The adverse pathophysiological effects of outdoor air pollution on the body tissues

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Abstract

Long-term exposure to outdoor air pollution is a serious and common public health concern associated with growing morbidity and mortality worldwide. There are many published studies about the pathophysiological mechanisms involved in response of the body tissues to outdoor air pollution exposure. The aim of our review was to investigate the problem of outdoor air pollution and health effects of pathological mechanisms, with specific goal to point out public health intervention strategies based upon a clearer understanding of pathophysiological mechanisms of outdoor air pollution. A systematic literature review was carried out in two bibliographic databases, Science Direct and PubMed, in the period from January 1995 to December 2015. We conducted a systematic analysis of 95 studies, 43 of them being review studies and 52 original studies. The systematic analysis was done in three steps, for each body tissue separately (respiratory diseases, cardiovascular diseases, neurologic diseases and diabetes mellitus). This insight into literature review may help foster more effective preventive measures at the public health level as well as potential intervention strategies based upon a clearer understanding of the involved pathways.

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1. Introduction

In the past decades, various pathophysiological effects of outdoor air pollutants on the respiratory tract (1-5) and cardiovascular (3,6-10) system have been well researched and reported in large epidemiological studies. Recently, epidemiological study have also demonstrated an association between outdoor air pollutants and central nervous system (CNS) diseases (11,12). An association was also indicated between a long-term exposure to outdoor air pollutants, insulin resistance and diabetes mellitus (type 2 diabetes) in adults and in children (13,14). Different findings of the studies investigating the influence of exposure to outdoor air pollution on health can be attributed to various study approaches. It should be pointed out, however, that epidemilogical studies are investigating the effects of exposure to outdoor air pollutants in different population groups. In correlation analysis, different groups of potential confounding

risk factors are taken into accout. Data on the obseved health outcome and exposure to pollutants are obtained in different ways, and different exposure periods are taken into account (12). According to the World Health Organization (WHO), the burden of disease due to air pollution is estimated to exceed 2 million pemature deaths annually, which could be attributed to urbane and indoor air pollution (15). The latest online news by WHO Media Centre reports as many as 7 million deaths as a result of air pollution in 2012 (16). The total contaminated outdoor air represents the presence of various and complex chemical mixtures, PM (PM) or rough particles, gases (terrestrial ozone (O_3), carbon monoxide (CO), sulphur dioxide (SO_2), methane and nitrogen oxides (NOx)), organic compounds (polycyclic aromatic hydrocarbons and bacterial endotoxins) and toxic metals (vanadium, lead, nickel, copper and manganese), which can be found in the indor and outdoor air (12). Although outdoor air pollutants can enter the interior spaces, there are pollutants that are unique to indoor-air pollution; these are substances generated in the combustion process (e.g. gases, particles of different sizes, tobacco smoke), biological contaminants (e.g. mites, molds) and chemical contaminants (e.g. vapours emanating from building materials, furniture, household cleaners) (17). Millions of people worldwide are chronically exposed to legally still acceptable high concentrations of outdoor air pollutants (12). Among all the outdoor-air pollutants, the most widespread and also harmful are particles of different sizes (12). Depending on the size, the PM is classified into rough particles (PM10) with an aerodynamic diameter of 2.5 to 10 μm, fine particles (PM2.5) and ultrafine particles (UFP) or nanoparticles (NP) of less than 0.1 μm (13,18). PM2.5 and UFP can pass through the lung alveoli and enter the bloodstream, thus causing various health effects (19-21). In our review, we focused on the effects of PMs (PM) of different sizes in outdoor air on various body tissues.

The aim of this review article is to examine the pathophysiological mechanisms involved in the effects of contaminated outdoor air, with the specific goal on the public health actions based on a better understanding of these mechanisms and their effects on the health of the population.

2. Methods

In a systematic review, we studied articles that investigated the relationship between the outdoor air pollution and pathophysiological mechanisms, and the effects on the body tissues. Information was derived from two bibliographical databases: Science Direct and PubMed. Our systematic analysis included articles published in the period from January 1995 to December 2015. In our search, we used the following key words: outdoor air pollution OR atmospheric pollution OR ambient outdoor air pollution, respiratory diseases, cardiovascular diseases, neurological diseases and diabetes mellitus.

In the process of searching and defining the articles for the final systematic analysis, the following inclusion criteria were taken into cosideration: a) review or original scientific articles describing pathophysiological mechanisms affecting body tissues as a result of exposure to outdoor air pollution, published between January 1995 and December 2015; b) abstracts; c) English language. All abstracts derived from both bibliographical databases using inclusion criteria were analysed. Not all the articles found in both bibliographical databases were

included in our systematic review, as some of them were focused on topics other than air pollution and pathophysiological mechanism response of body tissues. Also, many articles repeated the same findings as those that have already been included in the review. The final number of articles was determined for original scientific papers on the basis or new scientific findings reported, and for review articles on the basis of the summarised scientific findings.

2.1. Respiratory diseases

The initial key words (outdoor air pollution, respiratory diseases) for review articles in both bibliographical databases revealed 306 articles. By using more selective key words (outdoor air pollution, respiratory diseases; oxidative stress, local inflammation, systematic inflammation) in the second step, we determined a total of 52 articles for abstract review. In the third step, among these we identified 16 articles that met our inclusion criteria.

The initial key words (outdoor air pollution, respiratory diseases) for original scientific papers in both bibliographical databases revealed 77 articles. By using more selective key words (outdoor air pollution, respiratory diseases; oxidative stress, inflammation, autonomic system imbalance, mitochondrial dysfunction) we determined a total of 55 articles for abstract review. In the third step, among these we identified 17 articles that met our inclusion criteria.

2.2. Cardiovascular diseases

The initial key words (outdoor air pollution, cardiovascular diseases) for review articles in both bibliographical databases revealed 657 articles. By using more selective key words (outdoor air pollution, cardiovascular diseases; vasoconstriction, hypertension, neurological system imbalance, atherosclerosis, coagulation and thrombosis) we determined a total of 115 articles for abstract review. In the third step, among these we identified 5 articles that met our inclusion criteria.

The initial key words (outdoor air pollution, cardiovascular diseases) for original scientific papers in both bibliographical databases revealed 123 articles. By using more selective key words (outdoor air pollution, cardiovascular diseases; vasoconstriction, hypertension, neurological system imbalance, atherosclerosis, coagulation and thrombosis, mitochondrial dysfunction) we determined a total of 39 articles for abstract review. In the third step, among these we identified 16 articles that met our inclusion criteria.

2.3. Neurological diseases

The initial key words (outdoor air pollution, neurologic diseases) for review articles in both bibliographical data bases revealed 62 articles. By using more selective key words (outdoor air pollution, neurological diseases, inflammation, oxidative stress, neurological imbalance) in the second step we determined a total of 20 articles for abstract review. In the third step, among these we identified 19 articles that met our inclusion criteria.

The initial key words (outdoor air pollution, neurological diseases) for original scientific papers in both bibliographical databases revealed 30 articles. Among these we identified 19 articles that met our inclusion criteria.

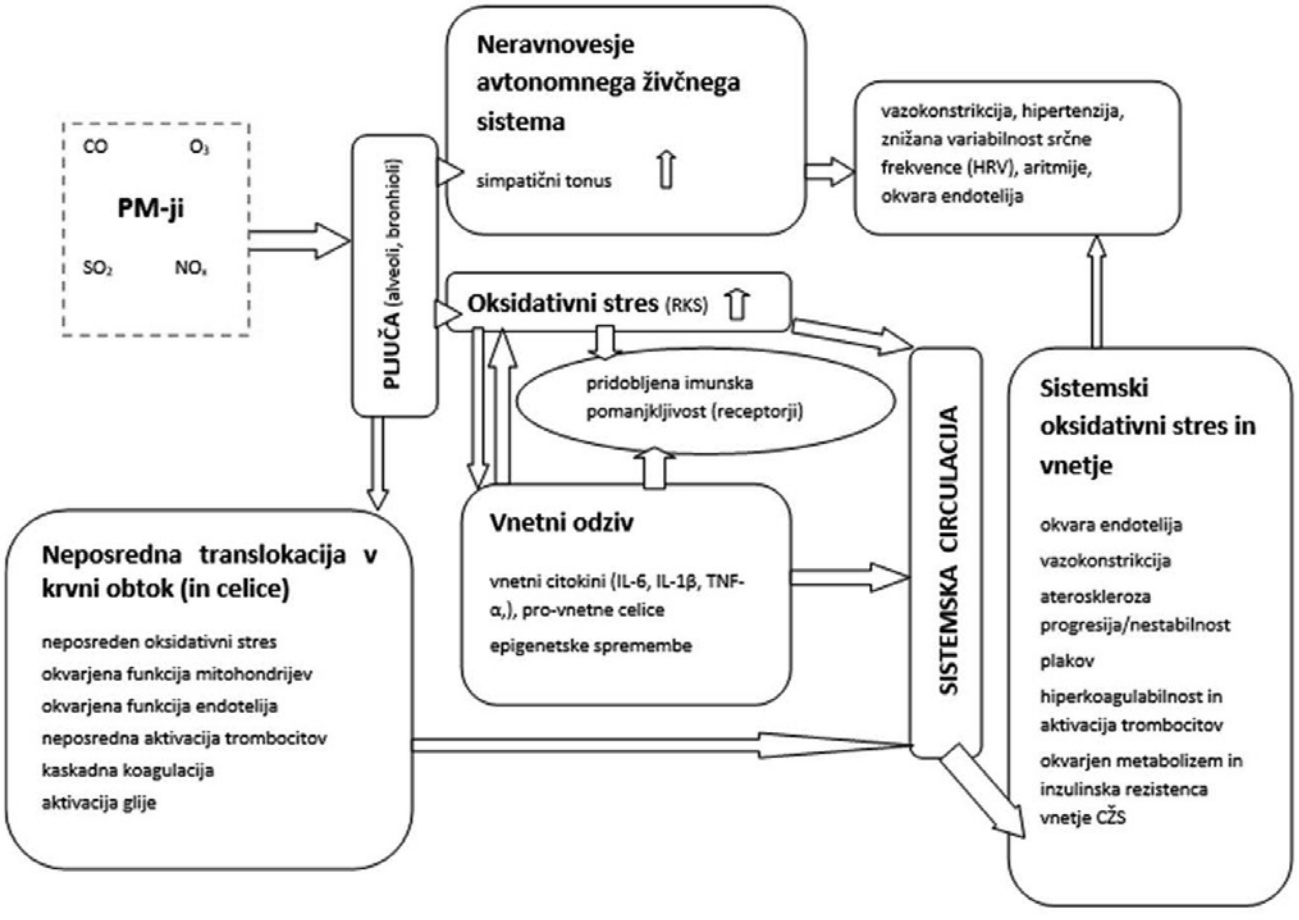

Figure 1: Pathophysiological mechanisms that link outdoor air pollutants with respiratory diseases, cardiovascular diseases, neurological diseases and metabolic disorders, including type 2 diabetes.

ROS – reactive oxygen species, IL-6 – interleukin-6, IL-1β – interleukin 1 beta, TNF- – tumour necrosis factor alpha, CNS – central nervous system

2.4. Diabetes

The initial key words (outdoor air pollution, diabetes mellitus) for review articles in both bibliographical databases revealed 38 articles. By using more selective key words (outdoor air pollution, diabetes mellitus, inflammation, adipose tissue, central nervous system dysfunction) in the second step we determined a total of 5 articles for abstract review. In the third step, among these we identified 3 articles that met our inclusion criteria. The initial key words (outdoor air pollution, diabetes mellitus) for original scientific papers in both bibliographical databases revealed 36 articles. Among these we identified 11 articles that met our inclusion criteria.

3. Results and discussion

There are three main pathways that associate exposure to PM of different sizes with respiratory diseases, cardiovascular diseases, neurological diseases and metabolic disorders, including type 2 diabetes. These pathophysiological mechanisms are presented in Figure 1.

Exposure to matriculate matter of different sizes causes (22):

1. oxidative stress and lung tissue inflammation with inflammatory response /oxidative stress that extends systemically and causes vascular impairment;
2. PM of different sizes also stimulates the pulmonary autonomic nerve endings and receptors, resulting in the prevalence of sympathetic tone over the parasympathetic one;
3. Ultra fine particles (UFP) may enter the bloodstream and cells and get in direct contact with endothelial cells and platelets, exerting potentially adverse effects on the blood vessels and haemostasis.

3.1. Respiratory diseases

Outdoor air pollutants affect one or more host defence mechanisms in the respiratory tract. Several pollutants act simultaneously in a cascade of intertwinned pathophysiological mechanisms. The pathophysiological mechanisms include triggering of oxidative stress, local and systemic inflammatory response, decline in mucocilliary clearance, increased respiratory response and bronchial irritation (23-26). These mechanisms vary with respect to the type of outdoor air pollutant and the duration of exposure (27,28). In addition, various health effects are more pronounced in particularly vulnerable population groups, such as patients with chronic cardiovascular diseases, children and the elderly (29).

3.1.1. Oxidative stress

Outdoor air pollutants can cause lung tissue damage due to oxidative stress through direct action of free reactive oxygen species (ROS) or indirect induction of inflammatory response. Free radicals can directly cause the production and activation of inflammatory mediators or indirectly induce the release of inflammatory mediators following tissue damage (29). ROS are normal products of cell metabolism and cause cell damage by affecting intracellular components, such as deoxyribonucleic acid (DNA) and membrane lipids (30). Antioxidant redox system and antioxidant enzymes neutralise ROS, while oxidative stress may cause posttranslational modification to proteins that modulate ROS activity (31). The activation of sensitive redox pathways, e.g. of nuclear factor Kappa beta (NF -κB), leads to the secretion of inflammatory cytokines (e.g. Interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α)) and chemokines, which accelerate immune response as well as oxidative stress, most probably as part of a coordinated tissue response in the fight against foreign matter. There is a hypothesis that this response extends throughout the whole organism, and rather than being limited to the lungs alone, it also involves the systemic circulation (22,23,29). Scientists presume that the majority of mediators originate from pulmonary tissue cells (e.g. macrophages), however, this hypothesis still needs to be confirmed, because the role of other cells cannot be excluded (22,29). Oxidative stress that affects cells may cause several chronic diseases (32). Body tissues have developed various mechanisms to cope with oxidative stress. The latter becomes harmful by producing free radicals in a quantity that the tissues can no longer control by cells' antioxidant mechanisms. Such excessive quantities of free radicals interact with DNA nucleotides, resulting in DNA mutations over a longer time period. Although there are cellular mechanisms that detect and repair oxidative DNA damage, the mutation accumulates over time, and as

a result, chronic diseases, cardiovascular diseases and cancer may also occur.

3.1.2. Direct inflammatory response

A persistent immune-response-mediated inflammatory condition is an important mechanism through which outdoor air pollutants may damage lung tissue (32,33). Molecular pathways involved in the respiratory inflammation related lung tissue damage have not yet been fully explained, however, several studies have shown that they undoubtedly include an increased IgE-mediated sensitivity to airborne allergens and immune response via Toll-like receptors (TLRs) (34-49). Regulatory T-cells probably play a key role in the inhibition of allergic sensitisation pathway and IgE production as a response to allergen exposure. Outdoor air pollutants exert influence on the IgE-mediated response by damaging the regulatory T cell function (38,39). With respect to the TLR-mediated innate immune response in lung damage due to airborne pollutants, TLRs are known to support defence against a plethora of antigens, and function as signal transmitters in the exposure to the so-called **pathogen-associated molecular patterns** (PAMP), such as lipopolysacharide (LPS) and various inflammatory mediators released in response to tissue damage (43). LPS is an endotoxin found on the cell membrane of Gramm-negative bacteria and is one of PM components. The bronchial epithelial cells are the main first PM sensors, expressing a considerable level of TLR 2 (44,45). TLR can be activated directly by biological components contained in PM of different sizes, such as e.g. LPS, peptides and gas pollutants such as O_3 (45). Different size PM components, such as LPS, play a key role in the urban environment in Asia, where the outdoor air pollution with LPS-rich sources is supposed to be the greatest. Studies have shown that exposure to O_3 and consequent increase in the number of neutrophils in the respiratory system indicate the same signaling pathway.. It has been shown that neutrophils released into the respiratory tract after exposure to O_3 and LPS produce ROS, which causes epithelial cell inflammation, hyper reactivity of the respiratory tract and lung tissue damage by so far unknown mechanisms (46).

3.1.3. Systemic inflammatory response

PM is a triggering agent for a range of abnormalities in the lung tissue, including innate and acquired cellular immune response and the release of inflammatory cytokines (32,33). For the time being, scientists can only hypothesize that there is a synergistic effect with other cells, such as bronchial epithelial cells, as regards the release of such cytokines (50,51). When studying the exposure to PM of different sizes in experimental animal models, scientists found elevated C-reactive protein (CRP), IL-6, and TNF-α values, and decreased expression of IL-10 gene (50-57). The rate of inflammation in the lung tissue is associated with an increase in systemic cytokines and a systemic vascular failure (55). Several related factors can therefore directly affect the cardiovascular system and may also cause changes in other organs that enhance local tissue or systemic cardiovascular responses, such as the release of adipocytokins (resistin, adiponectin) and acute phase proteins (CRP, fibrinogen and other coagulation factors) (22).

There is more evidence that supports the association between chronic exposure to PM of different sizes, inflammatory lung response and systemic vascular failure (29). The study found an

increased number of peripheral basophils in healthy adults four hours after their 2-hour exposure to $PM_{2.5}$ (58). The next study also revealed elevated leukocyte counts in healthy adults 12 hours after their 2-hour exposure to concentrated $PM_{2.5}$ (59). In physically active asthmatics, a decrease in the number of monocytes, basophils and eosinophils in the blood was found after exposure to black carbon (60).

3.1.4. Imbalance of the autonomic nervous system

It has been proven that severaly types of pulmonary receptors (e.g. several potential receptors) and nerve endings detect particles of different sizes or redox inactive compounds in the lungs (22,61). Afferent autonomic reflexes that are established cause a systemic autonomic sympathetic nervous response. This autonomic nervous system response causes the dominance of the sympathetic autonomic nervous system over the parasympathetic system. There may be several clinical consequences (e.g. changes in the heart rate at short-term exposure to high concentrations of $PM_{2,5}$, hypertension, ECG changes (ventricular repolarisation disorders)) (22).

3.1.5. Mitochondrial impairment

Because of their nanosize, UFP can enter the cell directly via a non-phagocytic route and thus impair organelles such as mitochondria (62). The damaged mitochondria thus contribute to increased oxidative stress through increased ROS production and thereby either burden the cell with excessive amount of ROS or impede the cell's antioxidant defence mechanisms. Mitochondria, which regulate cellular energy, metabolism and apoptosis, are critical organelles regulating various cellular responses that lead to death or survival of the cell (63,64).

3.1.6. Changes in the endoplasmic reticulum

Cellular resonses to oxidative stress may lead to changes in the endoplasmic reticulum and actually induce cell death (64,65). Disorders of calcium homeostasis in the endoplasmic reticulum also contribute to cellular damage. The endoplasmic reticulum is a critical organelle in the early protein synthesis of membrane and secretion proteins occuring in the lumen of the endoplasmic reticulum, which includes the whole pathway responsible for their structuring. The loss of homeostasis of the endoplasmic reticulum triggers a stress response, which is central to the pathology of inflammatory and degenerative diseases (66). Recent studies have shown that exposure to outdoor air pollutants causes stress to the endoplasmic reticulum in the lung tissue (67,68). Stress in the structuring of proteins in the endoplasmic reticulum leads to the activation of the Unfolded Protein Response (UPR) (69).

3.2. Cardiovascular diseases

There is increasing evidence of the association between cardiovascular mortality and exposure to outdoor air pollutants (8-10). The health effects due to the exposure to PM of different sizes depend on the aerodynamic diameter of the particles. It is well known that exposure to particles with a smaller aerodynamic diameter causes more severe adverse effects on health (13,18).

3.2.1. Vasoconstriction and vascular damage

When the particles enter the body, $PM_{2.5}$ and UFP can enter the systemic blood circulation directly with the potential of exerting a direct effect on the cardiovascular system. The ability of UFP

to pass through this barrier depends on several factors, such as particle size, their polarity, chemical composition and their potential to form clusters (19,70,71). Regardless of their route of entry, UFP in the blood circulation may exert direct effect on the cells of the vascular endothelium and cause local oxidative stress or inflammatory effects, comparable to their effects in the lungs. In addition, circulating cytokines secreted by peripheral tissue or endothelial cells stimulate peripheral cells of the innate immune response (73,74). Published studies report that exposure to PM of different sizes may cause acute vasoconstriction and impair endothelial function (22,61). Langrish et al. (75) has provided reliable evidence that a vascular impairment due to inhalation of diesel exhaust fumes actually occurs as a result of reduced levels of nitric oxide (NO), presumably due to excessive NO use in the vessels. Scientists have already proved that certain pathophysiological pathways of diesel exhaust fumes are caused by PM inhalation rather than by gas contaminants in outdoor air. Endothelial cells that were incubated with a serum of healthy individuals exposed to diesel exhausts produced higher levels of ROS. Studies have shown that acute vascular failure due to diesel exhausts is caused by endothelial dependent vasodilatation resulting from lower availability of NO, secondary to oxidative stress caused by inhaled particles (77). These vascular responses, including acute vasoconstriction and endothelial damage, play a key role in the genesis of acute cardiac ischaemia and chronic cardiovascular diseases (77).

3.2.2. Hypertension

It has long been known that the exposure to PM of different sizes causes hypertension (77). More recent research, however, provides insight into haemodynamic changes caused by PM of different sizes (8-10,78,79). There is a wealth of evidence on the association between outdoor air pollution and a higher prevalence of hypertension (80,81). Recent findings of studies with controlled exposure of healthy volunteers to PM support the hypothesis that an unbalanced autonomic nervous system with the prevalence of sympathetic over the parasympathetic one is a relevant factor (82). Important findings indicate that in the pathogenesis of hypertension it is also important to consider impaired elimination of sodium due to PM exposure (82). Scientists believe that the presence of endothelial damage, vasoconstriction, vascular hypertrophy, autonomic imbalance with an increased sympathetic tone, along with some other factors that have not yet been fully explained, are included in the pathophysiology of hypertension (77). These results support the hypothesis that outdoor air pollution may cause cardiovascular events (infarction and cardiac arrest), and acute increase in blood pressure leading to chronic hypertension (22).

3.2.3. Atherosclerosis

Chronic exposure to high concentrations of PM of different sizes is associated with an accelerated onset of systemic atherosclerosis (77). Scientists have already discovered some pathophysiological mechanisms involved in the process. These include: Systemic inflammation, oxidative stress in the endothelial vascular cells, activation of innate and acquired immune response, and impaired high-density lipoprotein activity (22,77). It has been shown that PM of different sizes cause prooxidative effects *in vitro* in cell types that play key role in the development of atherosclerotic changes. These are endothelial cells, macrophages and possibly also smooth muscle cells (83). It

has also been shown that PM of different sizes increase ROS production in human endothelial cells of the aorta, most likely by activating endothelial NADPH (nicotinamide adenine dinucleotide phosphate) oxidase and/or electronic failure in the mitochondrial electron complex. It is assumed that the oxidation of lipoproteins is also involved in the mechanism of accelerated atherosclerosis, i.e. in addition to systemic inflammation, since both pathways are deemed to be essential in the genesis of atherosclerosis (83). Several studies have linked the effects of contaminated outdoor air with hypertension, which is a known risk factor for atherosclerosis (77). Accelerated onset and progression of atherosclerosis pose a greater risk for acute cardiovascular events (22,77).

3.2.4. Accelerated blood coagulation and thrombosis

Research has shown that outdoor air pollution is associated with increased thrombotic potential, platelet activation and a higher tendency to blood clotting (22,77). The mechanisms involved in these prothrombotic changes have not yet been fully explained. The hypotheses are based on experimental data that the inhaled particles act quickly and directly activate thrombocytes, thus accelerating thrombosis independently of the mechanisms of systemic inflammatory response (84,85). The mechanisms include direct activation on platelets by particles entering the blood circulation, as well as inflammatory pulmonary endothelial cells that secrete adhesion molecules, which activate the circulating platelets via a P-selectin-dependent pathway (84,85). The sum of multiple small changes in hepatic expression of acute phase proteins and coagulation factors (e.g. fibrinogen) further enhances these responses (85). Recently it has been proven that hypomethylation of inflammatory genes is also involved. The endogenous thrombin generating potential increased with exposure to higher concentration of PM of different sizes. The activation of genes (reduced methylation) of nitric oxide synthetase-3 and endothelin-1 is also involved in the mechanisms of excessive blood coagulability (86). All these mechanisms pose an increased risk for venous thrombosis and other acute cardiovascular events (22).

3.2.5. Imbalance of the autonomic nervous system, cardiac variability, electrocardiographic changes and arrhythmias

Many published studies support the hypothesis that PM disrupt the autonomic heart balance (87). These physiological changes support the assumption that inhaled pollutants generally change the autonomous balance in favour of higher sympathetic activity. The pathways responsible for these changes have not yet been fully explained, but there is a hypothesis that they represent a systemic stress response and an integral neuronal reflex response mediated by activating vagal afferent pathways with various subgroups of receptors in the lung (77). Regardless of the mechanism details, inhalation of PM can induce arrhythmias, sudden cardiac death or haemodynamic changes (e.g. accelerated hear rate, hypertension) or cause cardiac ischaemia (22).

3.2.6. Myocardial damage

In a recent study in mice, dysfunctional mitochondria in the muscle tissue of the heart were found after exposure to PM of different sizes, which was associated with decreased contractility of the heart (88).

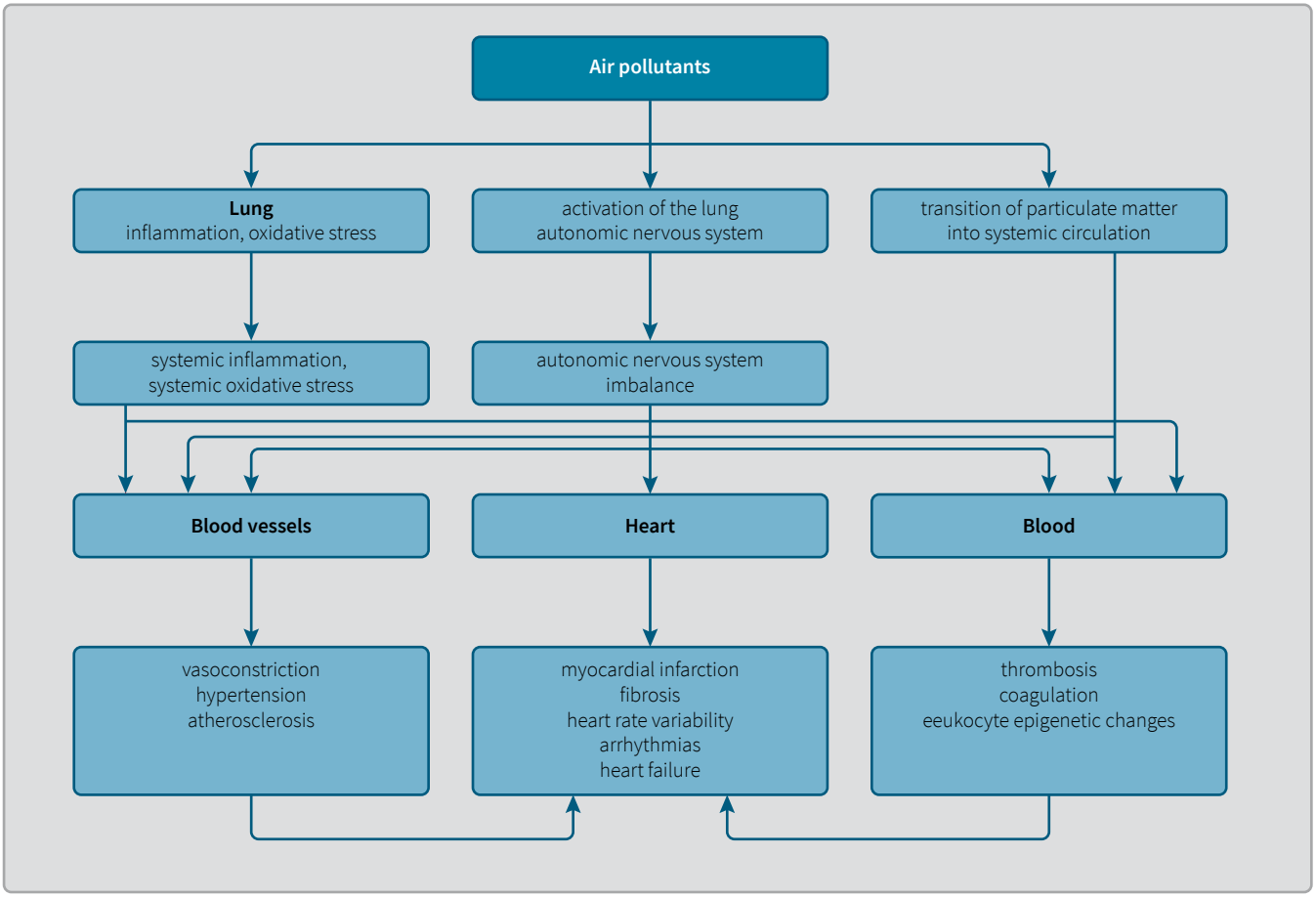

Figure 2: The effects of outdoor air pollutants on the cardiovascular system and blood

Figure 2 presents a systematic review of pathophysiological ways in which outdoor air pollutants affect the cardiovascular system.

3.3. Central nervous system

The mechanisms through which the outdoor air pollutants affect the central nervous system (CNS) are different; they exert their influence through various cellular, molecular and inflammatory pathways that directly impair brain structures or lead to a predisposition for neurological diseases (89-91). Copious evidence from recent epidemiological studies indicates that certain neurological diseases, such as Alzheimer's disease, Parkinson's disease and stroke are associated with outdoor air pollution (89-92).

3.3.1. Inflammation / oxidative stress in the central nervous system

CNS inflammation is a complex innate immune response of neural tissue to adverse factors, such as pathogens, damaged cells and other irritants within the CNS. A key component of the innate immune response in the CNS involves the production of proinflammatory cytokines that are mediated by inflammasome signalling. Cells of the innate immune response in the CNS, i.e. microglia and astrocytes, express TLR4, which takes part in the formation

and activation of inflammasomes (93). Inflammasomes are multiprotein complexes. Exact inflammasome composition depends on the activator that triggers its aggregation; thus dsRNA triggers its own inflammasome composition, which differs from that triggered by e.g. asbestos (94). Inflammasomes accelerate the maturation of inflammatory cytokines, such as IL-1β and IL-18. They were shown to induce cell pyroptosis, the process of programmed cell death, which differs from apoptosis (94). Although it has been proven that inflammasomes are included in the innate immune response, the specific pathophysiological significance of inflammasomes in neurodegenerative diseases has not yet been fully explained (95,96). The systemic inflammatory response is associated with the production of proinflammatory cytokines, which have already been described, and for which blood vessels in the brain express certain and induced receptors (11,96) Thus cytokines may activate endothelial brain cells, disrupt the blood-brain barrier integrity, or trigger a signalling cascade leading to activation of mitogen-activated protein kinase (MAP-kinase) and NF-κB, further leading to the local production of proinflammatory cytokines (e.g. interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α)) and chemokines, which accelerate immune response as well as oxidative stress (97). In addition, the circulating cytokines released from inflamed peripheral organs or endothelial cells also activate peripheral afferent neuron endings or enter the brain by diffusion and active transfer, thus synergistically impairing the condition (74,98). Therefore, nerve tissue shows an increased number of infiltrated monocytes or activated microglia, and increased expression of IL-1β, a damage of the blood-brain barrier, activation of endothelial cells, and changes in the prefrontal lobe of the brain (99,100).

Due to exposure to environmental stress, such as PM-related air pollution, ROS levels increase dramatically, which is reflected in a significant damage of cell components, including proteins, lipids and DNA (101,102). The brain is particularly vulnerable to oxidative stress related disorders due to their high metabolic activity, low activity of antioxidant enzymes (superoxide dismutase and catalase), low levels of endogenous radical scavengers (vitamin C), high content of cellular lipids and proteins, and high levels of redox metals such as iron and copper, which can react as catalysts to produce ROS (103,104). Oxidative stress is thus proven to be associated with age-related neurodegenerative diseases due to lipid peroxidase production, protein aggregation, and oxidative DNA in the tissue samples from the affected brain (103,105).

3.3.2. Direct penetration into the cerebrovascular system

Mechanisms through which outdoor air pollutants may affect body tissues depend on the size, structure and composition of contaminated outdoor air components (19-21). PM of different sizes can enter mammalian cells in various ways, including through phagocytosis, pinocytosis, passive diffusion, receptor endocytosis, directly by penetrating cell membrane or by transcytosis (62,106). PM of different sizes that do not enter the cell directly can still get in contact with surface proteins and alter the signalling and behaviour of the cell. UFP can easily and rapidly pass through the erythrocyte membrane, so that these particles can be observed intraluminally in the erythrocytes of some brain capillaries (106). They also have a large surface-to-volume ratio and are non-mem-

brane bound organelles, which allows them to interact directly with intracellular proteins, organelles and DNA. These particles can reach specific organelles, such as mitochondria, lysosomes and Golgi complex, and may cause oxidative stress in membranes by interfering with NADPH-oxidase activity. They can also trigger the cellular release of inflammatory mediators and cytokines (62). The study showed that exposure to UFP was associated with mitochondrial damage, as demonstrated by an increase in the number of mitochondrial DNA (mtDNA) copies (63). The damaged mitochondria contribute to increased oxidative stress through increased ROS production and thereby burdening the cell with excessive amount of ROS or through involvement in the cell's antioxidant defence mechanisms. UFP interaction with cellular proteins may result in their denaturation or degradation. Possible consequences are the loss of enzymatic activity and the production of autoantigens (107). UFP may also significantly increase the level of protein fibrillation, which may indicate a link between ambient air pollutants and neurodegenerative diseases (108,109). Other possible molecular pathways that are affected by neurodegenerative diseases include incorrect composition, accumulation and aggregation of proteins in the brain. UFPs that have the ability to penetrate into the nerve cells further exacerbate these processes in the same way as does the oxidative stress caused by ambient air pollutants. At cellular level too, mitochondrial damage is often characterised by aggregation and accumulation of malformed proteins, leading to neurodegenerative diseases (110,111).

3.3.3. Neuron uptake of ambient air pollutants

Ambient air pollutants may affect the afferent nerve cells and act on the *circumventricular* organs or change the permeability of the blood-brain barrier (112). The *circumventricular organs* are midline brain structures located around the third and fourth ventricles. They have extensive vasculature and no blood-brain barrier, so that chemicals circulating in the blood may enter neurons directly (112). Another important and more direct pathway through which UFPs enter the CNS is via the olfactory neural epithelium (113-115). $PM_{2,5}$ and UFP can reach the CNS via the olfactory receptors or the trigeminal nerve. The olfactory epithelium is covered with a layer of supportive cells, and olfactory sensory neurons extend their dendrites into the mucosal layer that covers the olfactory epithelium. Thus, they can directly get in contact with pollutants in the inhaled air. Pollutants that are inhaled through the nose can enter the cilia of the olfactory neural receptors by pinocytosis, simple diffusion or by receptor-mediated endocytosis. Once they enter the sensory neurons, they can enter the olfactory bulbus by slow transfer along axons. From there, the pollutants travel further into the CNS along the axons of the mitral cells projected from the olfactory bulb into multiple brain locations, including the olfactory cortex, the anterior olfactory nucleolus, the pyriform cortex, the amygdala, and the hypothalamus (116). Nasal absorption of contaminants is further accelerated by systemic inflammatory response due to contaminants that also affect the olfactory mucosal barrier, resulting in the accelerated destruction of neurons in these parts of the brain (113).

3.3.4. Imbalance of the autonomic nervous system

There is yet another mechanism of direct UFP's access to neurons, which includes retrograde and anterograde transmission in axons and dendrites, such as the transfer of inhaled UFP into the CNS via sensory nerve endings that transfer stimuli to the respiratory epithelium. Exposure to ground-level ozone (O_3) is activated by the CNS through the vagal nerves without involvement of the thoracic spinal nerves (103). The result is an increased sympathetic tone at the systemic level (22).

Figure 3 presents a systematic review of pathophysiological ways in which outdoor air pollutants affect the CNS.

3.4. Type 2 diabetes mellitus

There is increasing evidence that exposure to outdoor air pollutants is associated with susceptibility to type 2 diabetes 2 (13,14).

3.4.1. Systemic inflammation

PM of different sizes is a proinflammatory triggering agent; the result is a range of abnormalities in the lung, including innate and acquired cellular immune response and the release of inflammatory cytokines, which has already been described (34,-49). The level of lung inflammation correlates with an increase in systemic cytokines and systemic vascular damage, which also affects tissues responsible for insulin resistance (liver, adipose tissue, muscle, brain) and/or type 2 diabetes (55).

3.4.2. Changes in glucose homeostasis associated with outdoor air pollutants

An increase in blood glucose levels associated with exposure to $PM_{2.5}$ was demonstrated in mice fed normal and high-fat diet (119,120). Defective insulin signalling in tissues such as the liver is essential in the pathogenesis of insulin resistance and diabetes. Scientists have demonstrated a decrease in tyrosine phosphorylation in the liver at exposure to $PM_{2.5}$ with changes in the level of insulin receptor substrate (IRS). They have proven that changes in phosphorylation of the IRS in the insulin resistance result in the impairment of PI3K/Akt signalling. This is an intracellular signal transduction pathway that promotes metabolism, proliferation, cell survival, growth, and angiogenesis in response to extracellular signals. This pathway is via serine or threonine phosphorylation of several subsequent substrates in the cell. The key protein is phosphatidylinasitol 3-kinase (PI3K). The reduced phosphorylation of PI3K-Akt in the liver, skeletal muscle, white fat tissue and in the basal state aorta as well as in insulin response was demonstrated by the development of insulin resistance in these organs (122).

3.4.3. Visceral adipose tissue inflammation associated with outdoor air pollutants

Type 2 diabetes mellitus in humans and in animal models is associated with increased levels in the collection and/or activation of innate immune response cells in visceral adipose tissue. Exposure to PM results in an increased number of macrophages in the adipose tissue with a shift to proinflammatory phenotype, characterised by an increased number of F4/80 macrophages in visceral fat, and a "phenotype M1" inflammatory disease characterised by elevated levels of TNF-α, IL-6 and a decline in IL-10 and the expression of MGI1 gene (119). In order to further evaluate how the exposure to PM mediates infiltration in visceral adipose tissue, the effects of the expression of yellow-fluorescent protein that is

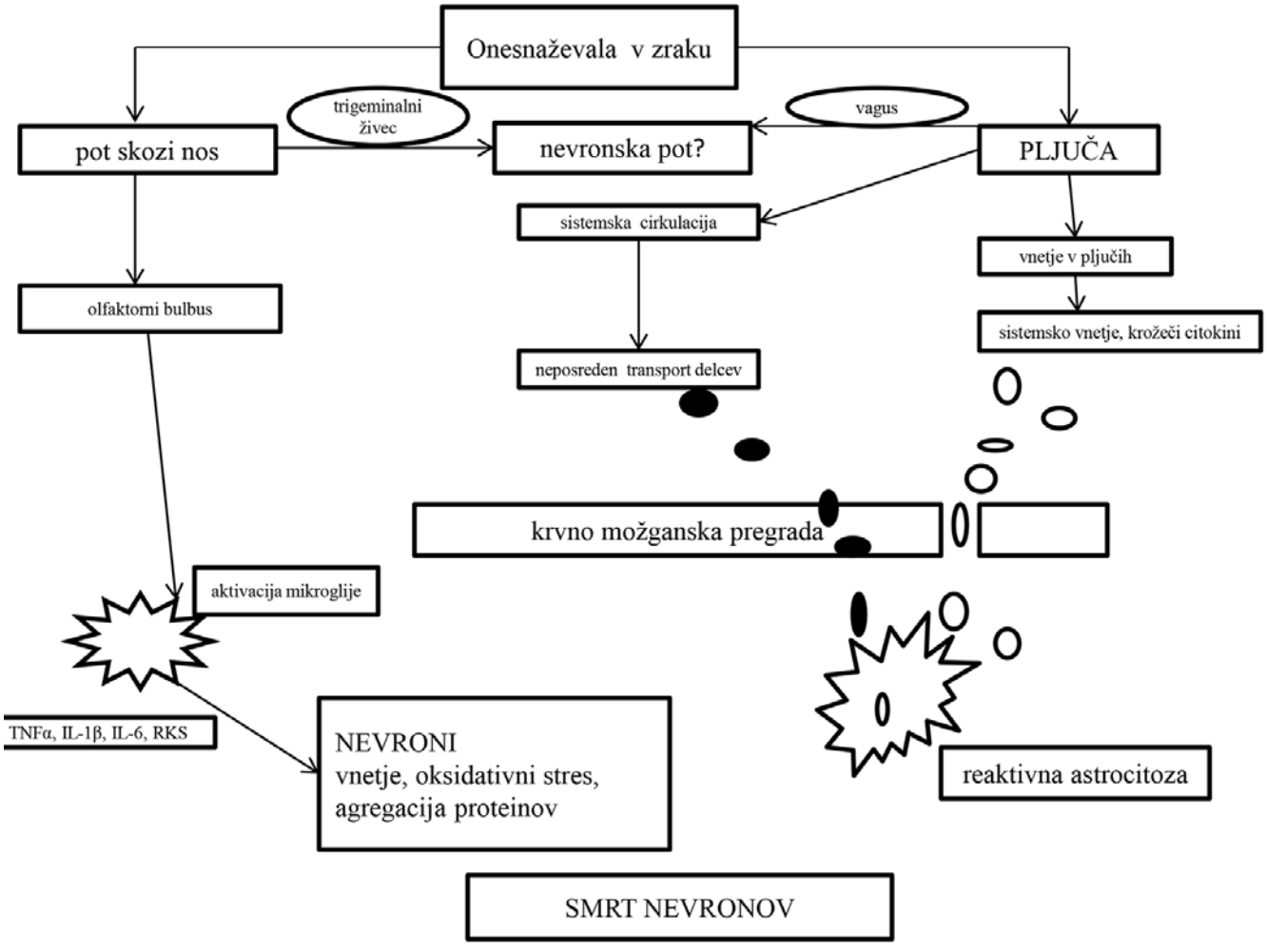

Figure 3: The effects of outdoor air pollutants on the brain via multiple pathways. TNF-α – tumour necrosis factor alpha; IL-1β – interleukin 1 beta; IL-6 – interleukin 6; ROS – reactive oxygen species.

characteristic of monocytes have been evaluated by introducing $PM_{2.5}$ into the trachea in the transgenic model (*c-fms*^{YFP}). However, when these mice were rendered insulin-resistant by high-fat diet, the exposure to $PM_{2.5}$ resulted in a doubled number of endothelial adherent YFP^+ cells in the mesenteric fat, while the number of monocytes in fat increased sixfold (119). Thus, $PM_{2.5}$ promotes the migration and adhesion of YFP^+ cells into visceral fat deposits. In the next study (123), the effects of early (at the age of 3 weeks) exposure to $PM_{2.5}$ on the development of insulin resistance in mice fed normal and high-fat diet. The intraperitoneal glucose tolerance test in mice on a normal diet exposed to $PM_{2.5}$ showed a significant increase in glucose levels. In the high-fat diet and $PM_{2.5}$ exposure in normally fed mice, there was an increase in HOMA-IR (homeostasis model assessment index-insulin resistance) and an increase in TNF-α compared to mice that were on a normal or high-fat diet (123). HOMA-IR is a method for quantifying insulin resistance and the function of beta cells. The authors of HOMA-IR made use of physiology studies data and developed a mathematical equation describing glucose control with a feedback loop (124). $PM_{2.5}$ and high-fat

diet combined statistically significantly increased total abdominal fat compared to the exposure of normally fed mice only to high-fat diet. Visceral and subcutaneous fat increased significantly after $PM_{2.5}$ exposure in normally fed mice, and the size of adipocytes in this case also increased in visceral and subcutaneous fat. The size of the adipocytes was the highest in mice that were exposed to high-fat diet only, and no further increase was noted after their exposure to $PM_{2.5}$. These data indicate that in mice on a normal diet the exposure to $PM_{2,5}$ alone may exacerbate adiposity and trigger proinflammatory effects (123).

3.4.4. $PM_{2,5}$–mediated stress of the endoplasmic reticulum in the lung and liver

Stress in the endoplasmic reticulum (ER), also called UPR, is an evolutionary conservative pathway intended to alleviate wrong protein bending in response to various pathophysiological stressors (125). An *in vitro* study (126) has shown that the exposure to $PM_{2.5}$ has the potential of triggering ER and UPR stress, which may represent pathophysiological mechanisms that link $PM_{2.5}$ exposure to liver insulin resistance. In response to inhaled high concentrations of $PM_{2.5}$ exposure over a 10-week period, a statistically significant increase in UPR-associated proteins was observed: ATF-4, Hsp70, Hsp90 and BiP (binding immunoglobulin protein) (126). GRP94 (glucose regulatory peptide) and BiP increased in the lung and liver, which reflects the activation of transcription factor 6 pathway (ATF6) in these organs. ATF is one of the three major sensors for ER-stress. Phosphorylated PERK (double-stranded RNA-activated protein kinase-like ER kinase) and eIF2a were also increased in the liver in addition to the induction of C/EBP-homologous transcription factor CHOP/GADD153 (126), the latter being in correlation with apoptosis in the lung and liver. UPR is known to intersect with several inflammatory and stress-signalling pathways, including NF-κB and c-Jun N-terminal kinase (JNK) as well as with oxidative stress response. All these may affect glucose and fat metabolism (126).

3.4.5. Mitochondrial and brown adipose tissue damage as a result of contaminants in the outdoor air

Mitochondrial damage is one of the key abnormalities in type 2 diabetes. Defective metabolism of fatty acids via β-oxidation in mitochondria leads to the accumulation of intracellular metabolites, including CoA fatty acid, diacylglycerol and ceramides in the skeletal muscle and liver (127). Scientists (120) have established several mitochondrial abnormalities in brown adipose tissue after both long-term (> 10 months) and short-term (2 months) exposure to PM2.5 in mice. Long-term exposure to PM2.5 resulted in a visible decrease in the quantity of brown adipose tissue and a decrease in the size of mitochondria in the brown adipose tissue deposits. These changes coincided with an elevated oxidative and nitrosative stress in brown adipose tissue. In order to better determine brown adipose tissue damage, specific adipocytic gene profiles of brown as well as white adipose tissues were evaluated. Certain genes specific for brown adipose tissue were statistically significantly reduced in white adipose tissue after prolonged exposure to PM2.5, so that changes in brown fat are probably due to reduced metabolism after exposure to PM2.5.

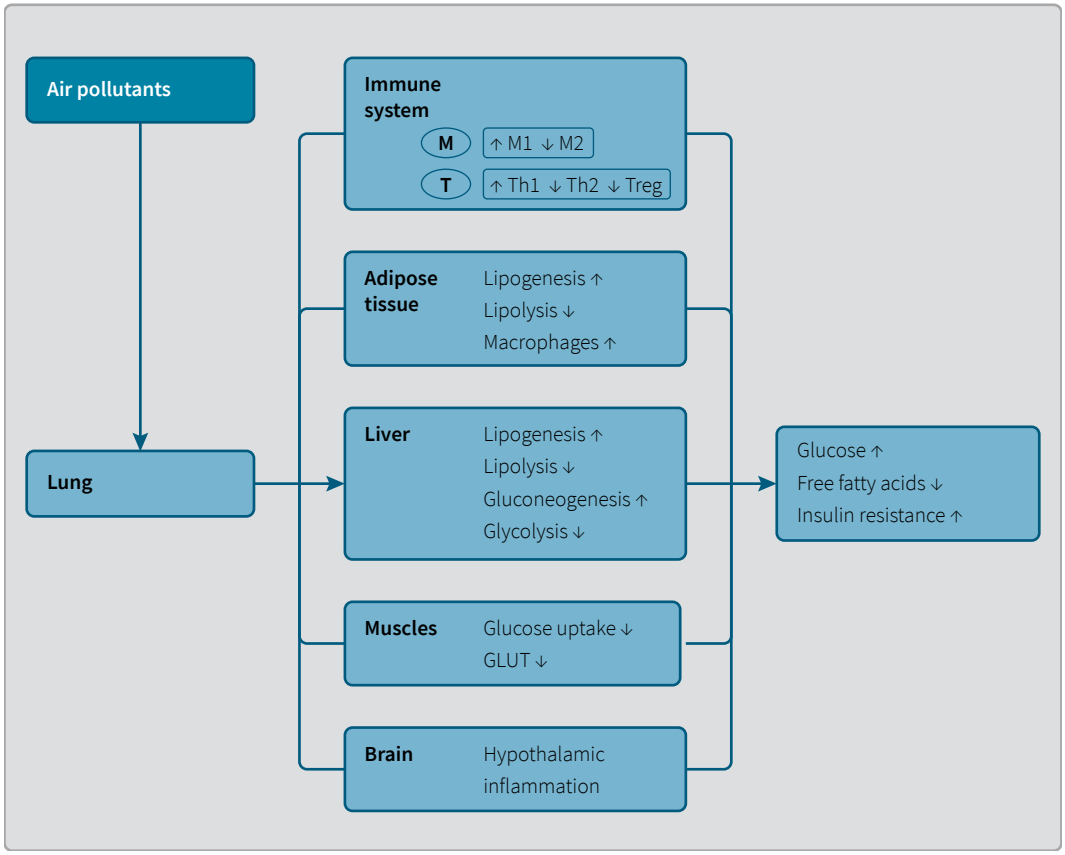

Figure 4: The effects of outdoor air pollutants on the immune system, adipose tissue, muscles, liver and brain. M1 - classically activated macrophages; M2 - alternatively activated macrophages; Th1 – T helper type 1 cells; Th2 – T helper type 2 cells; GLUT 4 - Type 4 glucose transporter.

3.4.6. Sample recognition receptors(PRR)TLR and NLR as sensors for exposure to PM of different sizes

It is known that pattern recognition receptors, such as TLR and NLR, play an important role in the diet-induced insulin resistance. Scientists have demonstrated in animal models and in humans that a large number of ligands, such as saturated fatty acids, lipopolysacharide (LPS) and ceramide, play a key role in obesity and insulin resistance (128). The bronchial epithelial cells are the main first cellular sensor for PM, widely expressing TLR and NLR. TLR can be activated directly by biological components, which are intrinsic in the exposure to PM of different sizes, such as LPS, peptides and gas pollutants such as O_3 (119,129). Although the LPS level is lower in $PM_{2.5}$ than in PM_{10}, data show the association of these components with insulin resistance (129). In a recent study of Suna et al. (130) in the urban population of Beijing, the results of a multivariate correlation analysis standardised for a majority of confounding risk factors, including CRP, have shown LPS-binding protein (LPB) to be an important triggering factor for the development of type 2 diabetes mellitus. Plasma LPB is a better substitute than LPS, and recent studies have found that it can serve as an indicator of inflammatory changes as it activates the innate immune response (131).

3.4.7. Central nervous system mechanisms and metabolic disorder

Recent studies report inflammation in the key areas of the hypothalamus as a mediator in the peripheral defects in glucose homeostasis and energy imbalance. Thaler et al. (132) studied hypothalamic inflammation as evidence of signal-enhanced regulation of IL-6 and NF-κB very much ahead of the onset of overweight gain. Furthermore, the experiment revealed reactive gliosis and markers indicating neuronal damage that was present in the hypothalamic arcuate nucleus in the first week following a high-fat diet (132). Other investigators (133) established an important role of hypothalamic ER in the induction of peripheral inflammation and glucose imbalance. Disruption of ER-stress with tauroursodeoxycholic acid (TUDCA) partially repaired obesity-dependent metabolic impairment and hypertension-associated impairment. The acute activation of NF-κB proinflammatory protein and its IκB kinase-β (IKK-β) activator in the mediobasal hypothalamus, the region rich in proopiomelanocortin (POMC) containing neurons, has been proven to rapidly increase blood pressure in mice, irrespective of obesity (133). PM of different sizes has been proven to enter the CNS directly through the translocation along the olfactory nerve into the olfactory bulb (134). In addition, $PM_{2.5}$ and/or exposure to O_3 directly affect vagal afferent endings, which may play an important role in the regulatory pathways that mediate blood pressure and peripheral inflammatory response (135). It has already been stated that outdoor air pollutants cause inflammation, oxidative stress and pathological changes in the CNS, which lead to pathological changes, such as reactive gliosis (11). Scientists have shown that prolonged exposure to $PM_{2.5}$ that lasts more than 10 months increases the hippocampal expression of proinflammatory cytokines, and affects memory impairment of spatial learning and behaviour (134).

Figure 4 presents a systematic review of pathophysiological ways in which outdoor air pollutants affect metabolism and insulin resistance.

3.5. Brief recommendations regarding outdoor air pollution proposed by Künzli and co-workers

People spend most of their time indoors. In the absence of indoor pollutant sources (fireplaces, gas cookers, tobacco smoke), the levels of contaminants in the indoor air depend significantly on the quality of the outdoor air. The concentrations of highly reactive gases, such as O_3, are considerably lower indoors. Thus practices like not opening windows during rush hour and when O_3 concentrations are high, may contribute significantly towards improving the quality of indoor air. Concentrations of some air pollutants are lower in air-conditioned rooms, such as modern offices and public indoor premises. On the other hand, air-conditioning consumes a lot of energy and thus contributes to increase in the level of outdoor air pollution, depending on the mode of energy generation. It is questionable whether patients, particularly those with respiratory conditions, should invest in the purchase of indoor air filters. While high-efficiency air filters actually lower the concentration of dust particles in an experimental indoor environment, few studies have confirmed that the use of such filters has improved the health situation in real-life conditions. The potential benefits should not be ignored, but we must weigh them against the price, energy consumption,

the noise emitted by the device, and the relevance of exposure relative to the time spent at other locations. People should be warned before purchasing air filters that produce O_3 or other gases with known adverse effects on health (137).

3.5.1. Adjusting the individual's exposure or changing the dose

In the coming years, air pollution will remain a reality, so that various adverse effects on health will be inevitable. In the light of these facts, people will become interested in the endeavours for reducing their exposure or dose despite the poor air quality. Personal exposure and dose depend on the location and time of the activity (137).

3.5.2. Local factors

People living at a distance of 50–100 m from a road with dense traffic are faced with much higher exposure to traffic-related pollutants. Health risk is significantly dependent on the distance from the road, traffic density and traffic characteristics (stop-and-go, up or down, diesel trucks / buses), as well as on the city structure and meteorological characteristics (e.g. wind direction and speed). Concentrations of primary pollutants resulting from transport are diluted in the vicinity of several hundred meters. They are also lower on the upper floors of modern high-rise buildings than in the ground floors (137).

Thus, patients and young families have the opportunity to choose a healthier option, provided that they have access to appropriate counselling. Since individuals cannot directly influence the level of outdoor air pollutants, and when relocation is not possible, they still have the option of deciding where to spend time.

Walking along the roads with dense traffic results in much higher exposure than walking on nearby roads where traffic is less dense or non-existent (pedestrian zone). People should be advised that rather than running along highways and roads with dense traffic they should use roads with less dense traffic where there is a lower level of air pollution. Also, kindergartens, schools and sports parks or playgrounds should not be built in close vicinity of major roads with dense traffic (137).

3.5.3. The factors of time and activities

Concentrations of many air pollutants in the environment show a typical daily trend with high pollution during rush hour or with peak oxidant values (summer smog) in the afternoon and early evening hours. Doses of pollutants reaching the target organs increase with physical activity. Consequently, the dose and exposure are influenced by the choice of time and the level of activity. Thus, during the summer smog, prolonged outdoor activities, such as football and other long-lasting events, should be carried out in the morning. It is recommended that during high PM contamination, rather than outdoors, sports events should be organised in indoor gymnasiums, halls etc.

In extreme air pollution, people can wear masks, which however do not provide 100 % protection against air pollution exposure. The exposure to PM, and in particular UFP and PM_{10} as well as to dust can be reduced to some extent. However, the long-term health effects of wearing mask have not yet been investigated. Some studies have shown that in occupational exposure, the choice of the correct mask size rather than the filter is important (137).

4. Conclusion

Polluted outdoor air is still one of the main risk factors for chronic diseases and mortality, and thus one of the major public health concerns. Due to the presence of various outdoor air pollutants and their long-range spread, it is a global problem and, in addition to climate change and environmental protection, it is becoming a major topic in the area of public health and environment. Much has already been done to clarify the pathophysiological mechanisms involved in the effects on human health, however there are many mechanisms that still remain to be explained. It is very important to provide credible explanations of mechanisms to assist policy-makers in preparing evidence-based measures.

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