The “exposome” concept – how environmental risk factors influence cardiovascular health

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INTRODUCTION

Environmental risk factors, disease burden and global mortality

The global burden of disease (GBD) has shifted within the last two decades from communicable, maternal, perinatal, and nutritional causes to non-communicable diseases such as atherosclerosis or metabolic disease (World Health Organization (WHO), Global Health Observatory (GHO) data). While scientific efforts over the last few decades have focused on traditional cardiovascular risk factors (e.g. diabetes, smoking, hypertension), the GBD Study indicates that also environmental factors such as air pollution (ambient and household) lead to development of chronic non-communicable diseases and contribute to global mortality (Lim et al., 2012; Murray et al., 2012). These factors play in concert with lifestyle risk factors such as smoking, unhealthy diet and physical inactivity, where all health effects that are associated with environmental exposures are described by the “exposome”. The four leading risk factors identified by the GBD Study to contribute to global mortality and disability-adjusted life years (DALYS) are high blood pressure, smoking, ischemic heart disease, and cerebrovascular disease (Fig. 1) (Lim et al., 2012; Murray et al., 2012). The GBD Study from 2015/2016 ranked the global risk factors for chronic non-communicable diseases and global mortality, placing particulate matter ($\text{PM}_{2.5}$) as the 5th most impactful factor (Cohen et al., 2017). Occupational noise was also indicated for the first time as a significant environmental health risk factor (Collaborators, 2017). Epidemiological research also suggests effects of other environmental stressors on cardiovascular complications, including social isolation, work stress (Fransson et al., 2015; Nyberg et al., 2014; Online-Link2; Rosengren et al., 2004), noise exposure (e.g. traffic/occupational sources) (Kempen, Casas, Pershagen & Foraster, 2018; Münzel, Schmidt, Steven, Herzog, Daiber & Sorensen, 2018; Online-Link3; Vienneau et al., 2015) and chemical pollution (e.g. heavy metals and pesticides) (Cosselman, Navas-Acien & Kaufman, 2015; Navas-Acien, Guallar, Silbergeld & Rothenberg, 2007; Online-Link1; Telliez-Plaza, Jones, Dominguez-Lucas, Guallar & Navas-Acien, 2013). The shift in the modern burden of disease is also reflected in these environmental stressors. Lead, ozone, and dioxins are all outranked by air pollution as the primary environmental cause of DALYS, with noise as the second rank in Europe (Stansfeld, 2015).

There is general consensus that environmental pollution and non-chemical stressors contribute to the incidence and prevalence of chronic noncommunicable disease (e.g. cardiovascular, metabolic and mental). Clinical and epidemiological studies support that air pollution and traffic noise are associated with a higher risk for cardiovascular disease and significantly contribute to overall mortality. In this respect, the “exposome” provides a comprehensive description of lifelong exposure history. A recent publication using an updated global exposure-mortality model found that the global all-cause mortality rate attributable to ambient air pollution by $\text{PM}_{2.5}$ and $\text{O}_3$ was 8.79 (95% CI 7.11–10.41) million in 2015 – much higher than previously calculated. For Europe this corresponds to 790,000 premature deaths due to ambient air pollution. Various large scale studies and expert commissions have identified air pollution as the leading health risk factor in the physical environment, followed by water and soil pollution with heavy metals, pesticides, other chemicals and occupational exposures, however neglecting the non-chemical environmental health risk factors: mental stress, light exposure, climatic changes and traffic noise. Especially for traffic noise-related health effects there are numerous clinical and epidemiological studies reporting significant impact on cardiovascular disease. We here provide an in-depth review on the health effects of the external exposome, with emphasis on air pollution and traffic noise and to a lesser degree mental stress and other environmental pollutants. In addition, we summarize our previously published experimental research investigating effects of aircraft noise exposure in mice and provide mechanistic insights on how noise contributes to noncommunicable disease.

Key words: Environmental risk factors; external exposome; air pollution; particulate matter; traffic noise; oxidative stress; cardiovascular disease.

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Abbreviations: CI, confidence interval; DALYs, disability-adjusted life years; EAWS, Environment-Wide Association Study; GBD, Global Burden of Disease; IHD, ischemic heart disease; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOX, NADPH oxidase; $\text{PM}_{2.5}$, particulate matter with a diameter ≤ 2.5 µm; ROS, reactive oxygen species; WHO, World Health Organization
social stress and its individual perception, which complicates the determination of its contribution to global DALYs and mortality, the associations for some of the social and behavioral variables are potentially more hazardous than factors of the physical environment (Sainani, 2016). Indeed, psychologists, neurologists and social scientists have reliable methods to assess the degree of mental stress (e.g. by self-report questionnaires).

With the world population estimated to reach 9 billion by 2050, we face a distressing health crisis as a result of the striking effects of worsening environmental pollution. The Lancet Commission on pollution and health concluded that “Pollution is the largest environmental cause of disease and premature death in the world today. Diseases caused by pollution were responsible for an estimated 9 million premature deaths in 2015 – 16% of all deaths worldwide – three times more deaths than from AIDS, tuberculosis, and malaria combined and 15 times more than from all wars and other forms of violence. In the most severely affected countries, pollution-related disease is responsible for more than one death in four” (Landrigan et al., 2018). The commission further emphasized that detrimental health outcomes stemming from exposure to environmental risk factors (with air pollution identified as the main contributor) is a circular socio-economic issue, as low-income countries are disproportionately affected, which can then result in further socioeconomic imbalances. The WHO provides data supplementing this assertion with the estimate that 12.6 million global deaths in 2012 were due to living in unhealthy environments (Online-Link5, 2016; Online-Link6, 2016).

The GBD study estimates that in total, all forms of pollution were responsible for 268 million DALYs. Interpretation of this figure illustrates 254 million years lost and 14 million lived with disability due to levels of pollution which are only increasing (DALYs & Collaborators, 2016). F. Collins, the director of the NIH, crystallized the relationship of environmental risk factors with health with the statement, “Genetics load the gun but environment pulls the trigger.” In light of these dramatic numbers, environmental pollution is unquestionably a cause for public health concern, however, it has not earned the recognition merited by such a critical situation. For example, despite that the majority of pollution-related diseases are non-communicable, the Global Action Plan for the Prevention and Control of Non-Communicable Diseases provides no recommendations for interventions (Landrigan et al., 2018). Additionally, investments made in research into environmental health risks pales in comparison to the investment in human genome research, a situation clearly at odds with F. Collins’ statement. Leading scientists in environmental health have suggested that environment-health-associations should be investigated as systematically as the genome has been, calling for an “Environment-Wide Association Study (EWAS)” in the same vein as Genome-Wide Association Studies (GWAS) (Sainani, 2016) (see Table 1 for EWAS examples). Such a study would take steps in characterizing the exposome – the sum of all exposures in the course of an individual’s life- and also in correlating these exposures with public health effects like risk for chronic disease or mortality. Though there are challenges in investigating the complex relationship be-

Figure 1. Global burden of disease and related deaths. Comparison of the magnitude of the ten leading diseases and injuries and the ten leading risk factors based on the percentage of global deaths and the percentage of global DALYs, 2010. The figure shows the leading 25 diseases, injuries, and risk factors contributing to disability-adjusted life years (DALYs) and global deaths. The leading 4 diseases and risk factors (see red mark-up) are all associated with increased risk for vascular disease and mortality. Orange color indicates lifestyle or behavioral risk factors, whereas red color indicates environmental risk factors. Redrawn from Murray et al., Lancet 2012 (Murray et al., 2012). This article is available under the terms of the Creative Commons Attribution License (CC BY). Adopted from (Munzel et al., 2018b) with permission. Copyright © 2018, Mary Ann Liebert, Inc.
between disease and environment, technological advances can facilitate measuring the exposome at a higher resolution and larger scale than ever before possible. An inconceivable amount of “big data” can be produced by modern – omics and technological approaches: metabolomics and adductomics measure the vestiges of chemical exposures in our blood, wearable sensors and smartphones track our locations, diet, and physiological data, social media sites collect our social experiences; electronic health records store our clinical, personal, and demographic attributes; and geographical information systems and survey data reveal the wider societal factors that influence health. Because of EWAS encompasses the transcriptome, proteome, metabolome, adductome, plus the chemical and physical pollutants along with the associations of all of these factors with the health status, the potential volume of data created by EWAS would even exceed that created by Genome-Wide Association Studies (GWAS), making a systems biology approach absolutely necessary for integration of all of these data.

### Table 1. Important exposome and environmental association studies and projects.

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<thead>
<tr>
<th>Study</th>
<th>Description and major aims</th>
<th>Reference</th>
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<tbody>
<tr>
<td>ENNAH project (The European Network on Noise and Health, funded by FP7)</td>
<td>highlighted in its final report the alarming epidemiological evidence for an increased incidence of cardiovascular disease due to increased mental noise exposure and stressed the importance of studies on the combined health effects by noise and air pollution</td>
<td><a href="https://cordis.europa.eu/project/rcn/92035/reporting/en">https://cordis.europa.eu/project/rcn/92035/reporting/en</a></td>
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<td>ERA-Planet project (funded by H2020)</td>
<td>focuses on monitoring technologies and data verification on air pollution particulate matter</td>
<td><a href="http://www.era-planet.eu/">http://www.era-planet.eu/</a></td>
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<td>ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project (funded by HEI)</td>
<td>is a Europe-wide collaboration to investigate mortality and morbidity effects of long-term exposure to low-level PM$_{2.5}$, Black Carbon, NO$_x$, and O$_3$ in European cohorts</td>
<td><a href="http://www.elapseproject.eu/">http://www.elapseproject.eu/</a></td>
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<td>NordicWelfare and NordSOUND projects</td>
<td>are dedicated to understand the link between air pollution levels, the chemical composition of the pollution, the traffic noise levels and the related health effects, socio-economics and welfare in the Nordic countries</td>
<td><a href="https://projects.au.dk/nordicwelfare/">https://projects.au.dk/nordicwelfare/</a> <a href="https://www.cancer.dk/nordsound/">https://www.cancer.dk/nordsound/</a></td>
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<td>BREATHE (BRain dEvelopment and Air polluTion ultrafine particles in school children, funded by FP7) project</td>
<td>to develop valid methods to measure children’s personal ultrafine particles exposure and to develop valid neuroimaging methods to assess correlations between neurobehavior, neurostructural alterations and particle deposition in order to reveal how traffic pollution affects children’s exposure to key contaminants and brain development, and identify susceptible subgroups</td>
<td>(Online-Link8) <a href="https://cordis.europa.eu/project/rcn/99632/factsheet/en">https://cordis.europa.eu/project/rcn/99632/factsheet/en</a></td>
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<td>HELIX (Human Early-Life Exposome) project</td>
<td>concentrates on only “early” life exposures and on the measurement of the external exposome (levels of pollutants) as well as endogenous and xenobiotic metabolite profiles in blood and urine, proteins in plasma, transcriptomics and DNA methylation in whole blood</td>
<td><a href="https://www.projecthelix.eu/">https://www.projecthelix.eu/</a></td>
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<tr>
<td>PACE (Pregnancy And Childho-d Epigenetics) project</td>
<td>a consortium is comprised of researchers at National Institute of Environmental Health Sciences and around the world who are interested in studying the early life environmental impacts on human disease using epigenetics</td>
<td><a href="https://www.niehs.nih.gov/research/atniehs/labs/epi/pi/genetics/pace/index.cfm">https://www.niehs.nih.gov/research/atniehs/labs/epi/pi/genetics/pace/index.cfm</a></td>
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<td>ESCAPE (European Study of Cohorts for Air Pollution Effects, funded by FP7) project</td>
<td>investigates all aspects of adverse health effects by air pollution including cancers, cardiovascular, metabolic and mental diseases in a cohort of 900,000 subjects</td>
<td>(Cesaroni et al, 2014) <a href="http://www.escapoproject.eu/">http://www.escapoproject.eu/</a></td>
</tr>
<tr>
<td>HEALS (Health and Environment-wide Associations based on Large population Surveys) project</td>
<td>conducts Health and Environment-wide Associations based on Large population Surveys (one of the largest research projects on environment and health in Europe)</td>
<td><a href="http://www.heals-eu.eu/">http://www.heals-eu.eu/</a></td>
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<td>HERCULES (Health and Exposome Research Center: Understanding Lifetime Exposures) project</td>
<td>bring investigators together to formulate a plan to define the exposome in a way that is useful to those in health care and public health, to identify gaps in knowledge or technique, and to help develop a new generation of scientists who focus on these complex environmental influences on health</td>
<td><a href="https://emoryhercules.com/">https://emoryhercules.com/</a></td>
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<td>EXPOSOMICS project</td>
<td>aims to develop a new approach to assess environmental exposures, primarily focusing on air pollution and water contaminants. Using ‘omic’ techniques the collected exposure data can be linked to biochemical and molecular changes in our body. The results will help to improve our understanding on how these pollutants influence the risk of developing chronic diseases</td>
<td>(Vineis et al, 2017) <a href="http://www.exposomics-project.eu/">http://www.exposomics-project.eu/</a></td>
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The exposome: “comprehensive description of lifelong exposure history”

The exposome, first described in detail by Christopher P. Wild in 2005, is the lifelong sum of all the environmental contributions to human physiology and pathophysiology (Wild, 2005). In addition to the above-mentioned environmental stressors, also behavioral or lifestyle (e.g. diet, smoking, alcohol abuse, physical activity) and more general environmental factors (e.g. socioeconomic status, urban environment, pathogens, UV radiation and climate) define the individual exposome. All these factors are subcategorized into the specific and general environment, with traffic-dependent noise and air pollution as components of the general external environment (Fig. 2) (Sainani, 2016). Another subset of the exposome is the newly introduced “pollutome,” defined as “pollutant exposures during gestation, infancy, childhood, adolescence, adult life (including occupational exposures), and old age” (Landrigan et al, 2018). In other words, the pollutome represents the pollutants specific...
to a place and time and impact human physiology. Exposome studies of any category correlate environmental factors with health outcomes by measuring the transcriptome (including the epigenome), proteome and metabolome, and also the microbiome, providing an estimation of the contribution of specific or general environmental factors to health risks, disease burden and mortality as well as information on the specific internal environment (Ghezzi et al., 2018). The mechanistic insight provided by the uncovered associations potentially allows interactome and diseasome bioinformatical mapping, which would be powerful data in the study of environment-triggered disease and the overlap/synergy with classical metabolic, cardiovascular, and neurodegenerative diseases in addition to cancer and interventional strategies. Importantly, if environment truly does “pull the trigger,” the influence of the exposome on development and progression of chronic diseases may even exceed those relating to genetic predisposition (Rappaport, 2016). Examples for exposome studies can be found in Table 1.

Especially the impact of environmental stressors during the developing stage (e.g. on fetuses, infants, and children) represent a largely unknown field, and even very low exposure levels could have detrimental effects on the development and of the brain and other organs (Bellinger, 2013). Exposure during these windows of vulnerability in early life could account for a number of long-lasting adverse effects, such as reduced cognitive function and also to juvenile delinquency, violent crime in adulthood, and lifelong reduction in economic productivity (Grandjean & Landrigan, 2014) but also manifest psychological disorders (summarized in (Landrigan et al., 2018)). Importantly, environmental “early fetal or child reprogramming” thereby creates a major burden of socioeconomic problems that represent a major challenge for all societies in the future (Fig. 2). With respect to adults, research on the impact of environmental stressors on development and acceleration of neurodegenerative disease (e.g. Alzheimer’s disease), representing another major challenge in our societies, is still in its infancy (Chen et al., 2017). Not surprising, the number 1–3 research recommendations of the Lancet Commission on pollution and health are to “define and quantify the burden of neurodevelopmental disease in children, of neurodegenerative disease in adults and of diabetes attributable to PM$_{2.5}$ air pollution”. The Lancet Commission also suggests that “funding of research to document and map the disproportionate effects of pollution upon the poor, women, and girls be adopted as a priority by international health agencies” in order to especially target the inequitable exposure of the poor and the marginal groups to pollution.

THE POLLUTOME: RISK FACTORS IN THE PHYSICAL ENVIRONMENT

As previously stated, the pollutome accounts for the sum total of all forms of pollution that could potentially impact human health (Landrigan et al., 2018), and
as such, is a fully nested subset of the exposome (Wild, 2005; Wild, 2012). All the ages at which exposure to pollutants can occur, whether it be during gestation, infancy, adulthood, adolescence, adulthood (including occupational exposures), or old age, are inherent in the pollutome model. Other than the aforementioned findings by the Lancet Commission and GBD identifying air pollution as leading health risk factors, there are other important risk factors in the physical environment mentioned in the reports, including water pollution, soil pollution, heavy metal and chemical occupational exposure. This report does not, however, mention other non-chemical environmental health risk factors, mental stress and noise exposure. Collectively, both reports attribute 9 to 12.6 million deaths in the years 2012–2015 to all forms of pollution, which reflects 16–20% of total worldwide mortality (Landrigan et al., 2018; Online-Link5, 2016; Online-Link6, 2016). These mortality numbers are likely to rise as newer and more expensive exposure-response relationships are defined, particularly after the inclusion of cardiometabolic disease in the calculation. The numbers reflecting reduction in quality of life, as measured in DALYs, are even more astounding with 254 million years of life lost and 14 million years lived with disability (DALYs & Collaborators, 2016). In addition to being a health crisis, these numbers also reflect an economic predicament. In 2013, air pollution-triggered diseases cost high-income countries approximately 3.5% of their total health expenditures and 7.4% for low-income countries. Comprehensive costs of air pollution exposure go beyond healthcare, as there is a loss of productivity in affected people, including an increase in sickdays. The costs associated with this loss of productivity amount to 1.6% of gross domestic product in low-income countries and 0.7% in low-middle income countries (Landrigan et al., 2018). Due to the dramatic effects of air pollution on health and socioeconomic burden, we will elaborate more on this risk factor of the physical environment.

**Air pollution – number one environmental hazard**

Air pollution, in the form of solid particles (e.g. ambient particulate matter with a diameter of ≤ 2.5 µm \(\text{PM}_{2.5}\)) or reactive gases such as ozone and nitrogen dioxide, is well-known to contribute to the development and progression of cardiovascular and cerebrovascular disease as well as to cardiovascular (Beelen et al., 2014) and all-cause mortality (for review see (Munzel et al., 2018a)). Furthermore, the BREATHE project revealed impairment of cognitive development in school children exposed to traffic-related air pollutants (Online-Link8). The association between air pollution exposure (in particular for \(\text{PM}_{2.5}\)) and cardiovascular morbidity and mortality is pronounced and is discussed in the guidelines of the European and American cardiovascular societies (Brook et al., 2010; Newby et al., 2015). The following aspects of air pollution exposure and cardiovascular events are widely acknowledged: 1. The chronic effects are more severe than acute effects. 2. Elderly and individuals with prior cardiovascular disease or additional risk factors such as obesity are at higher risk. 3. The

![Figure 3. Estimates of excess deaths from cardiovascular disease induced by \(\text{PM}_{2.5}\) in the year 2015.](Adopted from Münzel et al., Eur Heart J 2018 (Munzel et al., 2018a) with permission of the publisher. Copyright © 2018, Oxford University Press. The figure represents an update of data from Lelieveld et al., Nature 2015 (Lelieveld, Evans, Fnais, Giannadaki & Pozzer, 2015).)
relationship between exposure levels and cardiovascular events suggest a “no lower threshold” limit, as recent studies demonstrated a strong relationship at levels below current regulatory limits (Di et al., 2017). These dramatic facts were further reinforced by recent estimates that an excess mortality rate of 4.55 million deaths per year (95% CI 3.41–5.56) can be attributed to air pollution, which reflects a fraction of 8.1% of the annual global deaths from all causes (Lelieveld, Haines & Pozzer, 2018). In total, 2.43 million cardiovascular deaths per year (95% CI 1.70–3.08) can be attributed to air pollution, which reflects 4.3% in relation to the annual global deaths from all causes and 53% of all air pollution associated deaths (Munzel et al., 2018). Figure 3 shows a global map of the excess mortality from cardiovascular causes that can be attributed to air pollution, which was recently corrected to higher numbers using optimized exposure-response functions (Burnett et al., 2018; Lelieveld et al., 2019). Accordingly, the numbers reported in the map also reflect cardiovascular damage by PM$_{2.5}$ as a precursor of cardiovascular disease. The alarming bottom line of this image is that Europe, although not ranking among the top air pollution areas of the world, has a significant burden of cardiovascular/air pollution-triggered mortality that demands urgent action at the governmental, economical and industrial level to protect the health of the European population. Especially eastern and central European countries suffer from dramatically high numbers of cardiovascular deaths per capita requiring preventive measures. Recently, “The Lancet Commission on pollution and health” published a strong statement on the health impact of air pollution in Europe by asserting the right of all people to breathe clean air (Landrigan et al., 2018).

The substantial excess mortality rates for air pollution brought this risk factor into the public focus (Landrigan et al., 2018; Lelieveld, Haines & Pozzer, 2018; Online-Link5, 2016; Online-Link6, 2016). It includes 2.43 million cardiovascular deaths per year (95% CI 1.70–3.08), which reflects 4.3% of the annual global deaths from all causes and 53% of all air pollution associated deaths (see global map in Fig. 3) (Munzel et al., 2018a). According to the most recent estimate estimated by Lelieveld et al., the global all-cause mortality rate attributable to ambient air pollution by PM$_{2.5}$ and O$_3$ was 8.79 (95% CI 7.11–10.41) million in 2015 (Lelieveld et al., 2019), which is in agreement with the estimate of 8.9 (95% CI 7.5–10.3) by Burnett et al. (Burnett et al., 2018). With continual refinement of the exposure-response functions and inclusion of data from more and larger cohorts, the excess mortality rates attributable to air pollution are corrected towards higher values (Fig. 4) (Shiraiwa et al., 2017). It is alarming that especially in central and Eastern Europe, the air pollution-induced cardiovascular mortality rivals that in South and East Asia, which urgently requires preventive measures. As exemplified for PM$_{2.5}$, the legal thresholds in Europe are too high to effectively safeguard human health (25 µg/m$^3$) and it would be very important that the PM$_{2.5}$ and other related air pollution thresholds adhere to the WHO air quality guidelines in the future. The thresholds for PM$_{2.5}$ in Australia, Canada and the USA are significantly lower with 8, 10 and 12 µg/m$^3$, respectively (Munzel et al., 2018a). Indeed, there are only a few countries in the world that have higher legal thresholds for PM$_{2.5}$ than Europe. As shown in Fig. 4, excess deaths attributable to air pollution show a continuous increase (Shiraiwa et al., 2017), despite the fact that legal guidelines become more and more restrictive and air quality is improving in some areas, but constant growth of the world population makes poor air quality into a health risk in most parts of the world, especially the fast growing metropolitan areas in South-East Asia. Accordingly, more and more deaths are attributed to ambient air pollution because an increasing number of people lives in highly polluted areas/cities, and the knowledge on the mechanisms of air pollution dependent disease development/progression, the quality of air pollution measurements and accordingly the knowledge on health impacts by air pollution is continuously improved, all of which is considered within newly developed exposure-response functions. This constant rise in excess deaths to air pollution is also in accordance with the recent report

Figure 4. Literature estimates of global premature mortality attributed to outdoor air pollution by fine particulate matter (PM$_{2.5}$). GBD, Global Burden of Disease study. Redrawn and updated from Shiraiwa et al., Environ Sci Technol 2017 (Shiraiwa et al., 2017) with permission. Copyright © 2017, American Chemical Society.
of “The Lancet Commission on pollution and health” (Landrigan et al., 2018): The Commission concludes that “An analysis of future trends in mortality associated with ambient PM2.5 air pollution finds that, under a “business as usual scenario”, in which it is assumed that no new pollution controls will be put into place, the numbers of deaths due to pollution will further increase the next coming decades, with sharper increases in the cities of south and east Asia.”

There is also emerging evidence for a causal association between PM2.5 pollution and lowered cognitive function, autism and attention-deficit or hyperactivity disorder in children, neurodegenerative disease, including dementia in adults and stroke (Landrigan et al., 2018). However, a limited number of mechanistic details lack a full characterization, and some (bio)chemical processes are not fully understood. The impact of particulate matter and diesel exhaust on oxidative stress pathways and inflammation was reviewed in full detail in two recent articles within the Forum issue “Oxidative stress and redox signaling induced by the environmental risk factors mental stress, noise and air pollution” (Rao, Zhong, Brook & Rajagopalan, 2018; Wilson, Miller & Newby, 2018).

Traffic and occupational noise exposures – the underestimated environmental risk factor

Another important transport-related health risk factor (Cohen et al., 2017) is environmental noise (Online-Link3) (for reviews see: Munzel, Gori, Babisch & Basner, 2014; Munzel, Schmidt, Steven, Herzog, Daiber & Sorensen, 2018). A large proportion of the population is exposed to noise levels exceeding the guidelines, and although there is growing evidence linking traffic noise to cardiovascular morbidity and mortality, traffic noise is neither mentioned as a health risk factor in the GBD Study (only occupational noise is briefly mentioned contributing almost 5 Mio DALY’s (Collaborators, 2017) nor in the report “Health at a Glance: Europe 2018” (Online-Link9). According to the recently published WHO guidelines, the pooled relative risk for IHD was 1.08 (95% CI 1.01–1.15) per 10 dB(A) increase in road traffic noise exposure, starting at 53 dB(A) (Fig. 5) (Kempen, Casas, Pershagen & Forastier, 2018). According WHO, at least one million healthy life years are lost every year from traffic-related noise in the Western part of Europe (DALYs: 61,000 for IHD, 45,000 for cognitive impairment of children, 903,000 for sleep disturbance, 22,000 for tinnitus and 654,000 for annoyance). This prognosis is supported by the WHO environmental noise guidelines for the European region predicting that traffic noise significantly affects cardiovascular disease development/progression and may contribute to metabolic disease. For noise, the lack of binding legal thresholds is also dramatic: Whereas the European guideline threshold for noise exposure is 55 dB(A) L1eq,1 a particular one third of the people in Europe are exposed to higher levels (Online-Link7). Although no legal thresholds exist for USA, the mode for mean noise exposure is 55 dB(A) during the day and 50 dB(A) during the night, which is in accordance with the “WHO Noise Guidelines” specifying 50–55 dB(A) L1eq,2 during the day to be mostly free of adverse health effects, whereas those during the night should be 5–10 dB(A) lower.

The aforementioned statistics are further supported by a population-based study in Switzerland of morbidity and annual years of life lost (YLL) due to transportation noise (n=6,000; 95% CI 2,000–11,100) (Vienneau et al., 2015). The study demonstrated that air pollution from road traffic is the primary contributor to the annual years of life lost, while quality of life and morbidity was more strongly impacted by noise. Costs attributable to the burden of noise were also found to be equal to those associated with air pollution, probably owing to the pervasive nature of environmental noise. It is estimated that 125 million Europeans are affected by road traffic noise, along with nearly 8 million by rail traffic noise and nearly 3 million by aircraft noise. This amounts to a European “cardiovascular burden” of noise that consists of 1.7 million cases of hypertension, 80 thousand hospital admissions per year, and at least 18 thousand premature deaths per year related to coronary heart disease and stroke (https://acm.eionet.europa.eu/reports/docs/ETCACM_TP_2014_9_HIA-noise_europe.pdf). A noise level reduction of a mere 5 dB(A) was projected to reduce hypertension by 1.4 % and IHD by 1.8 %, saving 3.9 billion dollars health costs (SWinburn, Hammer & Neitzel, 2015). A striking underline to this projection is the fact that 20% (2,904) of Barcelona’s annual premature deaths were preventable upon compliance with international exposure recommendations for urban factors. Specifically, 599 of these premature deaths are connected with road traffic noise exposure above the WHO guideline thresholds (Mueller et al., 2017). As epidemiological research into effects of traffic noise on disease have attracted much lesser attention than air pollution during the last decades, the WHO Environmental Noise Guidelines still calls for additional high quality evidence based on longitudinal studies to comprehensively assess the impact of noise exposure on the cardiovascular and metabolic system (Kempen, Casas, Pershagen & Forastier, 2018).

Beyond chronic exposure, a field study found acute exposure overnight to aircraft noise caused endothelial dysfunction, a subclinical marker for atherosclerosis, in healthy subjects (Schmidt et al., 2013). Other evidence suggests that disruption of the autonomic nervous system/ or sympatho-adrenal activation (Recio, Linares, Banegas & Diaz, 2016) results in release of pro-inflammatory mediators, lipids or phospholipids modification and activation of leukocyte populations, endothelial dysfunction and activation of pro-thrombotic pathways, which are crucial to the induction of adverse cardiovascular effects. Recent insights from animal studies revealed an essential role of cardiovascular and cerebral oxidative stress (corrected by genetic gp91phox deficiency), impairment of the circadian clock and dysregulation of gene networks leading to endothelial dysfunction and vascular/cerebral damage by aircraft noise exposure, especially during the sleep phase (Kroller-Schon et al., 2018a). The precise mechanisms leading to noise-induced vascular damage at the molecular level and subsequently cardiovascular disease are only poorly characterized from a mechanistic point of view and biomarker perspective.

Evidence for independent or synergistic health effects of air pollution and noise exposure

Previous experimental studies on air pollution and noise exposure suggest that some pathophysiological pathways are similar for these environmental risk factors,
highlighting the importance of investigating whether synergistic effects of noise and air pollution exist. Also recent epidemiological/clinical studies suggest additive damage of noise on air pollution induced cardiovascular disease (Stansfeld, 2015). In the HUNT (n=144,082) and the Heinz Nixdorf Recall (n=4,814) cohorts, an independent association of a functional marker of atherosclerosis and biomarkers of cardiovascular disease with noise exposure and air pollution were demonstrated. In the ESCAPE study population of 41,072 subjects, the incidence of self-reported hypertension was positively associated with PM$_{2.5}$ (relative risk (RR) 1.22 (95% CI:1.08-1.37) per 5 µg/m$^3$) (Fuks et al., 2017), and these estimates decreased slightly upon adjustment for road traffic noise. Comparative burden of disease studies demonstrate that air pollution is the primary environmental cause of DALYs (Stansfeld, 2015). According to these data environmental noise is ranked second in terms of DALYs in Europe, even outcompeting lead, ozone and dioxins in terms of DALYs (Stansfeld, 2015). However, almost all studies on combined effects of noise and air pollution published so far rely on mathematical models, rather than experimental data. Therefore, studies on the synergistic effects of air pollution and noise exposure under controlled laboratory conditions are urgently needed in order to refine the exposure-hazard ratio functions used for the calculation of risks or deaths. Since mental stress and heavy metals also may share similar pathophysiology with noise exposure and air pollution, the environmental burden of cardiovascular and all-cause mortality could even exceed all actual estimations.

**Molecular insights from animal studies on aircraft noise exposure**

We established an animal model for aircraft noise exposure and could demonstrate for the first time that around the clock aircraft noise (L$_{eq}$ 72 dB(A), peak
level 85 dB(A) for 24h/d for 1, 2 and 4 d) caused an increase in stress hormones, blood pressure, oxidative stress (originating from phagocytic NADPH oxidase (NOX2) and an uncoupled nitric oxide synthase), inflammation by infiltrated immune cells (aortic FACS analysis), dysregulation of gene networks (revealed by next generation sequencing) within the vasculature and accordingly endothelial dysfunction (Munzel et al., 2017b). Blood pressure increases of 10–20 mmHg in response to around-the-clock aircraft noise exposure

Figure 6. Summary of the results on vascular oxidative stress and dysregulated gene expression of our recently established noise mouse model.

Aircraft noise exposure increases whole blood oxidative burst upon stimulation with zymosan A and the phorbol ester PDBu (measured by L-012 dependent chemiluminescence, unpublished) (A) and causes S-glutathionylation of eNOS as a marker of uncoupling in the aorta (left) and the heart (right) (determined by eNOS immunoprecipitation followed by immunoblotting using a specific S-glutathionylation antibody) (B). Nitrosotyrosine-positive proteins in plasma (measured by dot blot analysis) were increased in aircraft noise exposed mice (C).

Graphs were generated from data in Münzel et al., Eur Heart J 2017 (Munzel et al., 2017a) with permission of the publisher. Copyright © 2017, Münzel et al. (open access). Published by Oxford University Press on behalf of the European Society of Cardiology. (D) Summary scheme of most relevant signalling pathways as the result of the next generation sequencing (NGS) experiments. Upregulated genes are in green, downregulated genes are red solid boxes. PTGIR, prostaglandin I2 receptor; AC, adenylyl cyclase; s-GC, soluble guanylyl cyclase; cGMP, calcitonin gene-related peptide; CRLR, calcitonin receptor-like receptor; ADRA1, adrenergic receptor alpha 1; EDNRA, endothelin receptor type A; TGFβ, transforming growth factor beta; TGFβR1, transforming growth factor beta-receptor 1; Smad, group of intracellular proteins that act down-stream to extracellular TGFβ signals; PAI, plasminogen activator inhibitor; CHK1, checkpoint kinase 1; P48/PTF1, DNA binding protein involved in transcription and DNA repair; CyC, cytochrome c; ATM, Ataxia telangiectasia mutated is an important checkpoint kinase; ATR, Ataxia telangiectasia and Rad3 related is a protein kinase; Fas, CD95 (cluster of differentiation 95); B99, G2 And S-Phase Expressed 1, gene involved in cell cycle; CASP3/9, caspase-3/-9; Gadd45, growth arrest and DNA damage-inducible 45 proteins; SGK, serum- and glucocorticoid-induced protein kinase; p38, mitogen-activated protein (MAP) kinase; JNK, c-Jun N-terminal kinase; BIM, Bcl-2 interacting mediator of cell death; p130, RBL2, regulator of entry into cell division; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; GLUT4, glucose transporter type 4; IRS, insulin receptor substrate; Homer, homer scaffolding proteins; IKKα/β, inhibitor of nuclear factor kappa B kinase α/β; c-Myc, nuclear phosphoprotein that plays a role in cell cycle progression and apoptosis; FOXO, Forkhead box proteins O is a group of transcription factors involved in cell growth, proliferation and differentiation; SOD1, mitochondrial Cu,Zn-superoxide dismutase; GPX-1, glutathione peroxidase-1; Bcl-6, B-cell lymphoma 6 protein; ATG8, autophagy-related protein 8; EDG1/6, endothelial differentiation gene 1/6 or sphingosine-1-phosphate receptor 1/6. Modified from Münzel et al., Eur Heart J 2017 (Munzel et al., 2017a) with permission of the publisher. Copyright © 2017, Münzel et al. (open access). Published by Oxford University Press on behalf of the European Society of Cardiology.
for 1, 2, 3 and 4 days were detected by tail cuff plethysmography and endothelial dysfunction was observed after 1, 2 and 4 days of noise exposure using the isometric tension method (Fig. 5A and 5B). Endothelial dysfunction was associated with decreased nitric oxide bioavailability in aortic tissue as measured by electron paramagnetic resonance (EPR) spectroscopy and with enhanced vasoconstrictor activity of norepinephrine revealed by applying the isometric tension method (Fig. 5C and 5D). These adverse hemodynamic and vascular effects induced by transportation noise exposure in mice can be mechanistically explained by data of human studies: impaired endothelial function (measured by flow-mediated dilation) is based on oxidative inactivation of nitric oxide by superoxide (e.g. from xanthine oxidase and NADPH oxidase), which will also promote infiltration of immune cells such as neutrophils or macrophages (Fig. 5E). Our experimental findings are also well supported by epidemiological data indicating that transportation noise is associated with a higher risk for ischemic heart disease (Fig. 5F).

Our mouse studies also revealed substantial induction of oxidative stress at the vascular (eNOS uncoupling by S-glutathionylation) as well as systemic level (whole blood oxidative burst and plasma concentrations of 3-nitrotyrosine-positive proteins) (Fig. 6A–C). Of note, with our subsequent studies we revealed that noise-induced vascular and cerebral damage is prevented by Nox2 knock-out and it seems that aircraft noise exposure during the sleep phase of the mice is more detrimental than exposure during the awake phase (Kroller-Schon et al., 2018b).

Illumina RNAseq identified 224 genes that were significantly up- or down-regulated in response to noise exposure (Munzel et al., 2017b). The 4 strongest up-regulated genes compared to controls were Zbtb44, Setad4, Ypel2 and Ihh. Similarly, the amount of transcripts of Sac3, Nbeal1, PTPN4 and NRAP3 were significantly reduced by noise. Pathway analysis by gene ontology annotation from RNAseq data revealed major changes in vascular smooth muscle cell (VSMC) contraction pathway and TGFβ- and Smad signaling, in the NF-κB related pathways (Fig. 6D). Subsequent studies applying Illumina RNAseq to different tissues of aircraft noise exposed mice revealed substantial dysregulation of the circadian clock (Kroller-Schon et al., 2018a). The molecular mechanisms of vascular dysfunction in response to around-the-clock and nighttime aircraft noise were therefore strikingly similar to mechanisms by which traditional cardiovascular risk factors such as diabetes (Hink et al., 2001), hypertension (Mollnau et al., 2002) and hypercholesterolemia (Oelze et al., 2000) induce endothelial dysfunction suggesting that noise will substantially accelerate the process of atherosclerosis if cardiovascular risk factors are already present but also may contribute to cognitive impairment, mental disease and neurodegeneration by noise-dependent bonfire mechanisms.

As a limitation of the animal experimental studies we would like to mention that specific frequency components of traffic noise exert differentially pronounced health effects in human subjects (Chang et al., 2014; Liu, Young, Yu, Bao & Chang, 2016) and, accordingly, translation of animal experimental data may be hampered by species differences in noise perception. Moreover, we have shown that white noise exposure, despite application of similar sound pressure levels and despite presence of a continuous band of frequencies in white (or pink) noise, displayed no adverse cardiovascular effects in mice (Munzel et al., 2017b), suggesting that the noise pattern (e.g. crescendo and decongestant nature of aircraft noise as well as particular silent passages) may be of importance as well. Most importantly, the noise perception itself may be quite different in mice and men. Whereas human subjects show strong annoyance reactions in response to noise exposure during the day (e.g. due to interruption of cognitive activity and communication), the detrimental effects of noise in mice may be mainly mediated by sleep deprivation when exposed during the sleep phase.

**Susceptibility for environmental risk factors is most pronounced at early and late life**

Morbidity and mortality due to pollution occur most frequently in the very young and the very old. Deaths due to all forms of pollution show a peak among children younger than 5 years of age, especially in low- and middle income countries (Lelieveld, Haines & Pozzer, 2018), but most pollution-related deaths occur among adults older than 60 years of age (Fig. 7) (Collaborators, 2016). By contrast, DALYs resulting from pollution-related disease are highly concentrated among infants and young children, reflecting the many years of life lost with each death and case of disabling disease of a child (Fig. 7) (Collaborators, 2016). These data fit very well to the exposome concept, which is based on the life-long environmental exposures and the associated changes of the external and internal exposome. Therefore, the EWAS approach would be dedicated to the life-long measurement of these exposures and exposomic changes. Since most deaths and DALYs due to pollution are observed in late life (high age) and early life (probably prenatal, neonatal and early childhood) these age groups obviously represent populations with increased vulnerability and higher risk for environmental adverse health effects. Accordingly, these populations require specific protective legislation by decision makers but also represent study cohorts of special interest for exposomic studies since the dynamic process of exposomic changes is obviously highly active in these age groups. Possible explanations for the more pronounced impact of pollution on premature death at higher age may be that 1) environmental exposures represent comorbidity factors on top of age-related disease further accelerating natural aging and death or 2) life-long exposure effects escalate at a certain time point (when a certain threshold is exceeded). Possible explanations for the more pronounced impact of pollution on DALYs at younger age may be that 1) they are less “prepared” for environmental stressors (may be some kind of adaptation during life with improved stress-response and compensatory machinery, 2) children are exposed to higher doses (have maybe larger uptake/weight ratio than adults), 3) detrimental fetal reprogramming – i.e. what happened during pregnancy – plays an important role or 4) prenatal and early-life developmental stage per se makes cells and organs more vulnerable to environmental toxins and stressors.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

Within our previous Forum issue (Munzel & Daiber, 2018), we established that environmental stressors share common pathophysiological pathways that are centered on stress hormone signaling, oxidative stress and in-
flammation. Of note, oxidative stress and inflammation also represent major pathomechanisms in cardiovascular, neurodegenerative and metabolic diseases. These shared pathways suggest additive/synergistic adverse effects by environmental (and lifestyle) risk factors and aggravation of pathogenesis of noncommunicable disease in a bonfire fashion (summarized in Fig. 8). The non-chemical stressors noise and mental stress require neuronal perception followed by activation of the hypothalamic-pituitary-adrenal (HPA) axis with subsequent cortisol release or of the sympathetic nervous system (SNS) with subsequent catecholamine formation (Daiber et al., 2019; Golbidi, Li & Laher, 2018; Xia & Li, 2018). These stress responses are linked to oxidative stress and inflammatory pathways and thereby impair vascular signaling and endothelial function, cause hypertension and cardiac damage but also contribute to neuronal dysregulation such as impairment of cognitive functions. The chemical pollutant particulate matter can also cause neuronal activation (HPA and SNS) by known pathways (Li et al., 2017; Niu et al., 2018; Rao, Zhong, Brook & Rajagopalan, 2018). Importantly, chemical pollutants such as particulate matter or heavy metals that are often bound to ambient particles directly lead to oxidative stress via transition metal catalysis or reactive surfaces of particles and directly trigger inflammatory pathways (e.g. by immune cell activation during phagocytosis of particles or interaction of heavy metals with sulfur groups in cytokine signaling). Ambient air pollution alone leads to 790,000 premature deaths per year in Europe (Lelieveld et al., 2019). Although it is so far not possible to calculate the premature deaths caused by environmental noise exposure, occupational noise alone contributes to 6 Mio DALYs at the global level (Collaborators, 2017). In the Western part of Europe a total annual sum of 1,685,000 DALYs is inflicted by noise by triggering IHD, sleep disturbance, annoyance and other adverse effects. Given the co-localization of noise, air pollution and other environmental toxins but probably also psychosocial stress in big cities and large urbanized areas, the potential co-benefits of reducing several of these stressors should be considered. The health problems and disease burden associated with the sum of these environmental stressors may even outperform all previous estimations.

![Figure 7. Estimated global deaths (A) and DALYs (B) by different pollution risk factors and age at death in 2015. Redrawn from GBD Study Lancet 2016 (Collaborators, 2016). This article is available under the terms of the Creative Commons Attribution License (CC BY).](image-url)
Figure 8. Unifying concept to explain the adverse effects of the environmental (and life style) risk factors air pollution, noise exposure, mental stress and environmental toxins such as heavy metals.

Almost all environmental stressors cause a primary stress reaction that is mediated either by the hypothalamic-pituitary-adrenal (HPA) axis with subsequent cortisol release or by activation of the sympathetic nervous system (SNS) with subsequent catecholamine formation (only for heavy metals this remains to be shown). These stress reactions activate inflammatory or oxidative stress pathways via damage-associated molecular patterns (DAMPs), Toll-like receptors (TLRs), angiotensin-II (AT-II) and NADPH oxidase (particles from air pollution can directly activate immune cells and cause ROS formation by reactive surfaces). Inflammation and oxidative stress pathways can activate each other and together with stress hormones, vasoconstrictors and alterations of gene expression (including microRNAs) contribute to the classical risk factors leading to cardiometabolic diseases. Redrawn from Münzel et al., Antioxid Redox Signal 2018 (Münzel & Daiber, 2018) and modified from Daiber et al., Biofactors 2019 (Daiber et al., 2019) with permission. © 2019 International Union of Biochemistry and Molecular Biology.

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Conflict of interest

We certify that there is no conflict of interest with any financial organizations regarding the materials discussed in the manuscript.

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