

## Association of air pollution and hematologic parameters in children and adolescents

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### Abstract

**Objective:** To assess the relationship between air pollution and hematologic parameters in a population-based sample of children and adolescents.

**Methods:** This cross-sectional study was conducted in 2009-2010 among school students randomly selected from different areas of Isfahan city, the second largest and most air-polluted city in Iran. The association of air pollutant levels with hemoglobin, platelets, red and white blood cells (RBC and WBC, respectively) was determined by multiple linear and logistic regression analyses, after adjustment for age, gender, anthropometric measures, meteorological factors, and dietary and physical activity habits.

**Results:** The study participants consisted of 134 students (48.5% boys) with a mean age of 13.10±2.21 years. While the mean Pollutant Standards Index (PSI) was at moderate level, the mean particulate matter ≤ 10 μm (PM<sub>10</sub>) was more than twice the normal level. Multiple linear regression analysis showed that PSI and most air pollutants, notably PM<sub>10</sub>, had significant negative relationship with hemoglobin and RBC count, and positive significant relationship with WBC and platelet counts. The odds ratio of elevated WBC increased as the quartiles of PM<sub>10</sub>, ozone and PSI increased, however these associations reached significant level only in the highest quartile of PM<sub>10</sub> and PSI. The corresponding figures for hemoglobin and RBC were in opposite direction.

**Conclusions:** The association of air pollutants with hematologic parameters and a possible pro-inflammatory state is highlighted. The presence of these associations with PM<sub>10</sub> in a moderate mean PSI level underscores the necessity to re-examine environmental health policies for the pediatric age group.

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### Introduction

A considerable part of the global burden of disease is attributable to preventable environmental exposures. In most countries, cardiovascular diseases impose the highest burden of disease, and their association with environmental factors, notably air pollution, is well

documented,<sup>1</sup> although the underlying mechanisms remain to be determined. Consistent with some previous findings, a recent experimental study showed for the first time that respiratory exposure to particulate matter enhances the process of atherogenesis<sup>2</sup>; thus, it might be the link

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between air pollution and cardiovascular diseases. Moreover, it is suggested that a pro-inflammatory state contributes to cardiometabolic risk factors, and the association of air pollution with these risk factors is documented both in adults<sup>3</sup> and adolescents.<sup>4</sup>

Furthermore, some studies have suggested an association between hematological parameters and the pro-inflammatory state related to cardiometabolic risk factors. A population-based study in Taiwan found that a higher number of white blood cells (WBC) and red blood cells (RBC) increased the odds ratio (OR) of clustering of cardiometabolic risk factors.<sup>5</sup> Such association is also suggested between platelet and WBC counts and clustering of cardiometabolic risk factors.<sup>6</sup> Likewise, the association of hematologic parameters, notably WBC, with cardiometabolic risk factors is documented in children and adolescents.<sup>7,8</sup>

The relationship of air pollution with hematological factors remains controversial. While some studies reported the association of short-term<sup>9</sup> and long-term<sup>10</sup> exposure to air pollution with WBC count, some other studies did not confirm such association.<sup>11,12</sup> It is suggested that differences in the extent of the response to air pollutants are influenced by the variation in susceptibility among individuals. For example, those with old age or underlying cardiovascular risk factors may show stronger associations.<sup>10,13</sup> Children are particularly at risk when exposed to air pollution, because they receive a higher dose of pollutants than adults, with more extreme consequences.<sup>14,15</sup> However, limited experience exists about the association of air pollutants with hematologic factors in the pediatric age group. Studying the effects of environmental factors on children's health can serve for future studies exploring the pathophysiologic mechanisms of adverse health effects and may offer strategies for primary prevention of chronic diseases. This study aimed to assess the relationship of air pollution and hematologic factors in the pediatric age group.

## **Methods**

### **Participants**

This cross-sectional study was conducted from November 2009 to February 2010 on the target population of children and adolescents aged 10-18 years residing in Isfahan, Iran's second largest and most air-polluted city. Eligible individuals were those who lived in areas of the city which had air pollution measurement stations, who had lived in that area for at least 6 months, and whose homes and schools were in the same area. Students who had a history of active or passive smoking, chronic disease or long-term medication use, or a history of acute infectious diseases in the past 2 weeks were not included in the study.

The study was conducted on 134 students. The sample size was calculated based on the correlation ( $r = 0.24$ ) between air pollutants and blood cell counts found in a

previous study<sup>16</sup> and considering the statistical significance of 5%. Students were selected by random sampling, taking into account the proportion of the different types of schools (public/private) to avoid socioeconomic bias. Schools were randomly selected in each city area having air monitoring stations. Then, students from the chosen schools were allocated code numbers and randomly selected using random number tables.

The study was approved by the Research and Ethics Committee of the Faculty of Medicine, Isfahan University of Medical Sciences. Before the start of the study, written consent was obtained from parents and oral assent from students.

### **Study area**

Isfahan is an industrial city with nearly 2 million inhabitants, located in the center of Iranian plateau, with an average altitude of 1,500 m above sea level, and bounded by a northwest-southeast mountain range of 3,000 m. The average monthly temperature is 16 °C, with a maximum of 29 °C in July and a minimum of 3 °C in December, and mild winds from the west and the south. Moreover, the air of the city of Isfahan is predominantly affected by industrial emissions and motor traffic, which can lead to a build-up of elevated concentrations of air pollutants during stagnant conditions.<sup>17</sup>

### **Clinical study and laboratory methods**

According to government rules, blood collection from students cannot be done in schools. Therefore, the selected students were invited to health care centers. A trained nurse completed a questionnaire on demographic data, and physical examination was performed by a trained general practitioner, under the supervision of a pediatrician. Subcutaneous fat of the biceps and triceps muscles was measured with a skinfold caliper (Mojtahedi, Iran), and percent body fat was determined by bioelectrical impedance using a body fat monitor (Omron HBF-300, Japan).

For the assessment of dietary habits, the Healthy Eating Index (HEI) was computed as described before.<sup>4</sup> Physical activity level was assessed by the international Physical Activity Questionnaire for Children, previously validated in Iranian children.<sup>18</sup>

While one of the parents accompanied his or her child, blood samples were taken from the antecubital vein. A complete blood profile, including hemoglobin, RBC, WBC and platelet counts, was measured using an automated cell counter (SYSMEX K-1000, Japan).

### **Air pollution data**

After following the necessary procedures, we used the daily registered data of Isfahan Provincial Directorate of

Environmental Protection, obtained from five air pollution measurement stations in Isfahan city. On the day of blood sampling, the data of the last seven 24-hour levels of air pollutants and Pollutant Standards Index (PSI) of the monitoring station located in the area of residence of each participant were recorded and included in the statistical analysis.<sup>4</sup> Daily values pertaining to the main air pollutants, i.e. sulfur dioxide (SO<sub>2</sub>), ozone (O<sub>3</sub>), particulate matter ≤ 10 μm (PM<sub>10</sub>), nitrogen dioxide (NO<sub>2</sub>), and carbon monoxide (CO), as well as to the PSI, mean daily temperature, sunlight duration, humidity, and wind speed were recorded. Particles in the air are a mixture of solids and liquid droplets that vary in size and are often referred to as "particulate matter." Particles less than 10 μm in diameter (PM<sub>10</sub>) pose the greatest health concern because they can pass through the nose and throat and get deep into the lungs. The PSI converts air pollution concentrations to a simple number between zero and 500 and assigns a descriptive term such as "good" or "moderate" to that value. The reference values of air pollutants and PSI are presented in the footer of Table 1.

### Statistical analysis

SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA) was used for data analysis. We used log-transformed concentrations of air pollution markers to achieve normal distribution. The associations between air pollutants and hematologic parameters were assessed by multiple linear regression, after adjustment for age, gender, body mass index, waist circumference, meteorological factors, HEI, and physical activity level. The concentrations of biomarkers and air pollutants were categorized into quartiles, and the upper quartile was considered as elevated value. We examined the association of the dichotomized concentrations of hematologic parameters (upper quartile,  $y = 1$  vs. lower quartile,  $y = 0$ ) across the quartiles of air pollutants by using logistic regression analysis after adjustment for the abovementioned confounders. The significance level was set at  $p < 0.05$ .

### Results

The study participants consisted of 134 students (48.5% boys) with a mean age of 13.10±2.21 years. Mean and standard deviation values of the variables studied are presented in Table 1. The mean hemoglobin level was 13.1±1.0 g/dL (range: 11-16.2 g/dL) and the mean WBC count was 7,373±1,800/mm<sup>3</sup>. The mean PSI value was at moderate level, i.e. an inappropriate level for sensitive groups. Mean levels of O<sub>3</sub>, NO<sub>2</sub> and SO<sub>2</sub> were much higher than acceptable values, and the mean PM<sub>10</sub> level was remarkably high, reaching more than twice the normal level (120.48 vs. 50 μg/m<sup>2</sup>).

**Table 1** - Mean and SD values of the variables studied

Variables	Mean (SD)
Age (years)	13.1 (2.2)
Weight (kg)	49.2 (14.1)
Height (cm)	154.5 (12.4)
Body mass index (kg/m <sup>2</sup> )	20.2 (3.9)
Waist circumference (cm)	73.5 (4.2)
Percent body fat (%)	23.1 (4.3)
Fat mass (kg)	12.5 (2.6)
Subcutaneous fat (mm)	10.9 (2.1)
Hemoglobin (g/dL)	13.1 (1.0)
Red blood cell (million/uL)	4.7 (0.1)
White blood cell count (/mm <sup>3</sup> )	7,373 (1,800)
Platelets (/mL)	255,050 (47,854)
Temperature (°C)	9.3 (4.6)
Humidity (%)	49.4 (5.1)
Wind speed (km/h)	10.2 (2.6)
Sunlight duration (h)	8.4 (1.1)
PM <sub>10</sub> (μg/m <sup>3</sup> )	120.4 (62.8)
CO (ppm)*	3.9 (2.5)
SO <sub>2</sub> (ppb) <sup>†</sup>	43.7 (30.5)
NO <sub>2</sub> (ppb) <sup>‡</sup>	59.3 (35.5)
O <sub>3</sub> (ppb) <sup>§</sup>	33.6 (10.2)
PSI	74.6 (30.3)

CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>10</sub> = particulate matter ≤ 10 μm (acceptable level: 50 μg/m<sup>3</sup>); ppb = parts per billion; ppm = parts per million; PSI = Pollutant Standards Index (0-50: good; 51-100: moderate; 101-199: unhealthy; 200-299: very unhealthy; ≥300: hazardous); SD = standard deviation; SO<sub>2</sub> = sulfur dioxide.

\* Acceptable level: 9 ppm.

† Acceptable level: 0.03 ppb.

‡ Acceptable level: 0.05 ppb.

§ Acceptable level: 0.08 ppb.

Multiple linear regression analysis showed that, after adjustment for confounding factors, PSI, and most air pollutants, notably PM<sub>10</sub>, had significant negative relationship with hemoglobin and RBC count, and significant positive relationship with WBC and platelet counts (Table 2).

The OR of elevated WBC increased as the quartiles of PM<sub>10</sub>, O<sub>3</sub> and PSI increased, although these associations reached a significant level only in the highest quartile of PM<sub>10</sub> and PSI. The corresponding figures for hemoglobin and RBC were in opposite direction, i.e. the OR was lower in the highest quartiles of PM<sub>10</sub>, O<sub>3</sub> and PSI for WBC and in the lowest quartiles for hemoglobin and RBC (Table 3).

### Discussion

This study, which, to the best of our knowledge, is the first of its kind in the pediatric age group, documented significant associations between exposure to air pollution and hematologic parameters in a population-based sample of children and adolescents.

**Table 2 -** Regression coefficients\* for the relationship of air pollutants and PSI with serum concentrations of biomarkers

	Beta (SE)			
	Hemoglobin	Red blood cells	White blood cells	Platelets
PSI	-0.54 (0.17) <sup>†</sup>	-0.51 (0.12) <sup>†</sup>	0.57 (0.14) <sup>†</sup>	0.46 (0.15) <sup>†</sup>
O <sub>3</sub>	-0.49 (0.15) <sup>†</sup>	-0.41 (0.17) <sup>†</sup>	0.46 (0.11) <sup>†</sup>	0.41 (0.18) <sup>†</sup>
NO <sub>2</sub>	-0.32 (0.11)	-0.35 (0.16)	0.41 (0.18) <sup>†</sup>	0.34 (0.15)
PM <sub>10</sub>	-0.52 (0.16) <sup>†</sup>	-0.51 (0.18) <sup>†</sup>	0.51 (0.17) <sup>†</sup>	0.44 (0.12) <sup>†</sup>
SO <sub>2</sub>	-0.44 (0.12) <sup>†</sup>	-0.37 (0.15)	0.37 (0.11)	0.34 (0.16)
CO	-0.42 (0.18) <sup>†</sup>	-0.41 (0.15) <sup>†</sup>	0.45 (0.12) <sup>†</sup>	0.35 (0.11)

CO = carbon monoxide; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>10</sub> = particulate matter ≤ 10 µm; PSI = Pollutant Standards Index; SE = standard error; SO<sub>2</sub> = sulfur dioxide.

\* Standardized coefficient (SE) adjusted for age, gender, anthropometric measures, dietary and physical activity habits.

<sup>†</sup> p < 0.05.

**Table 3 -** Association\* of the quartiles of air pollutants and PSI with the upper quartile of hematologic parameters

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P (for linear trend)
PM <sub>10</sub>					
Hb	1	0.91 (0.67-1.86)	0.87 (0.67-1.62)	0.74 (0.65-0.91)	0.02
RBC	1	0.91 (0.62-2.15)	0.84 (0.82-1.7)	0.72 (0.68-0.89)	0.04
WBC	1	1.05 (0.81-1.25)	1.14 (0.71-1.32)	1.21 (1.09-1.45)	0.02
Platelets	1	1.03 (0.72-1.76)	1.07 (0.91-1.74)	1.17 (1.07-1.61)	0.04
CO					
Hb	1	0.89 (0.51-1.61)	0.91 (0.61-1.75)	0.94 (0.75-1.71)	0.27
RBC	1	0.90 (0.25-1.81)	0.92 (0.51-1.90)	0.91 (0.62-1.80)	0.21
WBC	1	1.05 (0.61-1.91)	1.11 (0.71-1.41)	1.14 (0.91-1.78)	0.06
Platelets	1	1.05 (0.61-1.91)	1.11 (0.71-1.41)	1.14 (0.91-1.82)	0.09
SO <sub>2</sub>					
Hb	1	0.91 (0.35-1.82)	0.92 (0.35-1.91)	0.90 (0.68-1.81)	0.10
RBC	1	0.92 (0.45-1.71)	0.91 (0.38-1.91)	0.91 (0.64-1.78)	0.21
WBC	1	1.04 (0.71-2.51)	1.11 (0.61-1.90)	1.10 (0.91-1.82)	0.09
Platelets	1	1.07 (0.82-1.92)	1.11 (0.61-1.90)	1.10 (0.91-1.82)	0.08
NO <sub>2</sub>					
Hb	1	0.92 (0.45-1.71)	0.91 (0.38-1.91)	0.91 (0.64-1.78)	0.10
RBC	1	0.90 (0.41-1.60)	0.91 (0.51-1.70)	0.95 (0.71-1.82)	0.35
WBC	1	1.03 (0.70-1.54)	1.07 (0.80-1.64)	1.11 (0.80-1.91)	0.08
Platelets	1	1.01 (0.61-1.79)	1.07 (0.91-1.87)	1.11 (0.78-2.15)	0.21
O <sub>3</sub>					
Hb	1	0.96 (0.82-1.54)	0.84 (0.89-1.71)	0.79 (0.66-0.85)	0.02
RBC	1	0.94 (0.72-1.45)	0.88 (0.82-1.86)	0.78 (0.68-0.91)	0.03
WBC	1	1.05 (0.71-1.65)	1.1 (0.6-1.4)	1.31 (1.08-1.4)	0.04
Platelets	1	1.02 (0.75-1.80)	1.08 (0.92-1.92)	1.15 (1.08-1.75)	0.04
PSI					
Hb	1	0.93 (0.75-1.82)	0.87 (0.69-1.65)	0.77 (0.56-0.92)	0.04
RBC	1	0.91 (0.71-1.84)	0.86 (0.69-1.65)	0.78 (0.62-0.89)	0.03
WBC	1	1.07 (0.81-1.93)	1.16 (0.78-1.46)	1.37 (1.16-1.82)	0.02
Platelets	1	1.06 (0.78-2.12)	1.18 (0.81-1.86)	1.26 (1.14-1.79)	0.04

CO = carbon monoxide; Hb = hemoglobin; NO<sub>2</sub> = nitrogen dioxide; O<sub>3</sub> = ozone; PM<sub>10</sub> = particulate matter ≤ 10 µm; PSI = Pollution Standards Index; RBC = red blood cells; SO<sub>2</sub> = sulfur dioxide; WBC = white blood cells.

\* Values represent odds ratio (95% confidence interval) adjusted for age, gender, anthropometric measures, and dietary and physical activity habits.

Our findings are in line with an experimental study that revealed a significant decrease in hematocrit and a significant increase in leukocyte number in mice placed in cages with polluted air.<sup>19</sup> Another experimental study showed that exposure to PM<sub>10</sub> causes a systemic inflammatory response including stimulation of the bone marrow and progression of atherosclerosis. Given the key role of monocytes in atherogenesis, by migration into subendothelial lesions and appearing as foam cells, this study suggested that exposure to PM<sub>10</sub> accelerates the process of atherosclerosis in relation to the amount of particles phagocytosed by alveolar macrophages.<sup>20</sup> Our findings in children are also consistent with the Third National Health and Nutrition Examination Survey in the United States, conducted among adults aged 20-89 years, which showed significant association between WBC count and estimated local PM<sub>10</sub> levels during 1 year.<sup>21</sup>

However, our findings contrast with those from a study in Turkey that compared hematological parameters before and after a period of exposure to heavy pollution and showed increased hemoglobin and hematocrit levels.<sup>22</sup> This difference might be because of the shorter exposure to air pollutants and the higher age group of this study compared to ours. Moreover, the findings of the study in Turkey might be because of the accumulative effect of chronic air pollution and an acute episode of heavy pollution. Such concomitant effect is documented for chronic exposure to air pollution and chemical agents; in a study among 42 non-smoker petrol filling workers, chronic exposure to solvents like benzene and to pollutants like CO was associated with a significant rise in hemoglobin and RBC levels and a significant decrease in WBC levels.<sup>23</sup>

Our results are consistent with the findings of a study on the effects of indoor pollution on 8 to 13 year-old Indian children, which showed that living in households that cook with traditional biomass fuels was associated with low hemoglobin and RBC counts and raised WBC count.<sup>24</sup> Health hazards of both indoor and outdoor air pollution depend on the pollutant type, its concentration in the air, length of exposure, other pollutants in the air, and individual susceptibility. Children are one of the most vulnerable groups for such health impacts.

The findings of this study highlight the importance of adverse health effects of air pollution on children's health. The present study might provide confirmatory evidence of the pro-inflammatory state induced by air pollutants,<sup>25</sup> and suggests that the association between air pollution and chronic diseases may be mediated through systemic inflammatory responses.

Our finding on the inverse association of air pollutants with hemoglobin level is in line with a study among an adult urban population in Canada.<sup>26</sup> Contrary to these findings, a study in Denmark on 50 university students, aged 20-33 years, found positive associations between

personal exposure to particulate matter  $\leq 2.5 \mu\text{m}$  (PM<sub>2.5</sub>) and both RBC and hemoglobin concentrations only in female students.<sup>27</sup> The difference between our findings and those of this study might be because we could not measure ultrafine particles, however, as a study in Guatemala found, exposure to indoor air pollution resulting from the burning of biomass fuels was associated with elevation of hemoglobin concentration.<sup>28</sup> Although we had no case of anemia and the statistical analyses were controlled for gender, we suggest that in future surveys the hematologic status of study participants and possible gender differences in the association of air pollutants with blood parameters should be addressed in more detail. We should also acknowledge that our study participants were much younger than those of the aforementioned studies, i.e. before the development of gender differences in the prevalence of anemia.

We found positive association of air pollutants and platelet counts, although we did not assess platelet activity and aggregation. However, the increase in platelets in relation to air pollutants may be a surrogate marker of early hematologic and hemostatic changes due to air pollutants. Experimental and human studies have proposed that the systemic pro-inflammatory and pro-coagulant response to inhalation of fine and ultrafine particulate matter suggests a role for platelet activation in such changes. However, some studies are inconsistent about the role of inflammation in this process. A human study found that air pollution increased platelet aggregation and coagulation activity but without clear effect on systemic inflammation. The study suggested that the prothrombotic effects may partly explain the effects of air pollution on ischemic cardiovascular diseases.<sup>29</sup>

A cross-over study among 29 participants with or without biking exercise and exposed to air pollutants did not find any significant association of air pollutants with hemoglobin, RBC and platelet count and markers of inflammation in healthy young adults.<sup>30</sup> The associations of air pollutants with hematologic parameters in our study are consistent with the chronic effects of air pollutants on hematological factors in adults,<sup>16</sup> hence our findings can be due to chronic exposure of children studied to air pollutants or due to the higher susceptibility of children to the health hazards of air pollutants.

In addition to suggested effects of air pollution on respiratory and immunologic diseases, and also on the early stages of atherosclerosis,<sup>4,31</sup> the findings of our study propose an association of air pollutants with bone marrow activity. By considering the carcinogenic effects of air pollutants in children,<sup>32</sup> our findings might be alarming for more worrisome effects of air pollution on children's health.

The findings of the present study may have implications for understanding the systemic effects and possible pro-inflammatory state induced by air pollutants; further studies in this regard are warranted.

Isfahan is the second most polluted industrial city in Iran, where the number of factories, cars and motorcycles is increasing.<sup>17</sup> Although the urban air generally had a moderate level of PSI during the time period of this study, air pollutants had significant association with hematologic parameters. This association might be due to the susceptibility of children to environmental threats, and/or due to the noticeably high level of PM<sub>10</sub> and other air pollutants as O<sub>3</sub>, NO<sub>2</sub>, and SO<sub>2</sub>. Moreover, this association might be due to the long-term exposure of the children studied to improper air quality year-round. Our findings are confirmatory evidence on the role of pediatricians to address environmental pediatric health care needs and to improve the health status of children and adolescents.<sup>33</sup>

### **Study limitations and strengths**

The main limitation of this study is that the findings from different analyses of air pollutants associated with hematologic factors should be interpreted with caution, given the cross-sectional nature of the associations. Such associations should be confirmed in future longitudinal studies. The existing equipment was unable to measure more specific particles such as PM<sub>2.5</sub>. Although we found significant association of larger particles (PM<sub>10</sub>) with the biomarkers studied, studying ultrafine particles might result in stronger associations. Another confounding variable which was not controlled was the possibility that there could be differences in the relative incidence of hemoglobinopathies among subsets of children living in the different regions where pollution indicators were measured, however the random sampling of the study reduces the possibility and effect of these confounding factors on the study findings. It should also be acknowledged that we did not study all hematologic parameters reflecting the bone marrow response. Furthermore, we measured systemic biomarkers, but more localized investigation, e.g. assessment of lung tissue in broncho-alveolar lavage, may yield better results.

The main strengths of this study are its novelty of enrolling of a very young age group and studying a population-based sample of healthy children, as well as assessing potential confounding factors and controlling them in statistical analysis for the study of the association between air pollutants and hematologic parameters.

### **Conclusion**

Our findings highlight the association of hematologic parameters with PM<sub>10</sub> (which is larger than PM<sub>2.5</sub>, usually considered more harmful) in a moderate mean PSI level (which is usually considered with few or no health effect for the general population) and a possible pro-inflammatory state. The presence of these associations with PM<sub>10</sub> in a

moderate mean PSI level underscores the necessity to re-evaluate the environmental health policies and standards for the pediatric age group. The findings of this study should be confirmed in future longitudinal studies. Environmental protection concerns should be considered a top priority for primordial and primary prevention of chronic diseases.

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