Atherosclerosis 405 (2025) 119222

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Cardiovascular risk posed by the exposome

Andreas Daiber [a,b,*], Sanjay Rajagopalan [c], Marin Kuntic [a,b], Thomas Münzel [a,b]

[a] Department of Cardiology – Cardiology I, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
[b] German Centre for Cardiovascular Research (DZHK), partner site Rhine-Main, Mainz, Germany
[c] Department of Medicine, Case Western Reserve University, Cleveland, OH, USA

ARTICLE INFO

Keywords:
Chronic non-communicable diseases
Environmental risk factors
Exposome
Environment-related cardiovascular diseases
Inflammation and oxidative stress
Atherosclerotic diseases

ABSTRACT

Chronic non-communicable diseases (NCDs) account for 2/3 of global deaths annually, primarily due to an aging population and external risk factors such as air/water/soil pollution, traffic noise, mental stress, and climate change emanating from the environment. These factors contribute to premature deaths and loss of healthy life years, as reflected by disability-adjusted life years. The exposome concept was proposed 16 years ago as a new research field to investigate environment-health associations, also by considering the underlying pathophysiological pathways. The exposome describes lifelong environmental exposures, besides pollutants also socioeconomic and lifestyle factors, aiming to explain the associated diseases and deaths. The exposome can be divided into the specific and general external environment and further subcategories such as organ-specific exposomes as well as spatially and temporally restricted pollutomes. The exposome also shows considerable interaction with genetic predisposition and pre-established chronic diseases, characteristics of the vulnerable groups. The present overview provides background information on the impact of the environment on health and disease by considering recent data of the Global Burden of Disease Study. We also explain the exposome concept with the help of selected studies, briefly describe how the exposome is measured, and discuss biomarkers identified by exposomic research and their impact on the development and progression of atherosclerosis. Major pathophysiological pathways comprise exacerbated stress hormone signaling, oxidative stress, inflammation and circadian rhythm dysregulation promoting impairment of cardiometabolic function. The present overview highlights the relevance of the exposome for future health research and preventive medicine, especially concerning cardiovascular diseases and therapy.

1. Introduction

The global burden of disease has shifted from communicable diseases to non-communicable diseases (NCDs), including cardiovascular diseases, cancer, respiratory diseases, and diabetes [1,2] [3]. This shift is largely due to demographic changes, improved childhood survival, improvements in hygiene, and elimination of many nutritional and infectious risk factors, at least in the high-income countries, whereas communicable diseases may still represent a significant part of the burden of disease in low/middle-income countries [4]. The prevalence of many NCDs continues to rise, driven by adverse environmental exposures and lifestyle factors. Leading risk factors for annual global mortality (in % of total) include high systolic blood pressure (19.2 %), tobacco smoking (15.4 %), dietary risks (14 %), and air pollution (11.9 %) as well as unsafe water/sanitation and non-optimal temperatures (Fig. 1) [5]. Cardiovascular diseases are the leading cause of death worldwide, accounting for over 44 % of NCDs followed by cancer (22 %), respiratory diseases (9 %), diabetes (4 %) and others (21 %) [6]. Understanding the interplay between genetic predisposition and environmental exposures is crucial for addressing the growing burden of NCDs [7]. However, environmental contributions outcompete genetic predisposition, since only 16.4 % of 1.53 million deaths in 2000 in Western Europe could be attributed to direct known genetic causes [8]. The Lancet Commission on Pollution and Health has deemed chemical pollution the leading environmental cause of chronic diseases and premature deaths globally [4]. In 2015, chemical pollution caused 9 million premature deaths, accounting for 16 % of all annual deaths - a similar number of deaths as caused by smoking and passive smoking [9]. This number is three times higher than HIV, tuberculosis, and malaria combined. The World Health Organization reported a global excess mortality of 12.6 million in 2012 due to unhealthy environments [10,11]. In low-income countries, one in four deaths is caused by environmental

* Corresponding author. Univ.-Prof., University Medical Center Mainz, Johannes Gutenberg University, Langenbeckstrasse 1, 55131, Mainz, Germany.
E-mail address: daiber@uni-mainz.de (A. Daiber).

https://doi.org/10.1016/j.atherosclerosis.2025.119222
Received 13 February 2025; Received in revised form 13 April 2025; Accepted 15 April 2025
Available online 30 April 2025

risk factors. A more recent GBD report already estimates that air pollution alone is responsible for 8.1 million global annual deaths [12], suggesting that all chemical pollution-associated deaths will rather align with the WHO figure.

The Global Burden of Disease Study estimates that environmental pollution contributes to 268 million disability-adjusted life years (DALYs), including loss of life years and severe disease or disability [14]. Air pollution is the most significant chemical environmental health risk, with particulate matter with a diameter $\leq$2.5 μm ($PM_{2.5}$) and ozone responsible for 8.8 million global premature annual deaths [15,16]. These numbers are expected to increase due to improved exposure-response functions and more accurate high-exposure level studies from highly polluted megacities (Fig. 2) [17,18]. In 2013, air pollution caused 3.5 % of all healthcare costs in high-income countries and 7.4 % in low-income countries [4]. However, these costs do not fully reflect the socioeconomic burden of air pollution, including productivity loss due to sick days and invalidity pensions for chronically exposed and disabled individuals. The importance of air pollution as a major health threat is confirmed by the significant lowering of cardiovascular disease risk and even the extended life expectancy observed during the 2008 Beijing Olympic Games due to highly restrictive air pollution control measures [19] or lower legal limits for diesel emissions by new restrictive laws in Tokyo [20] and banning leaded fuels in the USA [21,22]. In line with this previous evidence for high efficacy of air quality improvement measures, a projection estimates that 5.13 million excess deaths per year globally are attributable to ambient air pollution from

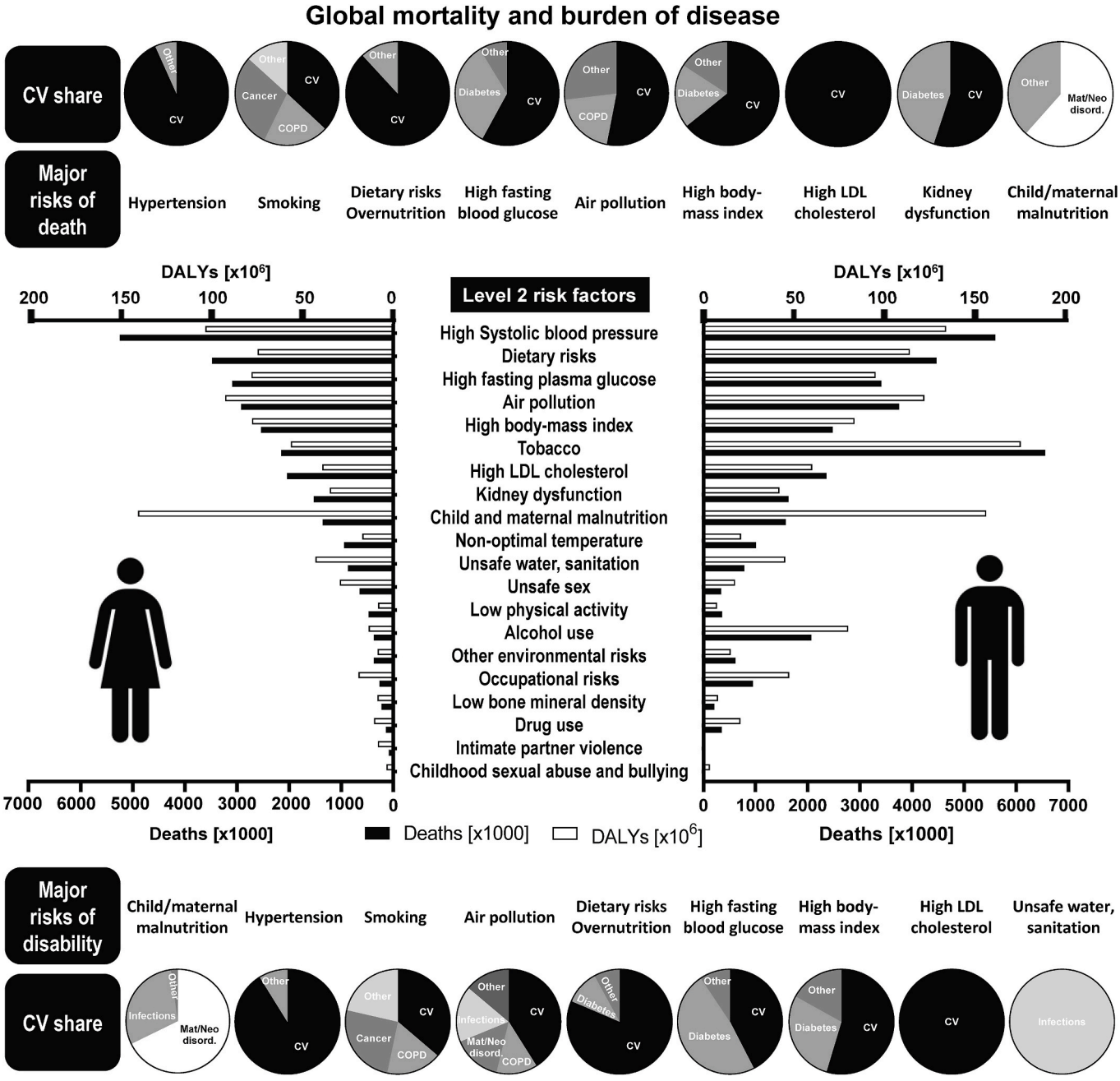


Fig. 1. Global number of deaths and percentage of DALYs attributable to Level 2 risk factors by cause and sex in 2019. Cardiovascular disease is the major category of sequelae in all leading risk factors, followed by respiratory disease, diabetes, cancers and infections (see pie charts for leading Level 2 risk factors). DALYs, disability-adjusted life years; LDL, low density lipoprotein; Mat/Neo disord., maternal/neonatal disorders; CV, cardiovascular disease; COPD, chronic obstructive pulmonary disease. Adapted and merged from data in Ref. [5] and graph in Ref. [13] with permission.

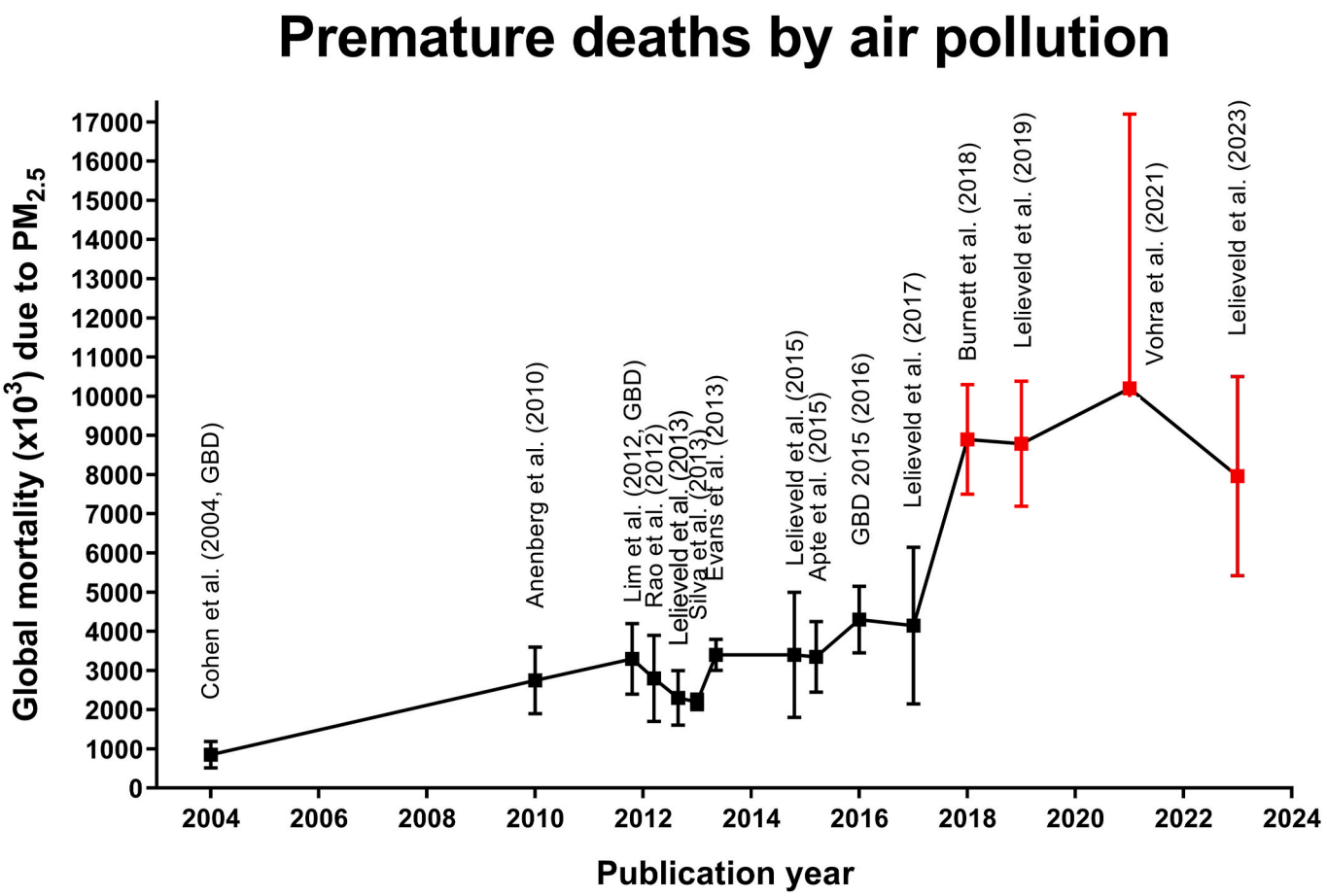


Fig. 2. Air pollution and global premature deaths. Literature estimates of global premature mortality attributed to outdoor air pollution by fine particulate matter (PM2.5). Black symbols represent data with mean ± SD; red symbols represent data with mean and 95 % confidence intervals. Approximated and updated from data in Refs. [17,18] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

fossil fuel use and therefore could potentially be avoided by phasing out fossil fuels [23].

The combined health impact and disease burden of environmental exposures in large cities, including air pollution, traffic noise, nighttime light, and psychosocial factors like mental stress [24–26] could exceed previous estimations based on single exposure models by far, potentially leading to higher socioeconomic savings when successfully mitigating these exposures. Assessment of multi-exposure scenarios is crucial for understanding and estimating the additive disease burden caused by interaction of different environmental stressors, e.g. as shown by cumulative increase of diabetes risk in the Danish population by combined exposure to $PM_{2.5}$, ultrafine particles, traffic noise, and lack of green space [27]. High-quality mechanistic studies on the combined health effects of two or more environmental stressors are needed in the future. For example, combined exposure of mice to ambient $PM_{2.5}$ and aircraft noise revealed dominant biochemical damage in the lung and brain, respectively, with key mechanisms centered on oxidative stress and inflammation that were additively increased in the aorta of co-exposed mice [28].

Lead toxicity, primarily from water and soil pollution, is significant due to its widespread use in car batteries, water pipes, and paints [13]. Contamination enters the food chain through plants, farm animals, and seafood, posing health risks. Lead-associated global deaths are estimated at 0.9 million per year highlighting its importance as an environmental risk factor [9]. Most chemical pollutants are linked to cardiovascular and metabolic issues like hypertension, ischemic heart disease and diabetes due to inflammation and oxidative stress (Fig. 3). Environmental pollution, lifestyle factors (e.g., smoking, nutrition, physical activity), climatic conditions (e.g., high temperature and humidity) are all considered important parts of the exposome by the Global Burden of Disease Study that significantly impact the biochemical phenotype. They can influence metabolic processes, inflammatory cascades, redox homeostasis, and circadian rhythm [29,30]. Smoking is the number one life style risk factor with a clear association with higher incidence of different forms of cancer and cardiovascular disease as well as increased mortality due to myocardial infarction and stroke [31]. According to estimations, the risk of myocardial infarction is 3-fold higher and a meta-analysis reported that overall cardiovascular mortality is 2-fold higher in active smokers and even years after tobacco use cessation, the risk of cardiovascular death is still increased by 37 % [32]. Clinically-induced and natural radiation poses an underestimated health risk. Meta-analysis data estimate an increased risk of all circulatory diseases by 2.5–8.5 % by low-level ionizing radiation [33]. Natural radon exposure increased the relative risk of different forms of cancers in children, adults and mine workers by 1–10 % [34]. Data from 3 large US prospective cohorts reveal that elevated UV radiation is associated with increased risk of both melanoma and noncutaneous cancers [35].

2. The exposome concept

2.1. Definition and examples

In order to account for the growing contribution of environmental and lifestyle risk factors to the global burden of disease, the “exposome” concept was developed. The term "exposome" was introduced in 2005 by Christopher P. Wild and encompasses changes in human physiology (the

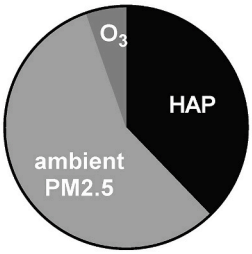
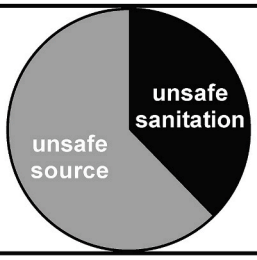
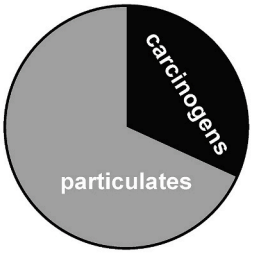
	Deaths [Mio] and 95% CI (conservative)*	Contribution of different components [%]*	Deaths [Mio] and 95% CI (progressive)	Risk estimate for hypertension or ischemic heart disease
 Air pollution	Female 2.92 (2.53-3.33) Male 3.75 (3.31-4.25)		8.8 (7.1-10.4)[a] 8.9 (7.5-10.3)[b] 10.2 (-47.1 -17)[c]	HR 1.11 (1.05-1.17) for incident hypertension per 10 µg/m³ increment of $PM_{2.5}$[d]
 Water pollution	Female 0.73 (0.40-1.26) Male 0.63 (0.46-0.95)		1.8[e] 3.56[f]	OR 2.3 (1.03-5.14) for prevalent hypertension for water with high fluoride levels[g]
 Occupational pollution	Female 0.22 (0.17-0.28) Male 0.65 (0.54-0.79)		1.2 (only NCDs) 1.5 (total without injuries)[h]	PR 2.20 (1.31- 3.71) for prevalent coronary heart disease for working with pesticides[i]
 Lead	Female 0.35 (0.19-0.53) Male 0.56 (0.36-0.77)	Lead-acid batteries Lead water pipes Other sources: pigments, paints, solder, stained glass, lead crystal glassware, ammunition, ceramic glazes, jewellery, toys, cosmetics, traditional medicines	almost 1[j]	HR 1.27 (1.01-1.59) for incident ischemic heart disease per one SD increase in blood lead[k]

Fig. 3. Contribution of major pollutants to global deaths and cardiovascular disease. *The conservative estimation from the Institute of Health Metrics and Evaluation was corrected for potential overlap of pollution-associated deaths. Data in 1st and 2nd column taken from Ref. [9]. Data of progressive studies were taken from a [36], b [37], c [38], e [39], f [40], h [41], j [42]. Last column shows selected risk estimates for different pollutants and hypertension/ischemic heart disease as a measure of contribution to NCDs and the global burden of disease; data taken from d [43], g [44], i [45], k [46]. HR, hazard ratio; OR, odds ratio; PR, prevalence ratio; SD, standard deviation; CI, confidence interval; HAP, household air pollution; PM2.5, particulate matter with a diameter of ≤2.5 µm; O_3, ozone. Tabular data in Ref. [13] used with permission.

"internal environment") due to environmental factors at a lifespan dimension [47]. These exposures include chemical and physical factors like air pollution, traffic noise, UV radiation, and climate-related stressors, as well as socioeconomic determinants related to social, urban, and work environments - social capital and mental stressors (e.g., social isolation, work strain) (the „general external environment") (Fig. 4) [1]. While this conventional definition of the exposome is rigorous, transcending the life span, a more practical definition refers to the exposome as a composite of measurable external factors with or without additional biomarkers at one or more time points [48]. This restricted definition recognizes the impracticality of having multiple samples across a lifetime for the vast majority of mankind, with recent studies measuring a more pragmatic set of factors to begin to understand complex interactions between many variables. We would like to stress that alternative concepts and hypotheses were put forward by other exposome experts that differ more or less from the here presented ideas and mechanisms [49–52].

The lack of availability or lack of green space is also an important environmental factor for our health [25,54]. Our lifestyle, including smoking, alcohol consumption, healthful eating, physical exercise, and use of consumer products, significantly influences the "specific environment" [1]. Importantly, individuals can easily alter their specific environment, but the general external environment cannot be easily altered. By definition, the exposome can be categorized into temporal periods (e.g., pre-birth, lactation, infancy, adolescence, adulthood, seniority), spatially distinct pollutomes (e.g., occupational exposome, urbanome) [4,55,56], and organ-specific representations, such as the blood exposome [57]. The external exposome also interacts with genetic predisposition [7] and pre-existing chronic diseases [13], leading to additive or synergistic biological responses. Environmental risk factors

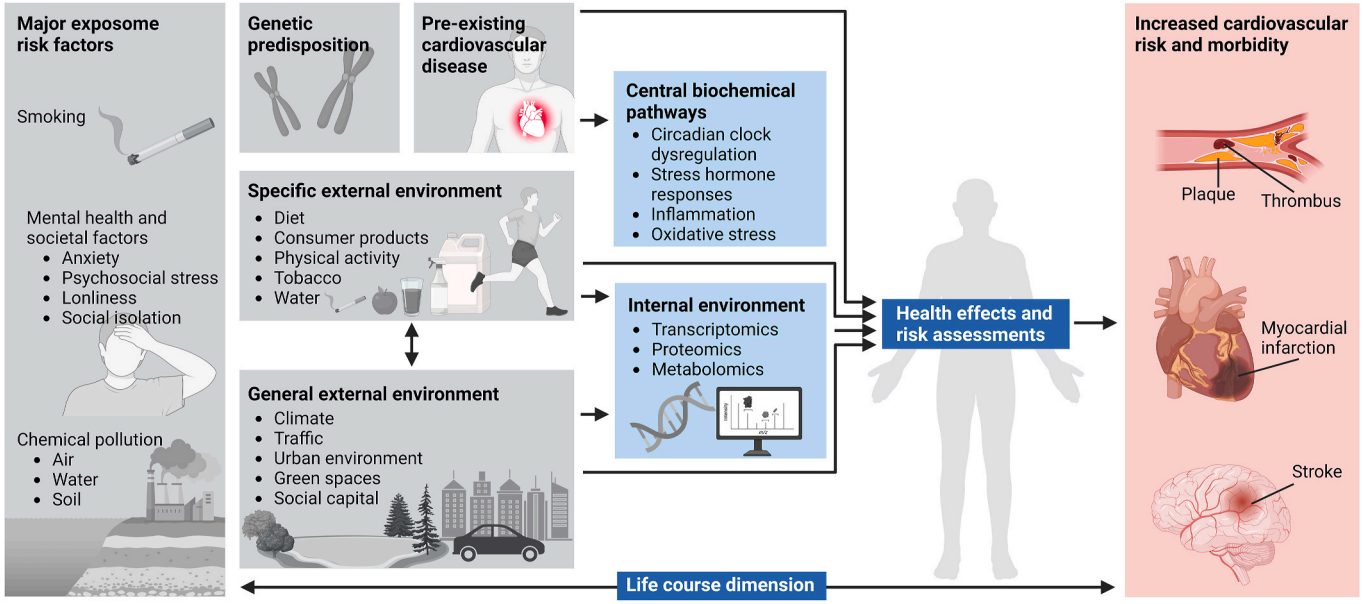


Fig. 4. The exposome concept. The exposome describes the totality of lifelong exposures to environmental risk factors, the induced pathological and mechanistic changes in central biochemical pathways, and the associated health effects [47] (also reviewed in [1,2]). Within the general external environment, the environmental factor with the largest effect on health is chemical pollution. Within the specific external environment, the environmental factors with the most substantial effect on health are tobacco smoking and unhealthy dietary habits. The general and specific external environment can have adverse effects on mental health (for example, by social isolation or work strain), but the contribution of environmentally triggered mental stress to the global burden of disease and global deaths might be underestimated owing to the lack of valid exposure–response relationship data for mental risk factors. Changes in the internal environment induced by exposures are most frequently quantified by changes in the transcriptome, epigenome, proteome and metabolome (and more rarely by analysis of the microbiome or adductome). Alterations in central biochemical pathways identified in exposome studies include dysregulation of circadian clock components that lead to impaired rhythmicity and phase shifts, the release of stress hormones (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 (reviewed previously [25,53]). Environmental exposures can act synergistically or additively with genetic predisposition or pre-existing cardiovascular disease. Environmental exposures can exacerbate detrimental cardiovascular health outcomes such as atherosclerosis, vascular stenosis, myocardial infarction, heart failure and stroke. Adapted from Ref. [13] with permission. Created using biorender.com.

primarily cause changes of the "internal environment" due to oxidative stress, inflammation, stress hormone signalling [17,24,58], and secondary dysregulation of circadian rhythms and metabolic pathways [29,30,59]. Indeed, an emerging viewpoint suggests that most environmental health impacts represent gene-environmental interactions at an epigenome level [60–62]. The epigenome could serve as a powerful buffer preventing large scale effects from the constant barrage of environmental risk factors [61]. Empirical evidence already suggests that environmental exposures (e.g., diet, stress, toxins) influence epigenetic states and suggests that the epigenome modulates phenotypic response to external cues, effectively attenuating or amplifying outcomes [60,62]. Indeed the vast majority of environmental exposures are transcriptionally silent with evidence that many epigenetic changes in response to exposures like air pollution exposure may be reversible [63].

Environmental stressors significantly impact human development during vulnerable phases of development, particularly in utero, during infancy and childhood. These vulnerable periods represent important opportunities to study exposure health effects given the relatively shallow thresholds for permanent end-organ damage and developmental delays [64]. Indeed exposures during early life can lead to long-term health complications and NCDs, e.g., reduced cognitive function, mental disorders, violence during adolescence, and economic unproductivity [4]. Fetal or infantile reprogramming of biological processes by environmental risk factors, e.g., by long-term epigenetic imprinting as seen by increased risk for major chronic NCDs in adults who experienced the great Chinese famines when being children [65,66], is a major socioeconomic challenge due to decreased productivity and higher long-term health care costs. Environmental exposures contribute to the rapid progression of neurodegenerative diseases like Alzheimer's and Parkinson's [67,68], and mental health in general [69].

Exposome studies such as HELIX [70,71], PACE [72,73], UK Biobank [74], and birth cohorts thus represent important assets to dissect complex exposomic impacts during vulnerable phases. Additional promising projects include EXPOSOMICS consortium [49,75], HERCULES [76], HEALS [77] and the EUROPEAN EXPOSOME NETWORK [78]. Other classical exposure-health association studies in Europe, like ESCAPE and ELAPSE, mostly lack information on biochemical changes of the internal environment, which is essential for a complete exposome study. As exposome studies typically began 5–10 years ago, robust data is expected within the next decade. Prominent examples are summarized in Fig. 5.

2.2. *Assessment of the exposome*

The exposome is a complex structure that requires two main methods [13]: bottom-up and top-down. The bottom-up method measures external factors like air and water quality, diet, and physical activity using advanced tools like geographic information systems (GIS), satellite data, and mobile sensors to collect real-time exposure data (Fig. 6). The top-down approach focuses on internal biological changes as biomarkers of exposure, analyzing blood, urine, and tissue samples to detect exogenous compounds and gene expression alterations. Metabolomics, proteomics, and transcriptomics are used to identify environmental exposure footprints in the body, with fields like epigenetics, lipidomics, adductomics, and microbiomics [79,80]. Both methods are essential for understanding the exposome by association with health outcomes (Fig. 6). Importantly, there are other approaches to assess the exposome with focus on different mechanisms, markers and specific health outcomes [80–82]. Also in the largest exposome initiative worldwide, the European Human Exposome Network, highly specific analytical

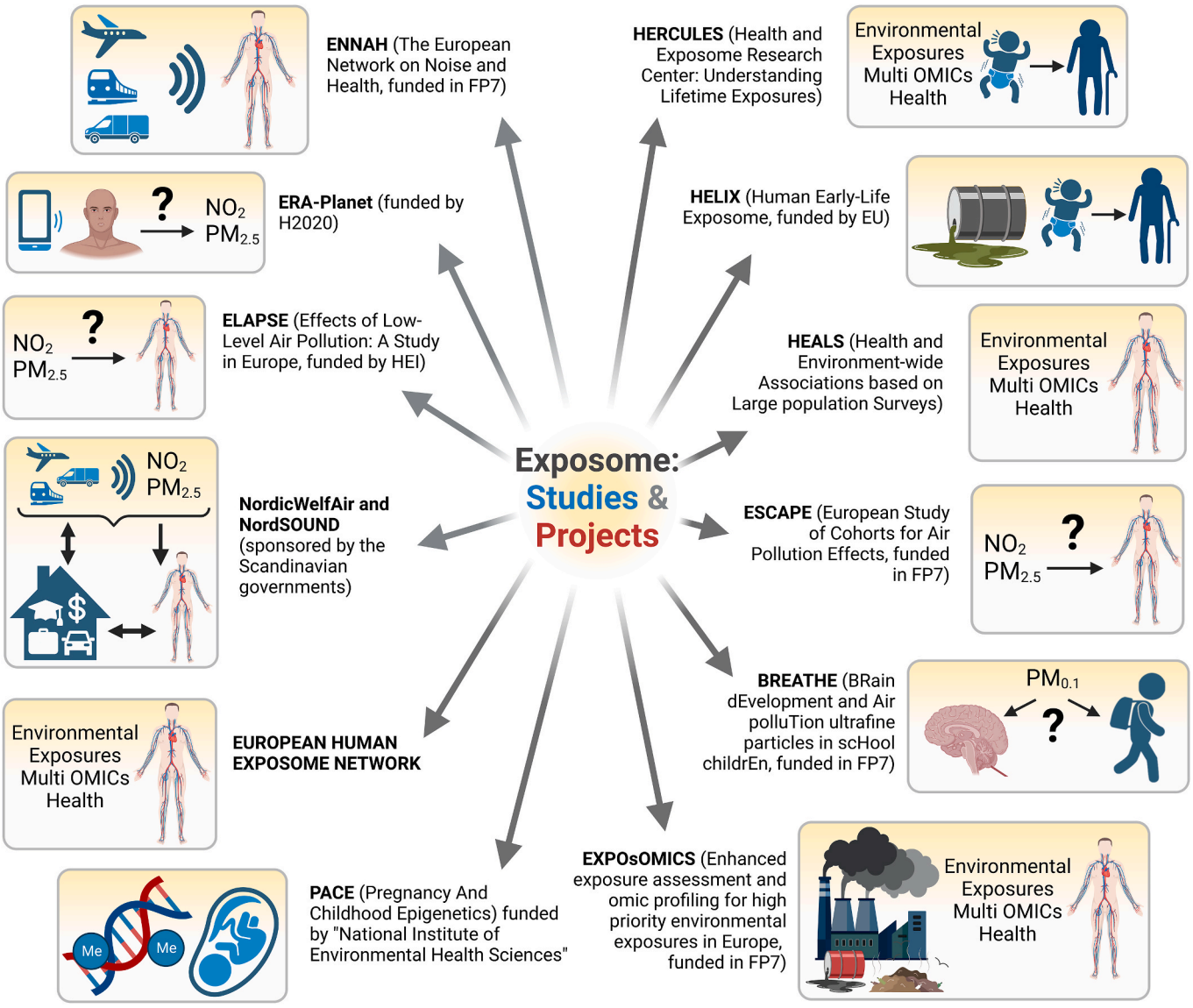


Fig. 5. Selected examples of exposome as well as environment-health-association studies and projects. Summarized from Ref. [17]. NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with a diameter ≤2.5 μm; $PM_{0.1}$, ultra-fine particles with a diameter ≤0.1 μm. Reused and translated from Ref. [2] with permission. Copyright © 2021, Rights Managed by Georg Thieme Verlag KG Stuttgart • New York. Created using biorender.com.

approaches are developed for different scientific questions related to the exposome [78]. Open acces databases further help to tackle the biochemical impact of environmental exposures [83,84].

Modern analytical methods like LC-MS are sensitive enough to monitor drug use in populations through wastewater analysis and detect over 30,000 small molecules in human serum [13]. However, untargeted high-resolution mass spectrometry may miss 90 % of pollutants and 30 % of endogenous and food chemicals, including hormones, carcinogens, and endocrine disruptors [57]. Genomic analyses have advanced, allowing for the measurement of 500,000–5 million single-nucleotide polymorphisms (SNPs) in a single test or approaches that sequence the entire genome. Targeted approaches like metabochips and immunochips offer cost-effective exposome studies [13]. Epigenetic changes are typically measured using DNA methylation techniques which may sample a representative methylome (EPIC or BeadChip) or the whole genome (whole genome bisulfite sequencing). Future advancements may include high-throughput assays for receptor activity and oxidative stress responses. "Enviromics" refers to high-throughput OMICs techniques used in exposome studies applied to a broad variety of health conditions including cardiovascular disease [85,86]. Exposure-health association studies measure stress hormones (e.g., catecholamines and cortisol), circadian rhythm disruption markers (e.g., melatonin), oxidative stress indicators (e.g., malondialdehyde), and inflammatory responses (e.g., cytokines), which are crucial for understanding how environmental exposures affect health. Fig. 7 provides a summary of biomarkers that are used for exposome studies.

2.3. *The exposome in early life and in the elderly*

Environmental risk factors play a significant role in global morbidity and mortality across all stages of life. The highest chronic disease burden, measured in disability-adjusted life years (DALYs), occurs in early childhood (<4 years). The substantial DALY burden from pollution in early life highlights the extensive lost life years and long-term disabilities that can result from the death or chronic non-communicable diseases (NCDs) of even a single child [4]. Environmentally triggered premature deaths dominate in the elderly (>60 years). Exposome studies are crucial to understand the pronounced impact of environmental risk factors in children and the elderly, mostly due to ongoing developmental processes and cellular decline [4]. According to one

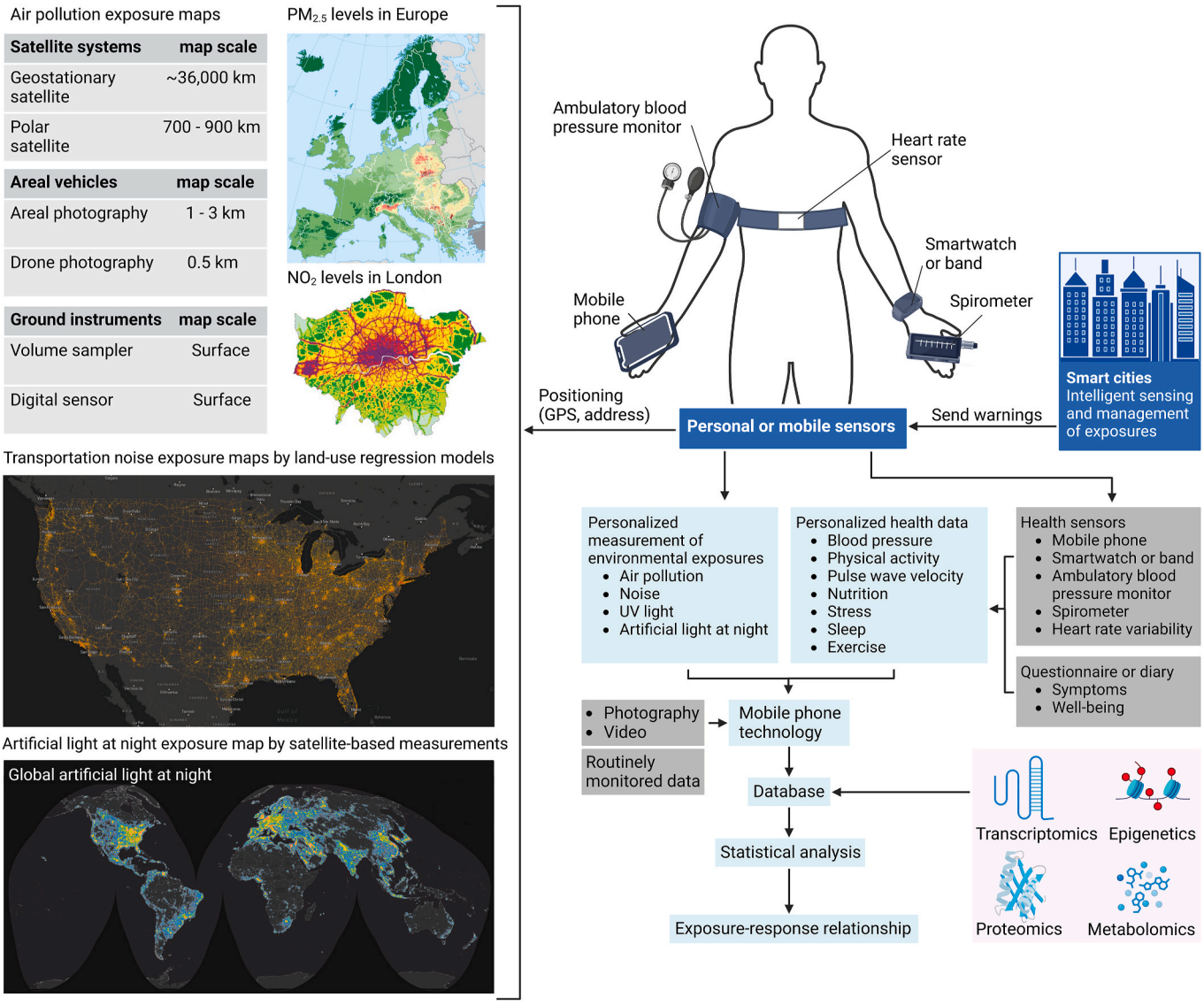


Fig. 6. Measurement of the external and internal exposome. Personal or mobile sensors enable the continuous assessment of environmental exposures (such as air pollutants, noise, ultraviolet (UV) and artificial light at night) and health parameters (such as blood pressure, physical activity, and sympathovagal and emotional parameters) of an individual. Personal data can also be acquired via daily questionnaires submitted via app-based software. Improved exposure data from satellite, aircraft, drone and ground-based measurements provide a detailed spatial and temporal exposure history in relation to the global positioning system (GPS) location of the target individuals. In addition, land-use regression models allow accurate exposure estimations for air, noise or light pollution at the address level. A combination of all assessment methods of exposure allows the creation of exposure maps. Smart cities can facilitate intelligent sensing of exposures and can protect the individual from environmental hazards via early warnings sent to the individual's mobile devices and through intelligent exposure management, for example, by advanced control of traffic, waste and nocturnal illumination and by the implementation of green spaces. The flow chart provides an example of a personalized sensor framework for continuous assessment of environmental exposures and lifestyle history for exposome studies. The exposure maps are reprinted with permission from the European Environment Agency (particulate matter with diameter ≤2.5 μm (PM2.5) levels in Europe), the UK Department for Environment, Food and Rural Affairs, © Crown 2004 (NO_2 levels in London), US Department of Transportation, Bureau of Transportation Statistics, National Transportation Noise Map (noise pollution in the USA), and the world atlas of artificial night sky brightness by Falchi et al., 2016, AAAS (global artificial light at night). Adapted from Ref. [13] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

hypothesis and potential explanation, excess mortality at old age attributed to environmental exposures, such as chemical pollution, due to diseases like cancer, neurodegeneration and cardiovascular events represent "tipping point" events, sometimes referred to in the epidemiologic literatures as "harvesting" [17,87]. Cumulative exposure impacts across a life time can rapidly escalate due to loss of endogenous defenses at a specific time point, in older age, when the acceptable threshold of biochemical damage is exceeded. The disproportionate effects of environmental factors in children on the other hand, could be attributable to their relatively immature immune system that is unable to defend against exposure to higher doses of environmental toxins due to a lower body weight to concentration ratio, unfavorable fetal reprogramming, and pre-birth and infantile development processes [17]. Also for the impact of the exposome during different periods in life, early life [70,88,89] and in the elderly [90–92], different concepts and hypotheses have been developed.

3. Impact of the exposome on development and progression of atherosclerosis

Exposomic determinants such as air pollution play a crucial role in the significant burden of atherosclerotic cardiovascular disease (ASCVD)

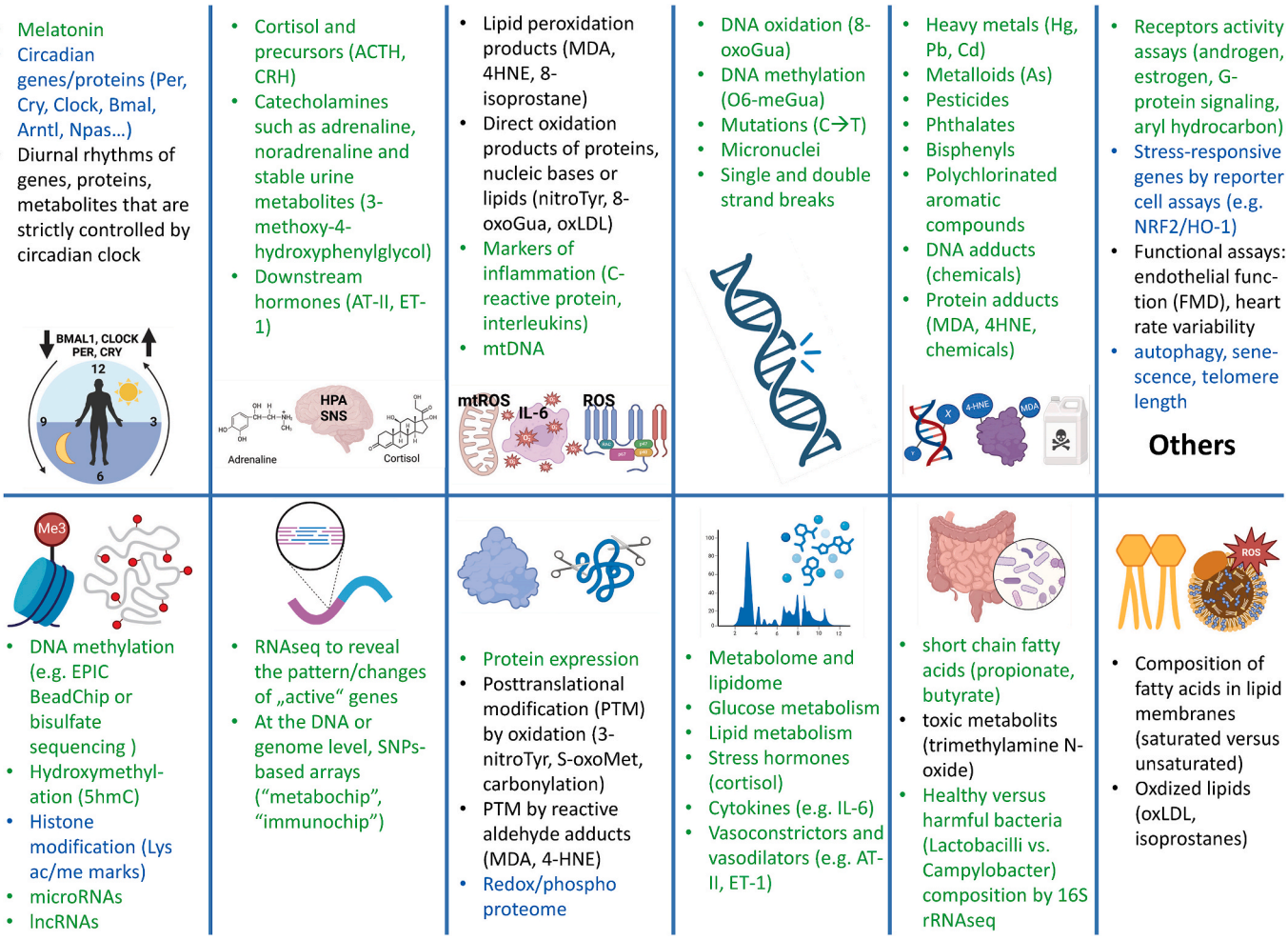


Fig. 7. Biomarkers of the exposome. Summary the major mechanisms and targets that respond to exposures and can be used for exposomic studies in the cardiovascular system. Color code: green, markers in the pipeline of the large exposome studies; black, markers reported by exposure field studies; blue, markers confirmed by animal exposure studies. Per, period; Cry, cryptochrome; Clock, clock circadian regulator; Bmal, brain and muscle arnt-like protein; Arntl, aryl hydrocarbon receptor nuclear translocator-like protein; Npas, neuronal PAS domain protein; 5hmC, 5-hydroxymethylcytosine; Lys ac/me, lysine acetylation/methylation; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; AT-II, angiotensin II; ET-1, endothelin-1; SNP, single nucleotide polymorphism; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; nitroTyr, 3-nitrotyrosine; 8-oxoGua, 8-hydroxyguanine; oxLDL, oxidized low-density lipoprotein; mtDNA, mitochondrial DNA; S-oxoMet, methionine sulfoxide; O^6-meGua, O^6-methylguanine; C→T, cytosine to thymine transition mutation; IL-6, interleukin-6; NRF2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; FMD, flow-mediated dilation. Adapted from tabular data in Ref. [13] with permission. There, multiple examples for the different biomarkers in exposome studies can be found with the respective references in Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

[93]. A significant portion of this attributable ASCVD burden may originate from non-genomic causes in the sense of “genetics loads the gun but environment pulls the trigger“ [7,25]. This does not preclude the importance of genetics but does reinforce the notion that the environment plays an important part in priming the genetic response. We will focus on a few exposomic risk factors with strong links to atherosclerosis, e.g. air pollution, transportation noise, non-optimal temperatures, soil/water pollution and socioeconomic factors. Of note, there are many more factors in the exposome that impact the risk of atherosclerosis, e.g. protective environmental “exposures” such as greenspace, neighborhood walkability [93,94], and more detrimental pollutants such as heavy metals, pesticides and microplastics [95,96]. Integrating vascular health markers into the exposome concept could improve our understanding of environmental influences on ASCVD onset and progression.

3.1. Air pollution and risk of atherosclerosis

Prior reviews have extensively covered the mechanisms underlying air pollution exposure and atherosclerosis events [97,98]. Indeed, short-term and long-term exposure epidemiologic studies, short-term human studies and experimental studies in atherosclerosis indeed implicate $PM_{2.5}$ air pollution as a causal factor in atherosclerosis. A susceptible individual who is high-risk for ASCVD, may experience an event when exposed to high levels of air pollution, often in concert with other poorly understood stressors. This is consistent with the available evidence that patients who are older, those with multiple risk factors and/or prior cardiovascular or pulmonary disease, experience most of the risk posed by air pollution [99,100]. While exposure over years may promote anatomic progression of the burden of atherosclerosis plaque, the development of “vulnerable plaque” features, which has also been noted with air pollution events, may ultimately precipitate an acute coronary event (plaque inflammation, weakening of fibrous cap and lipid content) [101]. Thus years of $PM_{2.5}$ exposure may facilitate a “vulnerable” state that may then confer risk to acute variations in $PM_{2.5}$ levels. Exposure to $PM_{2.5}$ has also been linked to several atherosclerosis surrogates including alterations in vascular function, carotid intima media thickness, coronary artery and aortic calcification, flow mediated

dilation and abnormal ankle brachial index [97,98].

The Heinz Nixdorf Recall Study from Germany (4384 subjects) investigated the link between urban air pollution and peripheral vascular bed atherosclerosis, using $PM_{2.5}$ levels, traffic exposure, and peripheral arterial disease (e.g. ankle-brachial index (ABI) < 0.9) [102] or coronary artery disease (e.g. coronary artery calcium content) as indicators [103]. Individuals living closer to a major road had a higher risk for peripheral arterial disease than those living more distant. The German KORA Study (4544 subjects) found that particulate matter was associated with high prevalence of low ABI [104]. The US American MESA Study (1147 and 5488 subjects) found a trend of elevated risk of aortic calcification [105] and decreased ratio of carotid intima-media thickness in association with higher air pollution levels [106], also confirmed by further increasing the sample size and measuring coronary artery calcium by CT in 6795 participants [107]. A study of 503 individuals found that higher air pollution exposure is linked to increased leucopoietic activity and arterial inflammation as envisaged by ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) imaging, and independently predicts major adverse cardiovascular events (MACE) [108]. A meta-analysis of a pooled sample of more than 10,000 subjects found an association between $PM_{2.5}$ exposure and subclinical atherosclerosis envisaged by carotid intima media thickness and arterial calcification [109], which was confirmed by meta-analysis data on European ESCAPE cohorts (9183 subjects) [110]. More examples on associations of air pollution with indicators of atherosclerosis can be found in Ref. [93]. The major mechanisms that promote atherosclerosis development by air pollution, specifically particulate matter, are oxidative stress and inflammation [98,111,112], thrombotic events [113], and enhanced vasoconstrictor activity [114,115]. These have also been previously reviewed extensively [116–118].

3.2. Transportation noise and risk of atherosclerosis

Traffic-related noise pollution negatively impairs endothelial function [119–121], an early predictor of atherosclerosis [122,123] coronary artery [124] and peripheral arterial disease [125]. One night of aircraft [126] or railway noise [127] was enough to impair endothelial function measured by flow-mediated dilation in healthy volunteers in association with increased stress hormone signalling and proteomic markers of thrombo-inflammation. The involvement of oxidative stress was suggested by restoration of endothelial function in noise-exposed individuals by administration of the antioxidant vitamin C. The effect of noise exposure on impairment of endothelial function was exacerbated in patients with pre-established coronary artery disease [128]. A study in Poland found that long-term aircraft noise exposure, exceeding 60 dB(A) L_{den}, led to higher pulse wave velocity and increased arterial hypertension [129]. The Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) also found that long-term exposure to railway and nighttime noise events increased brachial-ankle pulse wave velocity [130]. A 2020 study found a neurobiological link between noise exposure, inflammation, and MACE [131]. The study involved 498 healthy adults without active cancer or clinical CVD. Results showed that increased noise exposure at home was linked to heightened amygdala activity and arterial inflammation by PET-CT imaging, and a higher risk of MACE [132]. This pathway has also been implicated in the link between perceived mental stress and socioeconomic disparities and CVD [133,134]. However, large cohort studies show substantial variations. The Swedish SCAPIS Study found no association for risk of coronary artery disease and transportation noise levels (L_{den}) [135]. In contrast, a cross-sectional study on Indian populations in noisy areas (>60 dB(A) L_{den}) observed an odds ratio of 2.61 for males and 2.07 for females for risk of coronary artery disease per 5 dB(A) increment in the road noise levels [136]. Similarly, environmental noise exposure ($L_{Aeq,24h}$ and L_{night}) was associated with higher atherothrombotic risk in MI patients in the RICO survey [137]. The major pathophysiologic processes that promote atherosclerosis development by transportation noise are oxidative stress and inflammation [138–140], altered stress hormone signalling [141–143], enhanced vasoconstrictor activity [138,139,144], and dysregulated circadian rhythms and clock core components [139] – reviewed in Refs. [53,145].

3.3. Soil/water pollution and risk of atherosclerosis

Soil and water pollutants contribute to the progression of atherosclerosis. Exposure to cadmium in particular, has been linked to an increased incidence of coronary artery disease, peripheral artery disease, atherosclerosis and stroke, and increased cardiovascular mortality [146,147]. Also, arsenic and methylmercury promote carotid atherosclerosis and peripheral arterial disease, and lead concentrations in bone is associated with the incidence of and mortality from peripheral and coronary artery disease [95,148]. The risk of coronary heart diseases is increased by all the aforementioned heavy metals and metalloids, including copper [146,149]. Plastic-related chemicals such as phthalates [150] and bisphenols [151], polyhalogenated compounds [152,153] and dioxins [154] represent endocrine-disrupting and persistent organic pollutants, which increase the risk of coronary heart diseases related to atherosclerosis [16]. Important to note that many of these soil/water pollutants also represent toxic contaminants of air pollution constituents, especially of particulate matter, suggesting similar pathomechanisms. Also microplastic particles have been suggested to promote atherosclerotic plaque development, progression, and subsequent cardiovascular events [155]. The major mechanisms by which chemical pollutants promote atherosclerosis include, oxidative stress and inflammation, either by direct activation of reactive oxygen species producing enzymes, interference with thiol-dependent enzyme activities, oxidative disruption of circadian clock function or aryl hydrocarbon receptor-dependent processes, all of which has been previously reviewed [95].

3.4. Non-optimal temperatures and risk of atherosclerosis

Heat waves, are increasing in frequency with rising mean temperatures [156]. This may unequally affect low/middle- and high-income countries due to differential access to household and workplace air conditioning as well as access to the necessary energy for these cooling systems [157,158]. From 2008 to 2017, extreme heat was associated with higher all-cause mortality in the contiguous USA, particularly among older adults [159]. The absolute burden of temperatures related deaths are however overwhelmingly related to cold weather, rather than hot weather [160]. Heat exposure may result in severe volume depletion and cardiogenic shock in patients with cardiovascular disease, particularly those with heart failure with diuretics and β-blockers medication [161]. This worldwide study showed that exposure to extreme temperatures increased the risk of death from any cardiovascular cause, including ischemic heart disease, stroke, or heart failure compared to normal average temperatures, where heart failure was associated with the highest mortality due to non-optimal temperatures. While heat increases mortality, extreme cold also elevates cardiovascular mortality.

A study from North Carolina from 2007 to 2011 reported increased coronary artery disease-related hospitalizations and emergency department visits during heatwaves [162]. Meta-analysis data show a 2.8 % increased risk of coronary heart disease for every 1 °C rise above reference temperature, whereas the overall risk of cardiovascular disease-related mortality increased by 2.1 % [163]. The major processes that promote atherosclerosis development by non-optimal temperatures have been previously summarized [160,164]. Heat exposure triggers counter-regulatory processes to lower core body temperature, leading to peripheral vasodilatation and sweating, dehydration, and electrolyte imbalance. This can cause sympathetic activation and tachycardia, potentially causing myocardial infarction or stroke. Conversely, cold exposure triggers sympathetic activation, peripheral vasoconstriction, and increased muscle tone, raising blood pressure and encouraging

cholesterol crystal deposition within atherosclerotic plaques, potentially causing demand ischemia or plaque rupture [160].

3.5. Socioeconomic factors, built environment and risk of atherosclerosis

Urban design and land use can indirectly affect cardiovascular and metabolic health by influencing mobility, housing, transport modes, recreational and green spaces [25,165,166]. Prior reviews have extensively covered the association between the built environment and cardiovascular health [165,167]. A recent systematic review (63 studies, 31 cross-sectional and 32 longitudinal conducted across 21 locations) assessed the impact of urban design features, including residential density, land use mix, greenness and walkability, on cardiometabolic risk factors, including BP, the development of hypertensive heart disease and CV events [168]. Most studies focused on greenery and walkability, with a minority focusing on residential density and land use mix. Overall, strong associations were noted between lower neighborhood greenery indices with increased BP and the development of hypertensive heart disease, with a few studies showing an impact on cardiovascular events. Research indicates that neighborhood walkability is associated with a reduced risk of multiple risk factors [169].

A systematic review found that residential density, reduced traffic exposure, recreation facilities, street connectivity, and highly walkable environments were associated with increased physical activity [170]. A cross-sectional study in 14 cities in 10 middle-income and high-income countries found that the density of residences, public transport and parks was attributable to 90–150 min of physical activity per week [171]. Active transportation—such as walking or cycling for commuting—can increase physical activity and lead to reductions in BP. Compared to vehicular travel, it can also lower exposures to air pollution, noise and heat [166,172,173]. A number of quasi-experimental studies have suggested that switching from private to public and/or active transportation was associated with a decrease in BMI [165,166]. In a large prospective cohort study (n = 263,540) in the UK, active transportation by cycling and walking was associated with a lower risk of cardiovascular events (cycling HR 0.48, 95 % CI 0.25–0.92, P = 0.03; walking HR 0.64, 95 % CI 0.45–0.91, P = 0.01), independent of other factors [174]. The mechanisms may include reduced sympathetic nervous system activity, improved endothelial function and improved autonomic balance. A study comparing London and Hyde Park walking patterns found that walking in Hyde Park improved lung function and decreased pulse wave velocity and augmentation index, and thereby reduced indicators of arterial stiffness in patients with pre-existing chronic obstructive pulmonary disease or ischemic heart disease [175].

Prior meta-analyses and studies have suggested an association between green-spaces and multiple physical and mental health benefits [176–178]. The UK Biobank cohort examined the relationship between residential walkability index, greenness, and pulse wave velocity, showing that higher walkability exposure and greenness were associated with lower pulse wave velocity, particularly in women and older adults [179]. Prior studies have suggested a strong link between social determinants of health and cardiovascular outcomes [48]. The Gutenberg Health Study used cross-sectional and longitudinal data to examine the link between individual socioeconomic status and cardiovascular disease risk and mortality, with a total of 15,010 participants. At 10-year follow-up, low socioeconomic status was associated with a 68 % higher risk of incident CVD and 86 % higher all-cause mortality, effects that were stronger related to education and occupation than the household net-income [180]. Low socioeconomic status (here low income) may contribute to higher stress-related neural activity and arterial inflammation (measured by PET-CT) with an overall higher risk of MACE [181]. More examples are provided in Refs. [93,165,167].

4. New tools of exposomic assessment

The integration of climate, environmental, social and health data into common platforms and the use of machine learning and artificial intelligence (AI) to explore climate and human health effects provides an unprecedented opportunity for health impact assessment and policy [182–184]. Geo-spatial tools can markedly enhance the ability to integrate features in the built environment to predict heart disease. In a recent series of papers, we demonstrated that built environment features extracted from Google Street views of Satellite views, using deep learning predicted coronary heart disease and ASCVD prevalence. The addition of Google Street view features, improved a model that included census-tract level age, sex, race, income and education or composite indices of social determinant of health. Activation maps from the features revealed a set of neighborhood features that were associated with high coronary disease prevalence [185,186]. Integrated online mapping tools with embedded data enables researchers, community groups, and the public to identify communities burdened by multiple sources of pollution and socioeconomic vulnerabilities [187]. These scores are combined to calculate an overall cumulative impact score [188]. Newer generative AI approaches can further enhance our ability to estimate environmental risks, e.g. by automated assessment of the built environment [185,186]. The use of such tools may provide useful information for future policy recommendations. In the field of exposure science, new sensor technologies in wearable monitors that can capture multiple human microenvironments offer the promise of true exposomic assessment.

Integrated assessment of toxin exposures by OMICs methods (adductome, metabolome, proteome, transcriptome/epigenome) can substantially enhance exposomic assessment and is currently a limitation of current approaches [17,51,80,189]. Also, major limitations such as measuring biomolecules, metabolites, and toxic compounds from femto-to millimolar concentrations by mass spectrometric analysis need to overcome [57]. Although high-resolution mass spectrometric approaches are revolutionizing exposomics, identification of many chemical species is currently complicated, as chemicals undergo transformation. While computational tools can predict many transformations, predicting first order reactions alone can be challenging, let alone second order reactions. Approaches to reduce complexity and dimension reduction such as grouping of chemicals by their sources into groups as well as grouping “exposures,” analogous to genotype variants, and linking their relationship to a phenotype of interest is increasingly being employed. Environment-Wide Association Studies (EWAS) are currently allowing the assessment of exposures over lifetimes in thousands of individuals, correlating them with biochemical changes, and assigning them to health outcomes and mortality [17,190,191]. AI-based approaches are rapidly transforming many of the aforementioned challenges.

5. Outlook and conclusions

Although environmental risk factors have been linked to public health and socioeconomic burden, they are often overlooked in clinical guidelines, global prevention plans, and health politics [4,53,192]. This is also reflected by limited funding invested in environmental research as compared to substantial research support for characterization of the human genome and conduction of Genome-wide Association Studies (GWAS) to understand the correlation of genetic predisposition and NCDs, the „heritable diseases” [190]. Here are some facts and a road map for exposome research.

- Exposome research has shown that environmental factors play a major role in diseases [17,193], like diabetes [194], cardiovascular conditions [13,195], childhood illnesses [196], and unhealthy aging [90], accounting for up to 2/3 of all chronic disease [7,8]. However, understanding the exact impact of each exposure on disease and mortality requires better models that separate individual environmental effects [27,13].

- To achieve this, researchers need to track various environmental factors such as toxins, noise, UV radiation, temperature, and social influences at a detailed level [190]. Regular assessments - weekly or monthly - should measure internal body responses (e.g., blood pressure, heart rate [17,13], and biochemical changes [79,80]). These data must be collected across a person's entire lifespan, starting from before birth, to identify links with health outcomes.
- Analyzing such vast amounts of data will require advanced bioinformatics and statistical methods [190,197], as well as global cooperation in funding, ethics, and data protection [198] - similar to the Human Genome Project. As technology advances, exposome research will benefit from cheaper OMICs analysis [17,51,80,189], large-scale studies, and personal sensors [25,199] that can track multiple exposures with high precision to overcome the challenges mentioned in the **Graphical Abstract.** These improvements will enable more accurate environment-wide association studies (EWAS) [190,191], ultimately leading to better disease prevention strategies.

Author contributions

All authors were involved in writing the original manuscript and also critically revised it before submission.

Financial support

T.M. is PI, A.D. is Scientist and M.K. is Young Scientist of the German Cardiovascular Research Center (DZHK), Partner Site Rhine Main. The collaboration of the authors was funded by the environmental network EXPOHEALTH funded by the Science Initiative of the state Rhineland-Palatinate, Germany (chaired by A.D.). S.R. was supported by 1R35ES031702, R01ES017290, R01 ES033670-01 and P50 MD017351-01 from the National Institutes of Health and the National Institute of Environmental Health Sciences, USA. A.D. is the coordinator and T.M. is PI of the environmental research consortium MARKOPOLO, which is funded by the European Union (Grant Agreement Number 101156161) and the Swiss State Secretariat for Education, Research and Innovation (SERI). Views and opinions expressed are, however, those of the author (s) only and do not necessarily reflect those of the European Union, the European Health and Digital Executive Agency (HADEA) or the SERI. Neither the European Union nor the granting authorities can be held responsible for them.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

None of the contributing authors have a conflict of interest concerning this manuscript.

Financial support was provided as follows:

T.M. is PI and A.D. is Scientist of the German Cardiovascular Research Center (DZHK), Partner Site Rhine Main. The collaboration of the authors was funded by the environmental network EXPOHEALTH funded by the Science Initiative of the state Rhineland-Palatinate, Germany (chaired by A.D.). A.D. is the coordinator of the environmental research consortium MARKOPOLO, which is funded by the European Union (Grant Agreement Number 101156161) and the Swiss State Secretariat for Education, Research and Innovation (SERI). Views and opinions expressed are, however, those of the author(s) only and do not necessarily reflect those of the European Union, the European Health and Digital Executive Agency (HADEA) or the SERI. Neither the European Union nor the granting authorities can be held responsible for them.

References

[1] Vrijheid M. The exposome: a new paradigm to study the impact of environment on health. Thorax 2014;69(9):876–8. https://doi.org/10.1136/thoraxjnl-2013-204949.
[2] Daiber A, Kuntic M, Lelieveld J, Hahad O, Münzel T. Das Exposom charakterisiert die Auswirkungen unserer Umwelt auf Stoffwechsel und Gesundheit. Aktuelle Kardiol 2021;10:502–8. https://doi.org/10.1055/a-1546-7401.
[3] Lozano R, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012;380(9859):2095–128. https://doi.org/10.1016/S0140-6736(12)61728-0.
[4] Landrigan PJ, et al. The lancet commission on pollution and health. Lancet 2018;391(10119):462–512. https://doi.org/10.1016/S0140-6736(17)32345-0.
[5] Collaborators GBDRF. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. Lancet 2020;396(10258):1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2.
[6] WHO/THE GLOBAL HEALTH OBSERVATORY. Noncommunicable diseases: mortality. https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/ncd-mortality.
[7] Olden K, Wilson S. Environmental health and genomics: visions and implications. Nat Rev Genet 2000;1(2):149–53. https://doi.org/10.1038/35038586.
[8] Rappaport SM. Genetic factors are not the major causes of chronic diseases. PLoS One 2016;11(4):e0154387. https://doi.org/10.1371/journal.pone.0154387.
[9] Fuller R, et al. Pollution and health: a progress update. Lancet Planet Health 2022;6(6):e535–47. https://doi.org/10.1016/S2542-5196(22)00090-0.
[10] Webpage WHO. Ambient air pollution: a global assessment of exposure and burden of disease. http://apps.who.int/iris/bitstream/10665/250141/1/9789241511353-eng.pdf?ua=1; 2016.
[11] Webpage, WHO report. Preventing disease through healthy environments. https://www.who.int/quantifying_ehimpacts/publications/preventingdisease.pdf; 2016.
[12] Institute HE. State of global air 2024. Special report. Boston, MA: Health Effects Institute; 2024 (ISSN 2578-6873), https://www.stateofglobalair.org/resources/report/state-global-air-report-2024. [Accessed 23 September 2024].
[13] Munzel T, Sorensen M, Hahad O, Nieuwenhuijsen M, Daiber A. The contribution of the exposome to the burden of cardiovascular disease. Nat Rev Cardiol 2023;20(10):651–69. https://doi.org/10.1038/s41569-023-00873-3.
[14] Dalys GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet 2016;388(10053):1603–58. https://doi.org/10.1016/S0140-6736(16)31460-X.
[15] Lelieveld J, et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Eur Heart J 2019;40(20):1590–6. https://doi.org/10.1093/eurheartj/ehz135.
[16] Rajagopalan S, Landrigan PJ. Pollution and the heart. N Engl J Med 2021;385(20):1881–92. https://doi.org/10.1056/NEJMra2030281.
[17] Daiber A, et al. The "exposome" concept - how environmental risk factors influence cardiovascular health. Acta Biochim Pol 2019;66(3):269–83. https://doi.org/10.18388/abp.2019_2853.
[18] Shiraiwa M, et al. Aerosol health effects from molecular to global scales. Environ Sci Technol 2017;51(23):13545–67. https://doi.org/10.1021/acs.est.7b04417.
[19] Rich DQ, et al. Association between changes in air pollution levels during the beijing olympics and biomarkers of inflammation and thrombosis in healthy young adults. JAMA 2012;307(19):2068–78. https://doi.org/10.1001/jama.2012.3488.
[20] Yorifuji T, Kashima S, Doi H. Fine-particulate air pollution from diesel emission control and mortality rates in Tokyo: a quasi-experimental study. Epidemiology 2016;27(6):769–78. https://doi.org/10.1097/EDE.0000000000000546.
[21] Correia AW, Pope 3rd CA, Dockery DW, Wang Y, Ezzati M, Dominici F. Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007. Epidemiology 2013;24(1):23–31. https://doi.org/10.1097/EDE.0b013e3182770237.
[22] Pope 3rd CA, Ezzati M, Dockery DW. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 2009;360(4):376–86. https://doi.org/10.1056/NEJMsa0805646.
[23] Lelieveld J, et al. Air pollution deaths attributable to fossil fuels: observational and modelling study. Br Med J 2023;383:e077784. https://doi.org/10.1136/bmj-2023-077784.
[24] Munzel T, Daiber A. Environmental stressors and their impact on health and disease with focus on oxidative stress. Antioxidants Redox Signal 2018;28(9):735–40. https://doi.org/10.1089/ars.2017.7488.
[25] Munzel T, et al. Heart healthy cities: genetics loads the Gun but the environment pulls the trigger. Eur Heart J 2021;42(25):2422–38. https://doi.org/10.1093/eurheartj/ehab235.
[26] Munzel T, Hahad O, Daiber A. The dark side of nocturnal light pollution. Outdoor light at night increases risk of coronary heart disease. Eur Heart J 2021;42(8):831–4. https://doi.org/10.1093/eurheartj/ehaa866.
[27] Sorensen M, et al. Air pollution, road traffic noise and lack of greenness and risk of type 2 diabetes: a multi-exposure prospective study covering Denmark. Environ Int 2022;170:107570. https://doi.org/10.1016/j.envint.2022.107570.
[28] Kuntic M, et al. Co-exposure to urban particulate matter and aircraft noise adversely impacts the cerebro-pulmonary-cardiovascular axis in mice. Redox Biol 2023;59:102580. https://doi.org/10.1016/j.redox.2022.102580.

[29] Li H, et al. Influence of mental stress and environmental toxins on circadian clocks: implications for redox regulation of the heart and cardioprotection. Br J Pharmacol 2020;177(23):5393–412. https://doi.org/10.1111/bph.14949.

[30] Daiber A, et al. Redox regulatory changes of circadian rhythm by the environmental risk factors traffic noise and air pollution. Antioxidants Redox Signal 2022;37(10–12):679–703. https://doi.org/10.1089/ars.2021.0272.

[31] General ARotS. In: The health consequences of Smoking—50 years of progress, in: services, U. S. D. O. H. A. H. (ed), rockville, MD; 2014.

[32] Mons U, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. Br Med J 2015;350: h1551. https://doi.org/10.1136/bmj.h1551.

[33] Little MP, et al. Systematic review and meta-analysis of circulatory disease from exposure to low-level ionizing radiation and estimates of potential population mortality risks. Environ Health Perspect 2012;120(11):1503–11. https://doi.org/10.1289/ehp.1204982.

[34] Henyoh AMS, Laurent O, Mandin C, Clero E. Radon exposure and potential health effects other than lung cancer: a systematic review and meta-analysis. Front Public Health 2024;12:1439355. https://doi.org/10.3389/fpubh.2024.1439355.

[35] Chang MS, Hartman RI, Trepanowski N, Giovannucci EL, Nan H, Li X. Cumulative erythemal ultraviolet radiation and risk of cancer in 3 large US prospective cohorts. Am J Epidemiol 2022;191(10):1742–52. https://doi.org/10.1093/aje/kwac101.

[36] Lelieveld J, Pozzer A, Poschl U, Fnais M, Haines A, Munzel T. Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. Cardiovasc Res 2020;116(11):1910–7. https://doi.org/10.1093/cvr/cvaa025.

[37] Burnett R, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci U S A 2018;115(38): 9592–7. https://doi.org/10.1073/pnas.1803222115.

[38] Vohra K, Vodonos A, Schwartz J, Marais EA, Sulprizio MP, Mickley LJ. Global mortality from outdoor fine particle pollution generated by fossil fuel combustion: results from GEOS-chem. Environ Res 2021;195:110754. https://doi.org/10.1016/j.envres.2021.110754.

[39] Icahn School of Medicine at Mount Sinai, Philip J Landrigan MD. Pollution leading cause of death. https://www.mountsinai.org/about/newsroom/2017/pollution-leading-cause-of-death; 2017.

[40] The world counts: deaths from dirty water and related diseases. https://www.theworldcounts.com/challenges/planet-earth/freshwater/deaths-from-dirty-water; 2023.

[41] WHO/ILO. Almost 2 million people die from work-related causes each year. https://www.who.int/news/item/16-09-2021-who-ilo-almost-2-million-people-die-from-work-related-causes-each-year; 2021.

[42] WHO newsletter. Almost 1 million people die every year due to lead poisoning, with more children suffering long-term health effects. https://www.who.int/news/item/23-10-2022-almost-1-million-people-die-every-year-due-to-lead-poisoning–with-more-children-suffering-long-term-health-effects; 2022.

[43] Huang K, et al. Long-term exposure to fine particulate matter and hypertension incidence in China. Hypertension 2019;73(6):1195–201. https://doi.org/10.1161/HYPERTENSIONAHA.119.12666.

[44] Yousefi M, et al. Association of hypertension, body mass index, and waist circumference with fluoride intake; water drinking in residents of fluoride endemic areas, Iran. Biol Trace Elem Res 2018;185(2):282–8. https://doi.org/10.1007/s12011-018-1269-2.

[45] Bulka CM, et al. Association of occupational exposures with cardiovascular disease among US hispanics/latinos. Heart 2019;105(6):439–48. https://doi.org/10.1136/heartjnl-2018-313463.

[46] Jain NB, et al. Lead levels and ischemic heart disease in a prospective study of middle-aged and elderly men: the VA normative aging study. Environ Health Perspect 2007;115(6):871–5. https://doi.org/10.1289/ehp.9629.

[47] Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology, cancer epidemiology, biomarkers & prevention : a publication of the American association for cancer research, cosponsored by the. Am Soc Preventive Oncol. 2005;14(8):1847–50. https://doi.org/10.1158/1055-9965.EPI-05-0456.

[48] Khraishah H, Chen Z, Rajagopalan S. Understanding the cardiovascular and metabolic health effects of air pollution in the context of cumulative exposomic impacts. Circ Res 2024;134(9):1083–97. https://doi.org/10.1161/CIRCRESAHA.124.323673.

[49] Vineis P, et al. The exposome in practice: design of the EXPOsOMICS project. Int J Hyg Environ Health 2017;220(2 Pt A):142–51. https://doi.org/10.1016/j.ijheh.2016.08.001.

[50] Niedzwiecki MM, Walker DI, Vermeulen R, Chadeau-Hyam M, Jones DP, Miller GW. The exposome: molecules to populations. Annu Rev Pharmacol Toxicol 2019;59:107–27. https://doi.org/10.1146/annurev-pharmtox-010818-021315.

[51] Vermeulen R, Schymanski EL, Barabasi AL, Miller GW. The exposome and health: where chemistry meets biology. Science 2020;367(6476):392–6. https://doi.org/10.1126/science.aay3164.

[52] Deguen S, Amuzu M, Simoncic V, Kihal-Talantikite W. Exposome and social vulnerability: an overview of the literature review. Int J Environ Res Publ Health 2022;19(6). https://doi.org/10.3390/ijerph19063534.

[53] Munzel T, Sorensen M, Daiber A. Transportation noise pollution and cardiovascular disease. Nat Rev Cardiol 2021;18(9):619–36. https://doi.org/10.1038/s41569-021-00532-5.

[54] Nieuwenhuijsen MJ. Urban and transport planning pathways to carbon neutral, liveable and healthy cities; A review of the current evidence. Environ Int 2020; 140:105661. https://doi.org/10.1016/j.envint.2020.105661.

[55] Faisandier L, Bonneterre V, De Gaudemaris R, Bicout DJ. Occupational exposome: a network-based approach for characterizing occupational health problems 2011; 44(4):545–52. https://doi.org/10.1016/j.jbi.2011.02.010.

[56] Morawska L, et al. How to build urbanome, the genome of the city? Sci Total Environ 2022;810:152310. https://doi.org/10.1016/j.scitotenv.2021.152310.

[57] Rappaport SM, Barupal DK, Wishart D, Vineis P, Scalbert A. The blood exposome and its role in discovering causes of disease. Environ Health Perspect 2014;122 (8):769–74. https://doi.org/10.1289/ehp.1308015.

[58] Daiber A, et al. Environmental noise induces the release of stress hormones and inflammatory signaling molecules leading to oxidative stress and vascular dysfunction-signatures of the internal exposome. Biofactors 2019;45(4):495–506. https://doi.org/10.1002/biof.1506.

[59] Daiber A, Munzel T. Special issue "Impact of environmental pollution and stress on redox signaling and oxidative stress pathways". Redox Biol 2020;37:101621. https://doi.org/10.1016/j.redox.2020.101621.

[60] Baccarelli AA, Ordovas J. Epigenetics of early cardiometabolic disease: mechanisms and precision medicine. Circ Res 2023;132(12):1648–62. https://doi.org/10.1161/CIRCRESAHA.123.322135.

[61] Wu H, Eckhardt CM, Baccarelli AA. Molecular mechanisms of environmental exposures and human disease. Nat Rev Genet 2023;24(5):332–44. https://doi.org/10.1038/s41576-022-00569-3.

[62] Baccarelli A, Dolinoy DC, Walker CL. A precision environmental health approach to prevention of human disease. Nat Commun 2023;14(1):2449. https://doi.org/10.1038/s41467-023-37626-2.

[63] Rajagopalan S, et al. Metabolic effects of air pollution exposure and reversibility. J Clin Investig 2020;130(11):6034–40. https://doi.org/10.1172/JCI137315.

[64] Bellinger DC. Prenatal exposures to environmental chemicals and children's neurodevelopment: an update. Saf Health Work 2013;4(1):1–11. https://doi.org/10.5491/SHAW.2013.4.1.1.

[65] Li S, et al. Differential regulation of the DNA methylome in adults born during the great Chinese famine in 1959-1961. Genomics 2021;113(6):3907–18. https://doi.org/10.1016/j.ygeno.2021.09.018.

[66] Li Y, et al. Exposure to the Chinese famine in early life and the risk of hypertension in adulthood. J Hypertens 2011;29(6):1085–92. https://doi.org/10.1097/HJH.0b013e328345d969.

[67] Chen H, et al. Living near major roads and the incidence of dementia, parkinson's disease, and multiple sclerosis: a population-based cohort study. Lancet 2017;389 (10070):718–26. https://doi.org/10.1016/S0140-6736(16)32399-6.

[68] Cantuaria ML, et al. Residential exposure to transportation noise in Denmark and incidence of dementia: national cohort study. Br Med J 2021;374:n1954. https://doi.org/10.1136/bmj.n1954.

[69] Iglesias-Vazquez L, et al. Maternal exposure to air pollution during pregnancy and child's cognitive, language, and motor function: ECLIPSES study. Environ Res 2022;212(Pt D):113501. https://doi.org/10.1016/j.envres.2022.113501.

[70] Maitre L, et al. Human early life exposome (HELIX) study: a European population-based exposome cohort. BMJ Open 2018;8(9):e021311. https://doi.org/10.1136/bmjopen-2017-021311.

[71] Vrijheid M, et al. The human early-life exposome (HELIX): project rationale and design. Environ Health Perspect 2014;122(6):535–44. https://doi.org/10.1289/ehp.1307204.

[72] Felix JF, et al. Cohort profile: pregnancy and childhood epigenetics (PACE) consortium. Int J Epidemiol 2018;47(1):22–23u. https://doi.org/10.1093/ije/dyx190.

[73] Lozano M, et al. DNA methylation changes associated with prenatal Mercury exposure: a meta-analysis of prospective cohort studies from PACE consortium. Environ Res 2022;204(Pt B):112093. https://doi.org/10.1016/j.envres.2021.112093.

[74] Fu Z, et al. Association of ambient air pollution exposure with low birth weight. Environ Res 2022;215(Pt 1):114164. https://doi.org/10.1016/j.envres.2022.114164.

[75] Turner MC, et al. EXPOsOMICS: final policy workshop and stakeholder consultation. BMC Public Health 2018;18(1):260. https://doi.org/10.1186/s12889-018-5160-z.

[76] Niedzwiecki MM, Miller GW. The exposome paradigm in human health: lessons from the emory exposome summer course. Environ Health Perspect 2017;125(6): 064502. https://doi.org/10.1289/EHP1712.

[77] Steckling N, et al. Biomarkers of exposure in environment-wide association studies - opportunities to decode the exposome using human biomonitoring data. Environ Res 2018;164:597–624. https://doi.org/10.1016/j.envres.2018.02.041.

[78] Webpage. The EUROPEAN human exposome network (ehen). https://www.humanexposome.eu/; 2023.

[79] Dennis KK, et al. The importance of the biological impact of exposure to the concept of the exposome. Environ Health Perspect 2016;124(10):1504–10. https://doi.org/10.1289/EHP140.

[80] Dennis KK, et al. Biomonitoring in the era of the exposome. Environ Health Perspect 2017;125(4):502–10. https://doi.org/10.1289/EHP474.

[81] Cui Y, Balshaw DM, Kwok RK, Thompson CL, Collman GW, Birnbaum LS. The exposome: embracing the complexity for discovery in environmental health. Environ Health Perspect 2016;124(8):A137–40. https://doi.org/10.1289/EHP412.

[82] Hu X, et al. A scalable workflow to characterize the human exposome. Nat Commun 2021;12(1):5575. https://doi.org/10.1038/s41467-021-25840-9.

[83] Wishart D, et al. T3DB: the toxic exposome database. Nucleic Acids Res 2015;43 (Database issue):D928–34. https://doi.org/10.1093/nar/gku1004.
[84] Neveu V, et al. Exposome-explorer: a manually-curated database on biomarkers of exposure to dietary and environmental factors. Nucleic Acids Res 2017;45(D1): D979–84. https://doi.org/10.1093/nar/gkw980.
[85] Anthony JC. The promise of psychiatric enviromics. Br J Psychiatr Suppl 2001;40: s8–11. https://doi.org/10.1192/bjp.178.40.s8.
[86] Perry AS, et al. Proteomics, human environmental exposure, and cardiometabolic risk. Circ Res 2024;135(1):138–54. https://doi.org/10.1161/CIRCRESAHA.124.324559.
[87] Schwartz J. Harvesting and long term exposure effects in the relation between air pollution and mortality. Am J Epidemiol 2000;151(5):440–8.
[88] Vrijheid M, et al. Advancing tools for human early lifecourse exposome research and translation (ATHLETE): project overview. Environ Epidemiol 2021;5(5): e166. https://doi.org/10.1097/EE9.0000000000000166.
[89] de Prado-Bert P, et al. The early-life exposome and epigenetic age acceleration in children. Environ Int 2021;155:106683. https://doi.org/10.1016/j.envint.2021.106683.
[90] Misra BB. The chemical exposome of human aging. Front Genet 2020;11:574936. https://doi.org/10.3389/fgene.2020.574936.
[91] Pandics T, et al. Exposome and unhealthy aging: environmental drivers from air pollution to occupational exposures. Geroscience 2023;45(6):3381–408. https://doi.org/10.1007/s11357-023-00913-3.
[92] Kuntic M, Kuntic I, Hahad O, Lelieveld J, Munzel T, Daiber A. Impact of air pollution on cardiovascular aging. Mechani ageing Dev 2023;214:111857. https://doi.org/10.1016/j.mad.2023.111857.
[93] Hahad O, et al. Exposomic determinants of atherosclerosis: recent evidence. Curr Atheroscler Rep 2025;27(1):28. https://doi.org/10.1007/s11883-025-01274-2.
[94] Hahad O, Al-Kindi S, Lelieveld J, Munzel T, Daiber A. Supporting and implementing the beneficial parts of the exposome: the environment can be the problem, but it can also be the solution. Int J Hyg Environ Health 2024;255: 114290. https://doi.org/10.1016/j.ijheh.2023.114290.
[95] Munzel T, et al. Soil and water pollution and cardiovascular disease. Nat Rev Cardiol 2025;22(2):71–89. https://doi.org/10.1038/s41569-024-01068-0.
[96] Prattichizzo F, et al. Micro-nanoplastics and cardiovascular diseases: evidence and perspectives. Eur Heart J 2024;45(38):4099–110. https://doi.org/10.1093/eurheartj/ehae552.
[97] Bevan GH, Al-Kindi SG, Brook R, Rajagopalan S. Ambient air pollution and atherosclerosis: recent updates. Curr Atheroscler Rep 2021;23(10):63. https://doi.org/10.1007/s11883-021-00958-9.
[98] Bevan GH, Al-Kindi SG, Brook RD, Munzel T, Rajagopalan S. Ambient air pollution and atherosclerosis: insights into dose, time, and mechanisms. Arterioscler Thromb Vasc Biol 2021;41(2):628–37. https://doi.org/10.1161/ATVBAHA.120.315219.
[99] Rajagopalan S, Al-Kindi SG, Brook RD. Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 2018;72(17):2054–70. https://doi.org/10.1016/j.jacc.2018.07.099.
[100] Al-Kindi S, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. Nat Rev Cardiol 2020; 17(3).
[101] Yang S, et al. PM2.5 concentration in the ambient air is a risk factor for the development of high-risk coronary plaques. Eur Heart J Cardiovasc Imaging 2019;20(12):1355–64. https://doi.org/10.1093/ehjci/jez209.
[102] Hoffmann B, et al. Residential exposure to urban air pollution, ankle-brachial index, and peripheral arterial disease. Epidemiology 2009;20(2):280–8. https://doi.org/10.1097/EDE.0b013e3181961ac2.
[103] Hoffmann B, et al. Residential exposure to traffic is associated with coronary atherosclerosis. Circulation 2007;116(5):489–96. https://doi.org/10.1161/CIRCULATIONAHA.107.693622.
[104] Zhang S, et al. Long-term effects of air pollution on ankle-brachial index. Environ Int 2018;118:17–25. https://doi.org/10.1016/j.envint.2018.05.025.
[105] Allen RW, et al. Fine particulate matter air pollution, proximity to traffic, and aortic atherosclerosis. Epidemiology 2009;20(2):254–64. https://doi.org/10.1097/EDE.0b013e31819644cc.
[106] Kim SY, et al. Individual-level concentrations of fine particulate matter chemical components and subclinical atherosclerosis: a cross-sectional analysis based on 2 advanced exposure prediction models in the multi-ethnic study of atherosclerosis. Am J Epidemiol 2014;180(7):718–28. https://doi.org/10.1093/aje/kwu186.
[107] Kaufman JD, et al. Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the multi-ethnic study of atherosclerosis and air pollution): a longitudinal cohort study. Lancet 2016;388 (10045):696–704. https://doi.org/10.1016/S0140-6736(16)00378-0.
[108] Abohashem S, et al. A leucopoietic-arterial axis underlying the link between ambient air pollution and cardiovascular disease in humans. Eur Heart J 2021. https://doi.org/10.1093/eurheartj/ehaa982.
[109] Akintoye E, et al. Association between fine particulate matter exposure and subclinical atherosclerosis: a meta-analysis. Eur J Prev Cardiol 2016;23(6): 602–12. https://doi.org/10.1177/2047487315588758.
[110] Perez L, et al. Air pollution and atherosclerosis: a cross-sectional analysis of four European cohort studies in the ESCAPE study. Environ Health Perspect 2015;123 (6):597–605. https://doi.org/10.1289/ehp.1307711.
[111] Miller MR, et al. Inhaled nanoparticles accumulate at sites of vascular disease. ACS Nano 2017;11(5):4542–52. https://doi.org/10.1021/acsnano.6b08551.
[112] Sun Q, et al. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. JAMA 2005;294(23):3003–10. https://doi.org/10.1001/jama.294.23.3003.
[113] Mills NL, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. N Engl J Med 2007;357(11):1075–82. https://doi.org/10.1056/NEJMoa066314.
[114] Langrish JP, et al. Contribution of endothelin 1 to the vascular effects of diesel exhaust inhalation in humans. Hypertension 2009;54(4):910–5. https://doi.org/10.1161/HYPERTENSIONAHA.109.135947.
[115] Hajat A, et al. The association between long-term air pollution and urinary catecholamines: evidence from the multi-ethnic study of atherosclerosis. Environ Health Perspect 2019;127(5):57007. https://doi.org/10.1289/EHP3286.
[116] Munzel T, et al. Effects of gaseous and solid constituents of air pollution on endothelial function. Eur Heart J 2018;39(38):3543–50. https://doi.org/10.1093/eurheartj/ehy481.
[117] Al-Kindi SG, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. Nat Rev Cardiol 2020; 17(10):656–72. https://doi.org/10.1038/s41569-020-0371-2.
[118] Bevan GH, Al-Kindi S, Brook RD, Munzel T, Rajagopalan S. Ambient air pollution and atherosclerosis: insights into dose, time, and mechanisms. Arterioscler Thromb Vasc Biol 2020:ATVBAHA120315219. https://doi.org/10.1161/ATVBAHA.120.315219.
[119] Hahad O, et al. Noise and air pollution as risk factors for hypertension: part I-Epidemiology. Hypertension 2023;80(7):1375–83. https://doi.org/10.1161/HYPERTENSIONAHA.122.18732.
[120] Hahad O, et al. Noise and air pollution as risk factors for hypertension: part II-Pathophysiologic insight. Hypertension 2023;80(7):1384–92. https://doi.org/10.1161/HYPERTENSIONAHA.123.20617.
[121] Daiber A, et al. Targeting vascular (endothelial) dysfunction. Br J Pharmacol 2017;174(12):1591–619. https://doi.org/10.1111/bph.13517.
[122] Vita JA, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990;81(2):491–7.
[123] Garcia MM, Lima PR, Correia LC. Prognostic value of endothelial function in patients with atherosclerosis: systematic review. Arq Bras Cardiol 2012;99(3): 857–65.
[124] Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000;101(16):1899–906. https://doi.org/10.1161/01.cir.101.16.1899.
[125] Anderson TJ, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol 1995;26(5):1235–41. https://doi.org/10.1016/0735-1097(95)00327-4.
[126] Schmidt FP, et al. Effect of nighttime aircraft noise exposure on endothelial function and stress hormone release in healthy adults. Eur Heart J 2013;34(45): 3508–3514a. https://doi.org/10.1093/eurheartj/eht269.
[127] Herzog J, et al. Acute exposure to nocturnal train noise induces endothelial dysfunction and pro-thromboinflammatory changes of the plasma proteome in healthy subjects. Basic Res Cardiol 2019;114(6):46. https://doi.org/10.1007/s00395-019-0753-y.
[128] Schmidt F, et al. Nighttime aircraft noise impairs endothelial function and increases blood pressure in patients with or at high risk for coronary artery disease. Clin Res Cardiol 2015;104(1):23–30. https://doi.org/10.1007/s00392-014-0751-x.
[129] Wojciechowska W, et al. Blood pressure and arterial stiffness in association with aircraft noise Exposure:Long-Term observation and potential effect of COVID-19 lockdown. Hypertension 2022;79(2):325–34. https://doi.org/10.1161/HYPERTENSIONAHA.121.17704.
[130] Foraster M, et al. Exposure to road, railway, and aircraft noise and arterial stiffness in the SAPALDIA study: annual average noise levels and temporal noise characteristics. Environ Health Perspect 2017;125(9):097004. https://doi.org/10.1289/EHP1136.
[131] Osborne MT, et al. A neurobiological mechanism linking transportation noise to cardiovascular disease in humans. Eur Heart J 2020;41(6):772–82. https://doi.org/10.1093/eurheartj/ehz820.
[132] Munzel T, Steven S, Hahad O, Daiber A. The sixth sense is involved in noise-induced stress responses and vascular inflammation: evidence for heightened amygdalar activity in response to transport noise in man. Eur Heart J 2020;41(6): 783–5. https://doi.org/10.1093/eurheartj/ehz867.
[133] Tawakol A, et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 2017;389(10071):834–45. https://doi.org/10.1016/S0140-6736(16)31714-7.
[134] Tawakol A, et al. Stress-associated neurobiological pathway linking socioeconomic disparities to cardiovascular disease. J Am Coll Cardiol 2019;73 (25):3243–55. https://doi.org/10.1016/j.jacc.2019.04.042.
[135] Murzabekov M, et al. Road-traffic noise exposure and coronary atherosclerosis in the Swedish CArdioPulmonary bioImage study (SCAPIS). Environ Epidemiol 2024;8(5):e344. https://doi.org/10.1097/EE9.0000000000000344.
[136] Gilani TA, Mir MS. Association of road traffic noise exposure and prevalence of coronary artery disease: a cross-sectional study in North India. Environ Sci Pollut Res Int 2021;28(38):53458–77. https://doi.org/10.1007/s11356-021-14582-2.
[137] Koczorowski M, et al. Environmental noise exposure is associated with atherothrombotic risk. Sci Rep 2022;12(1):3151. https://doi.org/10.1038/s41598-022-06825-0.
[138] Munzel T, et al. Effects of noise on vascular function, oxidative stress, and inflammation: mechanistic insight from studies in mice. Eur Heart J 2017;38(37): 2838–49. https://doi.org/10.1093/eurheartj/ehx081.
[139] Kroller-Schon S, et al. Crucial role for Nox2 and sleep deprivation in aircraft noise-induced vascular and cerebral oxidative stress, inflammation, and gene regulation. Eur Heart J 2018;39(38):3528–39. https://doi.org/10.1093/eurheartj/ehy333.

[140] Sorensen M, et al. Health position paper and redox perspectives - disease burden by transportation noise. Redox Biol 2024;69:102995. https://doi.org/10.1016/j.redox.2023.102995.
[141] Baudin C, et al. Saliva cortisol in relation to aircraft noise exposure: pooled-analysis results from seven European countries. Environ Health : Global Access Sci Sou 2019;18(1):102. https://doi.org/10.1186/s12940-019-0540-0.
[142] Selander J, et al. Saliva cortisol and exposure to aircraft noise in six European countries. Environ Health Perspect 2009;117(11):1713–7. https://doi.org/10.1289/ehp.0900933.
[143] Babisch W, Fromme H, Beyer A, Ising H. Increased catecholamine levels in urine in subjects exposed to road traffic noise: the role of stress hormones in noise research. Environ Int 2001;26(7–8):475–81. https://doi.org/10.1016/s0160-4120(01)00030-7.
[144] Eckrich J, et al. Aircraft noise exposure drives the activation of white blood cells and induces microvascular dysfunction in mice. Redox Biol 2021;46:102063. https://doi.org/10.1016/j.redox.2021.102063.
[145] Munzel T, et al. Transportation noise pollution and cardiovascular health. Circ Res 2024;134(9):1113–35. https://doi.org/10.1161/CIRCRESAHA.123.323584.
[146] Chowdhury R, et al. Environmental toxic metal contaminants and risk of cardiovascular disease: systematic review and meta-analysis. Br Med J 2018;362:k3310. https://doi.org/10.1136/bmj.k3310.
[147] Tellez-Plaza M, Jones MR, Dominguez-Lucas A, Guallar E, Navas-Acien A. Cadmium exposure and clinical cardiovascular disease: a systematic review. Curr Atheroscler Rep 2013;15(10):356. https://doi.org/10.1007/s11883-013-0356-2.
[148] Cosselman KE, Navas-Acien A, Kaufman JD. Environmental factors in cardiovascular disease. Nat Rev Cardiol 2015;12(11):627–42. https://doi.org/10.1038/nrcardio.2015.152.
[149] Hu XF, Lowe M, Chan HM. Mercury exposure, cardiovascular disease, and mortality: a systematic review and dose-response meta-analysis. Environ Res 2021;193:110538. https://doi.org/10.1016/j.envres.2020.110538.
[150] Su TC, Hwang JJ, Sun CW, Wang SL. Urinary phthalate metabolites, coronary heart disease, and atherothrombotic markers. Ecotoxicol Environ Saf 2019;173:37–44. https://doi.org/10.1016/j.ecoenv.2019.02.021.
[151] Melzer D, et al. Urinary bisphenol A concentration and risk of future coronary artery disease in apparently healthy men and women. Circulation 2012;125(12):1482–90. https://doi.org/10.1161/CIRCULATIONAHA.111.069153.
[152] Mattsson K, et al. Levels of perfluoroalkyl substances and risk of coronary heart disease: findings from a population-based longitudinal study. Environ Res 2015;142:148–54. https://doi.org/10.1016/j.envres.2015.06.033.
[153] Winquist A, Steenland K. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. Environ Health Perspect 2014;122(12):1299–305. https://doi.org/10.1289/ehp.1307943.
[154] Lind PM, Lind L. Are persistent organic pollutants linked to lipid abnormalities, atherosclerosis and cardiovascular disease? A review. J Lipid Atheroscler 2020;9(3):334–48. https://doi.org/10.12997/jla.2020.9.3.334.
[155] Marfella R, et al. Microplastics and nanoplastics in atheromas and cardiovascular events. N Engl J Med 2024;390(10):900–10. https://doi.org/10.1056/NEJMoa2309822.
[156] Schiermeier Q. Climate change made North america's deadly heatwave 150 times more likely. Nature 2021. https://doi.org/10.1038/d41586-021-01869-0.
[157] Falchetta G, Cian E, Pavanello F, Wing IS. Inequalities in global residential cooling energy use to 2050. Nat Commun 2024;15(1):7874. https://doi.org/10.1038/s41467-024-52028-8.
[158] Romanello M, et al. The 2023 report of the lancet countdown on health and climate change: the imperative for a health-centred response in a world facing irreversible harms. Lancet 2023;402(10419):2346–94. https://doi.org/10.1016/S0140-6736(23)01859-7.
[159] Khatana SAM, Werner RM, Groeneveld PW. Association of extreme heat with all-cause mortality in the contiguous US, 2008-2017. JAMA Netw Open 2022;5(5):e2212957. https://doi.org/10.1001/jamanetworkopen.2022.12957.
[160] Munzel T, Khraishah H, Schneider A, Lelieveld J, Daiber A, Rajagopalan S. Challenges posed by climate hazards to cardiovascular health and cardiac intensive care: implications for mitigation and adaptation. Eur Heart J Acute Cardiovasc Care 2024;13(10):731–44. https://doi.org/10.1093/ehjacc/zuae113.
[161] Alahmad B, et al. Associations between extreme temperatures and cardiovascular cause-specific mortality: results from 27 countries. Circulation 2023;147(1):35–46. https://doi.org/10.1161/CIRCULATIONAHA.122.061832.
[162] Fuhrmann CM, Sugg MM, Konrad 2nd CE, Waller A. Impact of extreme heat events on emergency department visits in North Carolina (2007-2011). J Community Health 2016;41(1):146–56. https://doi.org/10.1007/s10900-015-0080-7.
[163] Liu J, et al. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. Lancet Planet Health 2022;6(6):e484–95. https://doi.org/10.1016/S2542-5196(22)00117-6.
[164] Khraishah H, et al. Climate change and cardiovascular disease: implications for global health. Nat Rev Cardiol 2022;19(12):798–812. https://doi.org/10.1038/s41569-022-00720-x.
[165] Rajagopalan S, et al. The urban environment and cardiometabolic health. Circulation 2024;149(16):1298–314. https://doi.org/10.1161/CIRCULATIONAHA.123.067461.
[166] Rajagopalan S, et al. Toward heart-healthy and sustainable cities: a policy statement from the American heart association. Circulation 2024;149(15):e1067–89. https://doi.org/10.1161/CIR.0000000000001217.
[167] Rajagopalan S, et al. Toward heart-healthy and sustainable cities: a policy statement from the American heart association. Circulation 2024;149(15):e1067–89. https://doi.org/10.1161/cir.0000000000001217.
[168] L.K. Y., Webster C, Gallacher JE. Sarkar, associations of urban built environment with cardiovascular risks and mortality: a systematic review. J Urban Health : Bull N Y Acad Med 2023;100(4). https://doi.org/10.1007/s11524-023-00764-5.
[169] Makhlouf MHE, et al. Neighborhood walkability and cardiovascular risk in the United States. Curr Probl Cardiol 2023;48(3):101533. https://doi.org/10.1016/j.cpcardiol.2022.101533.
[170] Mayne SL, Auchincloss AH, Michael YL. Impact of policy and built environment changes on obesity-related outcomes: a systematic review of naturally occurring experiments. Obes Rev : Official J Intern Assoc Study Obes 2015;16(5):362–75. https://doi.org/10.1111/obr.12269.
[171] Sallis JF, et al. Physical activity in relation to urban environments in 14 cities worldwide: a cross-sectional study. Lancet 2016;387(10034):2207–17. https://doi.org/10.1016/S0140-6736(15)01284-2.
[172] Nieuwenhuijsen MJ. Influence of urban and transport planning and the city environment on cardiovascular disease. Nat Rev Cardiol 2018;15(7):432–8. https://doi.org/10.1038/s41569-018-0003-2.
[173] Mueller N, et al. Urban and transport planning related exposures and mortality: a health impact assessment for cities. Environ Health Perspect 2017;125(1):89–96. https://doi.org/10.1289/EHP220.
[174] Celis-Morales CA, et al. Association between active commuting and incident cardiovascular disease, cancer, and mortality: prospective cohort study. Br Med J 2017;357:j1456. https://doi.org/10.1136/bmj.j1456.
[175] Sinharay R, et al. Respiratory and cardiovascular responses to walking Down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. Lancet 2018;391(10118):339–49. https://doi.org/10.1016/S0140-6736(17)32643-0.
[176] Liu XX, et al. Green space and cardiovascular disease: a systematic review with meta-analysis. Environ Pollut 2022;301:118990. https://doi.org/10.1016/j.envpol.2022.118990.
[177] Yuan Y, Huang F, Lin F, Zhu P, Zhu P. Green space exposure on mortality and cardiovascular outcomes in older adults: a systematic review and meta-analysis of observational studies. Aging Clin Exp Res 2021;33(7):1783–97. https://doi.org/10.1007/s40520-020-01710-0.
[178] Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. Lancet 2008;372(9650):1655–60. https://doi.org/10.1016/S0140-6736(08)61689-X.
[179] Lai KY, Kumari S, Gallacher J, Webster C, Sarkar C. Associations of residential walkability and greenness with arterial stiffness in the UK biobank. Environ Int 2022;158:106960. https://doi.org/10.1016/j.envint.2021.106960.
[180] Hahad O, et al. Cumulative social disadvantage and cardiovascular disease burden and mortality. Eur J Prev Cardiol 2024;31(1):40–8. https://doi.org/10.1093/eurjpc/zwad264.
[181] Abohashem S, et al. Additive effect of high transportation noise exposure and socioeconomic deprivation on stress-associated neural activity, atherosclerotic inflammation, and cardiovascular disease events. J Expo Sci Environ Epidemiol 2024. https://doi.org/10.1038/s41370-024-00734-2.
[182] Khoury MJ, Iademarco MF, Riley WT. Precision public health for the era of precision medicine. Am J Prev Med 2016;50(3):398–401. https://doi.org/10.1016/j.amepre.2015.08.031.
[183] Pearson TA, et al. Precision health analytics with predictive analytics and implementation research: JACC state-of-the-art review. J Am Coll Cardiol 2020;76(3):306–20. https://doi.org/10.1016/j.jacc.2020.05.043.
[184] Al-Kindi S, Paneni F, Brook RD, Rajagopalan S. Residual environmental risk in patients with cardiovascular disease: an overlooked paradigm. Eur Heart J 2023;44(44):4612–4. https://doi.org/10.1093/eurheartj/ehad412.
[185] Chen Z, et al. AI-Facilitated assessment of built environment using neighborhood satellite imagery and cardiovascular risk. J Am Coll Cardiol 2024;84(18):1733–44. https://doi.org/10.1016/j.jacc.2024.08.053.
[186] Chen Z, Dazard JE, Khalifa Y, Motairek I, Al-Kindi S, Rajagopalan S. Artificial intelligence-based assessment of built environment from google street view and coronary artery disease prevalence. Eur Heart J 2024;45(17):1540–9. https://doi.org/10.1093/eurheartj/ehae158.
[187] California office of environmental health hazard assessment (COEHHA), CalEnviroScreen 4.0. 2023.
[188] California office of environmental health hazard assessment (COEHHA), draft CalEnviroScreen 4.0. 2021.
[189] Jones DP. Sequencing the exposome: a call to action. Toxicol Rep 2016;3:29–45. https://doi.org/10.1016/j.toxrep.2015.11.009.
[190] Sainani K. Taking on the exposome - bringing bioinformatics tools to the environmental side of the health equation. Biomed Comput Rev Fall 2016;2016:14–21.
[191] Zheng Y, Chen Z, Pearson T, Zhao J, Hu H, Prosperi M. Design and methodology challenges of environment-wide association studies: a systematic review. Environ Res 2020;183:109275. https://doi.org/10.1016/j.envres.2020.109275.
[192] Webpage, World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. https://apps.who.int/iris/bitstream/handle/10665/94384/9789241506236_eng.pdf;jsessionid=71BCEA94B3F85737AB42F3C84216E54A. [Accessed 23 March 2023].
[193] Vineis P, Robinson O, Chadeau-Hyam M, Dehghan A, Mudway I, Dagnino S. What is new in the exposome? Environ Int 2020;143:105887. https://doi.org/10.1016/j.envint.2020.105887.
[194] Beulens JWJ, et al. Environmental risk factors of type 2 diabetes-an exposome approach. Diabetologia 2022;65(2):263–74. https://doi.org/10.1007/s00125-021-05618-w.

[195] Juarez PD, Hood DB, Song MA, Ramesh A. Use of an exposome approach to understand the effects of exposures from the natural, built, and social environments on cardio-vascular disease onset, progression, and outcomes. Front Public Health 2020;8:379. https://doi.org/10.3389/fpubh.2020.00379.
[196] Vrijheid M, et al. Early-life environmental exposures and childhood obesity: an exposome-wide approach. Environ Health Perspect 2020;128(6):67009. https://doi.org/10.1289/EHP5975.
[197] Santos S, et al. Applying the exposome concept in birth cohort research: a review of statistical approaches. Eur J Epidemiol 2020;35(3):193–204. https://doi.org/10.1007/s10654-020-00625-4.
[198] Vlaanderen J, et al. Developing the building blocks to elucidate the impact of the urban exposome on cardiometabolic-pulmonary disease: the EU EXPANSE project. Environ Epidemiol 2021;5(4):e162. https://doi.org/10.1097/EE9.0000000000000162.
[199] Munzel T, et al. Environmental stressors and cardio-metabolic disease: part II-mechanistic insights. Eur Heart J 2017;38(8):557–64. https://doi.org/10.1093/eurheartj/ehw294.