

INHALED AMBIENT PARTICULATE MATTER AND LUNG HEALTH BURDEN

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ABSTRACT

Increased ambient particulate matter (PM) has been associated with various cardio-respiratory disorders and emergency room visits due to short-term and long-term exposures. However, most of the efforts correlating PM exposure with human health hazards have primarily focused on cardiovascular impairments, although the lung acts as the primary port of entry, and is therefore also the primary target organ. Emerging evidences have shown an association between increased PM and respiratory illness, particularly chronic lung diseases. PM₁₀, PM_{2.5}, ultrafine particles, or nanoparticles (NPs) are of interest in this regard. Particle surface area increases with decreasing size and surface related parameters such as oxidative potency, solubility, and bioavailability, and are widely regarded as the parameters determining particle toxicity. Factory utility smoke stacks, vehicle exhaust, wood, and biomass burning act as the primary sources for ambient PM, coupled with composition variability. Revolution of nanotechnology during the last decade brought forward concerns about NPs as a potential new health hazard as well. Epidemiological, clinical, and experimental studies suggest oxidative stress, inflammation, impaired inflammation resolution, and altered coagulation cascade homeostasis as the causative mechanisms of both pulmonary and cardiovascular impairments due to PM exposure. Children, the elderly, and individuals with pre-existing conditions are found to be the most vulnerable subjects. Respiratory symptoms of increased PM exposure include increased infection, pneumonia, chronic bronchitis, emphysema, exacerbation of asthma and chronic obstructive pulmonary disease, declined forced expiratory volume in 1 second, and forced vital capacity, apart from the classically known phenomenon of asbestosis, silicosis, mesothelioma, lung cancer, and pneumoconiosis.

Keywords: Particulate matter, particle pollution, chronic lung disease, lung function, pulmonary inflammation.

INTRODUCTION

Particulate matter (PM) is a generic term representing the major portion of air pollution, which is made up of coarse but also extremely small particles, so called nanoparticles (NPs) - liquid droplets containing acids, organic chemicals, metals, and soil or dust.¹ Particles are present everywhere, but high concentrations, chronic exposure, and/or specific types of particles have been found to present serious human health hazards. Accidental inhalation of particles in the

workplace or environmental exposure where the lung serves as the primary port of entry as well as the primary target, thereby causing chronic lung diseases, is the focus of this review. However, PM-mediated cardiovascular (CV) effects are by far most widely investigated. Quartz or crystalline silica, asbestos, and coal are the three major particle types classically considered to be responsible for the vast majority of occupational and particle-induced lung diseases.²⁻⁴ Silicosis is caused primarily through silica exposure, particularly among miners. Asbestos exposure is causative for asbestosis,

lung cancer, pleural fibrosis, pleural plaques, and mesothelioma.⁵ Exposure to coal mine dust causes a form of pneumoconiosis along with emphysema. Towards the end of the 20th century, toxicological studies on environmental particles (PM₁₀) gained momentum after the rulings of various regulatory authorities affirming the lung disease relationship following silica, asbestos, and coal dust exposures.⁶ Subsequently, researchers also demonstrated an association between small variations in air pollution concentration and health effects such as heart attacks and exacerbations of asthma.

Ambient PM is a complex mixture of dust, ashes, and volatile and gaseous compounds, which come from diverse sources (factory/utility smokestacks, vehicle exhaust, wood burning).⁷ However, the composition of ambient PM also varies temporally depending on the seasonal condition, traffic density, and localised industrial and human activity. Air pollutants or ambient PM are respiratory irritants and increase susceptibility to acute respiratory infections and chronic lung diseases, particularly among compromised individuals.⁸ The effects of ambient PM on human health is a major concern as particles <10 µm (PM¹⁰) and <2.5 µm (PM^{2.5}) in aerodynamic diameter gain access to the deep lung. The US Environmental Protection Agency¹ listed the links between particle pollution exposure and a variety of health problems, including: premature death in people with heart or lung disease, nonfatal heart attacks, irregular heartbeat, aggravated asthma, decreased lung function, and increased respiratory symptoms, such as irritation of the airways, coughing, or difficulty breathing. People with pre-existing heart or lung diseases, children, and elderly individuals are the most vulnerable subjects for particle pollution exposure-related health risks. Healthy individuals may also experience temporary symptoms from exposure to elevated levels of particle pollution. Ultrafine particles (UFPs; <0.1 µm), also referred to as NPs following nano-technological revolution, contribute very little to the overall PM mass but more to PM number concentrations. UFPs have emerged as an important modern day air pollution hazard, mainly by virtue of their property to evade the effective mechanisms of mucociliary and alveolar clearance of the lung, compared to larger particles. Through our current understanding, PM exposure contributes to respiratory morbidity and mortality primarily through oxidative stress and inflammation which, in turn, may even result in anatomical and physiological remodelling of the lung. The localised particle-triggered reactions in

the lung have been shown to contribute to systemic effects particularly by disturbing the homeostasis of the blood coagulation cascade, thereby causing atherogenic reactions and cardiac impairments. The current knowledge on ambient PM-mediated lung health burden is primarily based on epidemiological, clinical, and experimental findings. In this review we addressed the topic broadly based on these three lines of evidence with emphasis on lung health burden.

EPIDEMIOLOGICAL EVIDENCE

The relationship between increased levels of air pollution and mortality/morbidity rates due to cardiopulmonary diseases is now well-established. To date, most of the effort in PM toxicology/PM-mediated health risk has focused on the CV system,^{9,10} although many studies evaluated the association between PM exposure and respiratory illness.^{11,12} Most of these studies reported that the emergency hospital admission in association with increasing ambient PM is mainly because of pneumonia, asthma, chronic inflammation, and chronic obstructive pulmonary disease (COPD). Exposure to PM shows a strong association with adverse respiratory health effects even when adjusted for other major risk factors such as cigarette smoking. Acute exacerbations of COPD (AECOPD), chronic bronchitis (CB), or emphysema have been associated with short-term exposure to air pollution. It has been reported that high levels of ambient particles are related to increased prevalence of CB, whereas recent studies predominantly related respiratory symptoms to the long-term effects of ambient particles. Several cross-sectional studies associated exposure to ambient urban traffic-related PM with declined forced expiratory volume in 1 second (FEV1) and onset of COPD. Schikowski and colleagues,¹³ using the Global Initiative for Chronic Obstructive Lung Disease criteria, showed, in a cross-sectional study among women, that an increase of 7 µg/m³ ambient PM (over 5 years) was associated with a 5.1% decline in FEV1 with an odds ratio of 1.33 for the development of COPD. Furthermore, they also associated that inhabiting <100 m away from busy traffic areas had significant detrimental effects on lung function. These findings suggest that both long-term exposure to ambient PM and habitation close to busy traffic may increase the risk of COPD progression and also accelerate a loss of lung function. Increased concentration of PM has been shown to be directly correlated to an increased mortality among individuals with

pre-existing COPD. Lee et al.¹⁴ have shown that asthmatics living in areas of high PM in London had significantly higher reductions in FEV1, forced vital capacity (FVC), and increased inflammatory response. A series of studies have reported that elderly patients or patients with pre-existing complications (viz. COPD) exhibit an accelerated decrease in lung function with an increase in PM_{2.5} concentration.^{15,16}

Gauderman et al.¹⁷ performed an explorative study on PM mediated respiratory risk over 1,759 children and found a strong association between reduced annual growth of FEV1 in children over the age of 8 and exposure to elemental carbon, nitrogen dioxide, and acid vapours. Islam et al.¹⁸ reported that sudden exposure to a highly polluted area (PM₁₀ and PM_{2.5}) can result in new onset of asthma, even in children with better lung function. Goss et al.¹⁹ demonstrated that predisposed children with lower lung function developed cystic fibrosis following exposure to higher levels of PM₁₀ and PM_{2.5}. Through the course of the children's respiratory health study, Grigg et al.²⁰ reported that chronic exposure to indoor PM following biomass burning (200 mg/m³) can lead to COPD, impaired lung function, and induce lung infection. There is mounting evidence suggesting that PM exposure leads to pulmonary inflammation and oxidative stress. Lung inflammation and redox imbalance plays a pivotal role in the development of chronic lung diseases such as asthma and COPD. Measurement of oxygen saturation in arterial blood was shown to be an important parameter to assess the respiratory risk or air pollution induced pulmonary burden. Decrease in oxygen saturation in arterial blood in association with PM₁₀ exposure at Utah valley was first reported by Pope et al.²¹ Similar findings have been also reported by DeMeo et al.²² through a study on 28 elderly Boston residents.

A series of studies on European, Asian, and Oceania cities have demonstrated a consistent and significant association between PM concentrations and emergency room visits for respiratory diseases such as chronic pulmonary inflammation.²³⁻²⁵ Accumulated evidence suggests that these PM induced chronic pulmonary inflammations may lead to further lung diseases - such as asthma, pneumonia, and COPD - and the effects are more pronounced among elderly patients, even following short exposures.²⁶ Recently, Hoek et al.²⁷ estimated the PM_{2.5} mediated respiratory mortality in a Dutch, Norwegian, and Chinese cohort study. The Norwegian study by Naess et al.²⁸ has demonstrated

an approximate 17% increase of respiratory mortality due to acute COPD for every quartile increase in PM_{2.5}. Similar results for increased respiratory mortality have been found in Asian cities where researchers have demonstrated excess respiratory mortality risk for increases in PM₁₀.²⁹ A cross-sectional study in India reported a significant negative linear relationship between higher concentrations of PM₁₀ with reduced FEV1 and increased concentration of PM_{2.5} with reduced peak expiratory flow rate and FEV1.³⁰ A 2.5% increase in COPD admissions for every 10 µg/m³ increase of PM₁₀ was observed with a lag of up to 0-5 days in an American study involving 10 cities and >1.84 million individuals >65 years of age.³¹ In another study, every 10 µg/m³ increase of PM_{2.5} was associated with 0.9% increased COPD hospitalisation with a lag of 0-1 day.³² In a European study involving six cities, the relative risk (95% CI) for 50 µg/m³ increase in the daily mean level of total suspended PM for AECOPD admissions was 1.02 with a lag of 1-3 days.³³ All these epidemiological studies demonstrated that the observed respiratory mortality is primarily due to the fraction of traffic-related pollutants.

Only very few studies have linked genes and respective polymorphisms to PM toxicity. Curjuric et al.³⁴ associated single nucleotide polymorphisms located in *SNCA*, *CRISP2*, and *PARK2* to declined FEV1/FVC and FEV1 following PM₁₀ exposures in the Swiss Study on Air Pollution and Lung and Heart Diseases in Adults. However, more epidemiological studies are warranted, especially those including particle quality, which are related to workplace and NP exposure to evaluate the long-term effect of PM and lung burden.

EXPERIMENTAL EVIDENCE

Epidemiological studies have established the close association between ambient PM exposures to respiratory diseases such as asthma, COPD, lung cancer, and declined lung function, apart from CV diseases. To substantiate the epidemiological associations and detect the plausible pathomechanisms causative of respiratory illness, researchers performed controlled human studies, animal exposures, and *in vitro* experiments. Particle exposure experiments mainly addressed two aspects: 1) oxidative stress and proinflammatory response; and 2) particle characteristics related to toxicity. Another phenomenon termed as translocation - where particles enter the deep lung, cross the alveolar-blood barrier to enter

systemic circulation, and thereby reach secondary target organs (heart, liver, kidney, and brain) - is an important aspect of particle toxicology and particularly relevant for sub 100 nm sized NPs. Even if particle translocation has been described only for NPs, its efficacy is considered to be low and far less than 1% of the pulmonary deposited dose, which may actually translocate to extra-pulmonary organs. In this context, long-term exposure and accumulation have to be considered.³⁵

Oxidative Stress Paradigm

Oxidative stress, leading to activation of pro-inflammatory reaction, is the most reported pulmonary effect of inhaled ambient PM. In this context, Li et al.³⁶ described the use of a stratified oxidative stress model to study the biological effects of ambient PM. This hierarchical and tier-based model suggests that the level of particle cell-interaction derived oxidative stress and the ability of the cell and tissue to cope with that stress, finally determines whether, upon PM inhalation, only anti-oxidant (tier 1), or pro-inflammatory (tier 2), or even cytotoxic responses (tier 3) are caused. Tao et al.³⁷ reported that activation of alveolar macrophages by particles leads to a release of proinflammatory/inflammatory cytokines and a production of reactive oxygen species. Particle charge, presence of transition metals, organic components, size, and surface area are considered to be defining properties for particle toxicity.³⁸ In ambient air, fine and UFPs are predominantly based on the number concentration among all particles, and represent the highest surface area per mass. Studies from Brown et al.,³⁹ Tran et al.,⁴⁰ and Renwick et al.⁴¹ established the idea of particle surface area instead of mass as the optimal dose metric for predicting the acute inflammatory response in the lungs (reviewed by Oberdörster et al.³⁸).

Later, Stoeger et al.⁴² investigated the acute adverse effects of six similar types of carbonaceous UFPs quantitatively following intratracheal (i.t.) instillation in healthy mice. The authors also concluded that the surface area measurement developed by Brunauer, Emmett, and Teller (BET) is a valuable reference unit for assessing the toxic effects of carbonaceous UFPs. BET surface area exhibited the most obvious dose-response relationship to the inflammatory effect in this study. From this result, the authors suggested particle surface area to be the most important parameter for evaluating the detrimental health effects caused by inhaled UFPs. Stoeger et al.⁴³ further established an *in vitro*, cell-free

ascorbate test for measuring oxidative potency (OX_{pot}) of particles using different types of combustion-derived NPs. For ambient particulate air pollution, however, it needs to be taken into account that the different size fractions also differ significantly in their composition and that these particles are not necessarily as non-soluble as carbonaceous model particles. Urban UFP samples, which mainly originate from combustion processes, consist of not only carbon but also metal oxides such as zinc and iron, as well as biological components, such as endotoxin. Investigation on the inflammatory potency of ambient PM samples therefore often reflects the amount of contained endotoxin,⁴⁴ and the presence of particular metal oxides (such as ZnO) may also contribute to their cytotoxicity.⁴⁵

Impact of Particle Size

Particle size is another important parameter driving the spatial deposition pattern within the respiratory system.⁴⁶ Fine and ultrafine inhaled PM deposits most effectively in the alveolar region of the lungs (~50% deposition efficiency for 3 μ m and 20 nm particles). Alveolar macrophage mediated clearance is described to work most effectively for microparticles compared to NPs. This explains why chronic exposures to high concentrations of NPs have been shown to cause the so called 'overload conditions', with impaired particle clearance and accumulation finally leading to chronic inflammation and even tumour development in rats.⁴⁷ These conditions occur as the cumulative deposited particle volume exceeds a threshold of 6% of the alveolar macrophage volume of the lungs.⁴⁸ At 40% of the macrophage volume, the mucociliary clearance (which is intrinsically slow in nature) for materials deposited in the alveolar zone comes to a complete standstill, causing extreme burden for the sensitive area(s) of the respiratory tissue. It must be noted that because of the biphasic clearance mechanism, clearance of the airway is fast and is characterised by a half-life for bronchiolar deposited particles <1 day, whereas the alveolar half-life is 700-900 days, or even longer for diseased individuals.^{49,50} Due to their small size, UFPs are known to enter deeply into the lung and eventually can cross the alveolar-capillary barrier, thereby directly interacting with extra-pulmonary organs and resulting in CV/cerebrovascular impairments in susceptible individuals. Kreyling et al.⁵¹ showed that translocation of UFPs across the air-blood barrier, and their accumulation/retention in the

secondary organ, is highly dependent on the particle characteristics such as size and surface charges.

EPIDEMIOLOGICAL AND ANIMAL STUDIES

A series of epidemiological and experimental studies have proposed that exposure to ambient PM results in pulmonary inflammation, lung injury, and procoagulant changes in the lung, which may finally lead to the observed cerebrovascular/CV effect. Therefore, it is conceived that PM mediated pulmonary inflammation or alteration of pulmonary homeostasis plays a central role in PM mediated localised lung burden as well as systemic burden. Gilmour et al.⁵² have suggested that increased levels of systemic fibrinogen or impaired blood coagulation in Wistar Kyoto rats may be due to pulmonary inflammation and injury following exposure to ZnO particles. Similarly, Budinger et al.⁵³ reported that inhalation of ambient PM results in interleukin-6 (IL-6) and tumour necrosis factor- α dependent lung and systemic activation of coagulation and prothrombotic state. Exposure of concentrated ambient particles (CAPs) on normal (F344) rats and hypersecretory airway (BN) rats showed no significant CAP mediated toxicity or inflammation in ovalbumin treated F344 rats.⁵⁴ However, significant increases in airway mucosubstances and pulmonary inflammation were observed in ovalbumin-challenged BN rats. This study demonstrated that adverse biological response to PM_{2.5} is highly dependent on the local sources of particles as well as the conditions supporting the epidemiological findings.

Several epidemiological studies indicated individuals with impaired lung function to be more susceptible to respiratory illness such as COPD following PM exposure.⁵⁵⁻⁵⁷ To approach this observation in an experimental setting, Ganguly et al.^{58,59} exposed two inbred mouse strains (C3H/HeJ and JF1/Msf) with extremely divergent lung function, as identified in the Mouse Phenome project, to CNP of moderate toxicity by i.t. instillation. Assessment of a comprehensive panel of proinflammatory cytokines and bronchoalveolar lavage cell differentials over a time course revealed impaired polymorphonuclear leukocyte resolution kinetics in JF1/Msf mice with lower lung function. Furthermore, at a time point when C3H/HeJ mice, with higher lung function, were able to resolve the inflammatory challenge completely, a sudden and sharp influx of macrophages and lymphocytes,

symptomatic of chronic lung diseases, was detected in the airspace of JF1/Msf mice. This differential response between the divergent lung physiological states was attributed to a defence/homeostatic response involving IL-1 β and IL-18, vascular endothelial growth factor, fibroblast growth factor 2, and endothelin in C3H/HeJ mice, which was absent in JF1/Msf mice. The contrasting effects of CAP (from two separate locations) on allergic airway response was observed by Wagner et al.⁶⁰ Exposure to CAP from both collection sites did not show any adverse pulmonary effect on non-allergic rats, whereas asthmatic rats showed a 200% increase of lung mucus along with influx of neutrophil, leucocytes, and protein leakage. This study therefore revealed that the pulmonary reaction and burden not only depended on the specific chemical components and size distributions of urban PM_{2.5} but also on the sensitivity of exposed individuals.

Xu et al.⁶¹ have shown exposure to diesel exhaust particles (DEPs) induces an adverse respiratory effect, such as irritation, reduced peak expiratory flow, and upregulation of inflammatory markers, within 75 minutes of controlled exposure. According to the estimates from US, DEP emissions constitute 4-16% of the total PM in non-urban and urban areas. The Umeå study by Sehlstedt et al.⁶² has provided extensive knowledge on the respiratory effects of an even moderate DEP exposure. The absence of lung function changes in conventional tests in most of the Umeå studies may have been due to the relatively short exposure and follow-up times. Overall, it is imperative that both outdoor (e.g. motor vehicle emissions) and indoor (e.g. cooking gas) air pollution play pivotal roles in onset, exacerbation, and progression of cardiopulmonary complications, with elderly or susceptible individuals being at the highest risk.

CONCLUSION

In summary, ambient PM exposure has been correlated to various respiratory diseases and symptoms such as asthma, COPD, and declined lung function. An efficient environmental risk evaluation will also need to consider the sensitivity and susceptibility of the exposed individuals, in addition to the conventionally used criteria such as: 1) the hazard or toxicity of air pollutants; and 2) specific exposure characteristics. Accordingly, numerous epidemiological studies describe the most significant pollution-related health effects for elderly and cardiopulmonary susceptible individuals.

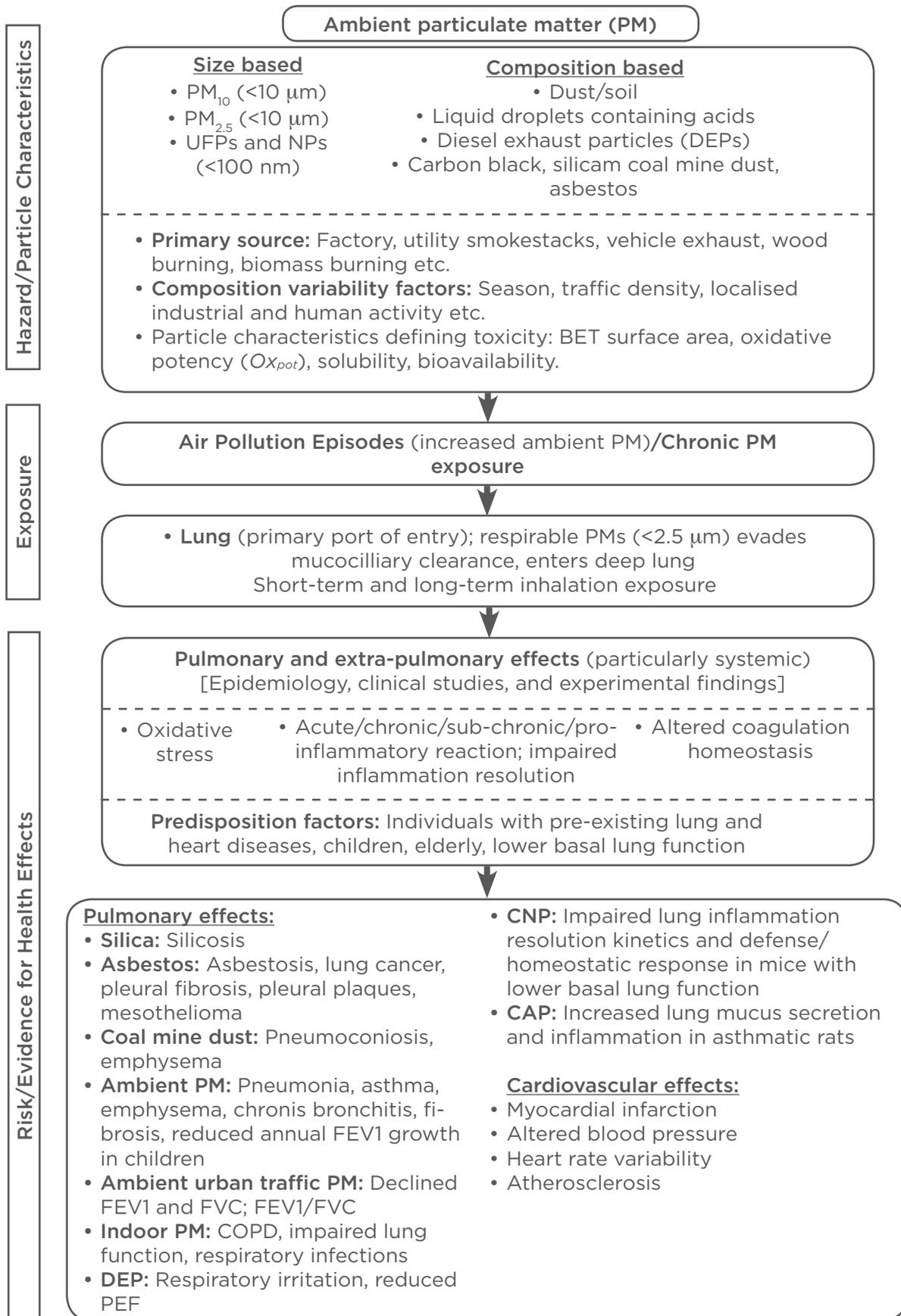


Figure 1: Summary sketch of the ambient particulate matter related lung health risk.

UFP: ultrafine particle; NP: nanoparticle; BET: Brunauer-Emmett-Teller measurement; CNP: carbon nanoparticle; CAP: concentrated ambient particle; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; PEF: peak expiratory flow.

Oxidative stress and pulmonary inflammation are by far regarded as the major mechanistic events driving the pathomechanism, as supported by epidemiological as well as experimental findings (Figure 1). BET surface area and Ox_{pot} measured in cell free systems may serve as important PM toxicity

indicators. The physiological status of the lung, as indicated by basal lung function or pre-existing condition, is also an important parameter to assess susceptibility to ambient PM that may be related to an inefficient inflammation resolution capacity or extent of an allergic response.

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