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The Latest Studies on the Impact of Ambient Particulate Air Pollution (PM_{10}, $PM_{2.5}$) on the Increased Risk for Cardiovascular Diseases, Respiratory Cancer and Neurodegenerative Diseases

Athanasios Valavanidis

Department of Chemistry, National and Kapodistrian University of Athens, University Campus Zografou, 15784 Athens, Greece
E-mail:valavanidis@chem.uoa.gr

ABSTRACT

Worldwide studies in the last decade have evaluated the short and long-term exposure of fine and superfine ambient particulate matter (PM) air pollution with mortality and morbidity. It has been established that ambient PM contribute to increased risk of cardiovascular diseases (CVD) certain types of respiratory cancer and neurodegenerative diseases. Also, scientifc evidence showed that there are specific population subgroups that are most susceptible to PM exposure. Individuals with underlying heart cardiometabolic conditions, including hypertension, diabetes mellitus, and obesity, may be at greater risk of morbidity and mortality from ambient PM exposure. Particularly, short-and long-term exposure to ambient air pollution $PM_{2.5}$ (2.5 aerodynamic diameter in μm) play an important role in cardiometabolic disorders exacerbating risk of future mortality connected to heart diseases. Size and chemical composition of PM are crucial for damage in the respioratory system. Fine and ultrafine particles can penetrate deeper into the airways reaching the alveoli in which 50% are retained in the lung parenchyma. Major chemical constituents of PM are transition metals (Fe, Cu, Ni, Cd, Pb, etc), sulfate and nitrate ions, polynuclear aromatic hydrocarbons (PAY), dioxins, quinoid (semiquinone) stable radicals of carbonaceous material, minerals, gases, and other materials. These components are involved in free radical generation, oxidative cellular mechanisms, oxidative stress, tissue inflammation, and production of chemoatractive molecules which activate pro-imflammators in the respiratory system. In the last 20 years epidemiological and clinical studies focused on adult population cohorts at various urban areas (in developed and developing countries) to investigate associations of levels of ambient PM air pollution and increased risk for CVDs, certain types of respiratory damage leading to lung and respiratory cancers. Also, a number of studies concentrated on the associated evidence for PM exposure and increased risk for neurodegenerative diseases. This review covers the most important experimental and epidemiological studies on PM and adverse health effects in the last 5 years, that have been published in authoritative scientific journals. Alkso, the review covers extensive reviews and meta-analyses for quantitative statistical comparison of several separate but similar studies in order to test the pooled data for statistical significance.

Introduction: particulate ambient air pollution and increased risk to morbidity and mortality

In the last decades growing evidence from epidemiological and clinical studies suggests that long-term exposure to fine particulate matter (PM_{10}, $PM_{2.5}$ and $<PM_{2.5}$ particles with aerodynamic diameter in nm, 1 nm $=10^{-9}$ m)) air pollution contributes to increased risk of cardiovascular disease (CVD) morbidity and mortality, and increased risk to certain types of respiratory cancer. Prospective cohort studies provide robust and consistent evidence that long-term exposure to particulate matter (PM) air pollution, especially fine PM (<2.5 μm in aerodynamic diameter, $PM_{2.5}$), is associated with increased risk of cardiovascular disease (CVD) mortality. A prominent research study covered mortality in 6 big urban areas of the USA. Most of the epidemiological studies were carried out by medical associations of USA and a national research in Canada.[1–6]

However, whether there are specific population subgroups that are most susceptible to the health effects of air pollution exposure in urban areas remains unclear. In the past decade, there has been a dramatic increase in chronic diseases like diabetes, hypertension, and obesity not only in industrialized nations but also in developing nations with emerging economies.[7] Scientific evidence from epidemiological studies suggests that individuals with underlying heart cardiometabolic conditions, including hypertension, diabetes mellitus, and obesity, may be at greater risk of morbidity and mortality after $PM_{2.5}$exposure when compared with those without these conditions. In addition, epidemiological and mechanistic studies support the possibility that $PM_{2.5}$ exposure is involved in the development of cardiometabolic conditions (prevalence of diabetes mellitus in the United States and Canada) and that long-term exposure to even modestly elevated levels of $PM_{2.5}$ may be linked to diabetes mellitus mortality).[8-13]

Studies for long-term exposure to $PM_{2.5}$could also play a joint role with cardiometabolic disorders exacerbating risk of future mortality in association to heart diseases. A study in 2015 recorded data for 669,046 participants from the American Cancer Society, Cancer Prevention Study II cohort were linked to modeled $PM_{2.5}$ concentrations (corresponding to home addresses of participants). Models of

Cox proportional hazards regression were used to estimate adjusted hazards ratios (hr) for death from CVD and cardiometabolic diseases based on death-certificate information. $PM_{2.5}$ exposure was associated with CVD mortality, with the hazards ratios (95% confidence interval) per 10 μg/m^3 increase in $PM_{2.5}$equal to 1.12. Deaths linked to hypertension and diabetes (death certificate as either primary or contributing cause of death) also were associated with exposure to ambient $PM_{2.5}$. Scientists concluded that air pollution-induced CVD mortality risk for those with and without existing cardiometabolic disorders. Long-term exposure may also contribute to the development or exacerbation of cardiometabolic disorders.[14]

Ambient air pollution in urban areas and megacities

Since 1950 the world population has more than doubled (7.4 billions, 2016), and the global number of cars has increased by a factor of 10 (in 2015, it was estimated, around 947 million passenger cars and 335 million commercial vehicles were in operation worldwide). In the last 60 years the prercentage of people living in urban areas has increased 4 times and from the 21st century more 50% of the world population live in big cities and their numbers are increasing dramatically. In 2014 around 28 megacities reached a total of 453 million people and projected to increase by 2030 to 735 million people in 48 megacities. Inevitably, ambient air pollution will increase if new measures do not improve the technology to reduce substantially the primary air pollution sources.[15]

Urban air pollution and the most important pollutans (CO, NOx, SO_2, O_3, airborne particulate matter-PM) is monitored routinely for the last decades in the majority of countries. Stricter regulations, technological improvements in car engines and vehicular exhaust catalysts, filters for industrial installations, have reduced substantially the air concentrations of these pollutants in most capitals and big cities worldwide. Since 1974 World Health Organization (WHO) and United Nations Environment Programme (UNEP) with the “Global Environment Monitoring System”, collaborated on a project to monitor urban air quality worldwide.

Also, concentrations of air pollutants are reported by national environmental organizationsin and in selected countries by the Organization of Economic Co-

operation and Development (OECD). The OECD Report 9/6/2016 estimated that outdoor air pollution could cause 6 to 9 million premature deaths a year by 2060 and cost 1% of global GDP – around $U.S. 2.6 trillion annually – as a result of sick days, medical bills and reduced agricultural output. The economic consequences of air pollution the OECD repot underline witll cause the reduction in global economic output by 2060 of around $U.S. 330 per person. Healthcare costs related to air pollution was U.S. $ 21 billion in 2015 worldwide and the number of work days lost to air pollution-related illness was 1.2 billion worldwide. The biggest rises in mortality rates from air pollution, the report emphasized, are in India, China, Korea and Central Asian (like Uzbekistan), where rising populations and congested cities mean more people are exposed to indutsrial and energy power plant emissions and traffic exhaust. Death rates are seen stabilising in the USA and falling in much of Western Europe thanks in part to efforts to move to cleaner energy production and transport (better technology of internal combustion engines, exhaust catalysts, electric and hybrid cars). [http://www.oecd.org/env/air-pollution-to-cause-6-9-million-premature-deaths-and-cost-1-gdp-by-2060.htm] (accessed Sept 2018).

A comprehensive presentation of urban air pollution in Europe (79 cities in 32 countries) are presented by the European Environment Agency (EEA). Also, The EEA by the European Air Quality Index allows users to understand more about air quality where they live. Displaying up-to-the-minute data for the whole of Europe, users can gain new insights into the air quality of individual countries, regions and cities**.** [https://www.eea.europa.eu/themes/air/air-quality-index/index, last modified May 2018, accessed Sept. 2018]. The EEA Report No 13/2017 "Air quality in Europe, 2017 Report" is an updated analysis of air quality and its impacts, based on official data from more than 2,500 monitoring stations across Europe in 2015 [https://www.eea.europa.eu/publications/air-quality-in-europe-2017].

But all epiodemiologicval and clinical studies in the last 20 years highlighted the damaging role of ambient airborne particulate matter (PM) as an important environmental pollutant for many different cardiopulmonary diseases, oxidative damage to respiratory organs and premature increased morbitity and mortality from lung cancer. Current research on airborne particle-induced health effects investigates the critical characteristics of particulate matter (size and chemical

composition) that determine their toxic biological effects. Several independent groups of investigators have shown that the size of the airborne particles and their surface area determine the potential to elicit inflammatory injury, oxidative damage, and other adverse biological effects. These effects are stronger for fine and ultrafine particles (less than $PM_{2.5}$) because they can penetrate deeper into the airways of the respiratory tract reaching the alveoli in which 50% are retained in the lung parenchyma. Composition of the PM varies greatly and depends on many factors.

The major components of PM are transition metals (Fe, Cu, Cd, Cr, Pb, etc), chemical ions (sulfate, nitrate), organic compound, stable radicals (semiquinones) of carbonaceous material, minerals, reactive gases, and materials of biologic origin. Results from toxicological research have shown that PM have several mechanisms of adverse cellular effects, such as cytotoxicity through oxidative stress mechanisms, oxygen-free radical-generating activity, DNA oxidative damage, mutagenicity, and stimulation of proinflammatory factors.[16,17]

Toxic mechanisms by ambient air pollution particulate matter (PM)

Several independent groups of investigators have shown that the size of the airborne particles, composition and their surface area determine the potential to elicit inflammatory injury, oxidative damage (enzymes, membrane lipids), and other adverse effects. These damaging effects are stronger for fine and ultrafine particles because they can penetrate deeper into the airways of the respiratory tract and can reach the alveoli in which 50% are retained in the lung parenchyma. Composition of the PM varies greatly and depends on many factors. Results from toxicological research have shown that PM have several mechanisms of adverse cellular effects, such as cytotoxicity through oxidative stress mechanisms, oxygen-free radical-generating activity, DNA oxidative damage, oxidative damage to proteins and enzymes, mutagenicity, and stimulation of proinflammatory factors. The smaller the size of PM the higher the toxicity through mechanisms of oxidative stress and inflammation.[18-20]

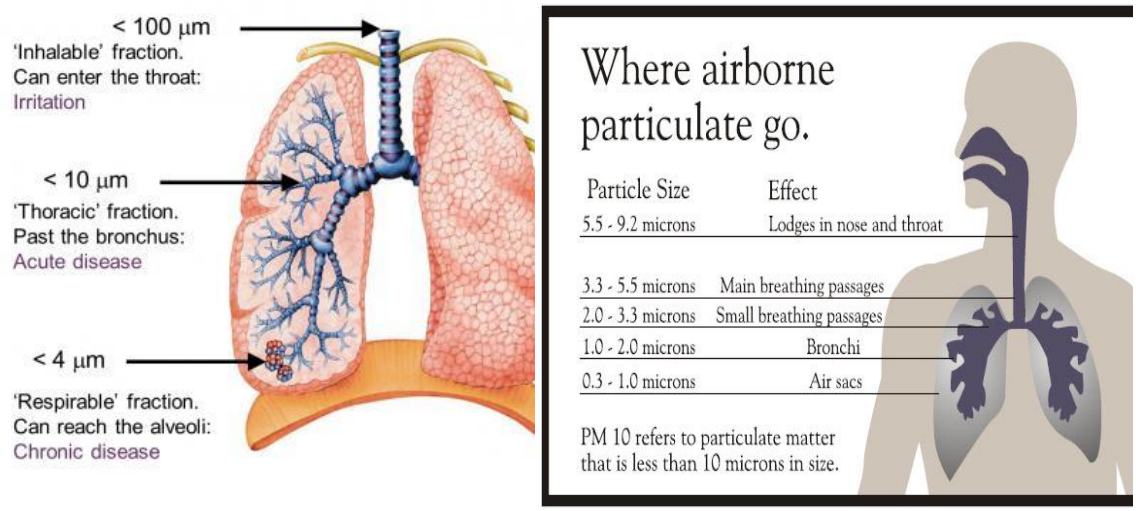

Figure 1. Airborne particulates enter easily and penetrate in the respiratory system where it settle or lodge in small breathing passages. Fine and ultrafine particles penetrate in bronchioles and alveoli because of their small size and are trapped in the parenchyma. PM transitional metals, PAH and stable carbon- centered radicals (semiquinones) increase substantially their toxicity mechanims.

Studies with samples of particulate matter, especially $PM_{2.5}$, exhibited the increased production of free radicals (detected by spin trapping and Electron Paramagnetic Resonance spectrometry, EPR). Semiquinone stable free radicals, that were trapped in the carbonaceous core of the particles, undergo redox cycling and ultimatelly produce reactive hydroxyl radicals ($HO^{\bullet}$) able to damage DNA and enzymes in human cells.[21]

Experimental studies in rats have shown that airborne fine particles sustain more lung injury and pathology due to their large surface area of PM available on smaller-sized particles. Studies showed that as airborne particles get smaller, their surface area for the same mass becomes greater, and hence their capacity to carry toxic substances (transition metals, PAHs) which in turn through redox mechanisms produce increasing free radicalss that cause oxidative lung damage.[22]

The extent of airborne particulate deposition in the respiratory system and especially in the lung tissues (for sizes smalle than 2.5 μm, $PM_{2.5}$) is determined by the inhaled concentration, tissue structure, and the clearing ability of airway mucociliar cilia clearance system. The resulting damage to airway cilia and the reduced ability to perform airway clearance prevent the timely elimination of

$PM_{2.5}$from the airway and lungs. Patients with chronic obstructive pulmonary disease (COPD) have restrictive clearance ability. [23]

During a pollution episode, each lung acinus (acinus refers to any cluster of lung cells that resembles a many-lobed "berry") could receive on average 30-million particles and each alveolus about 1,500 particles (for 24 h exposure) of which 50% are $PM_{2.5}$ being deposited.[24] Lung airways and alveoli retain mostly $PM_{2.5}$ rather than PM_{10}, a finding supported by various observations.[25] Analytical electron microscopy measurements showed that 96% of effectively retained particles in the lung parenchyma were $PM_{2.5}$ and only 5% were ultrafine particles (0.1 μm). The size of PM and their retention play an important role in PM cytotoxic effects.[26]

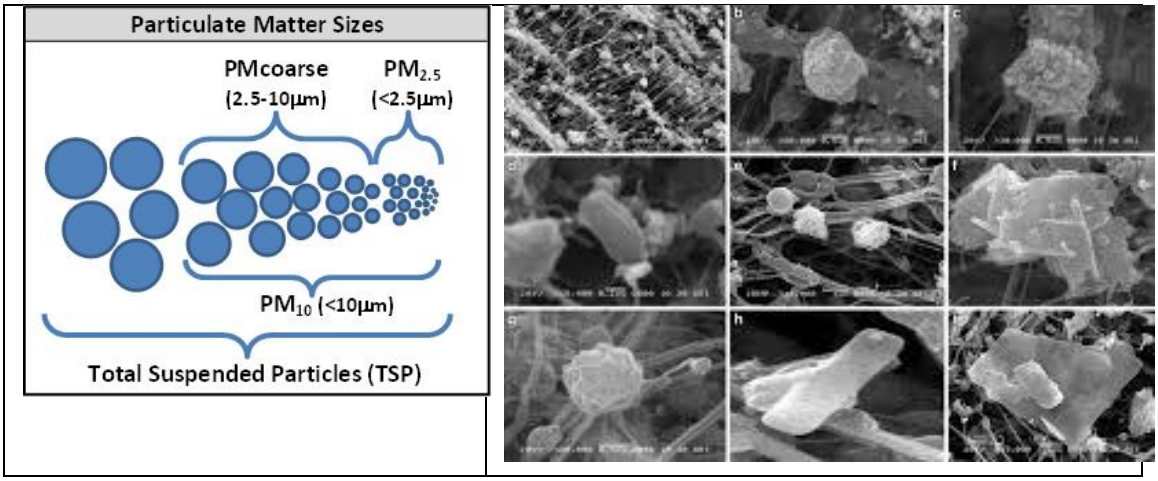

Figure 2. Characterization of $PM_{2.5}$ by X-ray diffraction and scanning electron microscopy-energy dispersive spectrometer (soot particles, halite crystal, gypsum, etc). [Satsangi PG, Yadav S. Characterization of PM2.5 by X-ray diffraction and scanning electron microscopy-energy dispersive spectrometer: its relation with different pollution sources. *Int J Environ Sci Technol* 11:217-232, 2014].

Experiments with animals showed that size and constituents of PM play an important toxicological role. The smaller the size and penetration and metallic constituents for example the greater the extend of oxidative damage (by generation of ROS) to pulmonary cells (membranes, proteins, DNA, RNA, mitochondrial, mtDNA), oxidative stress by depletion of antioxidant resistance, inflammation (from chemoatractive molecules and activated pro-imflammators) and finally pulmonary diseases or mechanisms of carcinogenesis.[27,28]

Experimental human studies with PM exposure show that the production of ROS leads to systemic inflammation. The inflammatory effects appear to be

mediated by the inflammatory cytokines IL-6, TNF-α, and C-reactive protein (CRP). Increases in both IL-6 and CRP have been associated with the development of acute myocardial infarction.[29-31] Also, studies with acute exposure to ambient PM showed that it causes changes in coagulation and platelet activation providing a more proximal link between PM and coronary artery disease (CAD). Results showed that fibrinogen to be an important risk factor for cardiovascular disease. Fibrinogen is a glycoprotein that circulates in the blood. During tissue and vascular injury it is converted enzymatically by thrombin to fibrin and subsequently to a fibrin-based blood clot. Other pro-coagulant factors, such as plasminogen activator fibrinogen inhibitor-1 (PAI-1), were also associated with PM elevations. Intratracheal instillation of diesel exhaust particles led to increased platelet activation in hamsters and rapid thrombosis formation. Also, further animal experiments suggested that small particles translocate into the blood stream and exert prothrombotic effects.[32-35]

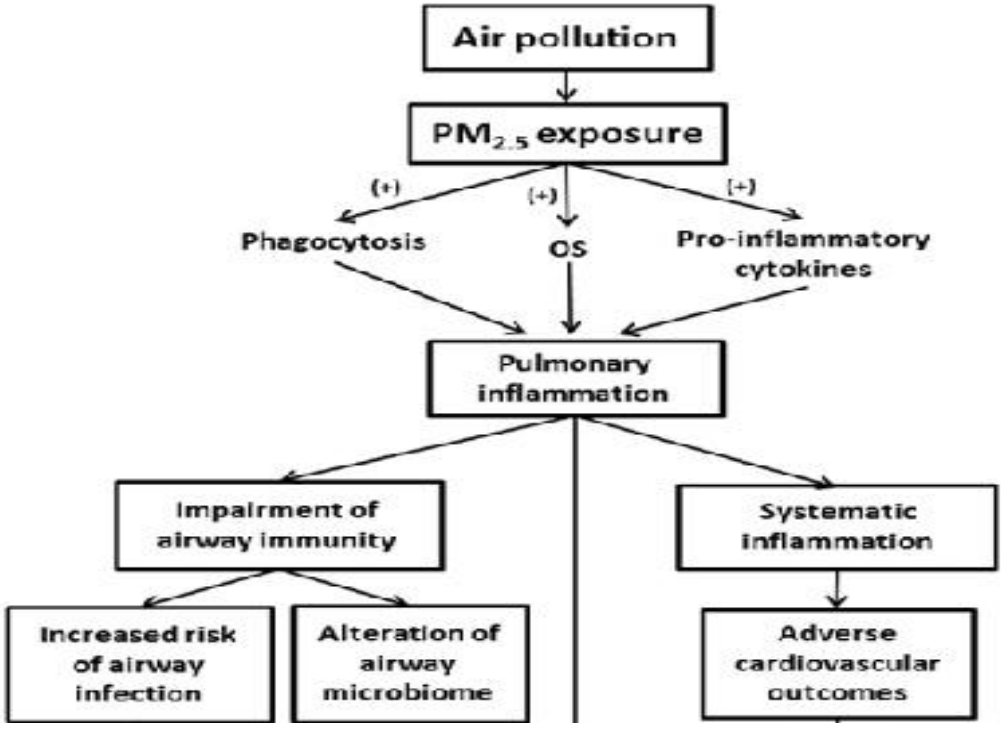

Figure 2. Schematic presentation of exposure to ambient $PM_{2.5}$. Particles increase airway inflammation by releasing pro-inflammatory cytokines (e.g., IL-6, TNF-α and IL-1) and ROS (phagocyotosis). Particles advance the production of chemoattractive and pro-inflammatory mediators and finally, PM generates ROS and proteases from the damaged alveolar epithelial or immune cells [Ni F, Chuang C-C, Zuo L. Fine particulate matter in acute exacerbation of COPD. *Front Physiol* 23.10. 2015. [https://doi.org/10.3389/fphys.2015.00294].

Particulate ambient air pollution and cardiorvascular and cardiorespiratory diseases

Most prospective studies in the last decades on the health effects of PM ambient air pollution exposure have focused on high-income countries (developed industrial countries, USA, Europe, Japan, etc), which have much lower air pollutant concentrations than low-income and middle-income countries (LMICs). A recent review (2017) focused on the cardiorespiratory health effects by PM exposure in LMICs exclusively. The review and meta-analysis was based on systematic searches of relevant studies on PM_{10} and $PM_{2.5}$ (in PubMed, Web of Science, Embase, LILACS, Global Health, and Proquest). The results were presented as excess relative risk per 10 $\mu g/m^3$ increase in PM. Reviewers used a random-effects model to derive overall excess risk. The review identified only 4 long-term exposure studies from China which were not included in the meta-analysis. A short-term 10 $\mu g/m^3$ increase in same-day $PM_{2\cdot5}$ was associated with a 0·47% increase in cardiovascular mortality and a 0·57% increase in respiratory mortality. Whereas a 10 $\mu g/m^3$ PM_{10} increase in same-day was associated with a 0·27% increase in cardiovascular mortality and a 0·56% increase in respiratory mortality.[36]

A research group reviewed studies that investigated the evidence on the association between air pollution and cardiorespiratory diseases (hospital admissions and mortality), including variability by energy, transportation, socioeconomic status, and air quality (PubMed and Web of Science, 2006-2016). They selected 529 for in-depth review, and 70 articles fulfilled the review's criteria. The 70 studies selected for meta-analysis encompass more than 30 million events across 28 countries. Analysis of data found positive associations between cardiorespiratory diseases and different air pollutants, in particular an association between exposure to $PM_{2.5}$ and respiratory diseases.[37]

A group of researchers investigated the relationship between ultrafine particles (<$PM_{2\cdot5}$) and particulate matter (PM) and daily mortality in 8 European urban areas [Finland (Helsinki), Sweden (Stockholm), Denmar (Copenhagen), Germany (Augsburg), and three adjacent cities in the Ruhr Area (Essen, Mülheim, and Oberhausen), Italy (Rome), Spain (Barcelona), Greece (Athens)]. Data were collected

for the period 1999-2013 for nonaccidental and cardiorespiratory mortality, particle number concentrations (as proxy for ultrafine particle number concentration), fine and coarse PM, gases and meteorologic parameterç. Resultys showed that mortality was increasing by approximately 0.35% per 10,000 particles/cm increases in particle number concentration occurring 5 to 7 days before death. A similar pattern was found for cause-specific mortality. Estimates decreased after adjustment for fine particles ($PM_{2.5}$) or nitrogen dioxide (NO_2). The study found weak evidence of an association between daily ultrafine particles and mortality.[38]

An adult population cohort in London was used to investigate associations of ambient air pollution and Cardiovascular Diseases (CVD) and respiratory effects. The study used data from 211,016 adults aged 40-79 years registered in 75 Greater London practices (2005 and 2011). A range of cardiovascular and respiratory outcomes were identified from primary care and hospital records. Annual baseline concentrations for nitrogen oxides (NO_x), particulate matter (PM) with a median aerodynamic diameter <2.5 μm ($PM_{2.5}$) attributable to exhaust and non-exhaust sources, traffic intensity and noise were estimated at 20 m^2 resolution from dispersion models, linked to clinical data via residential postcode. The largest observed associations were between traffic-related air pollution and heart failure (HR=1.10 for 20 $\mu g/m^3$ change in NO_x, 95% CI 1.01 to 1.21). However, no other outcomes were consistently associated with any of the pollution indicators, including noise. According to the research scientists, the associations observed with heart failure may suggest exacerbatory effects rather than underlying chronic disease. [39]

Hypertension and high (systolic, diastolic) blood pressure increase the risk for a variety of CVDs, including stroke, coronary artery disease, heart failure, atrial fibrillation and peripheral vascular disease. Although numerous studies have investigated the association of ambient air pollution with hypertension and blood pressure, the results were inconsistent. A new comprehensive systematic review and meta-analysis of a number of studies was performed (2018). Chinese research databases and 7 international were searched for studies examining the associations of PM [diameter<2.5 μm ($PM_{2.5}$), 2.5-10 μm ($PM_{2.5-10}$) or >10 μm (PM_{10})] and gaseous SO_2, NO_2, NO_x, O_3, CO air pollutants with hypertension or blood pressure. Odds ratios (OR), regression coefficients (β) and their 95% confidence intervals were calculated

to evaluate the strength of the associations. The overall meta-analysis showed significant associations of long-term exposures to $PM_{2.5}$ with hypertension (OR = 1.05), and of PM_{10}, $PM_{2.5}$, and NO_2 with diastolic bood pressure (DBP) (β values: 0.47-0.86 mmHg). In addition, short-term exposures to four (PM_{10}, $PM_{2.5}$, SO_2, NO_2), two ($PM_{2.5}$ and SO_2), and four air pollutants (PM_{10}, $PM_{2.5}$, SO_2, and NO_2), were significantly associated with hypertension. Stratified analyses showed a generally stronger relationship among studies of men, Asians, North Americans, and areas with higher air pollutant levels.[40]

A recent study (2017) investigated the associations of long-term exposure to ambient air pollution (PM_{10}, $PM_{2.5}$ and < $PM_{2.5}$) and cardiovascular effects in large-scale population of Seoul, South Korea. The study evaluated healthy participants (136,094 inhabitans or (X7)= 900,845 person-years) with no previous history of CVDs for 7 years, 2007--2013. Crude and adjusted analyses were performed using Cox regression models to evaluate the risk for CVDs (including cardiovascular mortality, acute myocardial infarction, congestive heart failure, and stroke). The risk of major CV events increased with higher mean concentrations of $PM_{2.5}$ in a linear relationship, with a hazard ratio of 1.36 per 1 $\mu g/m^3$ $PM_{2.5}$. Other pollutants, including ($PM_{2.5-10}$, CO, SO_2, and NO_2, but not O_3) were significantly associated with increased risk of cardiovascular events.[41]

A study in North Carolina, USA, collected data from 5,679 patients who had undergone a cardiac catheterization (2002-2009). Exposure to $PM_{2.5}$ for the year prior to catheterization was estimated using data from air quality monitors. The case status was either a coronary artery disease (CAD) index >23 or a recent myocardial infarction (MI). Logistic regression was used to model odds of having CAD index (the index ranges from 0 to 100 and is a risk indicator of events due to coronary atherosclerosis, higher CAD index corresponds with an increased risk of ischemic events due to atherosclerosis) or an MI with each 1-unit ($\mu g/m^3$) increase in $PM_{2.5}$, adjusting for sex, race, smoking status, socioeconomic status, and urban/rural status. The results of the study found that the elevated odds for CAD>23 and MI were nearly equivalent for all exposure assessment methods. The conclusions of the study are that long-term air pollution exposure (PM) was associated with increased coronary artery disease (CVD).[42]

Racial differences can play a role in CVD risk and PM exposure. A study investigated the associations of PM air pollution with racial differences (black Americans) in CVD risk (2018). The study used data from the HeartSCORE study (Heart Strategies Concentrating on Risk Evaluation) which had 1-year average air pollution measurements for exposure to $PM_{2.5}$ and black carbon (bc) using land use regression models (Cox proportional hazards mode). Data were available on 1,717 participants (66% women; 45% blacks; 59±8 years). The results showed that black Americans had significantly higher exposure to $PM_{2.5}$ compared with white Americans. Exposure to $PM_{2.5}$, but not black carbon, was independently associated with higher blood glucose and worse arterial endothelial function. $PM_{2.5}$ was associated with a higher risk of incident CVD events and all-cause mortality. Black Americans had 1.45 higher risk of combined CVD events and all-cause mortality than whites (models were adjusted for relevant covariates) partly explained by higher exposure to ambient $PM_{2.5}$.[43]

Athens (Greece) encountered for many decades high levels of ambient air pollution (the famous photochemical smog "nefos") and in the last decade measurements showed very high concentrations of PM_{10} and $PM_{2.5}$ in the central urban section of the city due to the car exhausts and central heating. The economic crisis in Greece started in 2008 and continued until now. The financial austerity of this period forced Greeks to reduce purchasing new cars and limited use of private cars, also Greeks used old pieces of wood and biomass (trash) for heating during the winder months.[44,45] The concentration of exhaust soot and PM_{10} probably decreased because of the economic crisis, but $PM_{2.5}$ might have increased. A group of scientists evaluated (2017) the change in mortality risk associated with short-term exposure to PM_{10} in Athens, during 2001-12. Time-series data on the daily concentrations of regulated particles (PM_{10}) and all cause, cardiovascular (CV) and respiratory mortality (RM) were analyzed using overdispersed Poisson regression models (for two periods 2001-2007 and 2008-2012). The results showed that the related mortality risks increased over the analyzed period, the difference before and after 2008 was significant only for total mortality. An interquartile increase in PM_{10} before 2008 was associated with 1.51% increase in deaths among ≥75 years, while after 2008 with a 2.61% increase. The researchers concluded that despite the decline in

PM concentration in Athens during 2001-12, the associated mortality risk has possibly increased, suggesting that the economic crisis initiated in 2008 may have led to changes in the particles' composition due to the ageing of the vehicular fleet and the increase in the use of biomass fuel for heating.[46]

China's has one the fastest rate of economic development in the last 20 years. The rate of economic growth affected the development of big cities, more cars, and influenced substantially the air pollution levels. Fine particulate matter ($PM_{2.5}$) monitoring started in 2013 in China's urban areas. A recent study (2018) einvestigated the association between $PM_{2.5}$ and cardiovascular disease (CVD), ischemic heart disease (IHD) and cerebral vascular disease (EVD) mortality in areas with light air pollution. The study collected data on resident mortality, levels of air pollution and meteorology in Shenzhen province during 2013-2015. Six pollutants were measured at seven air quality monitoring sites, including $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3. The $PM_{2.5}$ daily average concentration was 35.0 ± 21.9 μg/m³; the daily average concentration range was from 7.1 μg/m³ to 137.1 μg/m³. The study found association of $PM_{2.5}$ concentration with CVD, IHD and EVD mortality of the population Shenzhen. The excess risk (ER) of CVD mortality were 1.50%, the excessive risk of IHD mortality were 2.87%, and the excessive risk of EVD mortality. The research group concluded that $PM_{2.5}$ increased CVD mortality.[47]

India is another of the fastest developing countries in the world, but it is still a developing country, even after more than 60 years of independence. New Delhi, the capital, increased substantially and its population is at present 22 million. The World Health Organization (WHO) ranked New Delhi as the world's worst polluted city in 2014. A study (2018) investigated the association of short-term impact of poor air quality on cardiovascular and respiratory morbidity rate in Delhi. The data of the study were collected on monthly count of patients visiting hospitals due to respiratory and cardiovascular illnesses. Daily air pollution data were analysed from airquality monitoring stations of Central Pollution Control Board (CPCB), across Delhi for the period 2008 to 2012. A semi-parametric Quasi-Poisson regression model was used to examine the association of high pollution episodes with relative risk of hospital visit and hospital admission due to respiratory and CVDs. The results confirmed the substantial adverse health effects due to air pollution across criterion

air pollutants (including PM). The study reported the short-term effects of air pollution on morbidity (from CVDs and respiratory diseases) from a time-series study for the first time in India.[48]

A most recent review (2018) summarised the main scientific evidence, experimental clinical and epidemiological studies, for the role of ambient air pollutants (with emphasis on PM, coarse, fine and superfine particles) as important risk factors for cardiovascular diseases. The review presented the mecfhanisms involved in the processs linking PM air pollutants and the step by step development of CVDs.[49]

Ambient particulate air pollution and cancer risk of the respiratory system

Various epidemiological studies in the past 20 years investigated the association of PM ambient air pollution and increased risk for lung cancer mortal;ity. Most results from cohort studies of ambient particulate matter (PM) air pollution and lung cancer incidence or mortality in general populations showed associations that were statistically significant or of borderline significance.[50-57] There were also epidemiological studies that did not report association of increased risk for lung cancer after air pollution exposure to PM. [58,59]

Studies on the subject of ambient PM and lung cancer continued in the last 5 years. A study (2013) investigated the association between long-term exposure to ambient air pollution (especially PM) and lung cancer incidence in 17 European populations. The data of this study were obtained by the European Study of Cohorts for Air Pollution Effects (17 cohort based in 9 European countries). Ambient air pollution was for PM with diameter of less than 10 µm (PM_{10}), less than 2·5 µm ($PM_{2·5}$), and between 2·5 and 10 µm (PMcoarse), soot ($PM_{2·5\ absorbance}$), NOx and two traffic indicators. The research group used Cox regression models with adjustment for potential confounders for cohort-specific analyses and randomeff ects models for meta-analyses. The results for 312,944 cohort members contributed 4,013,131 person-years at risk (following for mean 12.8 years). During this study 2,095 incident lung cancer cases were diagnosed. Meta-analysis showed statistically significant association between risk for lung cancer and PM_{10} (hazard ratio [HR] 1.22 per 10

µg/m³. For $PM_{2·5}$ the HR was 1.18 per 5 µg/m³. The same increments of PM_{10} and $PM_{2·5}$ were associated with HRs for adenocarcinomas of the lung of 1.51 and 1.55, respectively. An increase in road traffic of 4,000 vehicle-km per day within 100 m of the residence was associated with an HR for lung cancer of 1.09. The results showed no association between lung cancer and nitrogen oxides (NOx) concentration.[60]

The association of $PM_{2.5}$ air pollution with lung cancer was established by a small number of epidemiological prospective studies. Researchers must take into account a serious confounding factor, active and passive tobacco smoking, which has been established as the most important risk factor (more than 80%) for lung cancer.

A prospective cohort study (2016) of the Canadian National Breast Screening (CNBS) collected data for 89,234 women (enrolled 1980-1985). The incident of lung cancers in the cohort was linked to the Canadian Cancer Registry and $PM_{2.5}$ concentrations were estimated using satellite data. Cox proportional hazards models were used to characterize associations and hazard ratios (HRs). Results were adjusted for several individual-level characteristics, including smoking (a serious factor for lung cancer). In total, 932 participants developed lung cancer. In fully adjusted models, a 10 $\mu g.m^{-3}$ increase in $PM_{2.5}$ was associated with an elevated risk of lung cancer (HR: 1.34; 95% CI = 1.10, 1.65). The strongest associations were observed with small cell carcinoma (HR: 1.53) and adenocarcinoma (HR: 1.44). Stratified analyses suggested increased $PM_{2·5}$ risks were limited to those who smoked cigarettes. The findings of the Canadian research were consistent with other previous epidemiological investigations of long-term exposure to $PM_{2.5}$ and increased risk for lung cancer.[61]

Another recent epidemiological study (2018) used health data from around 1.9 million people from Saxony (Germany) who were free of cancer in 2008 and 2009. Incident cancer cases (for the period 2010-2014) of mouth and throat, skin (non-melanoma skin cancer- NMSC), prostate, breast, and colorectum were collected. Air pollution exposures included PM_{10} and nitrogen dioxide ($N0_2$). Associations between air pollutants, green space, and cancer incidence were assessed by multilevel Poisson models (results adjusted for potential cofounders, age, sex, smoking, etc). 3,107 people developed mouth and throat cancer, 33,178 NMSC, 9,611 prostate cancer, etc, during the follow-up period 2010-2014. An

increase in PM_{10} of 10 μg/m^3 was associated with a 53% increase in relative risk (RR) of mouth and throat cancer and a 52% increase in RR of NMSC. Prostate and breast cancer were modestly associated with PM_{10} with an increase in RR of 23% and 19%, respectively. Colorectal cancer was not affected by any of the exposures. Researchers concluded that this study was able to provide evidence that higher ambient PM air pollution levels increase the risk of mouth and throat cancer as well as of NMSC. People living in higher residential green spaces showed a protective effect for skin cancer (NMSC) compared to people living in areas with low to moderate UV intensity (which is the main risk factor for skin cancer). [62]

Poland has some of the worst air pollution measurements in Europe according to a World Health Organization (WHO). The situation is worst in southern Poland, where towns in winter months frequently encounter high levels of particulate matter $PM_{2.5}$ and PM_{10}. The main culprit is the coal used to residential heat of people's houses and indurtial installations. Also, these areas have high vehicular exhaust pollution. A recent study in Poland (2018) investigated the health risk of exposure to airborne metals and benzo(a)pyrene (a well known carcinogen and mutagen in soot particulates) during episodes of high ambient PM_{10} concentrations. Scientists gathered data from 2002 to 2014 concerning the ambient concentrations of PM_{10} and PM_{10}-bound carcinogenic benzo(a)pyrene [B(a)P] and carcinogenic metals As, Cd, Pb, and Ni. With the use of the criterion of the exceedance in the daily PM_{10} mass concentration on at least 50% of all the analyzed stations, the PM_{10} maxima's were selected. During a 12-year period, 348 large-scale smog episodes occurred in Poland (307 in the winter season) with high concentrations of PM_{10}. During these events, a significant increase in the overall health risk was also observed. The highest probability of lung cancer occurrences was found in cities, and the smallest probability was found in the remaining areas outside the cities. Scientists concluded that the link between PM pollution and respiratory cancer risk in Poland is a serious public health threat.[63]

Particulate air pollution and risk to neurodegenerative diseases

In the last decade a growing body of epidemiological and clinical evidence has been published that link short- and long-term exposure to air pollutants with

adverse effects on neurodegenerative diseases. In particular, PM_{10} and $PM_{2.5}$ exposure has been linked to brain pathologies associated with Parkinson's and Alzheimer's disease.[64,65]

Studies implicated ambient particulate air pollution as a chronic source of neuroinflammation and reactive oxygen species (ROS) that produce neuropathology and central nervous system (CNS) diseases. Clinical evidence exists that increased risk for stroke incidence, Alzheimer's and Parkinson's diseases are linked to air pollution. While mechanisms driving air pollution-induced Centra Nevrous System (CNS) pathology are poorly understood, new evidence suggests that microglial activation and changes in the blood–brain barrier are key components.[66]

Also, scientific evidence has emerged that exposure to PM air pollution is associated with impaired cognitive functions at all ages and increased risk of Alzheimer's Disease (AD) and other dementias in later life; this association is particularly notable with traffic related pollutants (PM, NOx, etc). The exact mechanisms by which PM air pollutants mediate neurotoxicity in the CNS and lead to cognitive decline remain largely unknown. Studies using animal and cell culture models indicate that amyloid-beta processing, anti-oxidant defense, and inflammation are altered following the exposure to polluted air. A recent review (2018) summarized scientific research pubications supporting exposure to air pollution as a risk for cognitive decline at all ages and AD at later lifetime. [67]

Most investigations for the association of neurodegeneration and PM are supported by brain neuroinflammation. Neuroinflammation is connected with elevation of cytokines and reactive oxygen species (ROS) in the brain mediated by the known toxic effects of urban air pollution (PM and NOx, O_3 as oxidants and free radical promoters) on the central nervous system (CNS). Human and animal research documents that neuroinflammation occurs in response to several inhaled pollutants. Microglia are a prominent source of cytokines and ROS in the brain, implicated in the progressive neuron damage. The MAC1-NOX2 pathway (Macrophage antigen complex-1, Mac-1) has been identified as a mechanism through which microglia respond to different forms of air pollution, suggesting a potential common deleterious pathway. Multiple direct and indirect pathways in response to air pollution exposure likely interact in concert to exert CNS effects.[68]

A number of epidemiological (prospective) studies from various countries in recent years provided evidence for the association of neurotoxicity of the brain strucutre and impaired cognitive function with ambient particulate air pollution.[69-72]

A study in Denmark (2016) investigated the long-term exposure to traffic-related air pollution (particularly PM) and Parkinson's disease. In a case-control study of 1,696 Parkinson's disease (PM and NO_2) patients identified from Danish hospital registries and diagnosed for the period 1996-2009 and 1,800 population controls.
The study estimated the Odds Ratios (ORs) with logistic regression, adjusting for matching factors and potential confounders. The results found ambient air pollution from traffic sources to be associated with risk of PD, with a 9% higher risk. For participants living for ≥ 20 years in the capital city, ORs were larger (OR = 1.21; 95% CI: 1.11, 1.31) than in provincial towns (OR = 1.10; 95% CI: 0.97, 1.26), whereas there was no association among rural residents.[73]

A recent study (2017, population-based cohort study) investigated the influence of roads/traffic air pollution (PM, NOx, O_3, etc) on elevated risk for several neurodegenerative diseases. The results showed that dementia showed a significant relationship of patients living near a highly traveled roadway and exposure to traffic related air pollutants.[74]

Exposure to particular matter ($PM_{2.5}$) and increased risk to mortality

This section presents studies of the last years on the association between $PM_{2.5}$ and increased risk form premature mortality in various countries. The PM exposures can be from outdoor and indoor air pollution sources. The outdoor air pollution PM is mostly from transport vehicles, whereas indoor PM air pollution is mostly from solid fuels (heating and cooking) in unventilated kitchens, chimney smoke and passive smoking.

A paper (2018) in the prestigious *Proceeding of the National Academy of Science* journal (USA) published the results of a qualtitative estimate of increased risk for global mortality (41 cohorts from 16 countries) that was based on disease-specific hazard ratio models that incorporate risk information from multiple $PM_{2.5}$ sources. An experts group modeled the shape of the association between $PM_{2.5}$ and

nonaccidental mortality using data from 41 cohorts from 16 countries—the Global Exposure Mortality Model (GEMM). The GEMM predicted 8.9 million deaths in 2015, a figure 30% larger than that predicted by the sum of deaths among the five specific causes and 120% larger than the risk function used in the GBD (Global Burden of Disesase). According to the group these results suggest that $PM_{2.5}$ exposure may be related to additional causes of death than the 5 considered by the GBD and that incorporation of risk information from other, non-outdoor, particle sources leads to underestimation of disease burden, especially at higher concentrations.[75]

Another study from Chinese scientists (2018) assessed the associations and temporal relationships between ambient PM air pollution and daily mortality (short-term) in Guangzhou, China (during 11 year period, 2006-2016). The study correlated concentrations of $PM_{2.5}$, $PM_{10-2.5}$ and PM smaller that <10 μm (PM_{10}) to daily mortality in Guangzhou (China). Scientists applied overdispersed Poisson regression with adjustment for time trend and potential confounding factors. The study observed for 10 $\mu g/m^3$ increases (mean) at current day and 6 prior days of death (lag06) increases in total mortality risks of 0.55% for $PM_{2.5}$, 0.99% for $PM_{10-2.5}$, and 0.44% for PM_{10}. Stronger associations for PM were observed on cardio-respiratory mortality and people at age ≥ 65 years. The scientific group concluded that despite the decreased air pollution levels in Guangzhou in recent years, the short-term risk for CVDs remained significan from exposure to $PM_{2.5}$ and PM_{10}.[76]

In South and Southeast Asia countries (India, Bangladesh, East Pakistan, Indochina, Thailand, etc) air pollution has increased substantially in the last decades. Ambient fine and supefine PM in metropolitan areas (<$PM_{2.5}$) of big cities have reached high concentrations with substantial increases of premature mortality attributable to PM. A study (2018) investigated the long-term trends and spatial characteristics of $PM_{2.5}$ (in the period 1999-2014) and associated premature deaths were analyzed using trend analyses and standard deviation ellipses. Results showed that the numbers of premature deaths increased from 1,179,400 in 1999 to 1,724,900 in 2014, with a growth rate of 38% and net increase of 545,500. Stroke and ischemic heart disease were the two principal contributors, accounting for 39% and 35% of the total, respectively. High values were concentrated in North India, Bangladesh, East Pakistan, and some metropolitan areas of Southeast Asia.[77]

A recent (2018) meta-analysis collected 53 studies and invesatigated the all-cause and cause-specific mortality associated with long-term exposure to $PM_{2.5}$. The research group searched all published cohort studies for the association between long term exposure to $PM_{2.5}$ and increasd risk mortality (multivariate linear random effects meta-analysis). The 53 studies examined provided 135 estimates of the quantitative association between the risk of mortality and exposure to $PM_{2.5}$ (39 studies from USA-Canada, 8 from Europe, and 6 from Asia). This meta-analysis provides strong evidence for the adverse effect of $PM_{2.5}$ on mortality. Significant adverse effects were recorded for exposures even below 10 $\mu g/m^3$.[78]

From all these epidemiolgical results of the last 20 years there was a question among scientists, an uncertainty, whether the air temperature modified the mortality effects of ambient PM air pollution and vice versa. So, a recent study investigated whether the short-term associations of particle concentration ($PM_{2.5}$ and PM_{10}), and O_3 (ozone) with daily total natural and cardiovascular mortality were modified by air temperature in 8 European urban areas (for the period 1999-2013). Pooled associations between PM air pollutants and total mortality, and CV mortality were overall positive. Also, results showed that mortality was generally stronger on days with high temperatures, relatively compared on days with low air temperatures. Scientists concluded that high daily temperatures could modify the effects of air pollution on daily mortality and high air pollution might enhance the air temperature effects.[79]

In connection with the previous study, a group of scientists investigated the potential synergy between PM and ozone air pollution and temperature on mortality in 9 European cities (for the period 2004 to 2010). They used daily series of apparent temperature, measurements of PM_{10}, ozone (O_3), and nitrogen dioxide (NO_2) and the association with, non-accidental, cardiovascular mortality and respiratory deaths. In the warm season, the % increase in all deaths from natural causes per °C increase in apparent temperature tended to be greater during high ozone days, although this was only significant for all ages when all causes were considered. Results showed that interaction with PM_{10} was significant for CVD causes of death for all ages. For days with heat waves, no consistent pattern of interaction was observed. For the cold period, no evidence for synergy was found. Researchers concluded that some

evidence of interactive effects between hot temperature and the levels of ozone and PM_{10} was found, but no consistent synergy could be identified during the cold season.[80]

Although all studies indicate inreased risk from fine and supefine PM, ambient coarse PM particles (PMc), with diameters more than 10 μm, are also a risk factor for increased mortality at short-term exposures. A recent study in 3 cities in China (Pearl River Delta, 2013-2016) found a significant association between PM_c and mortality. Each 10μg/m^3 increase of a current day's PM_c was associated with a 1.37% increase in total mortality, a 1.63% increase in cardiovascular mortality, and a 0.97% in respiratory mortality in 3 Chinese cities.[81]

Conclusion

Long-term and short-term exposure to ambient air pollution particulate matter (PM) has beeen associated to a variety of adverse health effects. Numerous epidemiological and clinical studies linked exposure to fine and superfine PM levels to increased hospital admissions, increased risk for cardiovascular diseases, certain types of cancer and neurodegenerative diseases. The size and composition of particles are very important factors for the toxicological damage in the respiratory system. The particulates PM_{10}, $PM_{2.5}$ and $<PM_{2.5}$ have the potential to penetrate deep into the lungs, generate ROS, increase oxidative stress, initiate inflammatory damage and chemoactive cellular compounds which are directly linked to adverse cardiovascular and lung diseases. This review focused on the most important toxicological mechanisms of PM in the tissues of the respiratory system and the cardiovascular environment. Also, numerous studies contacted in the last 5 years explored the assocation of elevated levels of fine PM with increased risk of premature death, reduced life expectancy, increased risk of cardiovascular disease, and stroke, as well as certain types of cancer (breast, lung) and neurodegenerative diseases of old age. Ambient PM air pollution is now fully acknowledged to be a significant public health problem, responsible for a growing range of adverse health effects in humans. At present air pollution is the main environmental cause of premature death. According to the World Health Organization (WHO), the combined effects of ambient (outdoor) and household air pollution cause about 7 million

premature deaths every year, largely as a result of increasedmortality from stroke, heart disease, chronic obstructive pulmonary disease, lung cancer and acute respiratory infections.[82]

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