Air pollution and HTN

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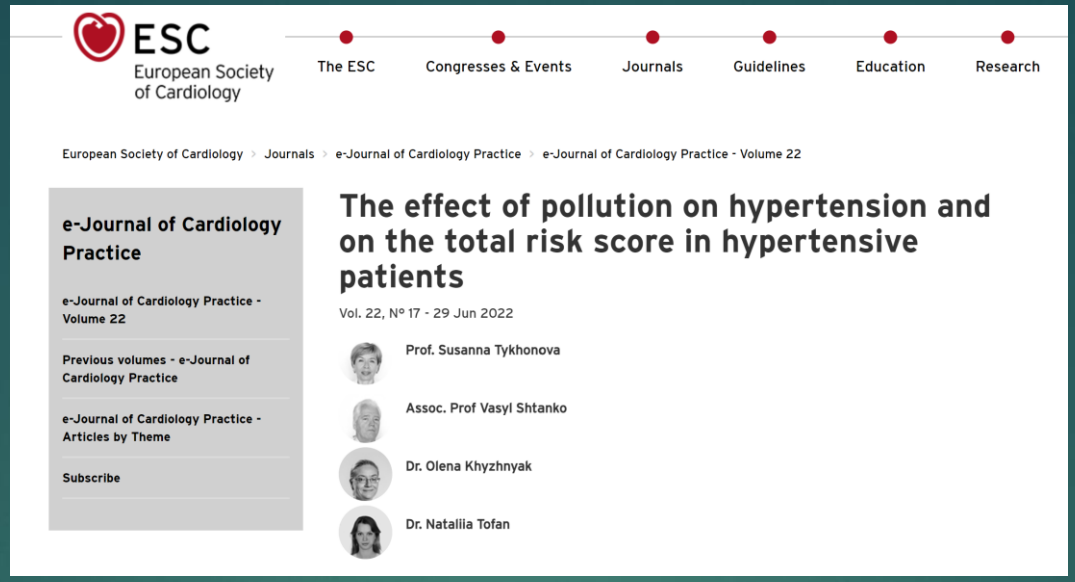
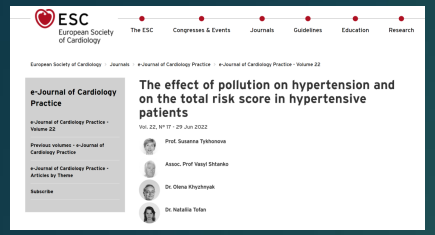


The development of hypertension is the result of the interaction between genetic predisposition to elevated blood pressure (BP) and environmental factors.

Among them are sedentary lifestyle, weight gain, increased sodium intake, unhealthy diet, and use of pro-hypertensive substances.

Environmental factors of greater geographical scale, such as air pollution, that are less subject to individual control are less frequently assessed.

- Given that hypertension is the leading risk factor for global disability and mortality, the relative contribution of environmental stressors to the development of arterial hypertension is, therefore, of substantial clinical interest.



- <u>Air pollution is a proven environmental risk factor of hypertension incidence and prognosis.</u>
- The inhalation of extreme concentrations of PM2.5 **for only 2-h** is capable of **acutely raising BP**.
- On the other hand ,**living in locations facing** higher ambient levels increases the risk for **developing overt** hypertension **over a few years.**
- **Determinants of susceptibility include:**
- **sex,**
- **age**,
- **baseline BP,**
- **anti-hypertensive medication use**, and
- **certain co-morbidities (e.g., obesity)**.

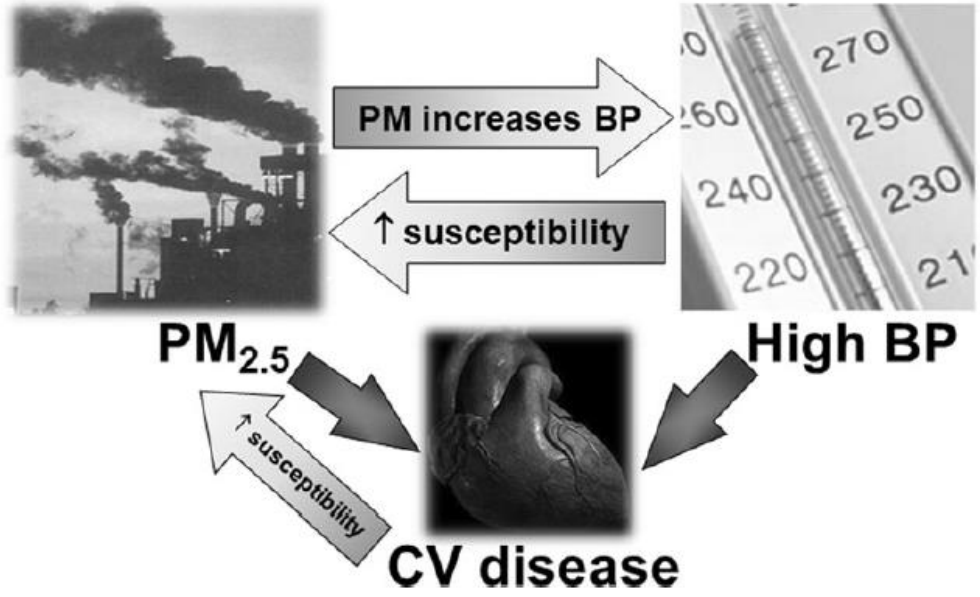


Fig. 1 Circular relationships among fine particulate matter air pollution, high blood pressure, and cardiovascular risk. BP blood pressure, CV cardiovascular, PM particulate matter, $PM_{2.5}$, particulate matter <2.5 μm. Higher BP and ambient $PM_{2.5}$ levels both directly increase cardiovascular risk. Higher ambient $PM_{2.5}$ levels also increase BP. Higher BP can increase the susceptibility to cardiovascular events related to $PM_{2.5}$ exposure. Preexisting cardiovascular diseases increase the susceptiblity to future events due to $PM_{2.5}$ exposures.

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PERSPECTIVE

Clearing the air to treat hypertension

Jonathan D. Newman[1] · Sanjay Rajagopalan[2] · Phillip Levy[3] · Robert D. Brook[4]

- The acute exposure-response relationship appears to be largely monotonic and independent of chronic concentrations of ambient PM2.5 [9, 10].

- This means that people living in heavily-polluted locations (e.g., Asia) are not immune to the acute BP-raising effects provoked by day-to-day increases in PM2.5.

- Their absolute BP responses are in fact larger compared to individuals residing in less-polluted regions because ambient concentrations and their variations are generally threefold to tenfold higher (50–100 ± 10–50 versus 5–25 ± 2–10 μg/m3) [14].

- Ambient air pollution is a heterogeneous complex mixture of particulate matter (PM) and gaseous components that vary considerably by season, source, and atmospheric conditions ,which can have an independent effect on the body, or through potentially synergistic and antagonistic effects.

- The statements of the European, American and World Health Organisations (WHO) on air pollution discussed aspects of this problem, such as fractions, sizes, chemical components and types of gaseous air pollutants, and their impact on health.

- The most common method to classify PM particles is based on size(aerodynamic diameter); coarse PM <10 μm (PM10), fine PM <2.5 μm (PM2.5), and ultrafine PM <0.01 μm (PM0.1).

- The chemical constituents of PM vary substantially by source.

- They may include transition metal ions, endotoxins, reactive aldehydes, and organic compounds such as toxic polycyclic aromatic hydrocarbons that largely determine its toxicity.

Table 1. WHO Air Quality Guidelines and National Air Pollution Legal Thresholds for Annual Average Concentrations (https://apps.who.int/iris/handle/10665/345329, https://www.epa.gov/criteria-air-pollutants/naaqs-table)

Air pollutant	WHO 2005	WHO 2021	EU threshold	US threshold
Nitrogen dioxide ($^{\bullet}NO_2$)	40 μg/m³	10 μg/m³	40 μg/m³	100 μg/m³ (53 ppb)
$PM_{2.5}$	10 μg/m³	5 μg/m³	25 μg/m³	12 μg/m³
PM_{10}	20 μg/m³	15 μg/m³	40 μg/m³	(50 μg/m³) canceled in 2006

PM indicates particulate matter; and WHO, World Health Organization.

Hypertension

REVIEW

Noise and Air Pollution as Risk Factors for Hypertension: Part I–Epidemiology

Omar Hahad, Sanjay Rajagopalan, Jos Lelieveld, Mette Sørensen, Katie Frenis, Andreas Daiber, Mathias Basner, Mark Nieuwenhuijsen, Robert D. Brook, Thomas Münzel

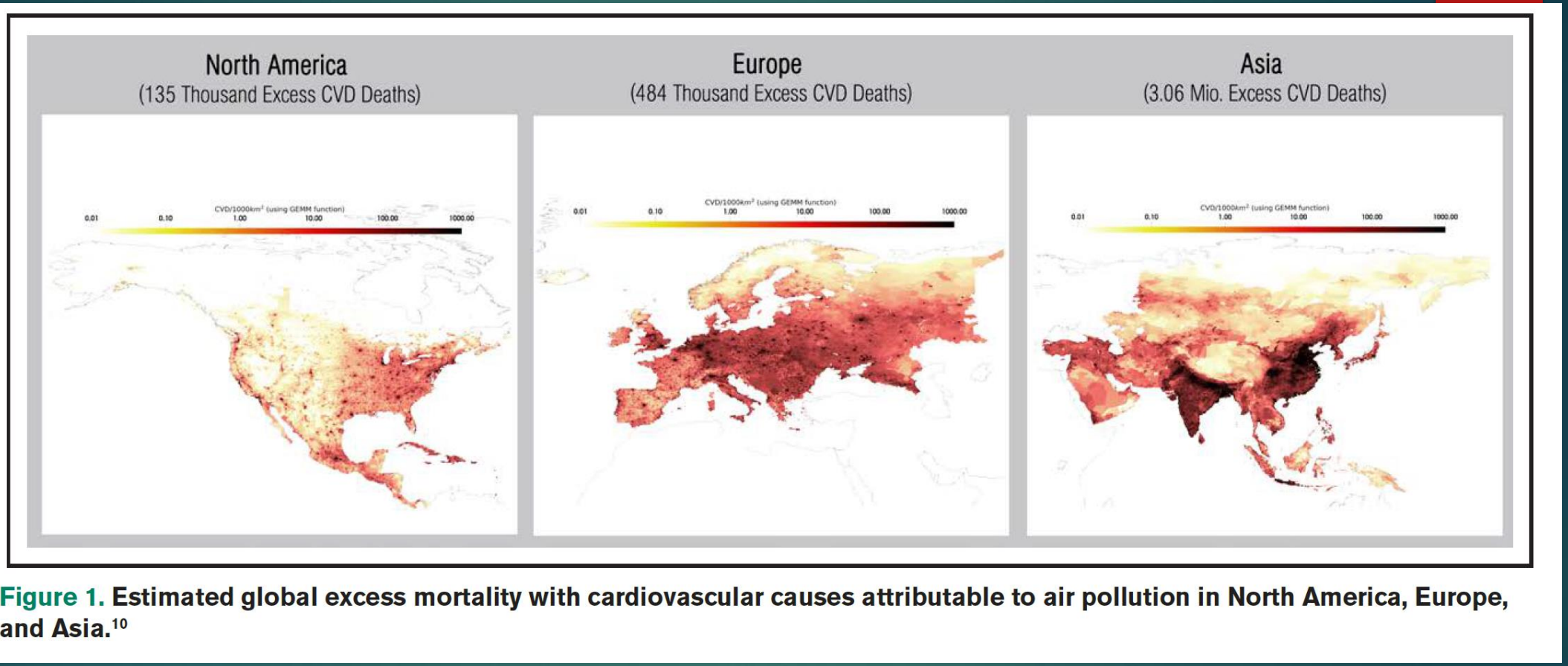


Figure 1. Estimated global excess mortality with cardiovascular causes attributable to air pollution in North America, Europe, and Asia.[10]

- WHO estimates that 97% of the world's population resides in places where annual mean air pollution levels exceed the annual WHO guideline level of 10 µg/m3, recently reduced to 5 µg/m3, a level at which air pollution continues to have a significant impact on the health.

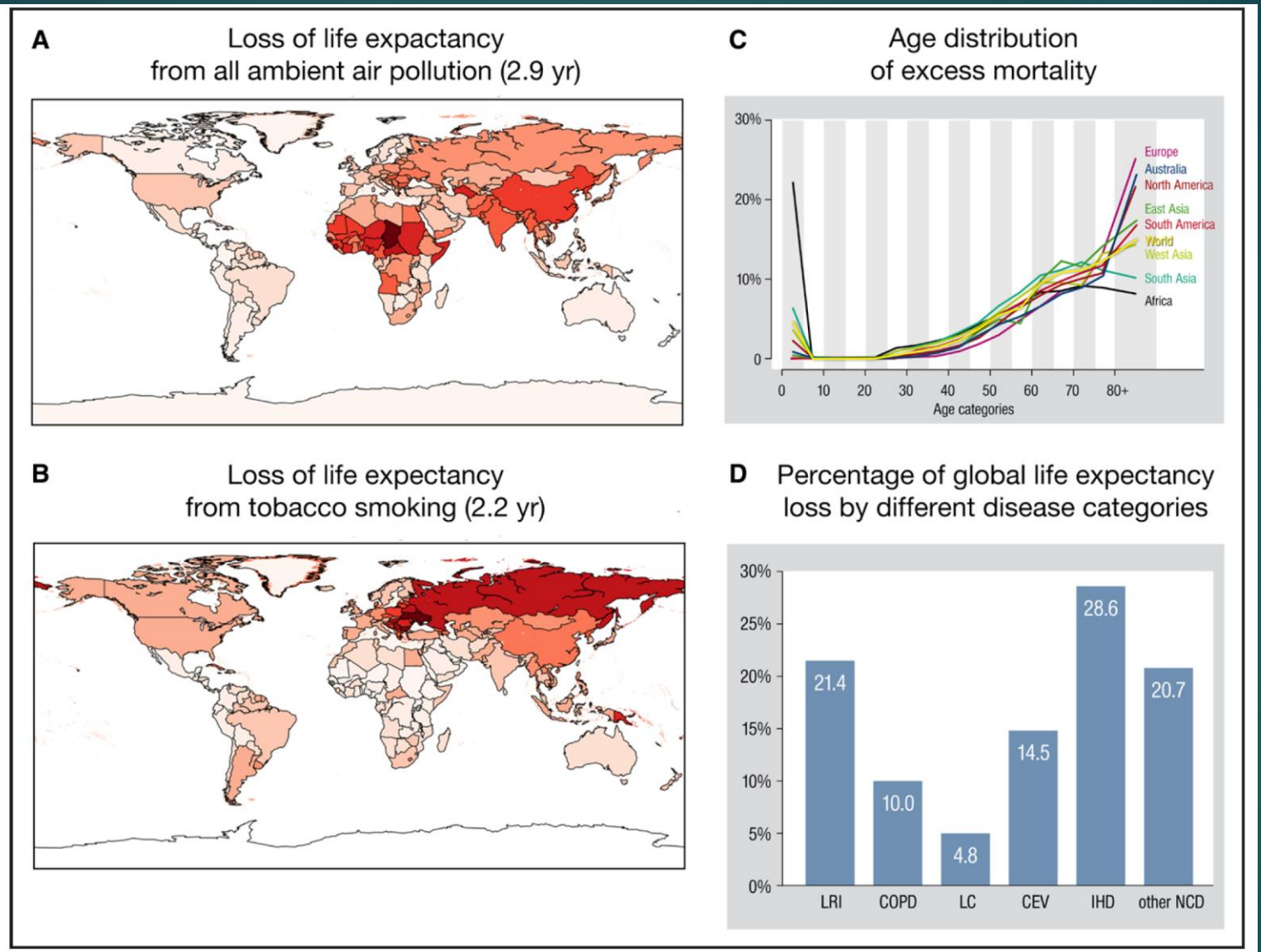
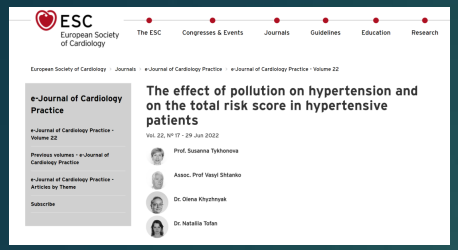


Figure 2. Impact of ambient air pollution and smoking on life expectancy.
Mean global, and country-level loss of life expectancy from ambient air pollution (**A**) and tobacco smoking (**B**) of death refers to 2015. **C**, Age

- Mean global, and country-level loss of life expectancy from ambient air pollution (A) and tobacco smoking (B) of death refers to 2015. C, Age distribution of excess mortality from ambient air pollution. Globally, about 25% of the attributable mortality occurs at the age of <60 years: in Europe, about 11%, and in Africa, about 55%.



- **The main pathophysiological mechanisms:**
- (a) disorders of the autonomic nervous system (ANS) and/or sympathoadrenal overactivity;
- (b) release of pro-inflammatory mediators, modified lipids or phospholipids and activation of leukocyte populations;
- (c) endothelial dysfunction caused by oxidative stress; and
- (d) activation of prothrombotic pathways [15].

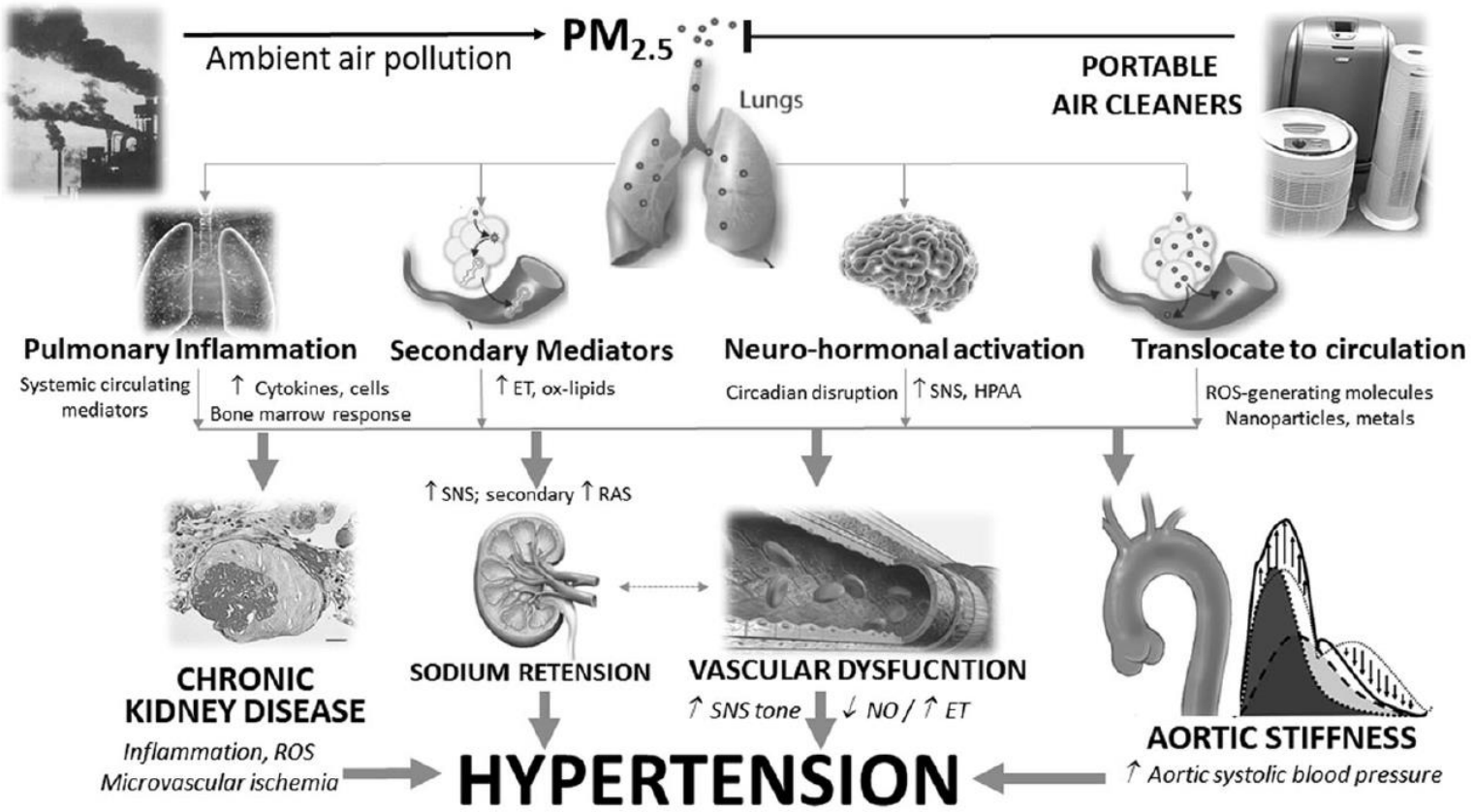


Fig. 2 Pathways and end-organ mechanisms whereby fine particulate matter air pollution exposures can increase blood pressure. ET endothelins, HPAA hypothalamic pituitary adrenal axis, NO nitric oxide, ox-lipids oxidized lipoproteins/ phospholipids; $PM_{2.5}$, fine particulate matter; ROS reactive oxygen species, SNS sympathetic nervous system.

- Direct and indirect effects of pollution on systemic vasculature
- An indirect effect of particulate matter exposure, mediated through systemic proinflammatory and oxidative responses, may lead to increased sympathetic tone and potentially cause arterial remodeling.
- Experimental and clinical data show that PM-induced oxidative stress and reduced NO bioavailability are likely to be key factors in systemic vascular dysfunction , and can result in an increased total peripheral resistance and a fixation of elevated BP .
- A direct effect of particulate matter exposure is vasoconstriction, which is a result of $PM_{2.5}$-induced ANS imbalance.
- Additionally, exposure to PM may reduce daytime sodium excretion and weaken nocturnal BP reduction, which over time may be one of the reasons for steady elevated BP [19].

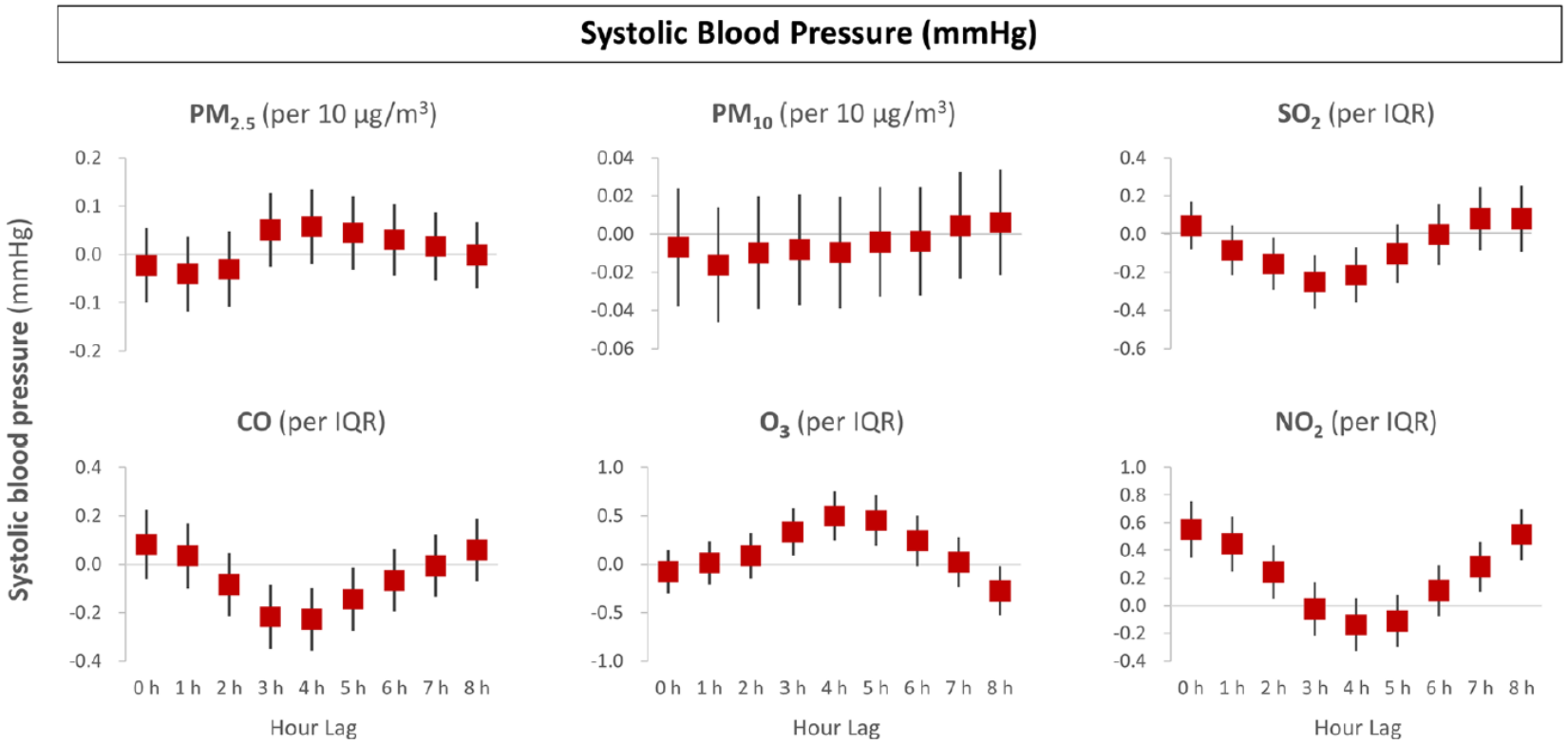


Figure 1. Time-lag effects of air pollution on systolic blood pressure. The x-axis represents hour lags, while the y-axis indicates adjusted effects on systolic blood pressure.

- In controlled studies in humans, **acute** exposure to particulate matter (PM)2.5 and dilute diesel exhaust (ultrafine particles) results in **rapid vascular dysfunction that manifests as conduit or microvascular endothelial dysfunction**, or **transient constriction of a peripheral conduit vessel, that is reversible.**
- **In some of these studies**, concentrated PM2.5 exposure diminished conduit artery **endothelial-dependent vasodilatation** in a **delayed fashion**, **post 24 hours (but not immediately**).
- Not all studies demonstrating endothelial dysfunction in humans have shown increases in BP.
- PM2.5 mass and tumor necrosis factor-a **level postexposure** have both been associated with the **degree of endothelial dysfunction**, suggesting that **systemic inflammation** induced by particles and the degree of pollution are likely responsible.

- BP and arterial **stiffness** increased in response to systemic nitric oxide (NO) synthase inhibition in humans with intravenous NG-Methyl-L-arginine (3 mg/kg), following exposure to ultrafine particle , suggesting a greater generation of NO and preservation of systemic BP with ultrafine particle exposure, which was unmasked by systemic NO synthase inhibition.

- The role of gaseous pollutants, such as ozone on BP, are mixed.
- A panel study noted reduction in brachial artery diameter without changes in endothelial function, and a marginally significant reduction in diastolic BP, with a lag period of 48 hours.

- This delayed temporal profile of reduction in BP with ozone was similar to another panel study that also demonstrated that a 5-day mean increase in the ozone of 13.3 ppb, was associated with a 5 mm Hg decrease in systolic BP.

- These results suggest but are not definitive of a counteraction of increased BP in response to PM2.5 noted in the same study.

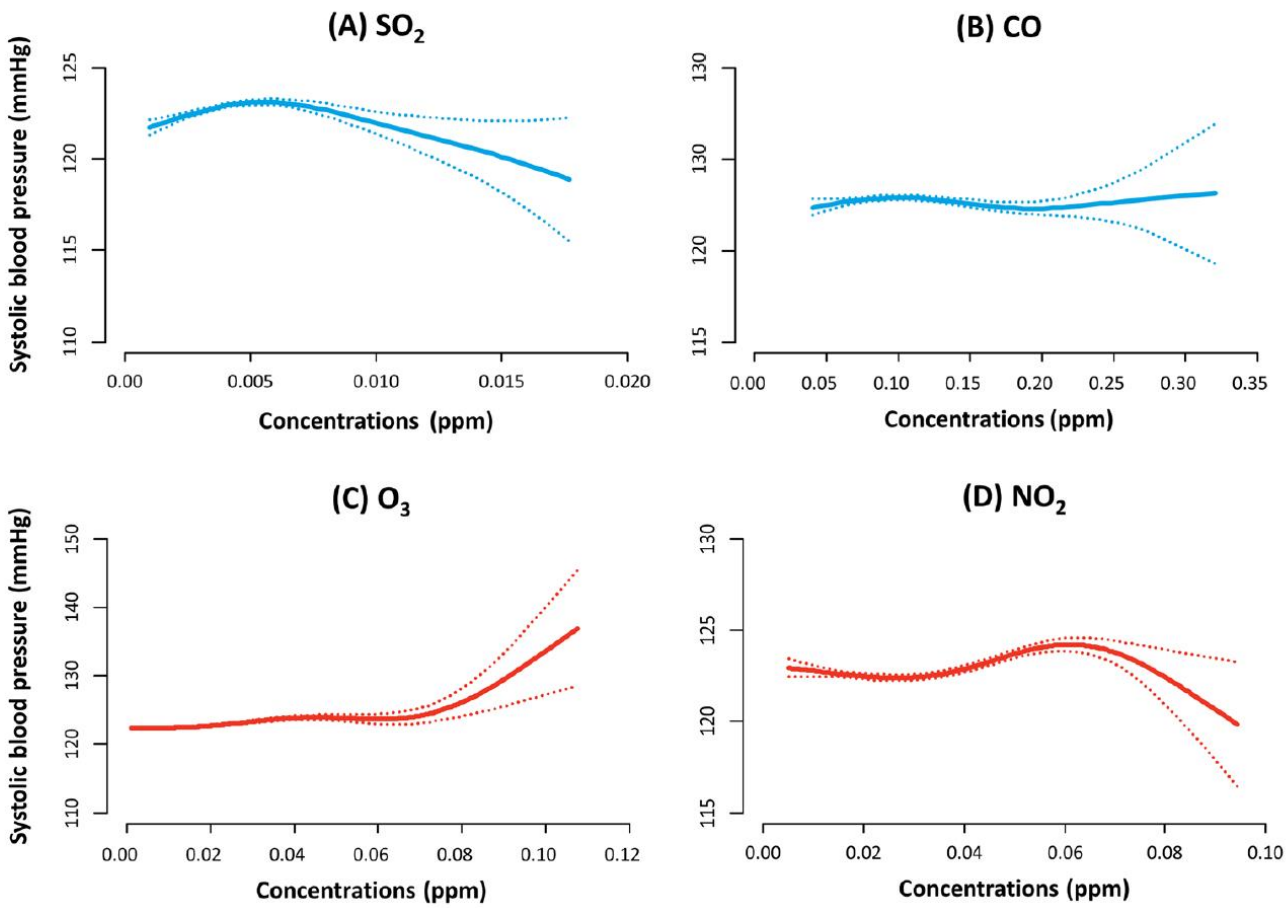


Figure 2. Spline curves showing the non-linear relationship of (**A**) SO_2, (**B**) CO, (**C**) O_3, and (**D**) NO_2 with systolic blood pressure. The running mean of lag hours 3–5 was used for SO_2 and O_3, and that of lag hour 2–4 for CO and lag hours 0–2 for NO_2.

- Other components of air pollution, such as volatile organic compounds such as acrolein and 1,3-butadiene have been associated with endothelial dysfunction and may contribute to elevated risk of hypertension in participants with an increased sympathetic tone, particularly in Black individuals.

- Short-term exposure to high levels of ultrafine, fine PM2.5 and coarse PM10 have been associated with increased BP in humans, with evidence based on heart rate variability measures that suggest sympathetic activation.

- **Receptor**s such as the **TRPA1** (transient receptor potential cation channel, subfamily A, member 1) receptors in **airway sensory neurons** can also **sense the environmental toxicants and aerogenic oxidants**, resulting in **neurogenic inflammation** and **facilitate rapid autonomic regulation of BPs**, also with impact on rapid changes in BP in humans.

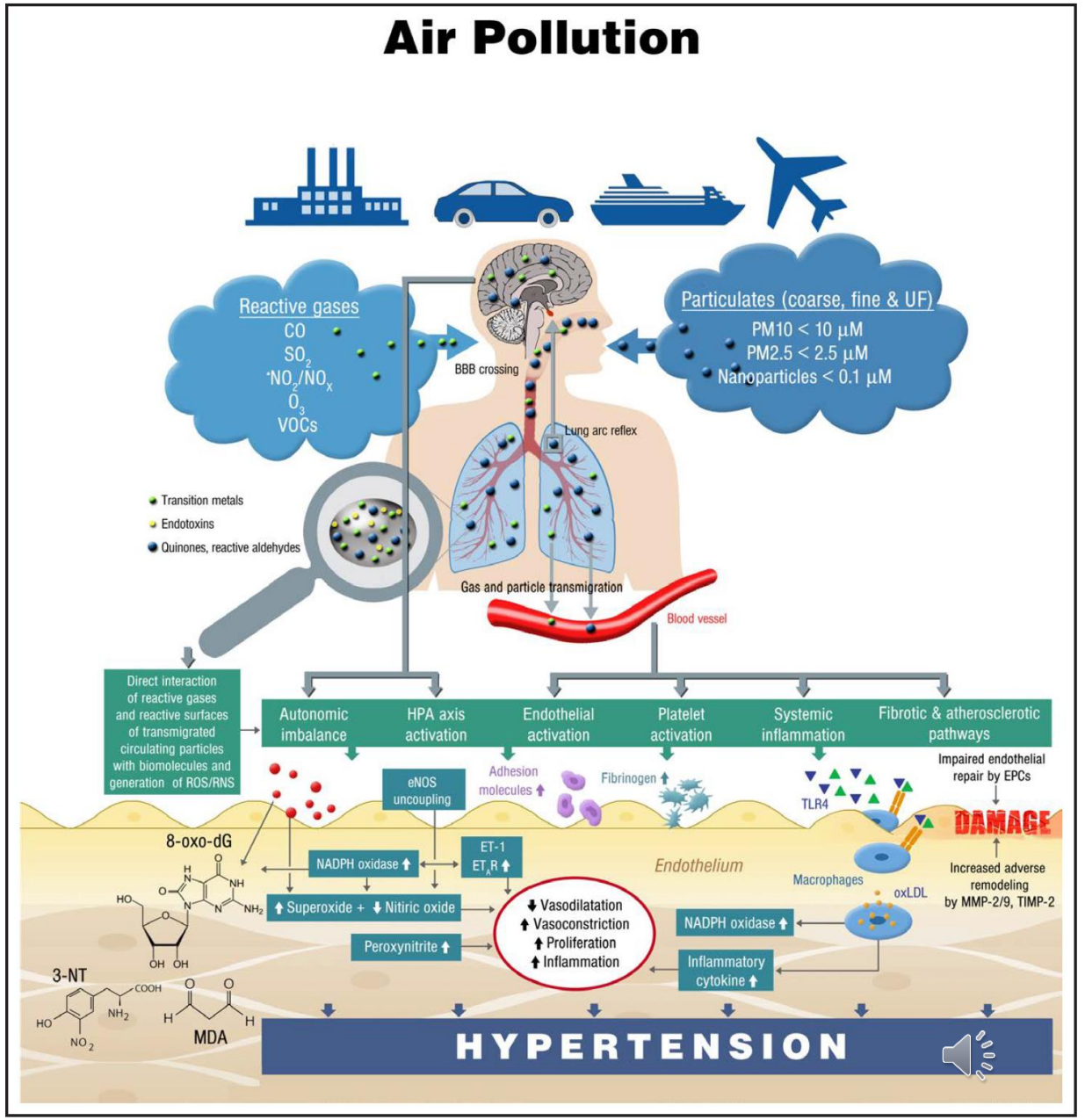


Figure 3. Pathophysiology of air pollution-induced endothelial dysfunction, increased oxidative stress, inflammation, and subsequently arterial hypertension.

- **Direct translocation** of particulate constituents and secondary damage-associated molecular patterns (**DAMP)** and **biologic intermediates** play an important role.
- However, their role in inducing BP changes remain unknown (summary in Figure 3).

- Air pollutants have been shown to **permeate the central nervous system**, **inducing inflammation** in several critical areas of the CNS responsible for BP regulation and metabolic control in animal models.

- In humans, there is evidence of systemic permeation of particles, including into the CNS , based on postmortem studies.
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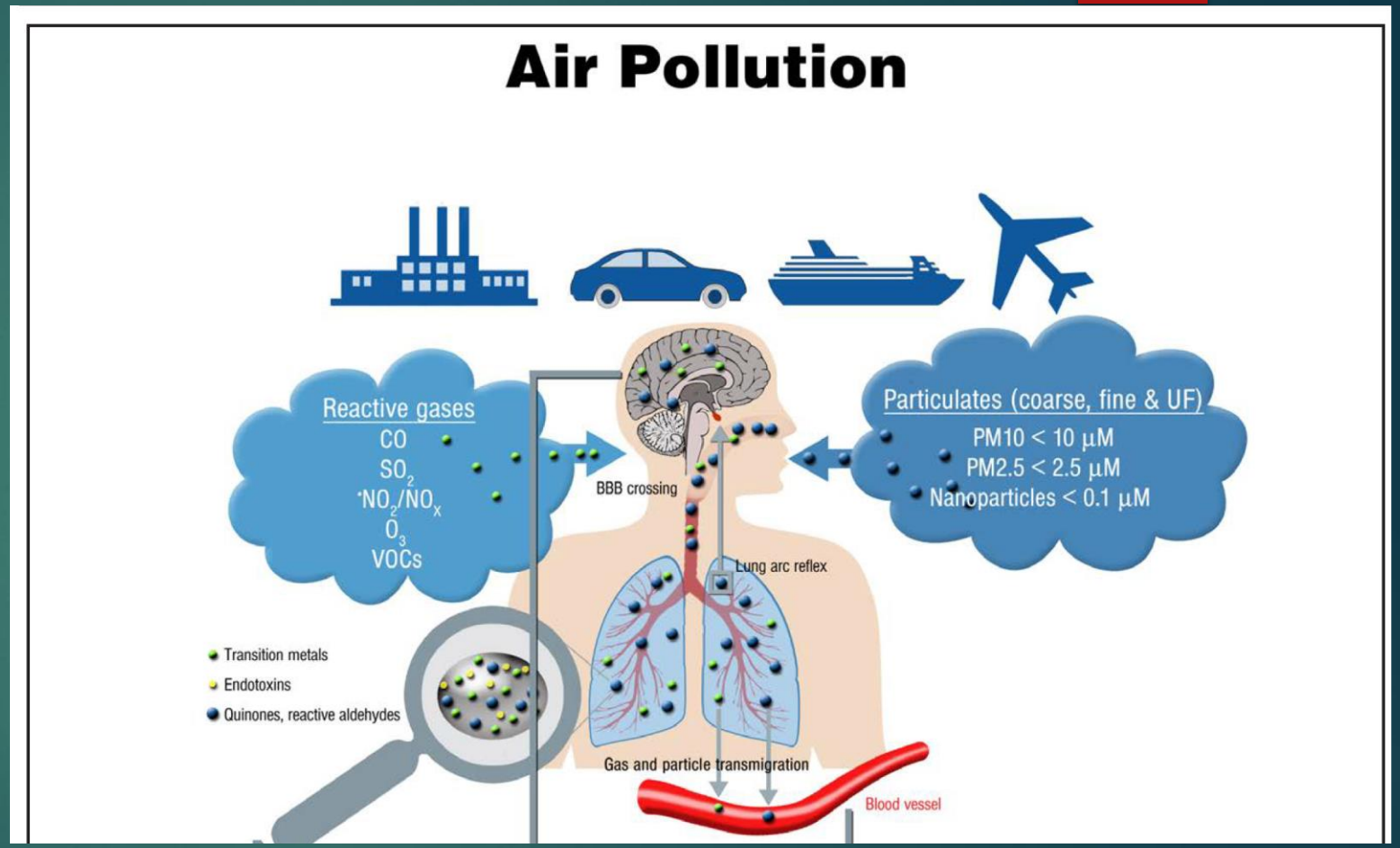
- Still, these are difficult to do because monitoring the particles in vivo is challenging, and postmortem studies may be subject to pathological artifacts.42,43



- Concentrated ambient PM2.5 exposure in C75/Bl6 mice, induced significant increases in **urinary angiotensin II** and **aldosterone**, along with the **decrease of ACE2** and **angiotensin (1–7)** in kidney compared with filtered air-exposed mice.

Several reports have found amplified **endothelin-1/ETA-receptor** signaling upon **exposure to diesel exhaust** which is consistent with the known involvement of **NADPH oxidase-driven endothelin-** 1 promoter activation, and conversely, activation of NADPH oxidase and O2•− production by endothelin-1.

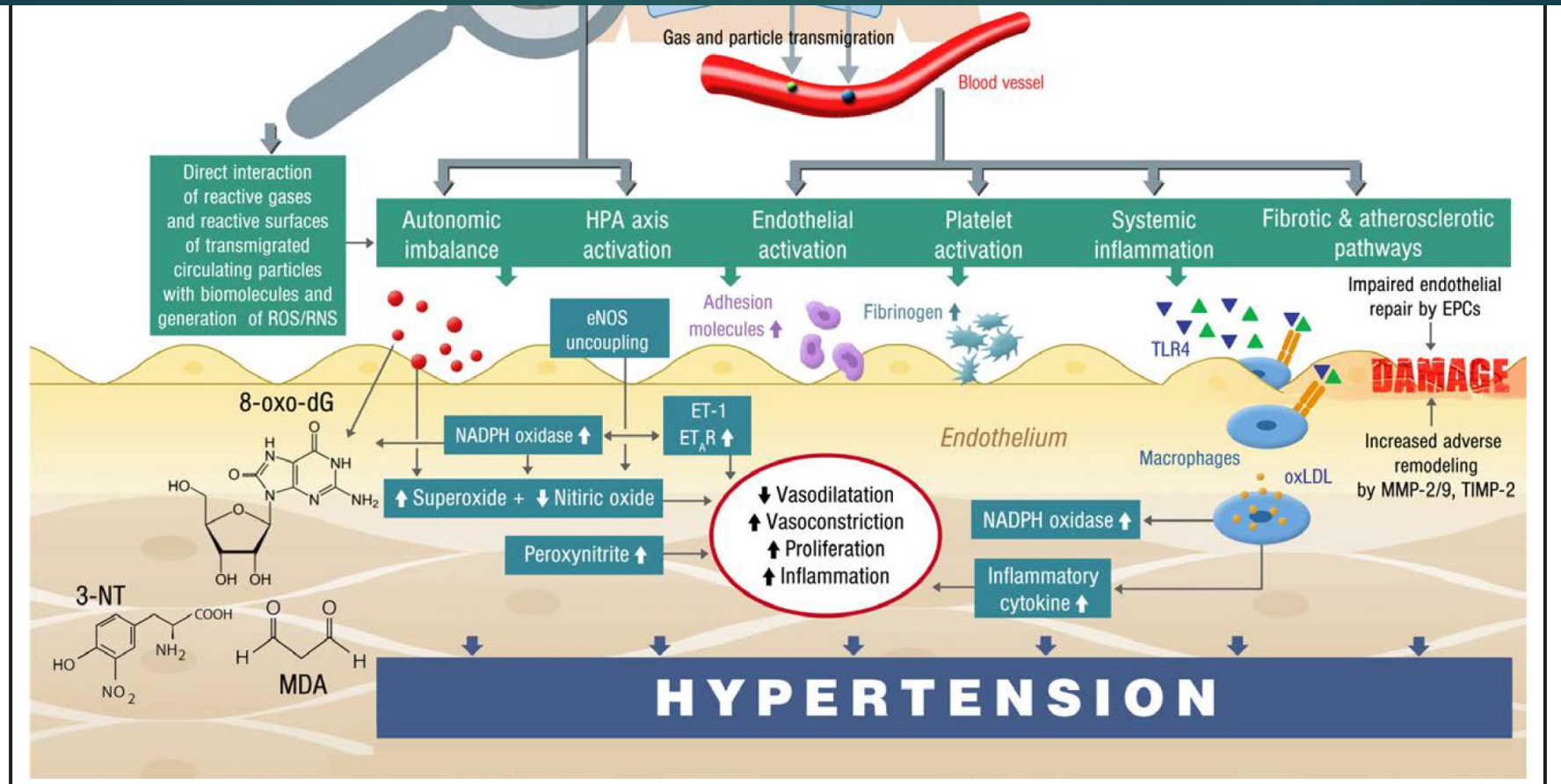
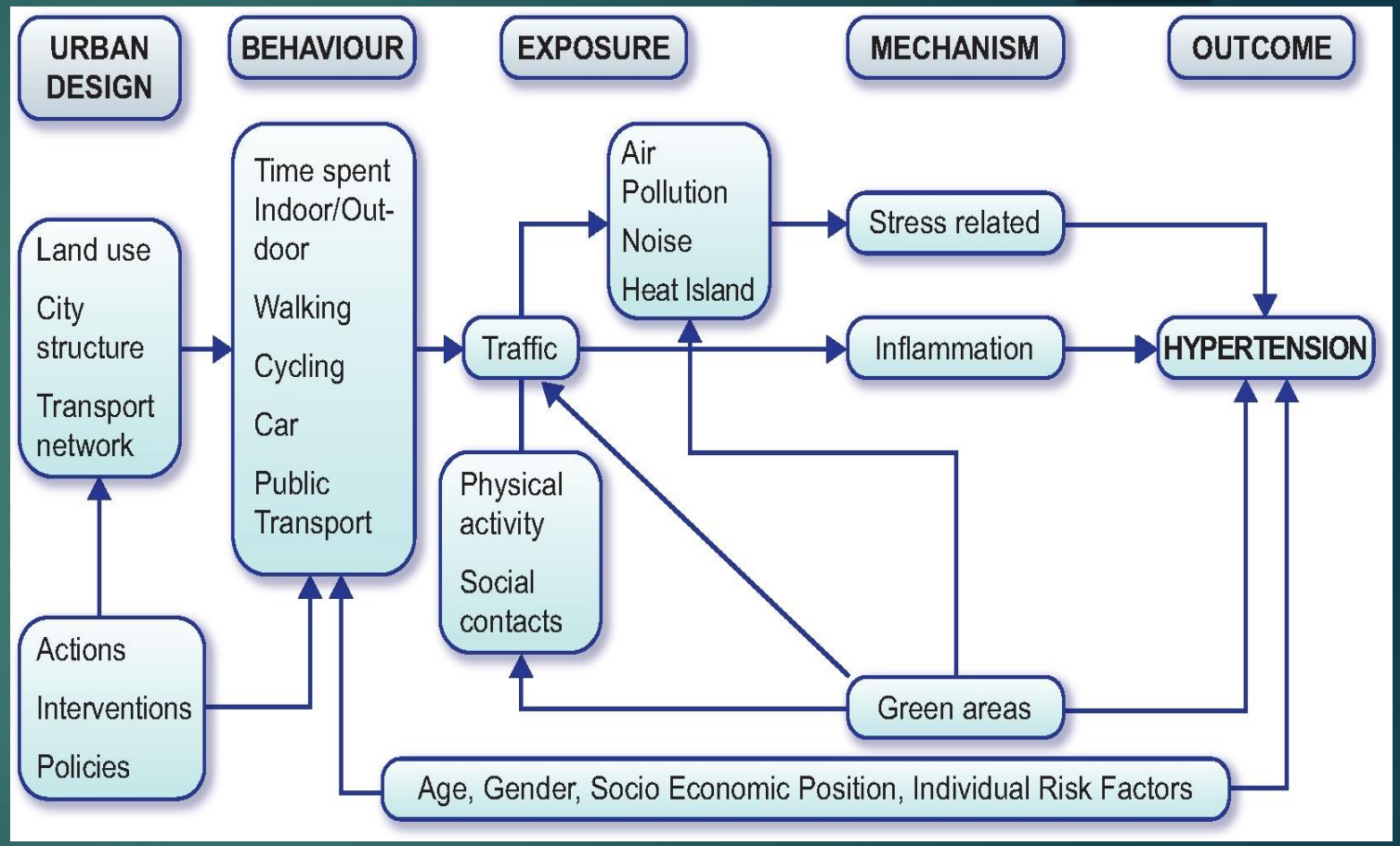


Figure 3. **Pathophysiology of air pollution-induced endothelial dysfunction, increased oxidative stress, inflammation, and subsequently arterial hypertension.**

- *An increase in oxidative stress is one of the earliest pathophysiologic mechanisms in response to air pollution exposure and appears to be a critical initiating event.*

- A number of important mechanistic questions remains to be addressed, including the
- magnitude and
- time course of response of coexposure,
- interactive effects of both factors on BP and metabolic risk
- and
- duration of effect/time course of reversal.

- Importantly, integrative mechanisms including the link between exposures and activation of central mechanisms and circadian rhythm need to be addressed.
- Importantly, the impact of mitigation measures including other of preventive measures on the pressor response is worth investigating.
- Integrating mechanistic studies with health impact assessment of noise and air pollution mitigation, in the context of climate interventions in cities may offer an extraordinary opportunity.



- Furthermore, motor vehicle traffic means not only air pollution and noise but also poor physical activity, which is in turn a cause of weight gain.

- Thus,there is widespread awareness of the need to reduce motor vehicle
- traffic, particularly in densely populated urban areas.

Thank you