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Fine Particulate Matter (PM_{2.5}) and Health Effects: An Unbridle Problem in Iran

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Abstract

Particulate matter (PM) is a complex mixture of solid and liquid particles from various sources. Fine PM or PM_{2.5} is defined as a mass with a size of less than 2.5 µm in aerodynamic diameter and has a large contribution to the world increasing annually. Iran is a developing country set in the Middle East that is not secured from this pollutant mainly due to its industries, desert dust and the travel of dust from the neighboring countries. Poor air quality caused by PM_{2.5} can induce multiorgan dysfunction including cardiovascular disease, respiratory impairment, and other adverse effects that lead to morbidity and even death. Since PM_{2.5} is a risk factor for health problems, the comprehension of the detailed molecular mechanisms of PM_{2.5} including oxidative stress and inflammation would be beneficial. The aim of this review is gathering information from epidemiological studies about the health effects of this pollutant in Iran for the sake of a healthy environment and proposing solutions which can be applied to every country that is concerned about the air quality. [GMJ.2017;6(2):81-94] DOI: 10.22086/GMJ.V6I2.755

Keywords: Particulate Matters; Air Pollution; Health Effects

Introduction

Nowadays, air quality and air pollution are big challenges around the world. The classification of atmospheric particulate matters (PMs) is as follows PM₁₀ (dp<10 µm), fine PM or PM_{2.5} (dp<2.5 µm), and ultrafine PM (dp< 0.1 µm) in aerodynamic diameter [1].

Among the air pollutants, PM_{2.5} is the most important pollutant deteriorating air quality [2], and it is putative due to its wide range of origins including combustion engines, power plants, industry, home energy consumption, cultivation, smokes from biomass burning,

and natural sources like desert dust. Also, PM_{2.5} is associated with a variety of health disorders (cardiovascular, respiratory, endocrine, cancers, etc.) as mentioned in epidemiological cohort studies [3-5]. The PM_{2.5} can cause death and have health impaction at very low concentration levels [6-9].

People living in the Middle East are exposed to PM_{2.5} [10], and Iran is one of the countries of the Middle East encountering a serious environmental problem because of the rapid growth in urban population, industries, desert dust, and deserts in its neighborhood [11]. Although the air quality index (AQI) in Iran differs from the standards of environmental

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protection agency [12], everyone agrees on the disaster of PM_{2.5} for Iran and other countries where the AQI ranges between 50-150 for PM_{2.5}, which equals a 24-hour average of 12 to 55.4 µg/m³.

The PM_{2.5} is not in accordance with the standards set by World Health Organization (WHO) which shows that public health is in danger in main provinces of Iran [13-15].

The purpose of this study is to evaluate and overview the hazards of PM_{2.5} in Iran and to propose solutions to make better decisions to solve this problem.

Epidemiology

The PM_{2.5} is noticed around the world mainly due to its impact on mortality rate and hospital admission; on the report of WHO it was responsible for 3.7 million deaths in 2012 [16, 17]. Atkinson *et al.* [18] suggested that the association of PM_{2.5} with respiratory mortality (1.51%) was larger than the percent reported for cardiovascular mortality (0.84%) and all-cause mortality ranged from 0.25% to 2.08% with an overall estimate of 1.04% which declared the public health importance of PM_{2.5}. However, a larger part of the population is affected by cardiovascular diseases (CVD) than by respiratory diseases.

Not only cardiovascular and respiratory mortalities are attributable to PM_{2.5} [19-21], but also it is a major risk factor for premature deaths globally [4]. However, PMs is the consequence of urbanization. Previous research in California demonstrated that surprisingly the mortality rate due to chronic exposure to PM_{2.5} was higher in rural areas [22].

According to the study conducted in Mashhad (one of the cities with high PM_{2.5} levels in Iran), total mortality rate related to PM_{2.5} was 1.61% (600 cases in a year due to short-term exposure) and results of the relative risks (RR) for the increase in total mortality and hospitalization caused by PM_{2.5} indicated that with every 10 µg/m³ increase in PM_{2.5} concentration, there was 0.3% increase in RR [23].

Also, dust is a powerful source of PM_{2.5} in Iran that is located in the dust belt, so dust can contaminate the atmosphere of cities and change the cloud characteristics and even soil prop-

erties [24-28]. The outdoor concentrations of PM_{2.5} are strongly correlated with indoor concentrations of PM_{2.5} in the schools which are built near the main roads in Iran [29]. The PM_{2.5} is one of the pollutants in dust which attenuates the air quality in metropolises of Iran. Hence, vulnerable groups such as children and older adults would be in danger [13]. Two studies conducted in Tabriz revealed that in February, there is the maximum daily mass concentration of total suspended PM_{2.5} (96.6µg/m³) and annual average concentration is 85.3 µg/m³ that mostly comes from natural sources especially soil and Urmia lake bed [15,30,31].

However, a study in Ahvaz (a city in Iran with many dust events) indicated that the average concentration of PM_{2.5} is 69.5µg/m³ and the peak concentration is in May and early July [32]. By evaporation of the water from semi-arid lakes, dust contains PM_{2.5} are created and transported by winds for thousands of kilometers [33,34]. A study claimed that the dust in Iran is similar to the dust around the world in their characteristics [35]. Unfortunately, there was 12 percent reduction in the air quality of Iran from the year 2002 until 2012 [36].

Mechanism

Several mechanistic pathways linking air pollution exposure to adverse health outcomes have been described [5]. The inhalation of air pollution can alter the autonomic balance leading to sympathetic activation which can for example cause changes in heart rate or impaired heart rate variability. Secondly, nanoparticles or their constituents may translocate into the circulation leading to direct harmful effects on the cardiovascular system. Thirdly, PM_{2.5} can induce detrimental effects by the impact of oxidative stress and inflammation (Figure-1).

The PM_{2.5} contains metals which can alter antioxidant enzymes, eg, glutathione (GSH) resulting in increasing reactive oxygen species (ROS), lipid peroxidation and redox imbalance. On the other hand, nuclear factor erythroid-2-related factor-2 (Nrf-2) translocation to the nucleus increases due to the ROS produc-

tion and attenuate the activity of antioxidant enzymes by changing their transcription [37]. Also, ROS overproduction occurs by altering electron transport chain and through Haber-Weiss and Fenton reactions in the cell cytosol [31, 38-40]. The ROS formation leads to the damage of DNA and proteins which can be the cause of cancers or apoptosis [41-43].

Inhaled PMs are capable of production of proinflammatory cytokines and adhesion molecules such as tumor necrosis factor (TNF α), interleukin-6 (IL-6).

Inflammation leads to activate the ataxia telangiectasia and rad3-related-tumor protein53 (ATR-TP53) axis and induces autophagy. Also, TP53 triggers autophagy in response to DNA damage [44-48].

However, DNA damage induced by PM_{2.5} causes apoptosis, ROS elevation increases AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) in-

hibition due to the activation of AMPK cause proliferation and inhibition of autophagy [49]. The PM_{2.5}-induced IL-8 expression occurs via activation of Toll-like receptor-2 (TLR2) [50]. The ROS increases transformation of procaspase-1 to caspase-1, and caspase-1 increases IL-18. The ROS activates nuclear factor kappa B (NF- κ B) and causes insulin resistance and IL-1 β promotion. The IL-18 and IL-1 β augmentation, transcription, and cleavage in endothelial progenitor cells (EPCs) accelerate EPC depletion [51].

The PM_{2.5} promote more inflammation and proliferation via NF- κ B and ROS-mediated signal transducer and activator of transcription-3 (STAT3) activation [52].

Some studies showed that using extracellular signal-regulated kinase-1/2 (ERK1/2) inhibitor and/or protein kinase B (AKT) inhibitor which block ERK/AKT/ NF- κ B pathway can reduce the number of adhesion molecules such

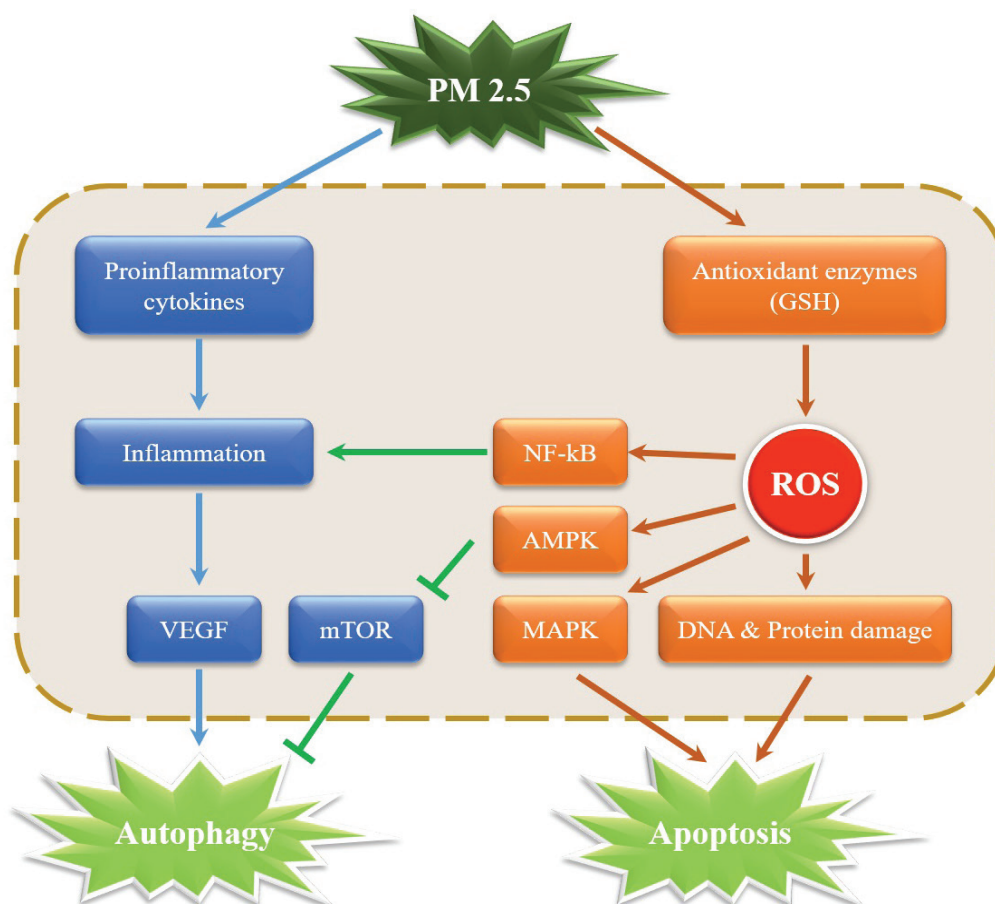


Figure 1. Mechanism of PM_{2.5} induced autophagy and apoptosis by various pathways in cell

as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) production due to the oxidative stress [53].

Cao *et al.* suggested that ROS elevation caused by PM_{2.5} activates mitogen-activated protein kinase (MAPK) and causes apoptosis in rat cardiac cells [54]. The PM_{2.5} effects on EGFR/PI3K/AKT and NLRP (ie, NACHT, LRR and PYD domains-containing protein) and leads to inflammation [55]. Besides, PM_{2.5} accelerates regulatory T cell (Treg) generation by altering forkhead box P3 (Foxp3) gene transcription [56]. The PM_{2.5} disrupts the metabolism of xenobiotics through Aryl hydrocarbon receptor (AhR) and increases transforming growth factor β (TGF β) [57].

Cardiovascular Impairment

Studies showed that there is a significant correlation between air pollution (PM_{2.5}) and CVD [58, 59].

Recent studies indicated that PM_{2.5} could decrease heart rate variability (HRV) a marker for cardiac parasympathetic tone modulation which may correlate with cardiac morbidity and sudden death [60,61]. The PM_{2.5} exacerbates the autonomic nervous system and can lead to cardiac arrhythmia [62]. Furthermore, polymorphisms in glutathione S-transferase enzyme-1 (GSTM1) and HFE (hemochromatosis) genes impairs HRV [63-65]. The HRV depressing is associated with aging, and low HRV causes CVD and coronary disease [66, 67]. As mentioned above, proinflammatory cytokine release occurs due to the exposure to PM_{2.5}. TNF- α and IL-6, two inflammatory markers associated with increased PM_{2.5} [5], increase the risk of myocardial infarction (MI) and out-of-hospital cardiac arrest [68-70].

Also, IL-6 increases C-reactive protein (CRP). The CRP is an indicator of inflammation in CVD as a rapid response to air pollution. With every 100 $\mu\text{g}/\text{m}^3$ in PM_{2.5} concentration, blood CRP level increases to 8.1 mg/L [71]. In this case, Dabass *et al.* suggested that PM_{2.5} is not significantly correlated with biomarkers of CVD, though can increase these biomarkers in the presence of metabolic disease [72].

Another adverse effect of PM_{2.5} is shortening prothrombin time and increasing fibrin-

ogen, tissue factor, hypercoagulable state, and thrombosis [73, 74]. The PM_{2.5} activates platelets at high shear rates through phosphoinositide 3-kinase/AKT (PI3K β /AKT) and glycogen synthase kinase 3 (GSK3) pathway and ultimately causes emboli [75].

Macrophages devour any xenobiotic that is foreign to them including PM_{2.5} and result in increasing adhesion molecules. The ROS leads to inflammation, endothelial damage, and apoptosis; thrombus formation, vascular damage, EPC depletion, high levels of endothelin-1 and imbalance between supply and demand occurs. Hence, all these events explain vascular pathologies, hypertension and coronary artery disease related to the PM_{2.5} [76-79].

In Tehran the capital city of Iran which trapped by air pollution with the largest population there was a significant relationship between the exposure to PM_{2.5} and changes in HRV in 2010.

Tehran is one of the most populated cities in the world, and approximately 20% of total population of Iran lives in Tehran; thus, the HRV, cardiac morbidities and mortalities should be more taken into consideration. Davoodi *et al.* conducted a study on 21 young people who had exposure to the polluted air and compared it to their situation in the clean air. Besides, they applied continuous Holter monitoring of electrocardiogram (ECG) and determined QT interval; they suggested that air pollution may increase nonsustained supraventricular tachycardia [80, 81]. Another study in Tehran demonstrated that tachycardia, cardiac dysfunction, endothelial damage and more atherosclerosis happens under the high PM_{2.5} concentration circumstances [82-84].

Lung Impairment

The PM_{2.5} passes the barriers deeply into the alveoli where it can exert respiratory problems [85]. It gives rise to cough hypersensitivity by increasing the expression of a non-selective cation channel [86]. Increasing asthma and asthma-like airway inflammation, reflect the danger of PM_{2.5} for the respiratory system [87, 88].

The PM_{2.5} is a risk factor for lung cancer and increases mortality from lung cancer [89, 90]. Sometimes, chemical components such as polycyclic aromatic hydrocarbons attach to the PM_{2.5} and go deep into the alveoli acting as a carcinogen [91].

The higher rate of phagocytosis, oxidative stress, and inflammation post PM_{2.5} exposure could impair immunity of the respiratory system which can lead to aggregation of microbes and infection. This process adds to decreasing cardiovascular function resulting in exacerbation of chronic obstructive pulmonary disease (COPD) [92]. The ROS and the activation of metabolic enzymes may induce pneumonia [93]. The PM_{2.5} correlates with the onset of asthma and higher asthma morbidity; also decreasing forced expiratory volume in 1 second (FEV1) due to the asthma is more noticeable in comparison with non-polluted air condition [94]. The presence of PM_{2.5} aggravates respiratory symptoms such as chest pain, dyspnea, sore throat, and wheezing [83, 95].

In Iran, a cross-sectional study gathered meteorological and air pollution information from 31 air quality monitoring station in Tehran and compared cardiovascular (68.36%) and respiratory admission (31.64%). This study showed that PM_{2.5} increases respiratory hospital admissions and also it is correlated with more respiratory admissions to emergency [96].

Neurodegenerative Impairment

A survey carried out on animals suggested that PM progresses to the brain through the nose and absorption from the digestive tract [97]. It revealed that lipid peroxidation and level of CRP had been associated with Parkinson's disease (PD) [98].

The PM_{2.5} correlates with neuroinflammation in the central nervous system, while some cohort studies showed that fine PM does not have potential effects on PD [99, 100]. Liu *et al.* observed a higher prevalence of PD among non-smoking women who inhaled PM_{2.5} [101].

Microglia (the resident innate immune cell in the brain) express TLRs on their surface which PM_{2.5} can attach these receptors leading

to a chronic activation of microglia. Chronic microglial activation results in more ROS production as a protective mechanism. However, the subsequent inflammation triggers a neuronal loss [102].

In an area covered with air pollutant, solar rays do not reach the earth properly, and vitamin D deficiency is prevalent among the people in such areas. Vitamin D deficiency is a risk factor for cognitive impairments. High concentration of lipids and poor level of vitamin D play a critical role in Alzheimer's disease (AD) [103]. Cyclooxygenase-1 (COX-1) and COX-2 increase during prolonged inhalation of particulate matter which reflects early changes in the brain in AD [104].

A pilot study in Iran suggested that there is a relationship between hypertension and AD [105]. The PM_{2.5} also is a trigger of stroke and raises the number of the emergency admissions posts cerebrovascular accident. A retrospective cross-sectional study in Iran indicated that increasing concentration of PM_{2.5} over 2 weeks and long-term changes in this pollutant elevates the risk of stroke admission 1.09 times [106].

Endocrine Disorders

According to the fact that the prevalence of diabetes is considerable in Iran and PM_{2.5} increases the risk of diabetes due to the insulin resistance along with aggravating the metabolic imbalance; it is more important to pay more attention to the air quality in Iran [107, 108].

Another effect of PM_{2.5} on the endocrine system is damaging the blood-testis barrier, oligospermia, and impairing testicular function as shown in animal studies [109]. There is some evidence that states the interaction between PM_{2.5} and AhR [57]. Furthermore, AhR-dependent apoptosis diminishes follicular maturation and has negative effects on the female reproductive system [110].

Having a child is one of the most vital issues in Iranian culture. Therefore, the clear mechanism of endocrine disruption by PM_{2.5} through AhR and other pathways remain to be understood. There is no extensive study conducted on the relationship between PM_{2.5} and

endocrine disorders in Iran; so, future studies should be done to fill our knowledge gaps.

Other Adverse Effects

Hypercoagulable state, hemodynamic problems, endothelial dysfunction, oxidative stress, and inflammation are five possible reasons for low birth weight children and infant mortality (add references for this statement). The PM_{2.5} competes with growth factors (add references for this statement); also, impairs the passage of nutrient and oxygen across the placenta which causes preterm birth.

Eosinophilic rise and nasal inflammation induce asthmatic allergy during childhood [111, 112].

Treg proliferation is the result of activation of Foxp3 transcription factor via TGFβ induction that happens following PM_{2.5} exposure. Besides, AhR promotes Treg differentiation that acts as an immunosuppressive agent [56, 113]. Genotoxic effects of PM_{2.5} as a fundamental aspect of various cancers and other disorders should be fully determined in Iran [114]. Finally, the detrimental effects of PM_{2.5} on gastrointestinal tract is another dilemma which should be surveyed broadly because of its intestinal absorption and evidence gave for more hospitalization due to the peptic ulcer disease after PM_{2.5} exposure [115].

In Iran, some studies conducted on particulate matter and defined the adverse effect of these matters (Table-1).

Suggestions

Since a mild to the moderate rise of PM_{2.5} would be harmful to a vulnerable group including old age people and children, one suggestion is to install air cleaners in the schools for school-aged children and nursing homes for elderly care [88]. Forasmuch as the mechanisms of PM_{2.5} is somewhat known; a possible solution is using the agents which modulate these mechanisms, for example, applying antioxidants like vitamin A, C, and E or β carotene may be beneficial in alleviating inflammation. However, more studies are necessary to prove this claim [116, 117].

Soy oil and fish oil supplements (rich in Ome-

ga-3) are the best sources to decrease oxidative stress. These polyunsaturated fatty acids should be more consumed in cities which are established in the deserts of Iran where far from the sea [118].

As discussed above wide range of disorders are related to PM_{2.5} (Figure-2); as a consequence wide range of treatments are enable for attenuating these effects.

Controlling HRV, hypertension, diabetes by the use of β blockers, antihypertensive agents, and managing diabetes is approximately a kind of constitutional treatment [119].

Other environmental interventions including using air purifiers, assessment of PM_{2.5} concentration by calibrator machines, the foundation of industries away from metropolises, seeding more plants, and using new technologies which are less harmful to the atmosphere are programs that should be performed by the government. For example, Tehran was equipped with subway system several years ago. Thus the concentration of pollutants is a key factor for the quality of underground stations [120].

On the other hand, people should follow some advice: avoid going out or exercising at high concentrations of PM_{2.5} (based on the daily reports), more use of public transports, more walking and cycling instead of using private cars and motorcycles, and ultimately cooperating with the government in order to improve air quality and advance healthy air [121, 122]. Characterization of PM_{2.5} and visibility measurement with professional satellites is another way to determine more accurate concentrations of this pollutant which can predict the exposure in Iran and the countries in its neighborhood [123, 124]. So, it could be helpful for civilization, migration, living and programming.

Conclusion

Iran is a country in the Middle East which wrestles with the PM_{2.5} pollution.

Many studies suggested that PM_{2.5} can be the cause of mortalities and morbidities in Iran and even trigger many diseases due to the multi-organ damage. Despite the discovery of mechanisms of adverse effects worldwide

Table 1. Overview Over the Iranian Studies on Particulate Matter

Authors	Publication Date	City	Source of Exposure	Outcomes
Sanobari <i>et al.</i> [13]	2007	Tabriz	Vehicle (traffic)	Non-standard AQI
Shahsavani <i>et al.</i> [28]	2010	Ahvaz	Dust	Maximum PM _{2.5} in May and early July
Davoodi <i>et al.</i> [77]	2010	Tehran	Polluted air	CVD
Poursafa <i>et al.</i> [81]	2010	Tehran	Polluted air	Cardiac dysfunction
Givhchi <i>et al.</i> [9]	2011	Tehran	Dust	Unsuitable atmosphere
Zarasvandi <i>et al.</i> [31]	2011	Khuzestan	Dust	Unhealthy atmosphere
Hojati <i>et al.</i> [23]	2012	Zagros	Dust	Poor atmosphere
Naddafi <i>et al.</i> [78]	2012	Tehran	Polluted air	CVD
Masoumi <i>et al.</i> [22]	2013	Zanjan	Dust	Poor atmosphere
Mohammadyan <i>et al.</i> [24]	2013	Sari	Vehicle (traffic)	Increased indoor concentrations of PM _{2.5}
Rashki <i>et al.</i> [30]	2013	Sistan	Dust	Uncontrolled dust storms
Arfaenia <i>et al.</i> [12]	2014	Tehran, Isfahan, Shiraz	Polluted air	Non-standard AQI
Gholampour <i>et al.</i> [25]	2014	Tabriz	Urmia lake bed	Maximum PM _{2.5} in February
Gholampour <i>et al.</i> [26]	2014	Tabriz	Dust	Increased total mortality
Shahi <i>et al.</i> [93]	2014	Tehran	Polluted air	Increased hospital admissions
Kamani <i>et al.</i> [116]	2014	Tehran	Subway system	High PM _{2.5} of underground stations
Gholampour <i>et al.</i> [29]	2015	Tabriz	Urmia lake bed	Uncontrolled dust storms
Hassanvand <i>et al.</i> [88]	2015	Tehran	Polluted air	Lung carcinogenesis
Hamedian <i>et al.</i> [11]	2016	Tehran	Polluted air	Non-standard AQI
Miri <i>et al.</i> [21]	2016	Mashhad	Polluted air	Increased mortality and morbidity rate
Saniei <i>et al.</i> [32]	2016	Tehran	Dust	Reduced AQI
Alimohammadi <i>et al.</i> [103]	2016	Tehran	Polluted air	Increased emergency admission
Bonyadi <i>et al.</i> [117]	2016	Mashhad	Variable sources	Increased total mortality

CVD: Cardiovascular Disease; **AQI:** Air Quality Index

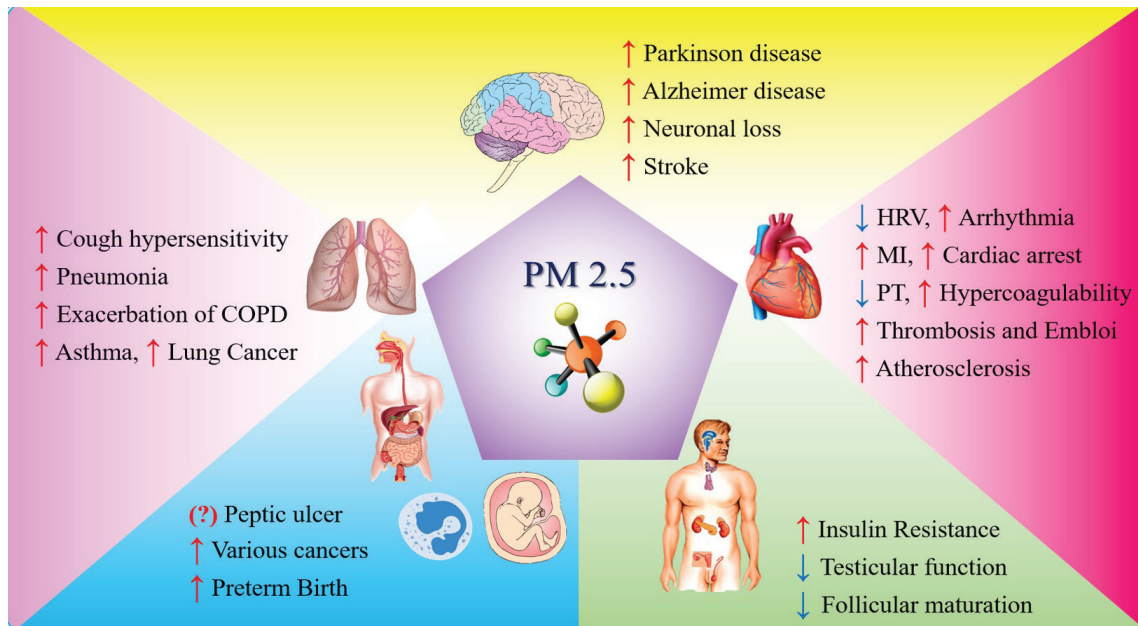


Figure 2. Effect of PM_{2.5} on the vital organs and systems.

such as inflammation and oxidative stress, no study demonstrates which mechanism is prominent in Iran to better overcome the detrimental effects.

Increasing PM_{2.5} is a major concern for public health effect. Since the countries are affected by each other in the air pollution, and Iran nearly is in the center of other countries in the Middle East geographically, new strategies should be scheduled to attenuate the amount of PM_{2.5} concentration and mitigate its detrimental effects. The accurate assessment and finding characterization PM_{2.5} in Iran are the priorities that should be tightly performed. There are some solutions to improve air quali-

ty and clean environment that WHO, the government of Iran and every individual should attempt to apply. Finally, more and more studies must be done to fill our knowledge gaps.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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