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Impact of the exposome on cardiovascular disease

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Air pollution, noise pollution, and light pollution have emerged as important but often overlooked risk factors for cardiovascular disease. In this review, we examine the emerging concept of the exposome, highlighting the close relationship between environmental exposure (e.g. $PM_{2.5}$, traffic noise, and night light) and cardiovascular disease, finally addressing the possible mitigation strategies that should be implemented to reduce the impact of air, noise, and light pollution on cardiovascular morbidity and mortality.

The concept of the exposome

Based on the growing awareness of the impact of environmental risk factors on human health, the exposome concept was introduced to identify an emerging research field that studies the effects of all environmental exposures on human health, such as air, noise, and light pollution.[1,2]

Air pollution is a complex mixture of particulate matter and gaseous material released into the environment by human activities, which includes environmental and household pollution.[3]Air pollution is the fourth leading cause of morbidity and mortality worldwide and, notably, more than 50% of these deaths can be attributed to cardiovascular disease (CVD).[4] Among the different components of air pollution, particulate matter with an aerodynamic diameter of 2.5 μm ($PM_{2.5}$) is the one with the strongest association with CVD. In fact, multiple evidences link exposure to $PM_{2.5}$ with an increased susceptibility to the development of coronary atherosclerosis and the progression of high-risk plaques.[5] Specifically, exposure to $PM_{2.5}$ can generate free radicals, including reactive oxygen species (ROS). This increased free radical production induces mitochondrial damage in macrophages, oxidation of circulating lipoproteins (ox-LDL) and foam cell apoptosis thus leading to the growth of necrotic core lipids in atherosclerotic plaques.

Furthermore, pulmonary exposure to $PM_{2.5}$, through the production of pro-inflammatory mediators, is able to stimulate the release of monocytes from the bone marrow and their activation and migration towards atherosclerotic plaques. $PM_{2.5}$ also determines the activation of the vascular endothelium responsible for the adhesion and migration of circulating leucocytes within atherosclerotic plaques. This pro-inflammatory vascular state determines a greater susceptibility to destabilization of atherosclerotic plaques and/or to the occurrence of thrombotic events, thus leading to a greater risk of acute ischaemic cardiac events.

Noise pollution may synergize with air pollution to mediate an increased risk of atherosclerosis and CVD.[6] Traffic noise can activate a stress chain response involving the hypothalamus, limbic system, and autonomic nervous system leading to activation of the hypothalamic–pituitary–adrenal axis and sympathetic–adrenal medulla axis, leading to increased heart rate and stress hormone levels, increased platelet reactivity, vascular inflammation, and oxidative stress.[7] A recent study reported that combined exposure to air and noise pollution is significantly associated with a greater risk of cardiovascular (CV) events than exposure to either or none of them; effect mainly mediated by arterial inflammation.[8] The adverse effects of traffic noise are more significant during the night, possibly due to sleep–wake cycle disruptions, sleep deprivation, and/or fragmentation and disruption of critical time periods for physiological and mental recovery.[9] In fact, a recent study demonstrated that exposure to aircraft noise at night increases vascular and brain oxidative stress through NOX [nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX)] activation and promotes vascular dysfunction leading to an increased risk of CV events.[10,11]

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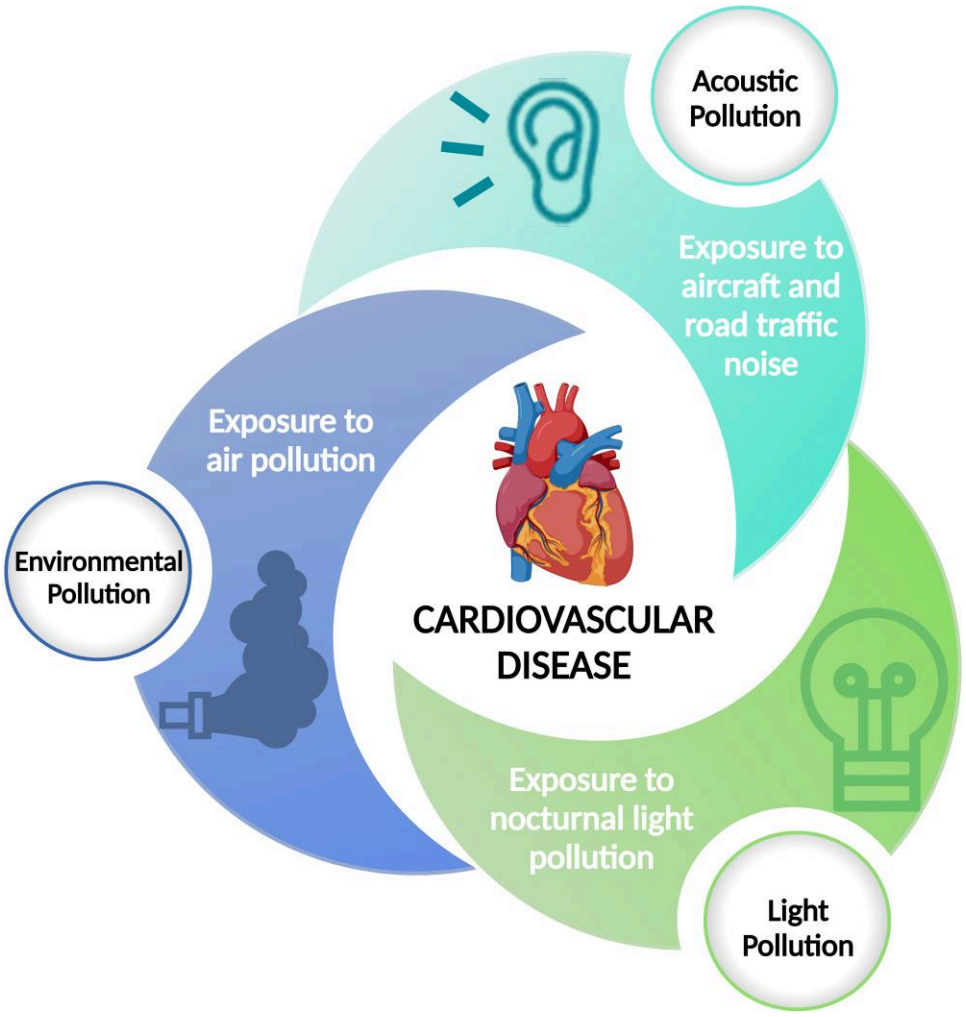

Finally, nocturnal light pollution is a potential risk factor for health, since light at night suppresses melatonin secretion and disrupts circadian rhythms; studies suggest that disruption of circadian rhythms may be associated with a higher risk of CVD. Considering this evidence, it is plausible that light at night may be an unrecognized risk factor for CVD; however, few studies have evaluated this hypothesis.

The purpose of this review is to address the concept of exposome, highlighting the close relationship between CVD and environmental exposure such as $PM_{2.5}$, noise pollution, and nocturnal light pollution, emphasizing the pathophysiological mechanisms and possible strategies of mitigation. Studying the mechanisms by which environmental, water, and light pollution mediate CV damage could pave the way for the development of new therapeutic strategies aimed at reducing the impact of the exposome on CV mortality worldwide (Central Figure).

Current evidence linking the exposome to cardiovascular disease

Environmental pollution

The health impact of urban air pollution, particularly from combustion, has been increasingly studied in recent years due to high urban population densities and rising levels of emissions from traffic worldwide. Particulate matter includes both organic and inorganic particles and the aerodynamic diameter is fundamental for its toxic effects; in particular, $PM_{2.5}$ and $PM_{0.1}$, being very small particles, could substantially contribute to the onset of CVD due to their ability to penetrate deeply into the alveoli and get directly into the bloodstream, causing damage and tissue and cellular dysfunction away from the lungs.[12]

Furthermore, a key determinant of the harmful effect of $PM_{2.5}$ on the CV system is the different exposure kinetics. Indeed, short-term exposure to $PM_{2.5}$ (hours) has been strongly associated with the risk of acute coronary syndrome (ACS), as immediate responses to $PM_{2.5}$ exposure are all potential initiators and promoters of atherothrombotic events (renal sympathetic activation, release of inflammatory mediators into the circulation, endothelial dysfunction, release of pro-coagulant proteins, and platelet activation).[13,14] However, acute exposure to $PM_{2.5}$ could trigger an ACS in the context of long-term chronic exposure (years), favouring the progression of the atherosclerotic burden and leading to the development of vulnerable plaque features and potentiating the deleterious effects of other traditional CV risk factors.[5,15]

Furthermore, the dose of exposure to air pollutants appears to be extremely relevant. Many epidemiological studies have demonstrated that rising levels of $PM_{2.5}$ are strongly associated with clinical markers of atherosclerosis, increased risk of myocardial infarction, and CV mortality.[18] The $PM_{2.5}$ dose–response curve demonstrates a non-linear relationship, with a sharp rise at low concentrations and flattening at higher levels, although there is no lower concentration threshold below which exposure can be considered safe.[16,17] In fact, the negative effects of $PM_{2.5}$ can also occur with exposure levels lower than the standards recommended by the WHO of 5 $\mu g/m^3$ per year.[18] Several studies have demonstrated a significant association between exposure to $PM_{2.5}$ and the progression of atherosclerotic plaques, making use of different imaging techniques such as computed tomography (CT) which allows the assessment of coronary calcium levels (CAC). Coronary calcium level is probably the best surrogate for atherosclerosis and has been shown to be a strong predictor of future CV events, as calcium-rich plaques tend to progress faster. In this regard, the Multi-Ethnic Study of Atherosclerosis (MESA) Air Pollution is the largest study that has evaluated the association between $PM_{2.5}$ and CAC. However, its results are inconsistent and CAC progression remains a surrogate for total atherosclerotic burden rather than plaque vulnerability; as a result, it may not accurately reflect the mechanism by which $PM_{2.5}$ mediates ACS risk and may rather be an indicator of other mechanisms. To overcome these limitations, intracoronary imaging techniques have been used to study plaque characteristics *in vivo*, in order to identify signs of plaque vulnerability after exposure to $PM_{2.5}$. Recently, our group evaluated the relationship between long-term exposure to air pollutants and coronary instability mechanisms assessed by optical coherence tomography (OCT) in patients with ACS and demonstrated that patients with plaque rupture (PR) as a mechanism of plaque instability were chronically exposed to significantly higher $PM_{2.5}$ levels than those with plaques with intact fibrous cap. $PM_{2.5}$ has been independently associated with PR and the presence of fibro-atheroma with a thin fibrous cap and the number of macrophages in the culprit plaque and with higher serum C-reactive protein (CRP) levels.[15]

Acoustic pollution

Due to constant urban growth and the increase in the demand for mobility of products and people, noise pollution is constantly increasing. The European Union in 2020 estimated that about 20% of the European population is exposed to traffic noise levels >55 dB and this number is probably underestimated.[19] In 2018, the guidelines for environmental noise were published by WHO; in this document, a consensus of experts highlighted, on the basis of various meta-analyses, how there is an association between road traffic noise and CVD, calculating a relative risk of CVD of 1.08 (95% CI 1.01–1.15) for an increase of 10 dB starting from the threshold value of 53 dB.[19] A study published in 2020 highlighted the key role of amygdala activation in mediating vascular inflammation and CV pathology in response to high noise exposures. A cohort of 498 adults was studied using 18-F-fluorodeoxyglucose PET-CT to assess amygdala activation and arterial (aortic) inflammation. Higher exposure to noise pollution was associated with higher levels of amygdala activation, aortic inflammation, and risk of major adverse cardiovascular events (HR 1.341, 95% CI 1.147–1.567, for a 5 dB increase).[9] In 2020, the European Society of Cardiology (ESC) guidelines on chronic coronary syndromes recognized noise pollution as a risk factor for CVD, stressing the importance of adopting policies aimed at reducing environmental noise and air pollutants.

Noise pollution is the subject of increasing studies suggesting that night-time aircraft noise can trigger fatal cardiovascular events.[20] The pathogenetic mechanisms with which noise pollution negatively affects health are stress and nocturnal sleep disturbance, with consequent activation of the hypothalamic–pituitary–adrenal axis with an increase in cortisol blood values and an increase in the secretion of pro-inflammation such as IL-1β and IL-6 and increased oxidative stress. In a randomized double-blind study, it was demonstrated that exposure to nocturnal noise pollution (aircraft noise) is associated with endothelial dysfunction in patients at risk of CVD.[21] Several works have shown the association between noise pollution and increased risk of arterial hypertension, dyslipidaemia, obesity, and type II diabetes mellitus.[19] Noise pollution, therefore, not only acts directly on the CV system but also indirectly, increasing the risk of developing CV risk factors considered traditional.

Light pollution

It is now known that nocturnal light pollution, through the alteration of melatonin secretion, is associated with alterations of the circadian rhythm and the sleep–wake cycle; these pathophysiological changes are associated with an increased risk of developing neoplasms, psychiatric disorders, metabolic syndrome, and increased blood pressure.[22] Several studies have suggested that these circadian rhythm alterations may be associated with an increased CV risk.[23,24] A cohort study with 58 629 patients evaluated the association between exposure to nocturnal light pollution and the risk of CVD incidence and CV mortality. In the 11 years of follow-up, 3772 hospitalizations for CVD and 1695 deaths for CVD causes were recorded demonstrating how exposure to nocturnal light pollution is associated with an increased risk of hospitalization for CVD with a hazard ratio of 1.11 (95% CI 1.03–1.18) and 1.10 for CV mortality (95% CI 1.00–1.22).[22]

While for environmental and noise pollution there is a large and solid evidence of their association with the increased risk of CVD, there are only a few studies investigating the role of nocturnal light pollution in CV pathology and new evidence is needed to corroborate this thesis.

Public and government risk mitigation strategies

Reducing the impact of the exposome with a primary prevention strategy through the implementation of social and governmental interventions is the main objective that should be pursued.[25] These interventions include urban planning reforms, the shift to renewable and clean energy sources, transport reforms that promote the use of low- and zero-emission vehicles and the limitation of traffic in city centres, and the reduction of traffic emissions

through the use of diesel particle traps, catalytic converters, or alternative fuels.

Vehicular traffic (cars, trains, and planes) is the main source of noise pollution and a growing public health problem. Given that car traffic is strongly linked to both noise and air pollution, the implementation of the same government strategies to reduce air pollution could also be effective for noise pollution, especially for transport, infrastructure reforms, and urban landscape. Furthermore, specific interventions to reduce noise pollution could include noise barriers in densely populated areas and near sensitive areas such as schools and hospitals, the insulation of buildings from noise, speed limits and the application of silent road surfaces. To reduce noise caused by aircraft, specific measures could include a ban on night air traffic (as noise during the night is associated with the most pronounced health effects), scaling up of new engine technologies, and improved air traffic management.[10] However, the implementation of these measures inevitably takes time and therefore the implementation of personal measures is crucial, especially for those individuals who may be more sensitive, such as patients with a previous history of coronary heart disease, pregnant women, and the elderly.

Personal exposure mitigation strategies

Current approaches include active personal exposure mitigation with the use of home air purifiers, face masks, and behavioural modifications to reduce passive exposures. While these strategies are readily available, relatively inexpensive, and highly effective, they are often overlooked. The use of FFP2 masks has been shown to improve systemic blood pressure at both high and low exposure levels of $PM_{2.5}$.[26] Portable or stationary air purifiers such as high-efficiency particulate air (HEPA) filters are a promising and cost-effective method that can significantly lower indoor $PM_{2.5}$ levels.

Behavioural strategies include closing car windows and home windows, using air conditioning filters, changing travel routes, staying indoors, and lifestyle changes, including physical exercise in green areas away from main roads.

Noise pollution can be reduced with simple gestures, such as turning off electronic devices when they are not in use, closing the doors when using noisy machines (dishwashers or washing machines) or turning them on before leaving the house, using earplugs or headphones to reduce loud noises, turn down the volume when listening through headphones or loudspeakers, and do not stay in noisy areas (industries or airports).

To reduce light pollution, personal mitigation strategies could be to use dimmers, motion sensors, and timers to reduce average lighting levels and save even more energy. Switching to LED lighting allows you to dim the lighting without compromising visibility. Turning off unnecessary interior lighting—particularly in offices at night—helps reduce overall light pollution. Another strategy may be to keep the shutters closed at night, after sunset, to prevent the internal lights from contributing to the light pollution of the external environment. Finally, night mode should be used on all devices, such as computers, tablets, and smartphones, as these have the potential to contribute as much, if not more, to light pollution than room lights.

Conclusions and future directions

From a clinical perspective, there is a strong need for randomized controlled trials to demonstrate the efficacy of specific exposome-targeted interventions, including personal equipment and/or drugs to reduce the incidence of CVD before their use can be recommended in clinical practice. Finally, social and governmental interventions aimed at reducing the burden of air pollutants are urgently needed, in order to decrease the significant impact of these environmental exposures on global CV morbidity and mortality.

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