.96	2.48	0.38
p	<0.0001	<0.0001	0.115	0.5396
χ^2 ($PM_{2.5}$)	16.88	19.35	0.28	0.86
p	<0.0001	<0.0001	0.5968	0.3548
χ^2 (NO_2)	54.25	37.53	2.28	0.46
p	<0.0001	<0.0001	0.1311	0.4988
χ^2 (SO_2)	155.56	12.33	8.89	1.35
p	<0.0001	0.0004454	0.002868	0.2453

Dg, J44-chronic obstructive pulmonary disease; Dg, J45-asthma bronchiale dg; D80-immunodeficiency with predominantly antibody defects; Dg, D83-common variable immunodeficiency; CI, confidence interval; χ^2, extended Mantel-Haenszel χ^2 for linear trend, p-value for one degree of freedom.

(SBR) region in the Czech Republic. Differences between long-term air concentrations in residential areas in the Czech Republic for the polluted and the unpolluted region are about 20 μg/m³ for PM_{10}, 15 μg/m³ for $PM_{2.5}$, 7 μg/m³ for NO_2, 25 μg/m³ for SO_2, 2 μg/m³ for benzene, 4 ng/m³ for B(a)P (shown in Table 1).

The results of longitudinal cross-section study show the statistically significant difference in prevalence and incidence of COPD in populations living in the polluted region compared to the population living in the unpolluted region in case of long-term exposure to all tested pollutants (OR = 2.105; CI = 1.730–2.563) (see Table 4). Even though, the ORs are calculated according to the whole health data occurred in both regions, there are no information about other risk factors. For this reason, it was not possible to assess the impact of some major socio-economic factors, and lifestyle factors (smoking, occupational exposure). Although, it is believed that these factors do not significantly differ in both of the selected populations, the effect of these factors might be significant. Therefore, the results should be rather tentative. The mortality to COPD was also observed. According to the theoretical calculation of health risk, the probability of mortality to cerebrovascular disease, ischemic heart disease and COPD in the case of long-term exposure to $PM_{2.5}$ should be statistically significant higher in the population living in the polluted region compared to the population living in the unpolluted region (RR = 1.1182; CI = 1.0413–1.2009). On the other hand, those results were not confirmed in our longitudinal cross-sectional study.

The key results of the longitudinal cross-section study is a confirmation of the association between long-term exposure to pollutants and the prevalence of immunodeficiency with predominantly antibody defects (OR = 1.779; CI = 1.374–2.304) (see Table 4). The strongest association was found for exposures to particulate matter ($PM_{2,5}$). The immunodeficiency with predominantly antibody defects is associated with increases IgG, IgE and IgM in the blood. The results of the analytical studies refer to the increase of these immunoglobulins together with reduction of T-lymphocytes and CD4 and CD8 cells. These associations encourage the hypothesis, that the long-term exposure to $PM_{2.5}$ might cause the activation of cellular immune response. Further research is needed to explore the correlative immunoregulatory mechanism linking $PM_{2.5}$ (and certain other pollutants, e.g. SO_2) and immune cells.

Nowadays, it is also believed that these associations are important in the increasing of incidence of immune inflammatory response which is a proven risk factor for cardiovascular disease (atherosclerotic disease, coronary heart disease and sudden cardiac death) [15].

Researched associations in earlier studies between exposures to pollutants and increase mortality were not confirmed in our cross-section study.

Conclusion

The results of the health risks assessment and longitudinal cross-sectional studies support the supposed association of long-term exposure to pollutants in ambient air and the occurrence of specific diseases. The statistically significant difference in the prevalence and incidence of COPD arising as a result of exposure to pollutants was proved. It is assumed that all non-carcinogenic pollutants contribute to this effect. Furthermore, this study provides the results of the possible hypotheses of an increased incidence of immunodeficiencies with predominantly antibody defects manifested itself by elevated levels of IgG, IgE and IgM antibodies in the blood. Based on these and other published results, the highest concern in connection with this disease is attributed to exposure to $PM_{2.5}$. These observed associations support the hypothesis that long-term exposure to $PM_{2.5}$ may cause the activation of cellular immune responses. Therefore, further research focused on exploring the mechanism of immunoregulation in case of exposure to $PM_{2.5}$ (together with other tested pollutants) is needed.

References

1. Ruiz S, Arruti A, Fernándes-Olmo O. Contribution of point source to trace metal levels in urban areas surrounded by industrial activities in the Cantabria region Northern Spain. Urban Environ Pollut 2011;4:76–86.
2. Amodio M, Caselli M, de Gennaro G, Tutino M. Particulate PAHs in two urban areas of Southern Italy: impact of the sources meteorological and background conditions on air quality. Environ Res 2009;1009:812–20.
3. Kazmarová H. Development of air pollution in the Czech Republic, Proceedings of the project: Sustainable Development of the Czech Republic. Prague: Creating the conditions, the State Health Institute 2000:62–78
4. Svecova V, Topinka J, Solansky I, Rossner P Jr, Sram RJ. Personel exposure to carcinogenic polycyclic aromatic hydrocarbons in the Czech Republic. J Expo Sci Enviton Epidemiol 2013;23(4):350–5.
5. World Health Organization. Health risks of air pollution in Europe – HRAPIE project. Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide. WHO 2013. Available at: http://www.euro.who.int/__data/assets/pdf_file/0006/238956/Health-risks-of-air-pollution-in-Europe-HRAPIE-project,-Recommendations-for-concentrationresponse-functions-for-costbenefit-analysis-of-particulate-matter,-ozone-and-nitrogen-dioxide.pdf.
6. Ostro B. Outdoor Air Pollution. Assessing the environmental burden of diseases in national and local levels. Geneva, World Health Organization 2004:ISBN 92-4-159146-3. Available at: http://www.who.int/quantifying_ehimpacts/publications/ebd5.pdf?ua=1.
7. Beelen R, Stafoggia M, Raaschou-Nielsen O, Andersen ZJ, Xun WW, et al. Long-term exposure to air pollution and cardiovascularmortality: an analysis of 22 Europeancohorts. Epidemiology 2014;25(3):368–78. Available at: http://ac.els-cdn.com/S0140673613621583/1-s2.0-S0140673613621583-main.pdf?_tid=3ecac730-20dd-11e6-8c3e-00000aacb361&acdnat=1464004709_38e06cd566234c2d2246ccc8390a312b
8. World Health Organization. Review of evidence on health aspects of air pollution – REVIHAAP Project. The WHO European Centre for Environment and Health. Copenhagen, Denmark 2013. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report-final-version.pdf?ua=1.
9. Frank J, Kelly and Julia C. Fussell. Linking ambient particulate matter pollution effects with oxidative biology and immune response. Ann N Y Acad Sci 2015;1340:84–94.
10. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 2010;121:2331–78.
11. Kelly FJ, Fussell JC. Air pollution and airway disease. Clin Exp Allergy 2011;41:1059–71.
12. Leonardi GS, Houthuijs D, Steerenberg PA, Fletcher T, Armstrong B, et al. Immune biomarkers in relation to exposure to particulate matter: a cross-sectional survey in 17 cities of Centtral Europe. Inhal Toxicol 2000;12(Suppl 4):1–14.
13. Wang L, Joad JP, Zhong C, Pinkerton KE. Effects of environmental tobacco smoke exposure on pulmonary immune response in infant monkeys. J Allergy Clin Immunol 2008;122:400–6, 406.e1–5.
14. Becker S, Soukup J. Coarse (PM(2.5-10)), fine (PM(2.5)), and ultrafine air pollution particles induce/increase immune costimulatory receptors on human blood-derived monocytes but not on alveolar macrophages. J Toxicol Environ Health A 2003;66:847–59.
15. Zhao J, Gao Z, Tian Z, Xie Y, Xin F, et al. The biological effects of individual-level PM2.5 exposure on systemic immunity and inflammatory response in traffic policemen. Occup Environ Med 2013;70:426–31.
16. Burchiel SW, Lauer FT, McDonald JD, Reed MD. Systemic immunotoxicity in AJ mice following 6-month whole body inhalation exposure to diesel exhaust. Toxicol Appl Pharmacol 2004;196:337–45.
17. van Eeden SF, Hogg JC. Systemic inflammatory response induced by particulate matter air pollution: the importance of bone-marrow stimulation. J Toxicol Environ Health A 2002;65:1597–613.

18. Li N, Sioutas C, Cho A, Schmitz D, Misra C, et al. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 2003;111:455–60.
19. World Health Organization: Health risks of air pollution in Europe – HRAPIE project. Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide. WHO 2013. Available at: http://www.euro.who.int/__data/assets/pdf_file/0006/238956/Health-risks-of-air-pollution-in-Europe-HRAPIE-project,-Recommendations-for-concentrationresponse-functions-for-costbenefit-analysis-of-particulate-matter,-ozone-and-nitrogen-dioxide.pdf.
20. World Health Organization. Review of evidence on health aspects of air pollution – REVIHAAP Project. The WHO European Centre for Environment and Health. Copenhagen, Denmark: WHO 2013. Available at: http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report-final-version.pdf?ua=1.