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Fine particle environmental pollution and cardiovascular diseases

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ABSTRACT

Air pollution affects 90% of the world's population and has caused 9 million deaths in 2015, becoming the most important cause of premature deaths in the world. Exposure to fine particulate matter, a major component of urban air pollution, has been associated with an increase in cardiovascular risk and associated mortality. Impact of fine particles on the cardiovascular system includes inflammation, activation of prothrombotic pathways, oxidative stress, vascular dysfunction and remodeling, and neurological dysfunction. Genetic and epigenetic factors might also increase the susceptibility to air pollution. Consequently, epidemiologic studies have identified correlations between air particulate matter concentrations and acute coronary events, ischemic cardiomyopathy, acute heart failure, and stroke. Interestingly, these effects are present even for fine particulate matter concentrations below current US and EU regulatory standards, and seems to be more harmful in the most fragile population such as low-income or elderly subjects, or patients with previous cardiovascular disease.
This review aims to summarize recent data on the pathophysiology and epidemiology of cardiovascular disease after particulate matter exposure. It will also discuss potential strategies to reduce the impact of air pollution on current and future populations' health.

1. Introduction

Due to urbanization, >90% of the world's population is exposed to air pollution levels exceeding World Health Organization Air quality guidelines [1] and especially to fine particulate matter (PM). As a result, air pollution has become a major public health concern for populations both in developed and developing countries. PM are constituted of a complex mixture of solid and liquid particles and of organic and inorganic substances suspended in the air. Sources may emit PM directly into the environment or emit precursors such as sulfur dioxide, nitrogen dioxide, and volatile organic compounds, which are transformed through atmospheric chemistry to form PM. Particles are generally classified by size into PM10 (<10 μm mean aerodynamic diameter), coarse (<10 μm and >2.5 μm diameter), fine (PM2.5; <2.5 μm diameter), and ultrafine (UFP; <0.1 μm diameter) fractions (Fig. 1). Air pollution due to PM_{10} is generally caused by dust, mining, construction, brake wear and road dust. These particles exhibit a short lifetime and travel small distances (inferior to 10 km). On the opposite, fine particle ($PM_{2.5}$) can last days or weeks, and travel up to 10^6 km. These particles are mainly generated by combustion, biomass and fossil fuel burning. Upon inhalation, particles <10 μm in diameter can deposit in the airways and lungs. Finest particle can reach pulmonary alveoli, enter the blood circulation and cause local and systemic inflammation [2].

The World Health Association estimates that air pollution was responsible for 9 million premature deaths in 2015 – 16% of all deaths worldwide –, with $PM_{2.5}$ being the cause of 1.2 million death [3,4]. Indeed, environmental pollution has become the current largest cause of reversible death and disability due to cardiovascular disease or cancer [5]. Moreover, populations are not equal regarding the impact of air pollution since 92% of these premature deaths involved populations of low and middle-income countries. These data illustrate the importance of a better understanding of the pathophysiology of PM inhalation on the cardiovascular system. Research and policy interventions to reduce environmental pollution are also urgently needed to limit morbidity and mortality associated with air pollution.

2. Pathophysiological mechanisms

Exposure to air pollution elicits cardiovascular diseases through several pathophysiological pathways that have not yet been completely

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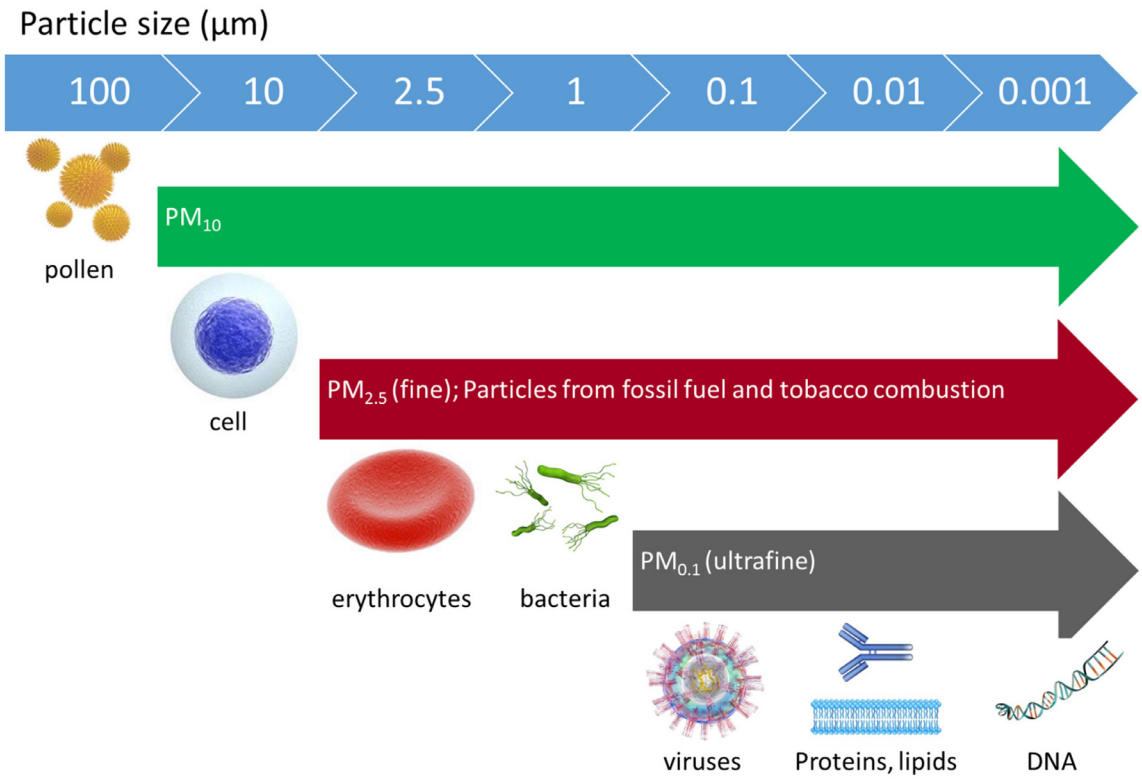

Fig. 1. Size categorization of airborne pollutants.

elucidated (Fig. 2). It's important to note that air pollution is more harmful for vulnerable subjects such as elderly people or patients with previous cardiovascular diseases.

2.1. Systemic inflammatory response

Several animal studies identified an association between air pollution and increased systemic inflammation biomarkers such as C-reactive protein or proinflammatory cytokines [2,5]. This proinflammatory effect of PM is activated even after short-term exposure, as illustrated by a study conducted during the Beijing 2008 Olympics. Pollutants and multiple biomarkers such as CRP, fibrinogen, von Willebrand factor, and white blood cell count, were measured daily in 125 healthy young adults before, during, and after the games. Lower levels of air pollution resulting from strict restriction of emission during the Olympics were associated

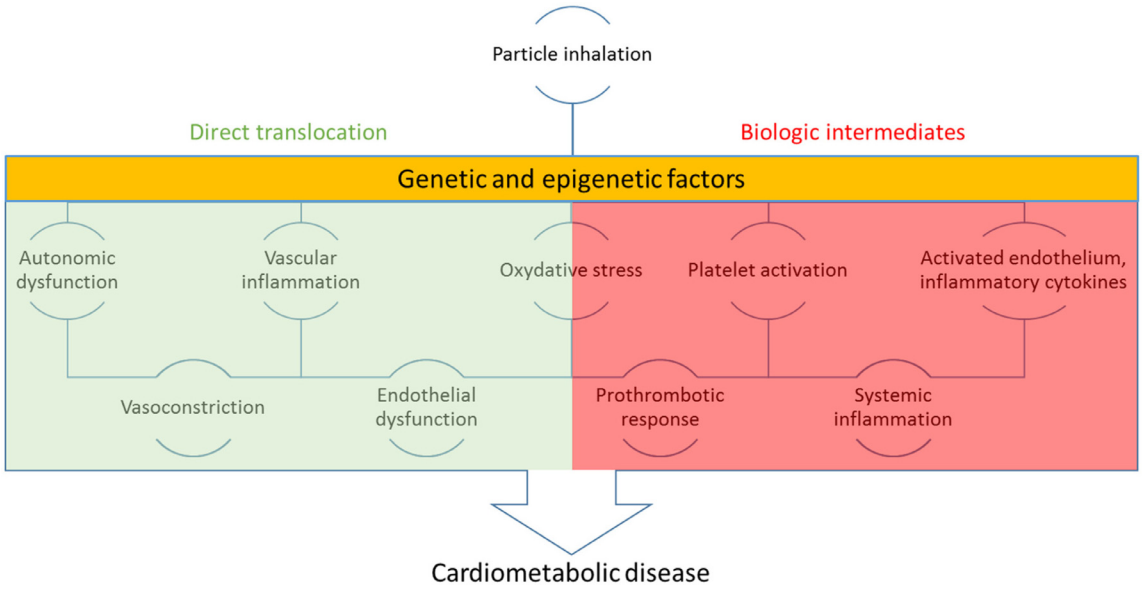

Fig. 2. Pathophysiological pathways leading to cardiovascular diseases after exposure to air pollution.

with a significant and rapid reduction in these biomarkers of inflammation and thrombosis [6].

2.2. Prothrombotic response

In parallel to this inflammatory response, PM increase fibrinogen concentration [6] and plasma viscosity, leading to a higher susceptibility to cardiovascular events. Acute exposure to diesel exhaust also significantly increased ex vivo thrombus formation, platelet activation [7] and hematocrit [8] in healthy subjects. Additionally, brief exposure to dilute diesel exhaust promoted myocardial ischemia and inhibited endogenous fibrinolytic capacity in men with stable coronary heart disease [9].

2.3. Oxidative stress

Inhalation of $PM_{2.5}$ stimulates reactive oxygen species production in the epithelial lining fluid of the human respiratory tract, reaching similar levels than those observed in respiratory diseases [10]. This increased pulmonary oxidative stress could elicit inflammation and insulin-vascular resistance, thus favoring cardiovascular disease even with short-term $PM_{2.5}$ exposure [11]. Recent studies also suggested that up-regulation of the pulmonary anti-oxidant barrier could protect from vascular effects of air pollution, illustrating the role of pulmonary oxidative stress in this setting [11,12].

2.4. Vascular dysfunction and remodeling

Several studies identified air pollution as a risk factor of endothelium and microvascular dysfunction. In particular, diesel exhaust encountered in urban environment impaired the regulation of vascular tone and endogenous fibrinolysis in healthy volunteers [7]. It has been associated with an acute endothelial response leading to endothelin-1 release and vasoconstriction [13]. Short exposure to $PM_{2.5}$ also induced vascular injury and the depletion of circulating endothelial progenitor cell [14]. In accordance with these observations, recent studies identified an association between $PM_{2.5}$ exposure and the development of hypertension [15–17].

2.5. Impact on central nervous system and autonomic dysfunction

Pulmonary receptors exposed to environmental pollution activate an autonomic reflex leading to increased blood pressure and heart rate, suggesting sympathetic predominance activation [18]. Experimental animal studies have also linked the development of hypertension in response to $PM_{2.5}$ exposure to increased hypothalamic inflammation [19].

2.6. Genetic and epigenetic factors

There is growing evidence that genetic and epigenetic factors [20] are associated with increased susceptibility to air pollution. Genes involved in oxidative stress and inflammatory pathways are potential candidates. For example, a significant two-way gene-air pollution interaction has been shown between glutathione S-transferase P (GSTP1) an enzyme regulating oxidative stress and PM10 on the risk of childhood asthma [21] and acute myocardial infarction [22]. Similarly, variant alleles of Toll-like receptor 2 and 4 genes influence the susceptibility to adverse effects of traffic-related air pollution on childhood asthma [23].

3. Effects on all-cause mortality

Due to its impact on the cardiovascular system and on lung inflammation, air pollution is responsible for the most important proportion of reversible death worldwide. Deaths related to $PM_{2.5}$ exposure have increased from 3 million in 1990 to 4.2 million in 2015 [3] and are mostly encountered in low or middle-income countries [24]. In the most severely affected countries, air pollution can be responsible for more than one in four deaths [4].

Impact of $PM_{2.5}$ on mortality also varies according to population socioeconomic status. A cohort of all Medicare beneficiaries in United States highlighted that effects were more pronounced in low income populations [25]. In addition, this study showed that all-cause mortality increased by 7.3% per 10 $\mu g/m^3$ increase in long-term exposure to $PM_{2.5}$ and that an increased risk existed even at levels below current standards defined by the National Ambient Air Quality Standard. Vulnerable subjects such as elderly people were at even higher risk of death when exposed to $PM_{2.5}$ [26–28].

4. Cardiovascular diseases and associated mortality

4.1. Myocardial infarction

Short-term exposures to fine particulate air pollution are predominantly associated with the onset of acute ischemic events (myocardial infarction and stroke) suggesting that some inhaled pollutants act as a trigger within hours of exposure. According to a meta-analysis of 34 studies, all air pollutants (with the exception of ozone) were identified as potential contributing factors of myocardial infraction, with a daily relative risk increase of 0.7% ($p < 0.001$) and 1.7% ($p = 0.03$) per 10 $\mu g/m^3$ increase in PM_{10} and $PM_{2.5}$, respectively [29]. Consequently, air pollution could be responsible for 5% of all acute myocardial infarction worldwide [30].

Long-term exposure to air pollution has also been associated with chronic ischemic heart disease and heart failure [31], especially in patients with preexistent coronary artery disease [32]. An observational study based on 65,893 postmenopausal women showed that each increase of 10 $\mu g/m3$ in $PM_{2.5}$ annual exposure was associated with a 24% increase in the risk of a cardiovascular event and a 76% increase in the risk of death from cardiovascular disease [33]. A meta-analysis of 11 European cohorts confirmed these results and identified a positive association between $PM_{2.5}$ and coronary events even with levels below the current European limit value of 25 $\mu g/m^3$ [34]. Accelerated coronary calcification, which has been associated with higher concentrations of $PM_{2.5}$ in a 10-years retrospective CT cohort study of 6795 participants may play a major role in this setting [35]. Lastly, roadway proximity was associated with elevated (8% increase per 100 m closer) and statistically significant risks of sudden cardiac death and fatal coronary heart disease, even after controlling for other cardiovascular risk factors [36].

4.2. Cardiac arrhythmias

Higher risk of atrial fibrillation when exposed to air pollutant such as $PM_{2.5}$ was reported in a systematic review including 461,441 subjects [37]. Data associating air pollution and ventricular arrhythmia are less obvious [5,38]. An observational study conducted in London suggested an association between air pollutant and activation of implantable cardioverter defibrillator [39]. T-wave alternans, which is a marker of cardiac electrical instability, was also increased after short-term exposure to traffic exhausts in patients with preexisting ischemic cardiopathy [40].

4.3. Heart failure

In a meta-analysis of 35 studies, rates of heart failure hospitalization or death increased by 2% per 10 $\mu g/m^3$ in $PM_{2.5}$ concentration, with strongest associations seen on the day of exposure. It was estimated that a mean reduction in $PM_{2.5}$ of 3.9 $\mu g/m^3$ would prevent 7978 heart failure hospitalizations and save a third of a billion US dollars a year [41]. A recent observational study conducted in 26 Chinese cities between 2014 and 2015 found similar results [42]. In addition to global

heart failure, right ventricular structure and function is also altered by air pollution. Magnetic resonance imaging of right ventricular structure of patients included in the multicenter prospective cohort study MESA (Multi-ethnic Study of Atherosclerosis) suggested an association between levels of NO_2 exposure and increased right ventricular mass and larger right ventricular end-diastolic volume [43].

4.4. Cerebrovascular diseases

The Women's Health Initiative Observational Study performed in United States first reported one of the largest cohort that allowed an estimation of stroke and death due to cerebrovascular disease, and identified a correlation between $PM_{2.5}$ exposure and concentration and stroke [33]. In a meta-analysis of 94 studies from 28 countries, including 6.2 million of stroke events, increase in $PM_{2.5}$ and PM_{10} concentrations was associated with hospital admission and mortality [44]. Similar association was identified with proximity to major roadways and poverty [45,46]. Older people may be at greater risk of cerebrovascular disease. In the ESCAPE cohort, there was a 40% increase in stroke per 5 $\mu g/m^3$ increase exposure to $PM_{2.5}$ in subjects $\geq$60 years of age [47]. Again, this increased risk was present at lower concentrations than set by the current air quality limit value [47].

4.5. Insulin resistance and diabetes

In a meta-analysis of cohort studies involving >2 million participants, the relative risk for incident type 2 diabetes mellitus increased by 39%, 34% and 11% per 10 $\mu g/m^3$ increment of concentrations of $PM_{2.5}$, PM_{10} and NO2, respectively [48]. Similar results were reported in a meta-analysis of 13 studies conducted in Europe or North America [49].

5. Interventions to reduce the cardiovascular impact of air pollution

Several studies have suggested that reducing exposure to outdoor air pollutant could lead to a significant decrease in cardiovascular morbidity and mortality. As already mentioned above, air pollution reduction during the 2008 Beijing Olympics led to a significant decrease in systemic inflammation and thrombosis [6], and oxidative stress [50]. Recently, the Lancet Commission on Pollution and Health reported a series of activities and interventions at different levels susceptible to reduce pollution and decrease mortality [4]. Societal and governmental interventions should include a reduction of traffic emission through transportation reform and shifting to clean fuel, urban landscape reform, and emission trading programs. Alternatively, personal interventions such as face mask and air purifiers [51], exercise and healthy diet may also mitigate the effects of pollution and particulate matter [52].

These activities should be led by multiple organizations and agencies involved in public health strategies in partnership with administrations. Populations and governments of low and middle-income countries should receive specific support and attention because of the impact of air pollution affects mainly their populations.

6. Conclusion

Air pollution is one of the most important cause of cardiovascular disease and premature death in the world and its impact continues to progress. Less-favored populations in low and middle-income countries and low socioeconomic level populations are at the higher risk of pollution-associated morbidity and mortality. Aggressive policies aiming at the reduction of fossil fuel consumption to decrease fine particle emission and global warming should be on the top list of the world leaders' agenda. However, these initiatives frequently face major economic and politic obstacles that might ultimately endanger the health of current and future world populations [53].

Declaration of Competing Interest

The authors declare that they have no conflicts of interest. AC is a member of the Collège International de Recherche Servier (CIRS).

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References

[1] WHO air quality guidelines - global update 2018, last accessed Nov 30th 2018.
[2] Brook RD, Rajagopalan S, Pope 3rd CA, Brook JR, Bhatnagar A, Diez-Roux AV. et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 2010;121:2331–78.
[3] Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 2017;389:1907–18.
[4] Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, et al. The Lancet Commission on pollution and health. Lancet 2018;391:462–512.
[5] Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:2054–70.
[6] Rich DQ, Kipen HM, Huang W, Wang G, Wang Y, Zhu P, et al. Association between changes in air pollution levels during the Beijing Olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA 2012;307:2068–78.
[7] Lucking AJ, Lundback M, Mills NL, Faratian D, Barath SL, Pourazar J, et al. Diesel exhaust inhalation increases thrombus formation in man. Eur Heart J 2008;29:3043–51.
[8] Krishnan RM, Sullivan JH, Carlsten C, Wilkerson HW, Beyer RP, Bammler T, et al. A randomized cross-over study of inhalation of diesel exhaust, hematological indices, and endothelial markers in humans. Part Fibre Toxicol 2013;10:7.
[9] Mills NL, Tornqvist H, Gonzalez MC, Vink E, Robinson SD, Soderberg S, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. N Engl J Med 2007;357:1075–82.
[10] Lakey PS, Berkemeier T, Tong H, Arangio AM, Lucas K, Poschl U, et al. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. Sci Rep 2016;6:32916.
[11] Haberzettl P, Conklin DJ, Abplanalp WT, Bhatnagar A, O'Toole TE. Inhalation of fine particulate matter impairs endothelial progenitor cell function via pulmonary oxidative stress. Arterioscler Thromb Vasc Biol 2018;38:131–42.
[12] Haberzettl P, O'Toole TE, Bhatnagar A, Conklin DJ. Exposure to fine particulate air pollution causes vascular insulin resistance by inducing pulmonary oxidative stress. Environ Health Perspect 2016;124:1830–9.
[13] Peretz A, Sullivan JH, Leotta DF, Trenga CA, Sands FN, Allen J, et al. Diesel exhaust inhalation elicits acute vasoconstriction in vivo. Environ Health Perspect 2008;116:937–42.
[14] O'Toole TE, Hellmann J, Wheat L, Haberzettl P, Lee J, Conklin DJ, et al. Episodic exposure to fine particulate air pollution decreases circulating levels of endothelial progenitor cells. Circ Res 2010;107:200–3.
[15] Cai Y, Zhang B, Ke W, Feng B, Lin H, Xiao J, et al. Associations of short-term and long-term exposure to ambient air pollutants with hypertension: a systematic review and meta-analysis. Hypertension. 2016;68:62−70.
[16] Chen H, Burnett RT, Kwong JC, Villeneuve PJ, Goldberg MS, Brook RD, et al. Spatial association between ambient fine particulate matter and incident hypertension. Circulation 2014;129:562–9.
[17] Yang BY, Qian Z, Howard SW, Vaughn MG, Fan SJ, Liu KK, et al. Global association between ambient air pollution and blood pressure: a systematic review and meta-analysis. Environ pollution (Barking, Essex: 1987) 2018;235:576–88.
[18] Perez CM, Hazari MS, Farraj AK. Role of autonomic reflex arcs in cardiovascular responses to air pollution exposure. Cardiovasc Toxicol 2015;15:69–78.
[19] Ying Z, Xu X, Bai Y, Zhong J, Chen M, Liang Y, et al. Long-term exposure to concentrated ambient PM2.5 increases mouse blood pressure through abnormal activation of the sympathetic nervous system: a role for hypothalamic inflammation. Environ Health Perspect 2014;122:79–86.
[20] Romieu I, Moreno-Macias H, London SJ. Gene by environment interaction and ambient air pollution. Proc Am Thorac Soc 2010;7:116–22.
[21] Su MW, Tsai CH, Tung KY, Hwang BF, Liang PH, Chiang BL, et al. GSTP1 is a hub gene for gene-air pollution interactions on childhood asthma. Allergy 2013;68:1614–7.
[22] Levinsson A, Olin AC, Modig L, Dahgam S, Bjorck L, Rosengren A, et al. Interaction effects of long-term air pollution exposure and variants in the GSTP1, GSTT1 and GSTCD genes on risk of acute myocardial infarction and hypertension: a case-control study. PLoS One 2014;9:e99043.
[23] Kerkhof M, Postma DS, Brunekreef B, Reijmerink NE, Wijga AH, de Jongste JC, et al. Toll-like receptor 2 and 4 genes influence susceptibility to adverse effects of traffic-related air pollution on childhood asthma. Thorax 2010;65:690–7.
[24] GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks

or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1659–724.
[25] Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. Air pollution and mortality in the Medicare population. N Engl J Med 2017;376:2513–22.
[26] Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ Health Perspect 2012;120:708–14.
[27] Di Q, Dai L, Wang Y, Zanobetti A, Choirat C, Schwartz JD, et al. Association of short-term exposure to air pollution with mortality in older adults. JAMA 2017;318:2446–56.
[28] Samoli E, Peng R, Ramsay T, Pipikou M, Touloumi G, Dominici F, et al. Acute effects of ambient particulate matter on mortality in Europe and North America: results from the APHENA study. Environ Health Perspect 2008;116:1480–6.
[29] Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. JAMA 2012;307:713–21.
[30] Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 2011;377:732–40.
[31] Tonne C, Wilkinson P. Long-term exposure to air pollution is associated with survival following acute coronary syndrome. Eur Heart J 2013;34:1306–11.
[32] Pope CA, Muhlestein JB, Anderson JL, Cannon JB, Hales NM, Meredith KG, et al. Short-term exposure to fine particulate matter air pollution is preferentially associated with the risk of ST-segment elevation acute coronary events. J Am Heart Assoc 2015;4.
[33] Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 2007;356:447–58.
[34] Cesaroni G, Forastiere F, Stafoggia M, Andersen ZJ, Badaloni C, Beelen R, et al. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project. BMJ 2014;348:f7412.
[35] Kaufman JD, Adar SD, Barr RG, Budoff M, Burke GL, Curl CL, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study. Lancet 2016;388:696–704.
[36] Hart JE, Chiuve SE, Laden F, Albert CM. Roadway proximity and risk of sudden cardiac death in women. Circulation 2014;130:1474–82.
[37] Shao Q, Liu T, Korantzopoulos P, Zhang Z, Zhao J, Li G. Association between air pollution and development of atrial fibrillation: a meta-analysis of observational studies. Heart Lung 2016;45:557–62.
[38] Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, et al. Expert position paper on air pollution and cardiovascular disease. Eur Heart J 2015;36:83–93b.
[39] Anderson HR, Armstrong B, Hajat S, Harrison R, Monk V, Poloniecki J, et al. Air pollution and activation of implantable cardioverter defibrillators in London. Epidemiology 2010;21:405–13.
[40] Zanobetti A, Stone PH, Speizer FE, Schwartz JD, Coull BA, Suh HH, et al. T-wave alternans, air pollution and traffic in high-risk subjects. Am J Cardiol 2009;104:665–70.
[41] Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, et al. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 2013;382:1039–48.
[42] Liu H, Tian Y, Song J, Cao Y, Xiang X, Huang C, et al. Effect of ambient air pollution on hospitalization for heart failure in 26 of China's largest cities. Am J Cardiol 2018;121:628–33.
[43] Leary PJ, Kaufman JD, Barr RG, Bluemke DA, Curl CL, Hough CL, et al. Traffic-related air pollution and the right ventricle. The multi-ethnic study of atherosclerosis. Am J Respir Crit Care Med 2014;189:1093–100.
[44] Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ 2015;350:h1295.
[45] Kulick ER, Wellenius GA, Boehme AK, Sacco RL, Elkind MS. Residential proximity to major roadways and risk of incident ischemic stroke in NOMAS (The Northern Manhattan Study). Stroke 2018;49:835–41.
[46] Wing JJ, Sanchez BN, Adar SD, Meurer WJ, Morgenstern LB, Smith MA, et al. Synergism of short-term air pollution exposures and neighborhood disadvantage on initial stroke severity. Stroke 2017;48:3126–9.
[47] Stafoggia M, Cesaroni G, Peters A, Andersen ZJ, Badaloni C, Beelen R, et al. Long-term exposure to ambient air pollution and incidence of cerebrovascular events: results from 11 European cohorts within the ESCAPE project. Environ Health Perspect 2014;122:919–25.
[48] Wang B, Xu D, Jing Z, Liu D, Yan S, Wang Y. Effect of long-term exposure to air pollution on type 2 diabetes mellitus risk: a systemic review and meta-analysis of cohort studies. Eur J Endocrinol 2014;171:R173–82.
[49] Eze IC, Hemkens LG, Bucher HC, Hoffmann B, Schindler C, Kunzli N, et al. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-analysis. Environ Health Perspect 2015;123:381–9.
[50] Huang W, Wang G, Lu SE, Kipen H, Wang Y, Hu M, et al. Inflammatory and oxidative stress responses of healthy young adults to changes in air quality during the Beijing Olympics. Am J Respir Crit Care Med 2012;186:1150–9.
[51] Hadley MB, Baumgartner J, Vedanthan R. Developing a clinical approach to air pollution and cardiovascular health. Circulation 2018;137:725–42.
[52] Tong H. Dietary and pharmacological intervention to mitigate the cardiopulmonary effects of air pollution toxicity. Biochim Biophys Acta 1860;2016:2891–8.
[53] Samet JM, Burke TA, Goldstein BD. The Trump administration and the environment - heed the science. N Engl J Med 2017;376:1182–8.