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INVITED REVIEW

Environmental risk factors and cardiovascular diseases: a comprehensive expert review

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Abstract

Non-communicable diseases (NCDs) are fatal for more than 38 million people each year and are thus the main contributors to the global burden of disease accounting for 70% of mortality. The majority of these deaths are caused by cardiovascular disease (CVD). The risk of NCDs is strongly associated with exposure to environmental stressors such as pollutants in the air, noise exposure, artificial light at night, and climate change, including heat extremes, desert storms, and wildfires. In addition to the traditional risk factors for CVD such as diabetes, arterial hypertension, smoking, hypercholesterolaemia, and genetic predisposition, there is a growing body of evidence showing that physicochemical factors in the environment contribute significantly to the high NCD numbers. Furthermore, urbanization is associated with accumulation and intensification of these stressors. This comprehensive expert review will summarize the epidemiology and pathophysiology of environmental stressors with a focus on cardiovascular NCDs. We will also discuss solutions and mitigation measures to lower the impact of environmental risk factors with focus on CVD.

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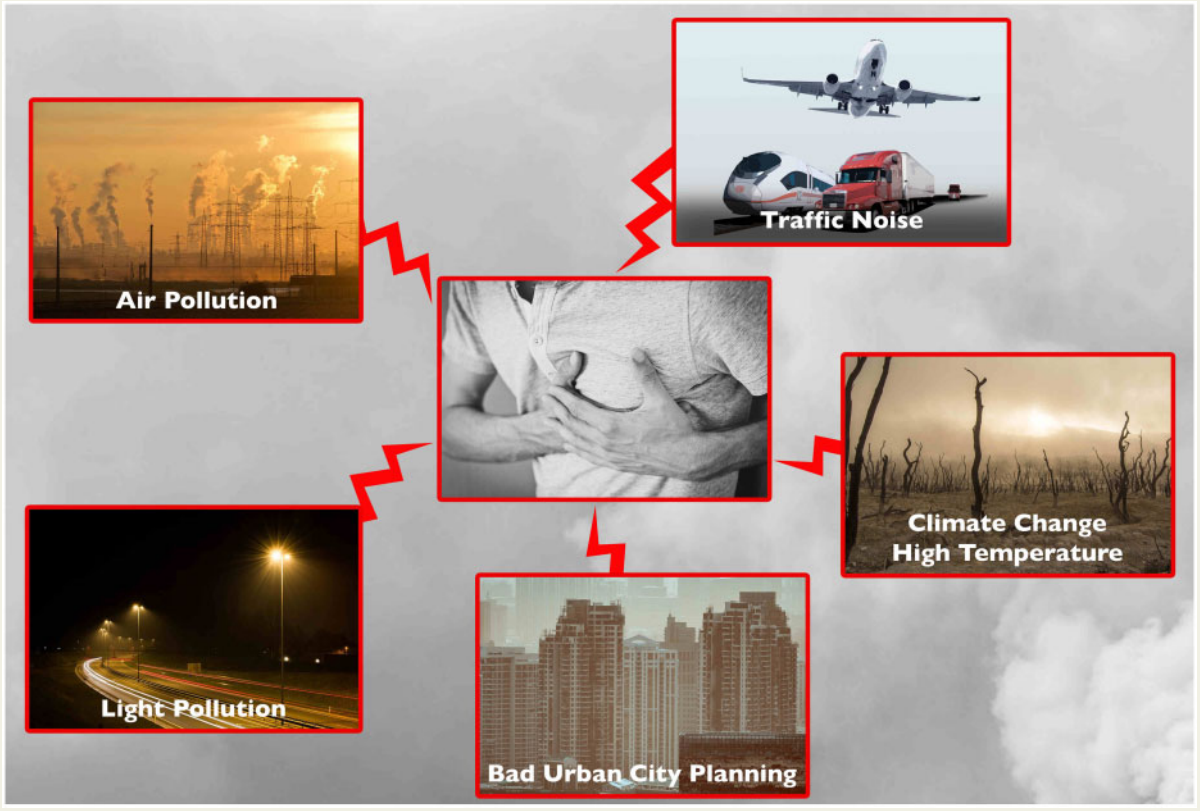
Graphical Abstract



Keywords Environmental stressors • Cardiovascular risk factors • Oxidative stress • Cardiovascular disease • Noise • Heat • Air pollution • Light pollution

1. Introduction

Cardiovascular diseases (CVDs), besides chronic respiratory and metabolic diseases, constitute a large part of non-communicable diseases (NCDs), including acute and chronic coronary artery disease, heart failure and arrhythmia, stroke and arterial hypertension. Importantly, 70% of annual global deaths (around 40 million people) can be attributed to NCDs and this share will further increase by 10% according to the World Health Organization (WHO) projections for the year 2030.[1] NCDs account for 80.6% [95% confidence interval (CI) 78.2–82.5] of age-standardized years lived with disability in 2016, as indicated by data of the global burden of disease (GBD) study.[2] CVDs are responsible for the majority of deaths that are caused by NCDs.[3] In the GBD study (2019 update), the contribution of CVDs to overall global mortality continuously increased from 12.1 million in 1990 to 18.6 million in 2019.[4] Interestingly, low- and middle-income countries have the highest share (86%) of premature deaths triggered by NCDs.[5,6] The economic burden caused by NCDs are severe, and may amount to global economic costs of $47 trillion within the coming 20 years.[7] Risk factors for NCDs are mostly originating from the environment, which is supported by observations that up to 25% of all ischaemic heart disease (IHD) are related to an unhealthy environment, especially to air pollution.[8] Nevertheless, the environmental share to NCDs is notoriously ignored as reflected by the failure to mention environmental risk factors in the 2013 WHO NCD Global Action Plan.[6] In addition research on, prevention of, and treatment of environmentally triggered NCDs are severely underfunded, relative to their disease burden in the general population.[9] This dramatic gap is now paid more attention by the emerging 'exposome' research field, investigating the life-long effects of all environmental exposures on biochemical pathways and health effects (*Figure 1*)[12,13] as well as 'healthy cities' campaigns.[14,15]

The exposome concept comprises a multiexposure perspective.[16] Besides external environmental risk factors (e.g. traffic noise and air pollution), our lifestyle and environmental factors on the whole (e.g. socioeconomic status and climate) also characterize the exposome of an individual,[10,17] the assessment of which requires a multidisciplinary approach using smart sensor devices, multi-OMICs techniques, and big data handling using bioinformatics and systems biology approaches.[18] In order to better address these multiexposure conditions, the refined 'envirome' concept was developed, which is defined by three consecutively nested domains, consisting of natural, social, and personal environments that are monitored in parallel and connected to biochemical changes and health effects using 'enviromics'.[19] Based on the increasing awareness of the major impact of environmental risk factors, the term

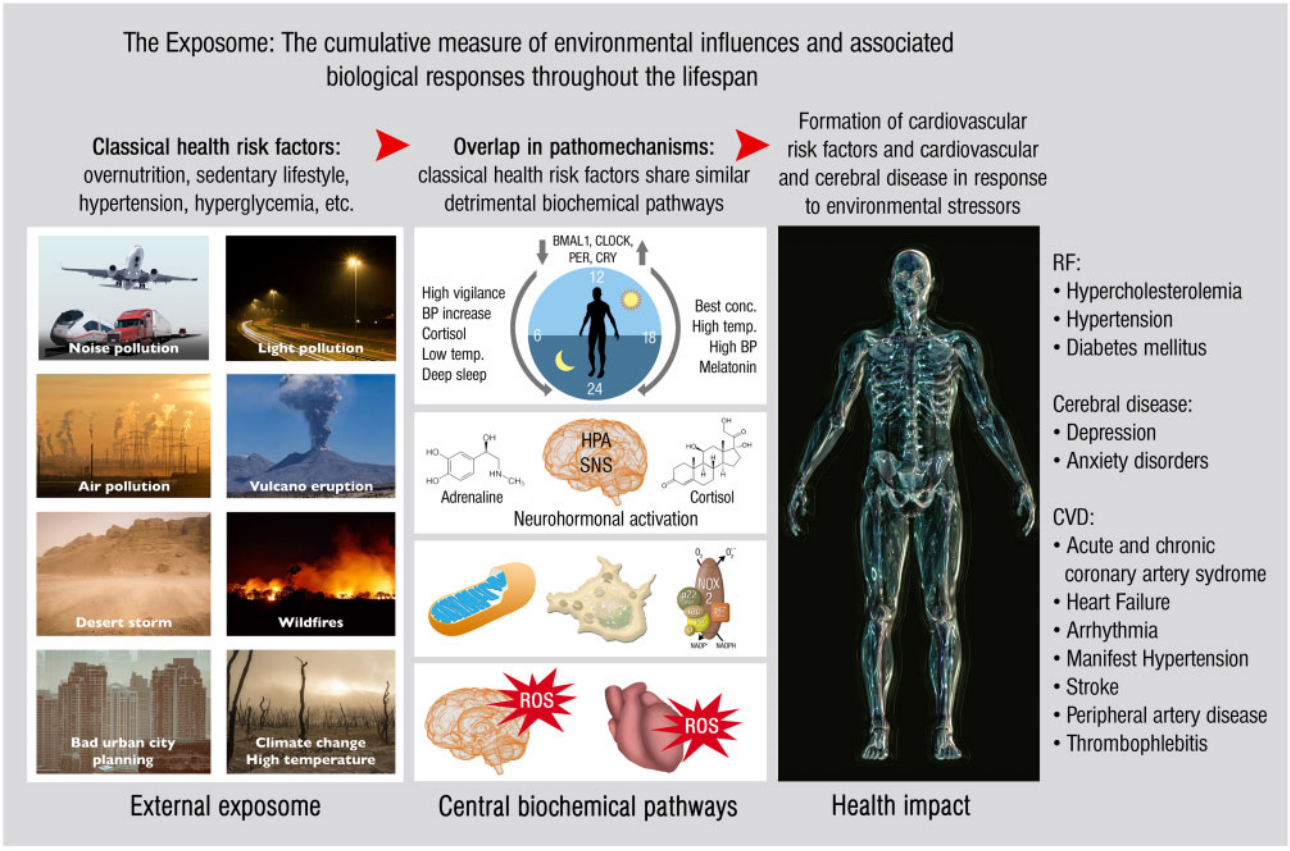


Figure 1 The exposome concept. Exposure to environmental risk factors (=external exposome) leads to changes of central biochemical pathways with associated health impact. The central biochemical pathways comprise changes in circadian clock genes leading to impaired rhythmicity and phase-shifts, stress hormone release (cortisol and catecholamines), production of reactive oxygen species by mitochondria and NADPH oxidase in activated immune cells, inflammation with tissue infiltration of activated immune cells, and oxidative damage in different organs. Because classical health risk factors share similar pathomechanisms, people with existing classical health risk factors or disease (e.g. diabetes or hypertension) may experience additive adverse health effects upon exposure to environmental risk factors. HPA, hypothalamic–pituitary–adrenal axis; NOX-2, phagocytic NADPH oxidase (isoform 2); ROS, reactive oxygen species; SNS, sympathetic nervous system. Merged and redrawn from previous reports refs[10,11] with permission; Copyright © 2020, The authors; Published by Elsevier B.V.

was coined 'Genetics load the gun, but the environment pulls the trigger'.[20]

This comprehensive expert review will summarize the epidemiology and pathophysiology of environmental stressors on NCDs, however without considering the contribution of other important environmental health risk factors, e.g. mental stress[21] and ionizing radiation (either by anticancer therapy[22] or ionospheric and geomagnetic exposures[23]). We will also discuss solutions and mitigation measures to lower the adverse health effects by environmental stressors with focus on CVDs.

2. Noise and cardiovascular risk

2.1 Epidemiological evidence for adverse effects of noise on our health

Noise pollution from traffic is an increasing public health problem. Road traffic noise is the dominant source of transportation noise-associated health effects, and mapping of the European Union (EU) in 2019 showed that 113 million Europeans (20%) are subjected to a burden of road traffic noise that exceeds the limit of 55 dB(A) (L_{DEN}: day-evening-night average) as suggested by the EU guideline.[24] This estimate is most likely underestimated, as the Environmental Noise Directive is not ubiquitously applied in all urban areas and roads in entire Europe.[24]

In 2018, a WHO expert panel stated that there was high quality of evidence to conclude that road noise was associated with IHD.[25] Based on a meta-analysis, the group of experts calculated that per 10 dB increase in road noise the relative risk (RR) for IHD was 1.08 (95% CI 1.01–1.15), starting at chronic exposure levels of 53 dB where significant health effects were observed. For noise from trains and aircrafts in relation to IHD, the expert panel ranked the quality of evidence as very low and low, respectively, due to few high-quality studies. However, recent studies covering Switzerland, the Rhine-Main region, and the island of Montreal have suggested that these noise sources may also be risk factors for myocardial infarction (MI), although results are not consistent and more evidence is needed.[26–28]

For all other cardiovascular health effects excluding IHD, the WHO group of experts found very low, low, or moderate evidence due to lack of high-quality studies.[25] However, high-quality studies have

subsequently emerged together with studies on new CVD outcomes and risk factors that were not studied in a noise context in the past, which we have summarized in the following Supplementary material online, *Table S1*.

Numerous studies addressed whether traffic noise is a risk factor for hypertension, but unfortunately using a cross-sectional design in most cases.[25] The WHO group of experts found >35 cross-sectional studies on traffic noise and hypertension, with a joined RR for prevalent hypertension of 1.05 (1.02–1.08) for road noise, but the quality level was judged as 'very low' due to the inherent problem of the cross-sectional design.[25] Later studies on noise and hypertension incidence have reported inconsistent results.[29–31] However, there is a large variation between the different studies with regard to the way hypertension was defined, which complicates reliable conclusions and warrants for more studies.

The quality of evidence for stroke incidence was by the WHO judged as moderate based on a single study that reported road noise to increase risk of stroke.[25] Subsequently, five studies on road traffic noise and incident stroke have been published: three large population-based studies that cover an entire region or country (London, Frankfurt, and Denmark) found road noise to aggravate stroke risk,[32–34] whereas smaller classical cohort studies from Sweden, Norway, and UK with a limited number of cases (900–1900) found no association.[35,36] Effects of noise on incident heart failure were not evaluated by WHO, but the few recent studies conducted have consistently showed transportation noise to increase the risk.[26,27,37–39] In contrast, the few studies investigating the impact of noise on atrial fibrillation have reported inconsistent results.[38,40]

Studies investigating transportation noise as a risk factor for cardiovascular death have been summarized in a meta-analysis from 2021.[41] This study reported a pooled RR for road traffic noise per 10 dB of 1.02 (0.97–1.08) for IHD mortality and 1.06 (0.94–1.20) for stroke mortality (based on cohort and case–control studies) suggesting that road noise is associated with a slightly increased risk of cardiovascular mortality. However, the quality level of evidence was judged as moderate and more longitudinal high-quality studies are required. Importantly, a study from 2021 investigating acute effects of aircraft noise led further support to noise from all sources of transportation as a risk factor of cardiovascular mortality.[42] The authors report that high aircraft noise exposure 2 h preceding death was found to trigger nighttime cardiovascular deaths, with an odds ratio of 1.44 (1.03–2.04) when comparing exposures >50 dB with <20 dB. As the first of its kind, this novel study needs to be reproduced.

Epidemiological studies suggest associations of transportation noise, mainly from road traffic, with several cardiovascular risk factors (Supplementary material online, *Table S2*). One of these is disturbance of sleep, which is hypothesized to be a key pathway through which noise is thought to impair the cardiovascular system.[43,44] A pooled analysis of polysomnographic studies on the adverse health effects of acute noise, found that the awakening probability was increased with greater exposure to road, rail, and aircraft noise.[45] The study also found an association of nighttime noise with severe sleep disturbance (self-reported questionnaires).

A cardiovascular risk factor consistently found associated with road noise is metabolic disease. A 2019 meta-analysis found a RR of 1.11 (1.08–1.15) per 10 dB higher road noise for incident diabetes based on five high-quality longitudinal studies.[46] In support of noise as an important metabolic risk factor, several studies have found road noise associated with adiposity markers and obesity.[47–50] Of note, results demonstrating that central obesity and waist circumference are associated with noise are more consistent than results on body mass index, which perfectly agrees with the concept that noise increases cortisol (stress hormone), which is known to cause mainly central obesity.

Some studies have reported on noise from all forms of transportation as a risk factor for an unhealthy lifestyle. According to two studies road noise exposure was associated with reduced physical activity, mainly with any leisure time sport and not intensity, implying that noise may influence whether people exercise at all.[51,52] Furthermore, a study suggested that road noise may potentially be associated with alcohol consumption and smoking.[53] More studies investigating noise-induced changes in health behaviour are important as these may represent an important link between noise and CVDs.

Lastly, studies have suggested that road noise may cause higher risk of depression.[26,54,55] However, a complicating factor in these studies is that they use different definitions of depression, e.g. interviews, self-reports, use of antidepressants, and hospital admissions, making between-study comparisons difficult, and a 2020 review judged that the evidence for an association may be insufficient for an overall conclusion.[56]

2.2 Mechanistic insights into noise-induced pathophysiology by clinical studies

The cognition of noise and the resulting cortical and sympathetic activation causes the generation of stress hormones (e.g. cortisol and catecholamines), with subsequent activation of the renin–angiotensin–aldosterone system. If chronically present, this pathway may first lead to development of cardiovascular risk factors (e.g. hyperglycaemia and hypercholesterolaemia), blood clotting factor activation, and high blood pressure, ultimately leading to MI, heart failure, arterial hypertension, arrhythmia, and stroke (*Figure 2A*).[62–64] Moreover, noise causes sleep disturbance, interferes with activities, and impairs communication, all of which can trigger annoyance and increased CVD risk. Recently, it was established that the limbic system, more precise the amygdala nuclei, becomes activated in response to transportation noise caused by cars and aircraft.[59] In this study, around 500 patients underwent a ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging investigation and the authors demonstrated that noise 'dose-dependently' increased amygdala activity, with coronary inflammation and major adverse cardiovascular events (e.g. CVD death, MI, stroke and coronary/peripheral revascularization) (*Figure 2B*).[59] In a subsequent investigation, the authors found that more pronounced resilience to chronic socioeconomic or environmental stressors such as transportation noise was clearly associated with lower risk for CVD events.[65]

Translational field studies found adverse effects of simulated noise from aircrafts and trains on vascular function, stress hormone release, sleeping quality, and inflammation markers in healthy subjects and coronary artery disease patients.[44,61,66] Furthermore, flow-mediated dilation (FMD) was found impaired by noise in an exposure dose-dependent manner, and the antioxidant vitamin C (2 g p.o.) significantly improved FMD, pointing to an important role of reactive oxygen species in this phenomenon (*Figure 2C*).[44,61] Proteomic analysis of plasma proteins revealed that redox, pro-thrombotic and pro-inflammatory pathways were significantly affected in noise-exposed subjects as compared with unexposed controls,[61] The impairment of cardiac function seemed to be aggravated by the number of noise events despite preserved average sound pressure level,[67] which may provide an explanation for the heart failure risk by transportation noise.[68]

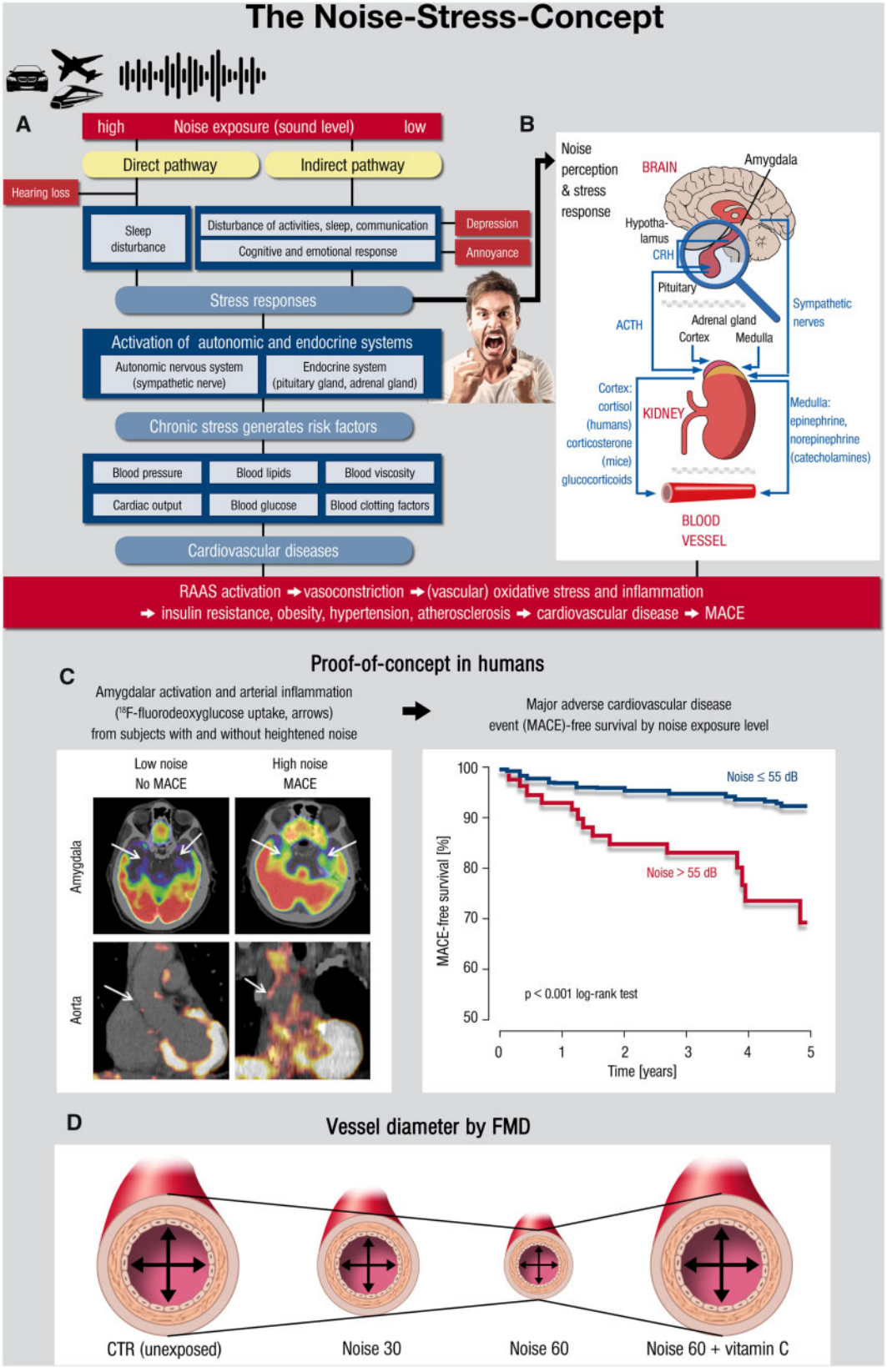


Figure 2 Noise–stress concept and the adverse health consequences in humans. (*A*) Noise reaction model for the direct (auditory) and indirect (non-auditory) effects of noise exposure. Adapted from ref.[57] with permission; Copyright © 2014, Oxford University Press. (*B*) Neuronal activation (arousals), e.g. by noise exposure, causes signalling via the hypothalamic–pituitary–adrenocortical (HPA) axis and sympathetic nervous system (SNS) via corticotrophin-releasing factor (CRF) in the pituitary gland and adrenocorticotropic hormone (ACTH) in the adrenal gland leading to activation of other neurohormones (e.g. the renin–angiotensin–aldosterone system), inflammation and oxidative stress. The adverse effects of cortisol (or corticosterone) and catecholamines

Figure 2 Continued
on cardiovascular function and molecular targets are well characterized. Adapted from ref.[58] with permission; Copyright © 2013, Campos-Rodríguez *et al.*; Creative Commons Attribution License (CC BY). (*C*) Neuronal activation (arousals) and subsequent atherosclerosis with a higher cardiovascular risk by noise exposure was proven in subjects by ^{18}F-PET scans indicating an association of amygdala activation, coronary inflammation, and increased incidence of major adverse cardiovascular events (MACE). Adapted from refs[59,60] with permission; Copyright © 2019, Oxford University Press. (*D*) Flow-mediated dilation (FMD) is measured by high-resolution B-mode ultrasound. Schematic presentation of adverse effects of simulated nighttime aircraft or train noise (either 30 or 60 events for one night) vs. unexposed control group (CTR) on FMD of the brachial artery in response to post-ischaemic hyperaemia and the beneficial acute effects of the antioxidant vitamin C. Results of own studies refs.[44,61]

It has been found that these noise-induced adverse health effects correlate with higher circulating cortisol levels and more pronounced noise sensitivity.[69,70] A Swiss cohort study (SAPALDIA) demonstrated that traffic noise and air pollution were associated with alterations of epigenetic DNA changes priming the tissues for altered inflammatory cascades and changes of immune responses.[71] The SAPALDIA consortium also found that intermittent nighttime railway and road noise may affect arterial stiffness as shown by measurement of pulse wave velocity.[72] These data were supported by results of a German cohort study, which found an association between nighttime traffic noise and subclinical atherosclerosis.[73,74] Altogether these studies support the concept that psychological stress in general and noise exposure in particular promotes the release of stress hormones, the activation and recruitment of immune cells and impairs cardiovascular function in men. This concept is also in accordance with the observation that the severity of immunological changes in response to psychological stressors correlates with the number of cardiovascular events.[75,76]

2.3 Cardiovascular effects of transportation noise exposure: mechanistic insights from animal studies

Early animal studies demonstrated that chronic noise exposure (85 dB(A) for 4 weeks to 9 months) caused a persistent increase in blood pressure in monkeys[77] or rats.[78] When rats were exposed to white noise (100 dB(A) for 1–4 weeks) an impaired endothelium-dependent vasodilation of the thoracic aorta[79] and the mesenteric artery[80] could be observed. These previous landmark studies are in accordance with strong evidence suggesting that background noise levels ≥42 dB(A) in animal housing buildings may induce a significant pathophysiology based on hypertension, impaired vascular function, endocrine stress responses, but also modulation of the immune system, slower wound healing, impaired fertility, and reproduction.[81] More animal studies on noise effects (≤100 dB(A)) can be found in Supplementary material online, *Table S3*.

Mouse studies conducted by Münzel *et al.*[82] showed dysregulation of vascular gene networks by noise (revealed by RNAseq) and downstream impairment of endothelial/vascular signalling. Their data also clearly showed that noise exposure of sleeping mice but not during their activity phase causes more pronounced cardiovascular complications via major pathomechanisms comprising endothelial dysfunction, oxidative stress, and inflammation in the vasculature as well as in the brain and by dysregulated *Foxo3*/circadian clock signalling (identified by RNAseq).[83] These adverse effects of noise were mostly normalized by *Nox2* knockout, supporting a major role of phagocytic cells. They also reported normalization of noise-induced microvascular dysfunction (in dorsal and cerebral arterioles), proinflammatory changes of the plasma proteome, and endothelial adhesion of leucocytes in Nox2 deficient mice.[84] This proposed concept was confirmed using a mouse model with lysozyme M (LysM)-specific overexpression of an inducible diphtheria toxin receptor (LysM^{iDTR} mice) allowing specific removal of LysM-positive myelomonocytic cells by diphtheria toxin treatment.[85] Detailed flow cytometric analysis demonstrated that genetic ablation of LysM-positive monocytes/macrophages prevented vascular inflammation and oxidative stress but also impaired endothelium-dependent relaxation and increased blood pressure in the peripheral circulation but failed to prevent neuroinflammation and stress hormone release in the brain as activation of microglia by noise was not suppressed in LysM^{iDTR} mice. Aircraft noise also caused lower expression and uncoupling of the neuronal nitric oxide synthase, which may explain at least in part the impaired cognitive development of noise-exposed children.[83] Of note, noise-dependent development of inflammation and oxidative stress, impairment of endothelial function and onset of hypertension were all improved by heme oxygenase-1 induction (using hemin) and NRF2 activation (using dimethyl fumarate).[86]

As the pathomechanisms of noise-induced cardiovascular damage show large overlap with traditional risk factors for cardiovascular events, such as diabetes,[87] hypertension,[88] and hypercholesterolaemia,[89] it may be speculated that noise exposure on top of an established CVD or risk factor contributes to accelerated vascular/cerebral atherosclerosis and neurodegenerative disease and adds to the severity of these disease in an additive manner. In line with this concept noise exposure has been found to aggravate arterial hypertension and all associated cardiovascular as well as cerebral complications in a mouse model of angiotensin-II infusion.[90] A similar observation was made regarding the more pronounced impairment of endothelial dysfunction by nighttime aircraft noise in coronary artery disease patients in comparison with healthy controls.[44,66]

3. Air pollution

3.1 Air pollution components

Air pollutants have been known since antiquity but their sources and composition have largely evolved with industrialization and urbanization and the generation of anthropogenic (combustion-derived) air pollutants that are now a major public health concern.[91] Air pollution is the result of complex chemical reactions of components from various emissions requiring new classification criteria of fine particles that are not solely based on size or mass of these particles but on the surface reactivity, loading with toxic contaminants such as transition metals or bacterial/fungal pyrogens.[92] Over 90% of the urban pollutant mass comes from gases or vapour-phase compounds such as O_3, $^{*}NO_2$, volatile organic compounds (e.g. benzene), CO, and SO_2. Combustion emissions that contain ultrafine particles (UFPs) or $PM_{0.1}$ (PM < 0.1 μm in diameter) display the most potent toxic cardiovascular capacity due to the high particle number, reactive surface (e.g. pro-oxidative) and high surface/mass ratio that together with high solubility and charge, facilitate the alveolar penetration, systemic circulation, and damage of various end organs by

these UFPs.[92] Importantly, CO is toxic at excessive levels that normally do not occur in ambient air. Its toxicity differs from that of other air pollutants, which e.g. exert oxidative stress. CO displaces O_2 in haemoglobin, depriving organs from oxygen. Additive effects of CO with $^{\bullet}NO_2$, O_3, and $PM_{2.5}$ are not expected. This may be different for oxidants such as $^{\bullet}NO_2$, O_3, and $PM_{2.5}$ components that generate reactive oxygen species. There is a need to address this issue through toxicological, modelling and epidemiological studies.[93–95] Importantly, the degree of air pollution is significantly modified by climate changes (highly reactive pollutants are formed by hot weather and high UV radiation)[96] but vice versa may contribute to global warming that may adversely affect cardiovascular health.[97]

3.2 Air pollution, global burden of disease, and mortality models

Air pollution is a main health hazard contributing to morbidity and excess mortality.[4,8,98] The WHO has identified gaseous and particulate pollutants as significant risk factors of infections of the respiratory tract, chronic obstructive pulmonary disease (COPD), lung cancer, and CVDs, leading to heart attacks and strokes. Of specific interest is the contribution of chronic exposure to low level air pollution to NCDs such as COPD that is currently studied within the ELAPSE project in pooled European cohorts[99] or all-cause mortality that is currently studied within the MAPLE project in pooled Canadian cohorts.[100] Of note, positive associations were also found at PM concentrations lower than the current European recommendations for the limits of annual $PM_{2.5}$ and PM_{10} exposure.[101] Worldwide, diseases due to air pollution cause greater loss of life than HIV/AIDS, tuberculosis, and malaria together and are responsible for trillions of US dollars in welfare losses each year.[8] Of note, higher air pollution concentrations and specific characteristics of particles or gases (e.g. diesel exhaust) were found to be associated with higher COVID-19 prevalence and fatality rates.[102] In contrast, COVID-19 pandemic induced lockdown decreased the air pollution and thereby cardiovascular events.[103]

We have to consider, however, that the drop in hospital admissions with respect to acute coronary syndromes (ACS), acute heart failure with decompensation, and arrhythmias, may have been not only due to the improved air quality during COVID-19-mediated lockdown but also due to the fear of the CVD patients to become infected.[104] This in turn caused more acute cardiovascular deaths, with almost 50% in the community that were not related to manifest COVID-19 infection, all of which points to the anxiety of patients to visit the hospital during the pandemic or to a high share of undiagnosed COVID-19.[105]

Long-term exposure to $PM_{2.5}$ can cause a chronic oxidant/antioxidant imbalance in the respiratory system, with inflammatory responses, and implications for the aetiology of respiratory and CVDs[106,107] (see also Section 3.3). Oxidative stress can occur directly by the inhalation of reactive oxygen species in $PM_{2.5}$, or indirectly from their catalytic generation within the epithelial lining fluid upon inhalation of toxic aerosol compounds, e.g. co-emitted by combustion sources.[17,93] The long-term inflammatory impacts within the respiratory tract can have local consequences, e.g. asthma and emphysema, as well as chronic outcomes such as circulatory and cardiovascular disorders.[92,108] Furthermore, ozone (O_3) is a strong oxidant that leads to respiratory and circulatory diseases through oxidative stress, likewise with immune-inflammatory responses within and beyond the lungs.[109,110]

Exposure of the global population to $PM_{2.5}$ and O_3 can be estimated with satellite and ground-based measurements and data-informed modelling.[4,111] To assess health outcomes, the Global Excess Mortality Model (GEMM) was developed, which utilizes hazard ratio functions based on 41 cohort studies performed in 16 countries.[112] Results include excess mortality rates and years of life lost from five disease categories: lower respiratory tract infections, COPD, IHD, cerebrovascular diseases (strokes), and lung cancer; and one general category that accounts for all NCDs, from which impacts by 'other' diseases are estimated through subtraction. The latter include neurological disorders, hypertension, and diabetes, for example.[113] *Figure 3A* shows percentages of excess mortality from exposure to $PM_{2.5}$ and O_3 by different disease categories. In middle- and high-income countries CVDs are predominant (IHD, strokes), while in low-income countries lower respiratory infections, in particular under children, are significant. In Africa, many children die from pneumonia, whereas in Europe, this is a minor cause of mortality. Globally, air pollution-induced CVDs contribute 45–50% to excess deaths. Because the 'other' category includes hypertension and diabetes, which contribute to cardiovascular disorders, it follows that these diseases make up the leading health outcome of air pollution. In the European Union (EU-27), $PM_{2.5}$ and O_3 together cause about 592 000 (483 000–701 000) excess deaths per year.[113] About 247 000 (206 000–285 000) per year are directly attributed to IHDs and strokes.

It was estimated that global excess mortality from the chronic impacts of $PM_{2.5}$ and O_3 amounts to 8.8 (7.11–10.3) million per year,[111] in accordance with Burnett *et al.*,[112] but significantly higher than estimated by the GBD,[4] which accounts for $PM_{2.5}$, not O_3, and selected disease categories, not including the 'other' NCDs. However, it is lower than the recent global estimate by Vohra *et al.*,[114] which exceeds 10 million per year for the part of $PM_{2.5}$ from fossil fuels only. Global excess mortality estimates range from about 4.5 to more than 10 million per year, depending on the pollutant compounds, disease categories and exposure–response functions considered.[4,98,111,112,114]

The loss of life expectancy attributed to air pollution has been evaluated against other health risk factors (*Figure 3B*). Because about two-thirds of worldwide air pollution are anthropogenic and can be prevented, it follows that the global mean life expectancy loss from smoking and avoidable air pollution are similar. *Figure 3B* also shows the global life expectancy loss from all forms of violence, which is nearly an order of magnitude less than from air pollution. In Europe, the life expectancy loss by air pollution is about 2.2 years, of which 1.7 years count as avoidable if the emissions would be controlled. Therefore, the mitigation of air pollution is an effective health promotion intervention, like the banning of smoking[115] and can make a major contribution to the prevention of CVDs.

3.3 Epidemiology: air pollution and CVDs

Increased levels of air pollution, mainly PM_{10} and/or $PM_{2.5}$ show an association with higher risk of ACS, chronic coronary and peripheral artery disease, heart failure, and arrhythmia (reviewed in refs107,108,116). The classification of air pollution particles and the WHO interim target threshold concentrations for $PM_{2.5}$ are shown in (*Figure 4A*). Clinical/epidemiological studies on association of air pollution with cardiovascular outcomes can be found in Supplementary material online, *Table S4*. Associations of air pollution with cardiovascular risk factors can be found in Supplementary material online, *Table S2*.

3.3.1 Ischaemic heart disease

In general, there is a higher incidence of fatal or non-fatal coronary artery disease in response to air pollution. The Women's Health Initiative

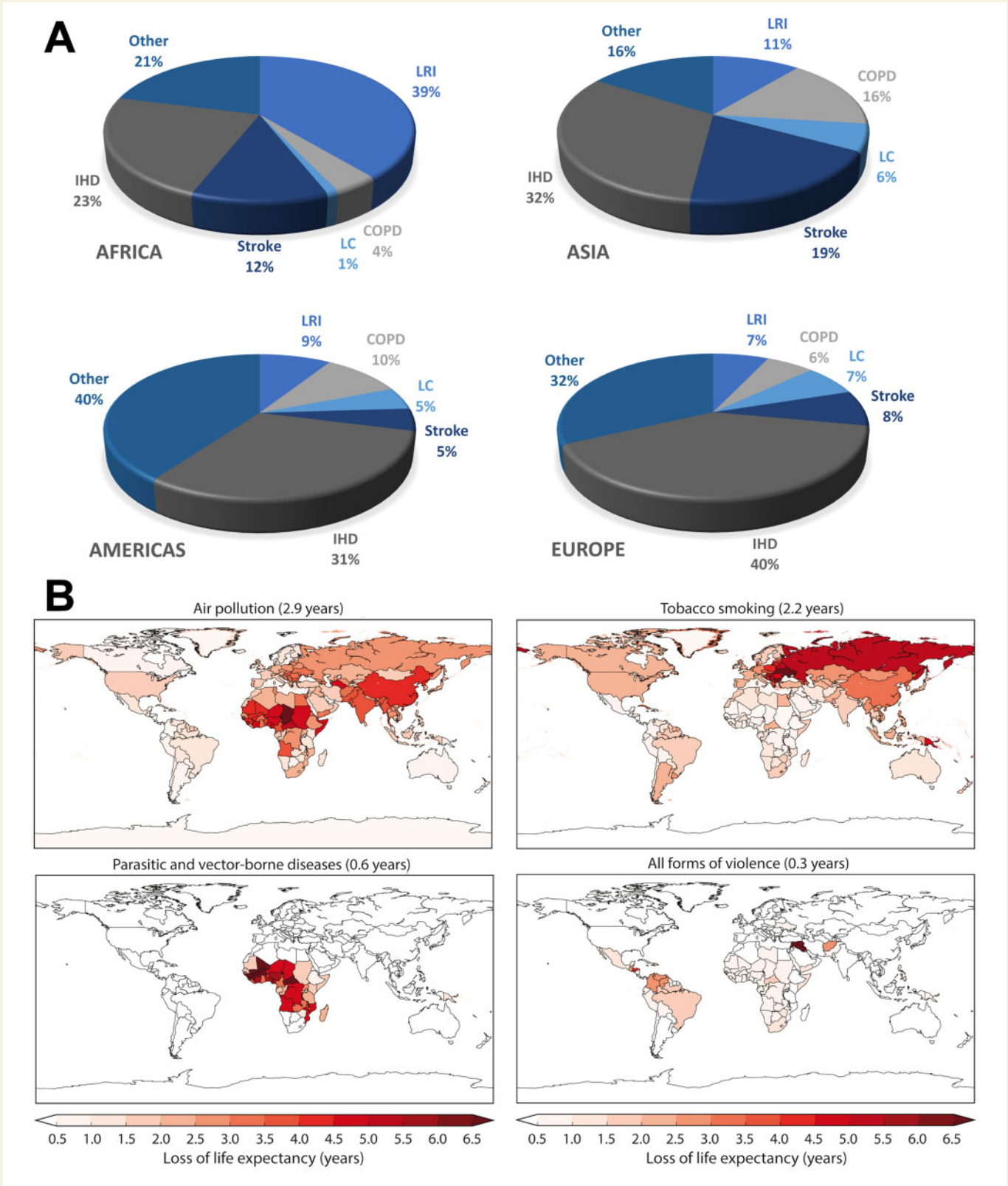


Figure 3 Global burden of disease of air pollution. (*A*) Disease categories that contribute to excess mortality from the long-term exposure to ambient $PM_{2.5}$ and O_3. COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart diseases; LRI, lower respiratory infections. (*B*) Mean global and country-level loss of life expectancy from air pollution, tobacco smoking (active and passive), parasitic and vector-borne diseases (e.g. malaria), and all forms of violence (interpersonal, collective conflict, and armed intervention). Adapted from ref.[111] with permission; Copyright © 2020, Oxford University Press.

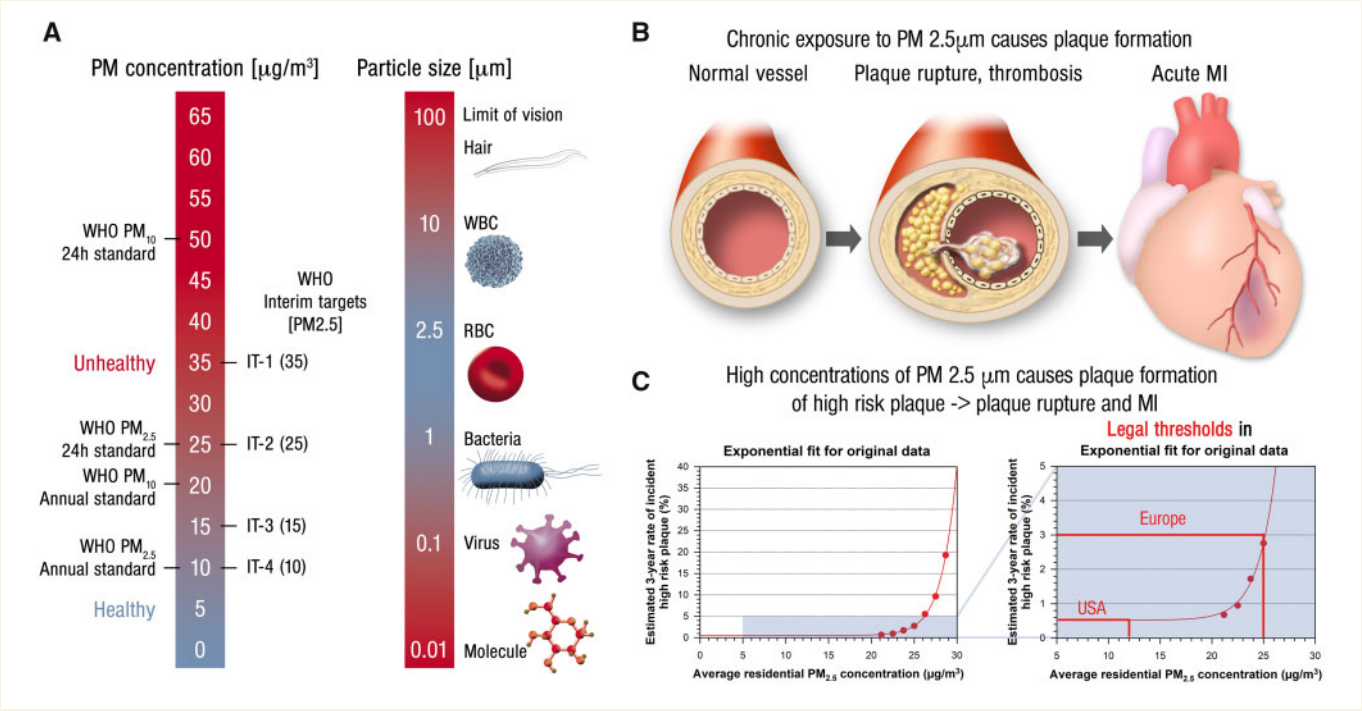


Figure 4 Air pollution thresholds and guidelines as well as health effects. (*A*) Data for air pollution obtained from WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide, and sulphur dioxide (update 2005 and summary of risk assessment) (http://apps.who.int/iris/bitstream/10665/69477/1/WHO_SDE_PHE_OEH_06.02_eng.pdf). Comparison of particle size with biochemical and biological entities. Reused from ref.[117] with permission; Copyright © 2017, Oxford University Press. (*B*) $PM_{2.5}$ exposure acutely triggers plaque rupture. Adopted from ref.118 (*C*) Effects of different legal thresholds for ambient particulate matter ($PM_{2.5}$) concentrations in USA and Europe on cardiovascular health risk by development of high-risk plaques depicted as exponential fit for original data (left) and zoomed exponential fit with legal thresholds (right). Reused from ref.[119] with permission; Copyright © 2019, Oxford University Press; generated from original data in ref.[120]

Study revealed a 21% (95% CI 4–42%) higher incidence of (non-)fatal coronary heart disease (CHD) with increment of 10 µg/m^3 in long-term $PM_{2.5}$ in 65 000 women studied.[121] The European Study of Cohorts for Air Pollution Effects (ESCAPE) trial (100 000 participants, 11 EU cohorts) established a 12% higher risk with increment of 10 µg/m^3 in long-term PM_{10} and a 13% higher incidence of coronary events with increment of 5 µg/m^3 in long-term $PM_{2.5}$.[101] A meta-analysis addressing the effects of short-term air pollution exposures and incident ACS revealed that $PM_{2.5}$, along with nitrogen dioxide (NO_2), and sulfur dioxide and carbon monoxide were linked to a higher incidence of MI.[122] Importantly, patients with already established diagnosis of coronary artery disease are at higher risk than healthy individuals for developing an acute coronary syndrome upon short-term exposure to $PM_{2.5}$. In coronary artery disease patients ($N = 16\,314$, diagnosed by angiography), odds ratios of 1.06 (95% CI 1.02–1.11) for ACS, 1.15 (95% CI 1.03–1.29) for ST-elevation MI, 1.02 (95% CI 0.97–1.08) for non-ST-elevation MI, 1.09 (95% CI 1.02–1.17) for unstable angina, and 1.05 (95% CI 1.00–1.10) for incident non-ST-segment elevation ACS were found with increment of 10 µg/m^3 in short-term $PM_{2.5}$ (on the same day, exceeding 25 µg/m^3).[123] Of note, higher odds ratios by air pollution were only observed in patients with coronary artery disease that was diagnosed by angiography.[123] Also prognosis after an acute coronary syndrome is worse in response to chronic $PM_{2.5}$ exposure.[124,125] It should be noted that an appreciable part of the cited literature deals with acute effects of air pollution on IHD as the evidence for these short-term effects are really substantial. In contrast, chronic effects of air pollution on MI incidence may be less conclusive as reported by a meta-analysis.[126]

In general, it is believed that long-term $PM_{2.5}$ exposure enhances cardiovascular risk through a continuous plaque progression, whereas short-term $PM_{2.5}$ seems to acutely trigger plaque rupture, and short- and long-term exposure in concert increases the risk for cardiovascular events (*Figure 4B*) (reviewed in ref.118).

Overall, the higher burden of IHD by air pollutants is also paralleled by higher plaque vulnerability at $PM_{2.5}$ >20 µg/m^3 indicating that even short-term high concentrations of $PM_{2.5}$ µg/m^3 may cause acute plaque rupture and that the European threshold (PM2.5 ≤ 25 µg/m^3) is clearly too high (*Figure 4B and C*) to protect exposed people from acute and chronic cardiovascular adverse events.[119,120]

3.3.2 Heart failure

Heart failure is an established major and escalating health problem in the population of Western societies with ageing populations and heart failure has a very high prevalence (64 million individuals at the global level).[127] Many cardiac diseases lead to heart failure as a final outcome, leading to high hospitalization numbers (3–5% of all affected patients) and high mortality numbers (30% within 1 year after diagnosis).[127] (Re)hospitalization of the elderly (age above 65 years) is most often due to heart failure (5% of all-cause hospitalization).[127] The sources of acute decompensated heart are therefore a major concern of public health systems. A cohort study from UK revealed that chronic exposure to PM

and NO_2 was linked to a higher incidence of heart failure.[128] A meta-analysis of 35 studies, reported an association of short-term increase in reactive gases and PM_{10} as well as $PM_{2.5}$ with higher incidence of heart failure hospitalization or death.[129] As also described in subjects with pre-existing coronary artery disease, heart failure, hypertension, and arrhythmia are the major cardiovascular risk factors for air pollution associated major cardiovascular events. According to the Air Quality Health Index, an increase of 10 μg/m^3 in $PM_{2.5}$ caused a higher hospitalization rate and higher number of deaths from heart failure with an increase in RR of 2.1% (95% CI 1.014–1.028).[130] A Chinese study in 26 cities with highly polluted air, higher long-term $PM_{2.5}$ exposure caused a 1.3% higher incidence of hospitalization for heart failure.[131] However, high-quality studies on the effects of chronic air pollution exposure on the risk of chronic heart failure are highly needed. Recent large population data show that risk for incident heart failure is increased by chronic exposure to PM at different sizes in an additive manner.[132]

3.3.3 Heart rhythm disturbances

Controlled exposure studies in general (healthy) populations failed to provide convincing evidence that air pollution directly affects arrhythmias or the frequency of ventricular ectopic beats,[133] which is also supported by studies in subjects with high cardiovascular risk as indicated by an implanted defibrillator.[134] On the other hand, it was found that out-of-hospital cardiac arrest is associated with short-term air pollution such as ozone[135] and particulate matter (especially $PM_{2.5}$).[136]

3.3.4 Cerebrovascular disease

Korean studies showed that long-term air pollution is associated with stroke mortality.[137] In support of this, large scale studies showed an association of hospital admissions for stroke with PM in the USA (intermediate to long-term effects)[138] and Denmark (short-term effects).[139] According to the Women's Health Initiative study, the risk of stroke and death from cerebrovascular disease was 35% higher and the risk of death from cerebrovascular disease was 83% higher with increment of 10 μg/m^3 in chronic $PM_{2.5}$ exposure.[121] In line with this, additive effect of PM_{10} and NO_2 exposure for 12 years contributed to higher cerebrovascular mortality in China.[140] The ESCAPE study reported a 19% (95% CI 12–62%) higher risk of stroke with increment of 5 μg/m^3 in long-term $PM_{2.5}$ (almost 100 000 participants, 11 EU cohorts).[141] An increased risk was observed specifically in the elderly (>60 years) and the non-smoking population and effects were already observed at low $PM_{2.5}$ concentrations (<25 μg/m^3).[141] A meta-analysis (94 studies from 28 countries), an increment of 10 μg/m^3 in short-term $PM_{2.5}$ and PM_{10} was linked to a 1% higher risk of hospitalization for stroke and stroke mortality.[142] The proximity of the home address to main roads and low socioeconomic status showed an association with ischaemic stroke and stroke severity.[143,144] Two independent meta-analysis have shown that long-term exposure to air pollution in the form of $PM_{2.5}$ or PM_{10} were associated with a higher risk for incident stroke by 13%[126] or 6.4%, respectively.[145] In summary, a systematic study and analysis of the impact of air pollution on cerebrovascular disease is urgently required.

3.3.5 Cardiovascular mortality

An appreciable number of single-city and multicentre studies as well as meta-analyses demonstrated a higher mortality rate in relation to short-term exposure to PM, NO_2, and ozone (reviewed in ref.108). For a short-term exposure scenario pooled RRs of 1.0060 (95% CI 1.0044–1.0077) for PM_{10} and 1.0092 (95% CI 1.0061–1.0123) for $PM_{2.5}$ were reported for the cardiovascular mortality by a recent meta-analysis.[146] Another meta-analysis reported that increment of 10 μg/m^3 in NO_2 concentration on the previous day was linked to 0.37% (95% CI 0.22–0.51%) higher numbers of cardiovascular mortality.[147] A position paper by the American Heart Association reported a higher all-cause mortality rate in association with chronic as compared with acute $PM_{2.5}$ exposure.[148] A 11% (95% CI 6–16%) higher cardiovascular mortality rate with increment of 10 μg/m^3 in $PM_{2.5}$ was demonstrated.[149] The pooled hazard ratio for cardiovascular mortality per 10 ppb NO_2 increase was 1.11 (95% CI 1.07–1.16).[150] However, in the ESCAPE study (22 EU cohort, >300 000 subjects), no statistically significant association of long-term $PM_{2.5}$ exposure with the number of cardiovascular deaths was found.[151] In contrast, the effect of $PM_{2.5}$ on all-cause mortality is well accepted and population-based studies estimate a gain of life expectancy (>22 months at age 30) when strictly following the recommended WHO threshold for $PM_{2.5}$ of a mean exposure of 10 μg/m^3 per year.[151,152]

3.4 Pathophysiology of air pollution induced CVDs

Animal studies show appreciable variation of results, which is mainly due to the exposure duration, strain/susceptibility of animals, and the particle characteristics (mostly size and chemical composition). Air pollution-induced oxidative stress mechanisms are responsible for cardiovascular and cerebral damage, also triggering subsequent inflammation and gene activation, which is largely consistent over a wide range of different particles (and reactive gases) such as diesel exhaust, wood smoke, $PM_{2.5}$, or UFPs (*Figure 5*).[154–157] Inflammatory responses to PM exposure are repeatedly demonstrated in experimental animal models starting with adhesion and infiltration of Ly6C^{high} immune cells via CCR2/VCAM interaction, TLR/CD36-mediated activation of NFkB, NLRP3, IL1β, which is associated with foam cell formation and plaque instability due to MMP-2/9 up-regulation.[158–160] A direct activation of the lung-neural reflex arcs facilitates systemic inflammation as well as neuronal activation/neuroinflammation linking pulmonary exposures to cerebral as well as systemic health effects of air pollution.[161–163] The activation of central sympathetic mechanisms is also leading to arterial hypertension.[164] Importantly, also other environmental pollutants such as traffic noise and artificial light at night share an appreciable part of these pathomechanisms that likely curdle at the level of oxidative stress and inflammation (*Figure 5*).[10,15,165]

Nanoscale (ultrafine) particles and toxic contaminations on the particle surface (e.g. heavy metals, polycyclic aromatic hydrocarbons or fungal pyrogens/bacterial endotoxins) can directly penetrate the lung tissue into the systemic circulation and lead to additional activation of immune cells or inflict direct (oxidative) damage to endothelial cells.[159,166,167] Other toxic mediators originate from air pollution and inflammation induced formation of oxidized biomolecules such as 7-ketocholesterol (7-KC) or oxidized phospholipid derivatives of 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (oxPAPC) that have their own biochemical toxicity (*Figure 5*)[168,169] promoting the infiltration of bone-marrow derived CD11b$^+$Ly6C^{high} cells into atherosclerotic plaques.[170] $PM_{2.5}$, UFPs and in particular diesel exhaust can cause endothelial dysfunction due to diminished vascular nitric oxide availability in response to augmented production of reactive oxygen species as a consequence of a higher vascular and/or phagocytic NADPH oxidase activity and/or endothelial nitric oxide synthase uncoupling.[171–174] In animals, $PM_{2.5}$ activates pathways that are analogous to those of angiotensin II such as

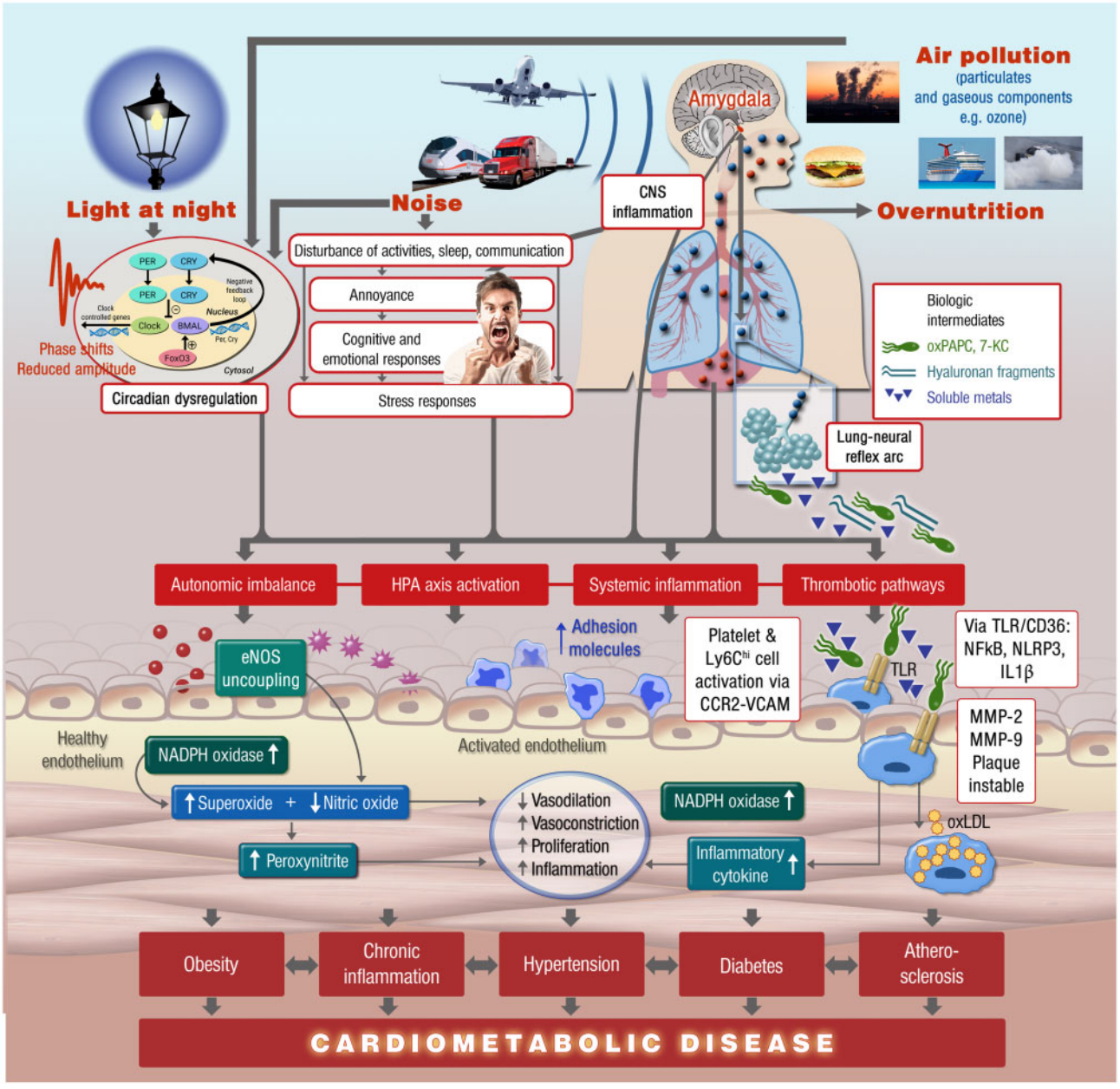


Figure 5 Proposed pathophysiological mechanisms of cardiovascular disease induced by environmental air, light, and noise pollution. Major pathomechanisms comprise neuronal activation and stress response, disruption of circadian rhythms, all of which initiates cerebral and systemic inflammation as well as oxidative stress leading to endothelial dysfunction, atherothrombotic changes, dysregulated metabolism, and manifest cardiometabolic diseases. Modified from ref.[153] with permission; Copyright © 2016, Oxford University Press.

induction of Rho/ROCK signalling and more pronounced calcium sensitivity.[174,175]

A more recent identified pathomechanism of air pollution-mediated cardiovascular damage and disease is the dysregulation of the circadian clock, which is also the major pathophysiological target of nocturnal light or noise at night (*Figure 5*).[165] It was shown that $PM_{2.5}$ exposure also impairs circadian rhythms as observed by phase shift and altered amplitudes of circadian gene expression including BMAL1, CLOCK, periods, and cryptochromes that was quite similar to circadian dysregulation observed in response to light at night.[176] $PM_{2.5}$ exposure impairs oscillations of circadian genes and thereby alters the lipid metabolism in white and brown adipose tissues providing a direct link to $PM_{2.5}$-induced obesity and diabetes.[177] Importantly, impaired circadian rhythm (e.g. as observed in shift workers or people with chronic sleep fragmentation/deprivation) is acknowledged as a potent trigger of CVDs.[11,178]

Of note, the results established in animal studies have mostly been translated to the human setting. $PM_{2.5}$ and transportation-based pollutants such as diesel exhaust cause acute peripheral endothelial dysfunction, ischaemia and prothrombotic changes of the vasculature of humans within a few hours after exposure.[155,179–182] Diesel exhaust acutely

impairs resistance vessel responses to endothelium dependent dilators such as acetylcholine and bradykinin and the direct NO-donor sodium nitroprusside coupled with increase in vasoconstrictor potency of ET-1 in mice but also humans.[179–181,183] Short-term exposure to diesel causes ischaemia in patients with already established coronary artery disease.[182] Diastolic dysfunction and impaired contractile reserve may be explained by $PM_{2.5}$-induced up-regulation of the β-myosin heavy chain and lower expression levels of SERCA2a, indicating abnormal calcium signalling.[184] PM also impairs the anti-inflammatory and antioxidant properties of HDL, and thereby promotes the adverse health effects of upregulated LDL.[185] More animal studies on air pollution-mediated cardiovascular damage can be found in Supplementary material online, *Table S5*.

The above described pathomechanisms may explain at least in part the accelerated development of atherosclerosis and inflammatory processes in the plaques observed in response to exposure of animals to $PM_{2.5}$, diesel exhaust, reactive gases, and UFPs.[186–188] Diesel exhaust particles were demonstrated to cause activation of platelets in murine models of arterial thrombosis.[189] These animal data were in accordance with enhanced fibrinolytic function in healthy individuals and in CHD patients in response to exposure to diesel exhaust particles.[180,182] Previous reviews provided an excellent summary of the experimental evidence and pathomechanisms, underlying the contribution of air pollution to cardiometabolic disease such as diabetes.[161,162] Also the mechanisms leading to a higher risk of CVD by air pollution, as indicated by enhanced carotid intima media thickness and impaired ankle brachial indices, was reviewed in the past.[108] This also includes $PM_{2.5}$ triggered mechanisms of inflammation and impairment of insulin response pathways, induction of brown adipose tissue dysfunction, and adverse central nervous system activation involved in glycaemic control, regulation of satiation, and metabolic pathways.[92]

4. Outdoor light pollution and cardiovascular disease (epidemiology and pathophysiology)

A rather novel environmental risk factor of concern is light pollution and its potential large impact on NCDs.[190] Anthropogenic sources of natural nighttime sky brightness represent a major challenge in huge cities and metropolitan areas but can additionally cause effects in distant rural places such as national parks.[191,192] Up to 83% of the population on earth and >99% of the people in the USA and EU may live under light-polluted skies (>14 $\mu cd/m^2$ artificial nighttime sky illumination).[191] This unfortunate situation was nicely summarized with the title of the review article 'Missing the Dark—Health Effects of Light Pollution', where satellite images document the progression of artificial light at night in the USA over a period of seven decades.[190] Light pollution induces premature mortality and loss of biodiversity of insects, animals, and birds by impairment of their circadian rhythm.[190] In humans, the dysregulation of circadian genes is a major contributor to NCDs, also due to the circadian control of inflammatory and metabolic pathways (*Figure 5*).[178,193] Mutations and expression changes of key circadian genes can contribute to obesity and hyperglycaemia[194–196] and the 'chronotype' (morningness or eveningness person) has a significant health impact in humans, specifically with respect to metabolic diseases[197,198] and is based on genetic profiles as revealed by genome-wide association studies.[199,200]

In elderly subjects, blood pressure was increased by 3–4 mmHg per 5 lux (=1 lumen/m^2) increase in outdoor nighttime light pollution.[201] In addition, artificial light at night is associated with a higher risk of CHD and mortality in the older population.[202] An increment of hazard ratios for CHD hospitalizations of 1.11 (95% CI 1.03–1.18) and for CHD mortality of 1.10 (95% CI 1.00–1.22) was reported per change of 60 Units of radiance (nW/cm^2/steridian). Of note, there was an additive increase of hazard ratio for CHD mortality in the upper light pollution quintiles in combination with highly polluted air based on the measured $PM_{2.5}$ concentrations (1.32 and 1.39, respectively),[202] which goes hand in hand with data on combined $PM_{2.5}$ and light at night exposure-induced circadian phase shifts and reduced amplitudes that, however, induced distinct epigenetic changes along with a specific pattern of circadian gene disruption.[176] As all of these studies were conducted in East-Asia and often in aged participants, replications of these studies in a wider context (e.g. different age groups and geographical locations) are urgently needed.

5. Climate change, increases in temperature, desert storms, and wildfires

A growing body of evidence also supports an association of particles from natural sources (e.g. desert dust, wildfires, and volcano eruptions) with adverse effects on public health. Based on estimations an annual number of 400 000–500 000 global deaths from cardiopulmonary causes (approximately 18% of all premature deaths), can be attributed to air pollution.[203] In line with this, Asian desert dust was found to potentially contribute to the risk of CVD hospital admissions,[204] also supported by a significant association of Asian dust storms up to 4 days before hospitalization and the risk of incident acute MI.[205] Also a recent meta-analysis reported higher mortality rates and more hospital admissions for major adverse events of cardiopulmonary origin in association with desert dust.[206] Forest fires in Southeast Asia create extremely high levels of PM_{10} that are linked to higher all-cause mortality and hospitalization for IHD in Malaysia.[207] Also the generation of $PM_{2.5}$ and other air pollutants from wildfires in California,[208] Brazil,[209] Australia,[210] Southern Europe,[211] and at a global scale[212] was reported to affect respiratory and cardiovascular health, whereas forest fires in Siberia were so far rather mentioned in the context of global warming. Although it is unclear to what extent wildfires and dust events are anthropogenic, the rapidly growing populations in Africa and Southeast Asia foster projections that more and more people will suffer from mixed exposure to natural and human-made air pollution in the future, including the exacerbated number of wildfires in California and Southern Europe with high population density. This warrants more clinical studies on the potential health harms of natural air pollution sources.

In addition, with increases in wildfire frequency, volcano eruptions, and desert storms, there will be also a substantial increase in the temperature further aggravating the heat wave in a positive feedback fashion (global warming by greenhouse gases). Wildfires release smoke that mainly consists of particulate matter. Importantly, PM from wildfires causes more pronounced effects on mortality than urban PM, which is mostly due to smaller particle size[213,214] and contamination with oxidative and proinflammatory compounds[213] causing an amplification of the adverse health effects of the increasing global warming[215] and O_3.[216]

The healthcare industry is a huge and socioeconomically powerful branch of trade, and by itself contributes significantly to global CO_2

emissions. Interestingly, healthcare in world's largest economies account for around 5% of all CO_2 emissions making this sector comparable to the importance of the food sector.[217] Importantly, the Lancet Commission on Health and Climate Change recommended that greenhouse gases emissions from the healthcare sector should be also considered as an indicator in evaluations of health and climate.[218]

Concerning the influence of climate change, changes in temperature and specifically subsequent CVDs such as acute coronary syndrome, epidemiological studies have postulated that high ('heat waves' and 'heat islands') but also low ('cold effect') temperatures may cause an increase in cardiovascular mortality and morbidity.[219–221]

There is evidence for an association between air temperature and acute MI. Many studies established a significant cold effect on MI occurrence,[222–224] while other studies suggested a higher risk of MI as a consequence of heat exposure.[225] Chen *et al.*[226] reported in a study over 28 years, which was based on a registry with time-stratification and cross-over design, that the risk of MI in relation to higher temperature increased over time, when comparing the period from 2001 to 2014 with the one from 1987 to 2000. Importantly, the risk of MI in relation to cold decreased during the study. In the late study period, the authors established that heat-induced MI was more pronounced in rural populations.

Associations between (climate change-related) high temperatures and cardiovascular events may occur through several direct and indirect mechanisms:

(1) Higher surface blood circulation and sweating is associated with high temperature, all of which contributes to higher cardiac strain, blood viscosity, plasma cholesterol, and interleukin-6 levels.[227]
(2) Warmer temperature causes sleep disturbance[228] such as too short sleep (<6 h) or fragmentation of sleep, which conversely increases the risk of CVD.[229]
(3) Very high temperature reduces physical activity,[230] which is conversely associated with higher cardiovascular risk.[231] Vice versa, physical activity at very high temperature may represent a risk factor of its own.

In summary, there is emerging evidence that the rising temperature in part triggered by wildfires and substantial greenhouse gas emissions due to biomass burning may in addition to inner cities heat islands (see below heart healthy cities) increase the susceptibility to heat related-MIs, which is further exacerbated by co-exposure to high $PM_{2.5}$ concentrations.[221] This indicates that, similar to air pollution exposure, heat exposure should be considered as an acute environmental stimulus of acute coronary syndrome especially in light of global warming.

6. Gaps in knowledge

There are only few high-quality animal or human studies that consider potential additive effects of combined noise, air, and light pollution. Although it is known that also air pollution from natural sources are associated with higher morbidity and death rates there are numerous gaps in knowledge with respect to their adverse health effect.

Mechanistic studies in animals may help to provide a direction for future human studies. The questions that should be answered comprise: (i) the of the additive effects and time-dependent biological/functional responses of different co-exposures; (ii) are the induced effects reversible; (iii) impact on circadian rhythm; and (iv) the effect of lifestyle modifications (e.g. diet, stress, and exercise). Finally, the development of novel technologies that enable personal measures of health together with public data on environmental pollutants would foster an advanced understanding of the interactions between environmental and non-environmental risk factors.

7. Mitigation measures

7.1 Societal/political noise exposure mitigation strategies

People in industrialized and urbanized societies are largely exposed to traffic noise, as reflected by >30% of the people in Europe being exposed to residential noise levels above 55 dB(A) L_{den}.[232] As this contributes to a higher incidence and mortality of major CVDs,[232] the implementation of new and effective mitigation measures is urgently required. Several noise interventional approaches are already in use, as propagated by the European Commission (*Table 1*).[233]

Buildings can be insulated against noise, which efficiently reduces exposure to all outdoor noise sources. However, this intervention has a low cost-effectiveness ratio due to the very high costs, especially when retrofit is required. Novel technologies and advances such as less noisy engines and tires for vehicles as well as silent brake blocks for trains are key to reduction of noise levels from all traffic-related sources.

Traffic noise pollution is significantly determined by road noise, which can be effectively mitigated by lower speed limits, silent road surfaces, and construction of noise barriers at main streets. However, in light of the continuously increasing traffic volume and accordingly constantly rising noise exposure levels, superior traffic management and regulation may represent key concepts for the future (see *Table 1*).

Aircraft noise exposure levels continuously increased over the last years, which has led to the ban of nocturnal air traffic at many airports because noise during nighttime is associated with the most pronounced adverse health effects.[66,73,234] However, noise exposure, in particular during the night has severe adverse effects on health,[235] which may be prevented by new engine technologies (fleet evolution), lower noise thresholds, longer night bans, and better air traffic management. Further measures include zoning, which means the restricted land-uses in areas of highest noise sensitivity, e.g. when housing complexes, schools, hospitals are in close proximity to airports or flight paths. Other mitigation measures also include facade insulation of residential buildings, tax incentives and fines for noise initiators (polluter liability), movement

Table 1 Noise-abatement approaches

Abatement procedures	Reduction in noise (dB)	Cost-effectiveness score (1–5)[a]
Noise barriers	3–20	2
Brake blocks for trains	8–10	4
Building insulation	5–10	1
Building design	2–15	3
Changing driving styles	5–7	3
Quiet road surfaces	3–7	5
Low-noise tires	3–4	3
Land-use planning and design	Unknown	4
Electric cars	1	1
Traffic management	3	3

dB, decibel.
[a]Evaluated by the European Commission in '10 ways to combat noise pollution' 231 lowest score = 1; highest score = 5.

limitations, and noise quotas. Also new air traffic protocols such as the continuous descending approach that is based on high altitude of the aircraft until shortly before landing or GPS-assisted starting/landing procedures, which both may significantly reduce the noise exposure levels of residents nearby airports.[164]

In summary, new noise reducing technological advances and legislative mitigation approaches are important to protect the general population from adverse effects of noise on health. These preventive measures are urgently needed in light of a growing global traffic load.

7.2 Air pollution

7.2.1 Personal exposure mitigation strategies

It is important to note that so far no personalized intervention for reduction of air pollution exposure has been demonstrated to improve life expectancy or to reduce cardiovascular events. Recently, the topic of personal exposure mitigation strategies has been extensively summarized (*Figure 6*). Here are some important notices. Portable air cleaners are inexpensive and can be employed in nearly all homes and apartments in locations with electricity. High Efficiency Home Air Filtration Systems: Central HVAC units with inbuilt filters can be an effective means for particle removal in residential indoor environments. There are, however, currently no clear studies demonstrating health benefits of filters in forced air systems in residences. Fisk and Chan[237] have estimated their potential benefits during wildfires in a modelling analysis and found that they are likely to be less effective than using other methods such as portable air cleaners. Personal air purifying respirators is a personal protective device that covers the nose and mouth and is used to reduce inhalation of $PM_{2.5}$ and other particles depending on their rating efficiency (removal of >95% or 99% of inhaled particles at 0.3 μm in size by N95 or N99). Some studies suggest that at least under conditions of high ambient exposures, there could be meaningful reductions in blood pressure in response to an N95 respirator intervention.[238] Some concerns over potential adverse cardio-pulmonary stress induced by wearing a respirator thereby mitigating health benefits, have been raised. However, there is no evidence that the short-term use of a respirator adversely affects health parameters such as blood pressure, heart rate, or aortic haemodynamics.[239]

Face masks (typically made of gauze, cotton, or cloth) and surgical masks are commercially available, but show large differences in filtering $PM_{2.5}$. FFP2 face masks provide a certain protection from solid air pollution components. While not directly relevant here, it was shown that face masks (all types and especially FFP2) effectively prevent SARS-CoV-2 infections through the spreading of droplets and aerosols.[240]

In summary, the current level of evidence demonstrates that wearing validated N95 respirators over a few hours to days in supervised experiments may improve surrogate markers of cardiovascular risk in

Figure 6 Personal mitigation manoeuvres and air pollution (significantly modified from ref.[236])

environments with high $PM_{2.5}$ levels, although the data are inconsistent across studies and no evidence exists regarding their impact on cardiovascular events. Nonetheless, their brief use during extremely poor $PM_{2.5}$ air quality events might be beneficial. It is logical to question if the use of surgical masks should be advocated if N95 respirators are not available. On the one hand, some degree of protection against $PM_{2.5}$ exposure, even if only incomplete (e.g. 25–75%), among many millions of people facing high levels of exposure might translate into significant public health benefits considering the well described linear dose-risk response. Unlike a viral contagion in which an unknown threshold of exposure reduction is required to prevent the spread of infection to an individual, any decrease in exposure to air pollution should reduce health risks in a population. Conversely, arguments have been made that these masks might engender a false sense of security, thereby worsening overall exposure. While they can reduce the inhalation of $PM_{2.5}$ by a variable degree, any health benefits of wearing less cumbersome facemasks (e.g. surgical style) have yet to be shown. At this point, there is insufficient evidence to support or proscribe against the use of simple face masks.

Automobile air filters and air-conditioning are approaches to reduce $PM_{2.5}$ and UFPs exposure during travel that may be of use for highly susceptible individuals, but also for those staying for significant parts of their daily life in transportation microenvironments.

Simple strategies implemented into one's lifestyle can help to reduce air pollution exposure. Some of these practical strategies are general and may not necessarily reduce exposures to $PM_{2.5}$, which is considered a regional pollutant. However, they may exert health benefits through their impact on UFPs and/or gaseous co-pollutants (in particular ozone), which have also been associated with health risk.

Other more simple recommendations include air pollution avoidance, staying indoors, and closing windows. An important question is at which level of air pollution ($PM_{2.5}$), exercise may be allowed without adverse health effects.

7.2.2 Personal mitigation strategies by physical activity

There is an ongoing discussion on the health benefits of physical exercise and the potential adverse health effects of higher exposure to air pollution during outdoor physical activity. In order to answer this question, Kim *et al.*[241] conducted a nationwide cohort study (1 469 972 young adults with an age of 20–39 years). Air pollution exposure was calculated by the average cumulative level of $PM_{2.5}$ and PM_{10} per year at the residential addresses and physical exercise was determined by the minutes of metabolic equivalent tasks per week (MET-min/week) for each participant for the years 2009 to 2012. As a major outcome of the study, there was a clear benefit of outdoor physical activity, even when exposed to low or moderate PM concentrations. Those participants with a sedentary lifestyle had a clearly increased cardiovascular risk. Of note, extremely high levels of outdoor physical exercise (≥1000 MET-min/week) in highly polluted air also caused a higher cardiovascular risk. These observations are also in accordance with the reported 'break-even point' for lowering of air pollution-associated RR of all-cause mortality by physical activity, which was calculated by the authors at 100 $\mu g/m^3$ of $PM_{2.5}$ making 1.5 h cycling or 10 h walking per day in more polluted air detrimental.[242]

7.2.3 Societal/political exposure mitigation strategies by improved air quality

The most promising manoeuvres to protect people from air pollution induced CVDs is the lowering of the allowed emission levels. Since 2015, the EU recommends an annual mean air quality limit of 25 $\mu g/m^3$ for $PM_{2.5}$, which is 2.5-fold higher than the WHO recommendation of 10 $\mu g/m^3$. Even at PM concentrations of 10 $\mu g/m^3$, hazard ratios are greater than 1.0 as based on calculation using the GEMM or the GBD model from the year 2015. A hazard ratio of approximately 1.5 for the risk of IHD was found at PM levels of 25 $\mu g/m^3$, which clearly indicates that the EU-28 air quality standard is not effective. This becomes even clearer, when comparing the annual mean limits in the USA of currently 12 $\mu g/m^3$ (since 2012), and in Canada of 10 $\mu g/m^3$ since 2015, with a further intended reduction to 8.8 $\mu g/m^3$. The Australian annual $PM_{2.5}$ limit is 8 $\mu g/m^3$ with another intended reduction to 7 $\mu g/m^3$ within the next years. The EU had the intention to reduce PM exposure limits until 2020 to a target concentration for $PM_{2.5}$ of 20 $\mu g/m^3$. However, even the current recommended $PM_{2.5}$ limit is exceeded in several European countries[113] and the targets for 2020 have not yet been ratified by the EU member states and it seems that this will not happen soon. Therefore, additional efforts are urgently warranted to improve air quality in Europe.

7.3 Mitigation strategies for light pollution exposure and of adverse health effects

The easiest mitigation approach to decrease light pollution is to switch-off lights, especially when light is not absolutely necessary.[190,191] Also technical advances may help to reduce light pollution: light shielding helps to send light rather to the base than to the sky, energy-efficient lights emit yellow light within a nanometer range where the human eye is most sensitive and smart city techniques control light dimming when nobody is around or when the weather/time of the day allows light reduction.[190,243] Reduction in 'blue' light emissions (LEDs display peak light spectrum at 400–490 nm) is highly effective as this kind of light is most detrimental for dysregulation of circadian rhythms.[243] An impaired circadian clock can also be 'reset' by chronotherapy (e.g. melatonin), which can especially help to prevent sleep disorders,[11] not only for those caused by light pollution but also ones triggered by nocturnal traffic noise[235] and air pollution.[244,245] Circadian dysregulation by these environmental factors resembles the desynchronized profile observed in shift workers who have an increased risk for CVD and events.[246,247]

7.4 Strategies for mitigation of climate change including greenhouse gas emission, temperature, desert storms, and wildfires

Human use of resources and energy generation has caused a 1.0°C global warming above preindustrial level, which will probably reach 2.0–2.5 or even higher in 2030–2052 if the emissions are not dramatically reduced. The natural disasters in 2018 were mainly climate related and involved almost 70 million people with wild fires, storms, extreme temperature, flooding, and landslides.[248] With respect to economic losses this summed up to 131.7 billion dollars. The economic loss by wildfires in 2018 reached almost the similar amount as all losses from wildfires during the last decade combined.[249]

Conventional mitigation strategies may focus on the reduction of CO_2 emissions from fossil sources. Negative emission technologies have the capacity to trap and bind atmospheric carbon to reduce CO_2 concentrations. Geoengineering techniques of radiative forcing may positively affect the radiative energy budget of our planet to stabilize or even decrease the global temperature. In light of global warming and climate disaster respective mitigation measures are urgently needed. Carbon emission fines that foster carbon removal should be introduced now.[250]

What can a cardiologist do to reduce greenhouse gases emissions? Should it be important also in decision-making of clinicians in cardiology? More recent studies compared the environmental impact (with respect to emissions and energy consumption) of magnetic resonance imaging (MRI), single photon emission tomography and cardiac ultrasound (echo) that are used for the diagnosis of cardiovascular complications. The data indicate that ultrasound is the most eco-friendly method and only caused 1–20% of the effects on human health, ecosystem effects, and resource use compared to MRI and tomography.[251]

7.5 Heart healthy city design: mitigation of the cardiovascular risk

Urban environments are still hotspots of all environmental stressors together including climate change, air pollution, noise and light and heat in form from heat island effects.[252] Further risk exposures that may affect the risk of NCD's include safety from crime, social isolation, prolonged sitting, sedentary lifestyle, and unhealthy nutrition with, just concerning physical inactivity, disabilities life years lost up to 70 million DALYS including 3.2 million deaths annually.[252] More recently, compacts cities are being promoted as they are considered more sustainable and healthier.[252,253] Compact cities are cities with higher density, shorter travel distances, and higher diversity that are healthier because of increased land use mix and the healthier mobility opportunities, all of which leads to lower CO_2 emissions.[254]

Boston and Melbourne are low-density sprawling communities with a high share of 80.1% and 85.1% attributable to transportation by cars and the health of these cities could be significantly improved by altered land use and transport mode.[254] However, compact cities are not without their problems if the existing (public) space is not used well. Many compact cites like Barcelona or Paris still suffer considerable adverse health impacts due to their air pollution levels and other exposures related to urban and transport planning.[255,256] Therefore, we need a better use of the new and existing public spaces.

Several novel urban concepts are currently implemented in various cities that partly solved these problems, such as the Superblocks, the low traffic neighbourhood, 15-min city (*Figure 7*), car free city, or mixed models. All of these models are aiming at reduction of private car use and promoting public and active transportation (walking and cycling) as well as reducing CO_2 emissions. The benefits are clear and comprise reduction of air pollution, noise, and heat island effects, whereas physical activity is increased, all of which has beneficial health effects.[253] Cars use a lot of public space (road) network and parking, which could be used much better for the creation of green spaces and infrastructure. Barcelona uses 60% of public space for cars, while their share in overall transportation is only 25%.[253]

The construction of over 500 superblocks are intended in Barcelona, which will decrease motorized traffic in a part of the roads of a block providing more room for people, active travel, and green space. The aim is to generate a healthy, greener, fairer and safer public environment promoting social relations and local economy. Air pollution lowering and noise mitigation, heat island prevention and better green space implementation for physical activity are the other beneficial side effects of this renewing city design, which can easily prevent up to 700 annual premature deaths in Barcelona (effects on premature deaths are by air quality > noise > heat island > green space).[260]

Similar concepts provide the basis of low traffic neighbourhoods that can be implemented by cheap and quick streetscape changes.[261,262] These measures are implemented by some governments already to create safer walking and cycling environments (lower COVID-19 and traffic injury risk).[262]

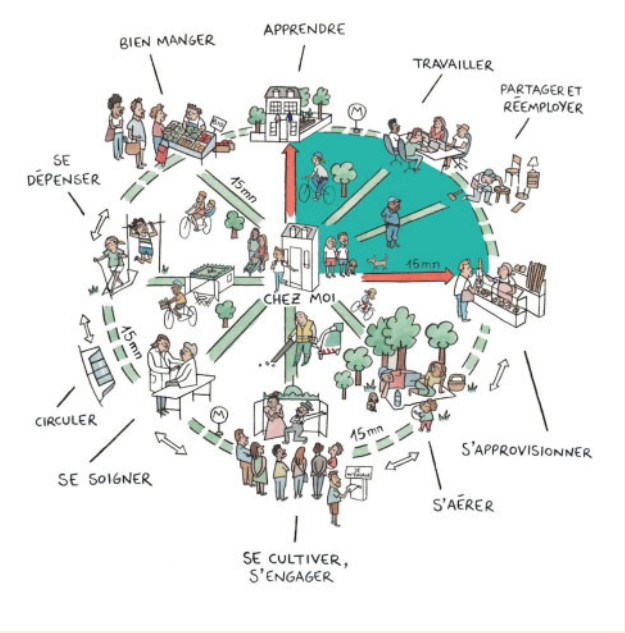


Figure 7 The present figure depicts the 15-min city, the brain child of Carlos Moreno, where work, school, entertainment, and other activities are reachable within a 15-min walk of the home.[257,258] The 15-min city involves the creation of a city of villages and a return to more traditional city design. The 15-min city will encourage more physical activity through more active transport, and is likely to reduce urban inequalities and health inequities.[259] Critically, it will also reduce the need for long distance travel and thereby reduce CO_2 emissions, and air pollution and noise levels (for review see ref.[15]) Translation of French words: apprendre = to learn; travailler = to work; partager et réemployer = to share and reuse; s'approvisionner = to supply oneself; s'aérer = to get some fresh air; se cultiver, s'engager = to subdue, to be committed; se soigner = to nurse oneself; circuler = to be on the move; se dépenser = to wear oneself out; bien manger = to eat well; chez moi = at home. Reused from ref.[257] with permission of the copyright owner Micael queiroz, www.micaeldessin.com.

Paris will implement the 15-min city, where work, school, shops, entertainment, culture, leisure, and other social activities can be reached within a 15-min walk or bicycle ride from the residence.[263,264] The 15-min city comprises formation of a city of villages and retro city design. Ecology (green space), proximity, solidarity among citizens, and participation of citizens are some of the key aspects.[265] The envisaged new trees and cycle ways, community facilities and social housing, homes and workplaces all go hand-in-hand with a new vision for urban planning, and will result in better health.

Even further go car free cities. For example, Hamburg intends to become a car-free city by 2034, mostly in response to the climate crisis. Car free cities or neighbourhoods decrease private motorized traffic and promote active and public transportation. A successful example is Vauban and to a lesser extent Rieselfeld in Freiburg, Germany, that are neighbourhoods without cars and with housing with higher sustainability.[266] Pontevedra is a small car-free city in Spain. Cars are prohibited in Pontevedra's city centre, representing an excellent example of a pedestrian-friendly living with low CO_2 emissions.[267] The transition to a

city without cars will result in a significant improvement of the livability of neighbourhoods also preventing disproportional burdens of pollution, social disadvantage, crashes, and public transport disinvestment. Car free cities or neighbourhoods will reduce air and noise pollution, promote physical activity, and foster generation of green space, and thereby reduce heat island effects and improve public health.[268]

Some of these changes take longer to implement, while we need to have faster action. New and easier to implement policies such as introducing 30 km/h speed limits on all roads in urban areas could have a significant impact on accidents and health. Further temporary tactical urbanism could help transform public urban space fairly quickly. Tactical urbanism refers to low-cost, temporary, and scalable interventions and policies intended to improve urban environments.[269] Although these tactical urbanism interventions are designed to be implemented in a temporary and low-cost approach, these interventions can be considered as pilot programs that could involve the community in selecting future permanent infrastructure. Except for the compact city concept,[254] these new urban models have not specifically evaluated CVD effects, but there are likely beneficial effects on the heart as an increase in active transportation and green space and a reduction in air pollution, noise and heat island effects have all been associated with better cardiovascular health.[14,15]

8. Major conclusion and resulting political/societal needs for action

The exposure to almost all environmental risk factors triggers a specific set of pathophysiological mechanisms that are centred on stress hormone signalling, oxidative stress, and inflammation.[10,16,17,107] As a result, exposome studies will face the problem of identifying specific biochemical signatures (footprints) of different environmental risk factors.[270] In addition, oxidative stress and inflammation also represent major pathomechanisms of cardiovascular, neurodegenerative, and metabolic diseases, which further complicates exposome research. Considering that environmental stressors, unhealthy behaviour (e.g. smoking, sedentary lifestyle), and classical risk factors (e.g. hypertension, diabetes, obesity) all trigger similar pathomechanisms, additive/synergistic effects should be present, leading to more pronounced development and faster progression of NCDs (*Figure 1*).[10,17] Smart city planning may be a key mitigation strategy of unhealthy environmental exposures because environmental stressors such as noise, air pollution or heat islands show an accumulation in big cities and large urbanized areas and their combination aggravates health problems and disease burden that may exceed even the most pessimistic projections.[16]

Concerning all environmental stressors societal action is highly needed. Without fast actions to decrease the environmental stressors at all levels (chemical, physical, and mental sources), the sum of all 'pollution' and climate change will likely form a reinforcing feedback loop. Currently, around 96% of public health funding is spent for treatment and only 4% for prevention.[271] Additionally, the funding for prevention is mostly spent at the individual level with only limited effort or money dedicated to the collective social and physical environment for prevention of environmental exposures. What we need are intersectoral actions for better city design, which has to be done by urban, transport and health planners, all of which has the largest impact on health. Unfortunately, these experts often do not realize the impact of their work on human health and how they can improve health.

We as health professionals have to play a leading role in addressing and in acknowledging environmental stressors such as noise and air pollution as cardiovascular risk factors that are as important as e.g. smoking, diabetes and hypercholesterolaemia. We also have to take care that environmental researchers are getting integrated into these guidelines writing teams to ensure that in the very near future environmental stressors (e.g. climate change, air pollution) rather than classical risk factors (e.g. high cholesterol or diabetes) are defined as the cardiovascular risk factors of the future. Funding for environmental research, teaching and education of the consequences of climate change has to be intensified dramatically, especially medical/health care field, in order to protect the health of our current and future generations.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

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