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The "exposome" concept – how environmental risk factors influence cardiovascular health

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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 $PM_{2.5}$ and 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.

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Abbreviations: CI, confidence interval; DALYs, disability-adjusted life years; EWAS, Environment-Wide Association Study; GBD, Global Burden of Disease; IHD, ischemic heart disease; NADPH, nicotinamide adenine dinucleotide phosphate; ·NO, nitric oxide; NOX, NADPH oxidase; $PM_{2.5}$, particulate matter with a diameter ≤ 2.5 µm; ROS, reactive oxygen species; WHO, World Health Organization.

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) leads 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 ($PM_{2.5}$) 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 cardio- and cerebrovascular 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; Munzel, 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; Tellez-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). Although there are no "hard" methods to measure psycho-
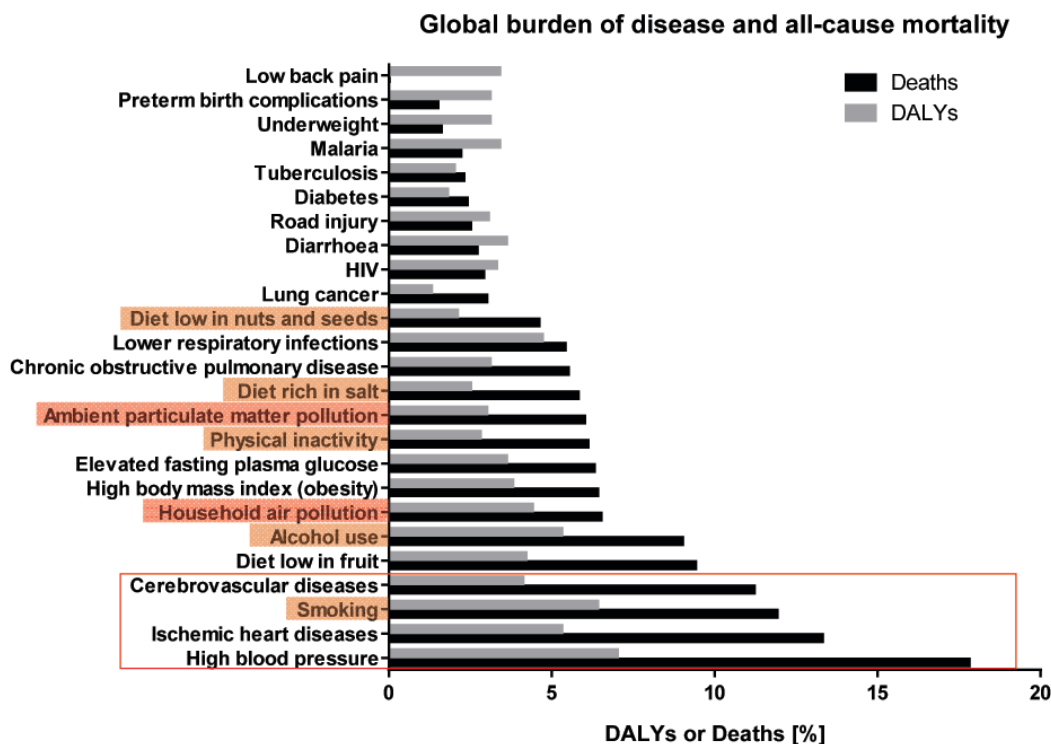
Figure 1. Global burden of disease and related deaths.
Comparison of the magnitude of the ten leading diseases and injuries and the ten leading risk factors based on the percentage of global deaths and the percentage of global DALYs, 2010. The figure shows the leading 25 diseases, injuries, and risk 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 life-style 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.

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 (Saina-ni, 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-

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

Study	Description and major aims	Reference
ENNAH project (The European Network on Noise and Health, funded by FP7)	highlighted in its final report the alarming epidemiological evidence for an increased incidence of cardiovascular disease due to environmental noise exposure and stressed the importance of studies on the combined health effects by noise and air pollution	https://cordis.europa.eu/project/rcn/92035/reporting/en
ERA-Planet project (funded by H2020)	focuses on monitoring technologies and data verification on air pollution particulate matter	http://www.era-planet.eu/
ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project (funded by HEI)	is a Europe-wide collaboration to investigate mortality and morbidity effects of long-term exposure to low-level $PM_{2.5}$, Black Carbon, NO_2 and O_3 in European cohorts	http://www.elapseproject.eu/
NordicWelfair and NordSOUND projects	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	https://projects.au.dk/nordicwelfair/ https://www.cancer.dk/nordsound/
BREATHE (BRain dEvelopment and Air polluTion ultrafine particles in scHool children, funded by FP7) project	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	(Online-Link8) https://cordis.europa.eu/project/rcn/99632/factsheet/en
HELIX (Human Early-Life Exposome) project	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	https://www.projecthelix.eu/
PACE (Pregnancy And Childhood Epigenetics) project	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	https://www.niehs.nih.gov/research/atniehs/labs/epi/pi/genetics/pace/index.cfm
ESCAPE (European Study of Cohorts for Air Pollution Effects, funded by FP7) project	investigates all aspects of adverse health effects by air pollution including cancers, cardiovascular, metabolic and mental diseases in a cohort of 900,000 subjects	(Cesaroni et al., 2014) http://www.escapeproject.eu/
HEALS (Health and Environment-wide Associations based on Large population Surveys) project	conducts Health and Environment-wide Associations based on Large population Surveys (one of the largest research projects on environment and health in Europe)	http://www.heals-eu.eu/
HERCULES (Health and Exposome Research Center: Understanding Lifetime Exposures) project	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	https://emoryhercules.com/
EXPOsOMICS project	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	(Vineis et al., 2017) http://www.exposomics-project.eu/

tween 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 pollutomes 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.

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 abovementioned 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
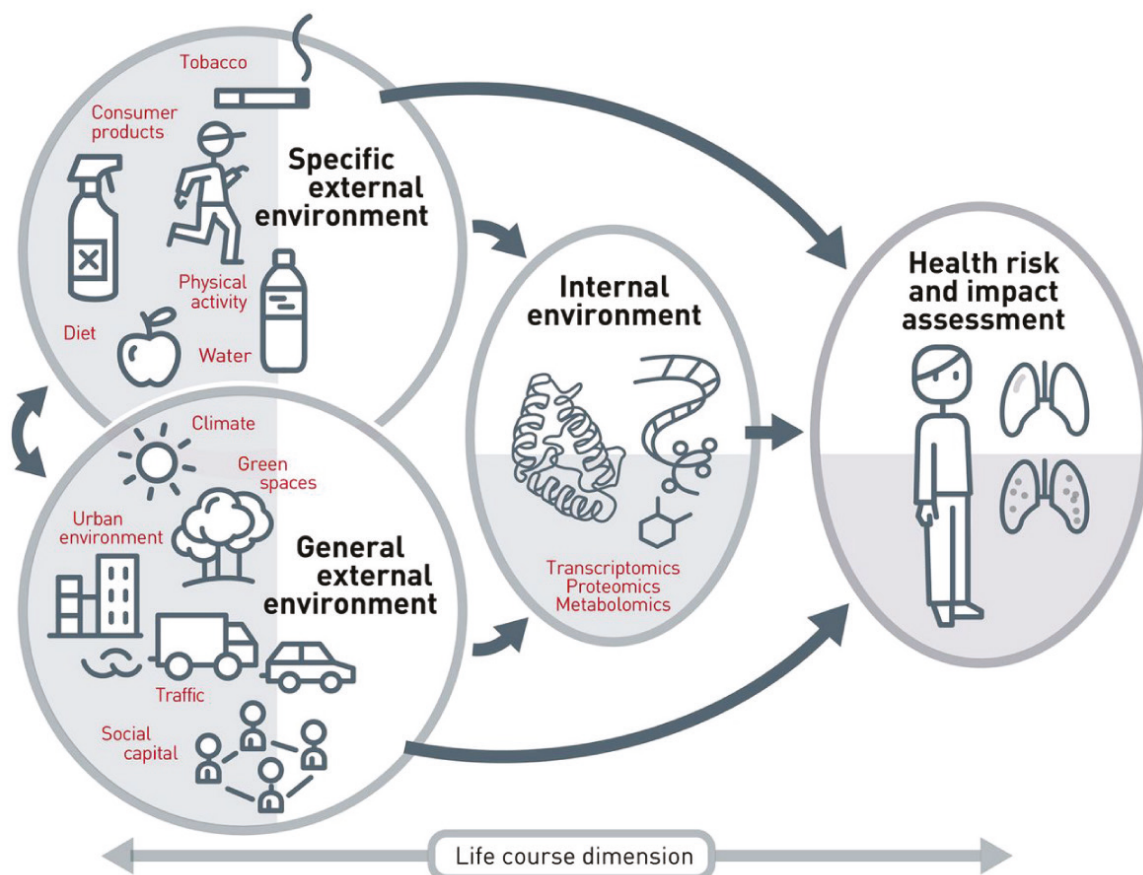
Figure 2. THE EXPOSOME: The exposome encompasses the entirety of a person's exposures from birth to death, including internal exposures such as gut bacteria, lifestyle choices such as smoking, and social determinants such as poverty.
Traffic-related noise exposure and air pollution belong to the general external environment. Reprinted from Vrijheid *et al.*, *Thorax* 2014 (Vrijheid, 2014) with permission of the publisher. Copyright © 2014, BMJ Publishing Group Ltd and the British Thoracic Society.

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 expansive 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 [$PM_{2.5}$]) 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 $PM_{2.5}$) 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

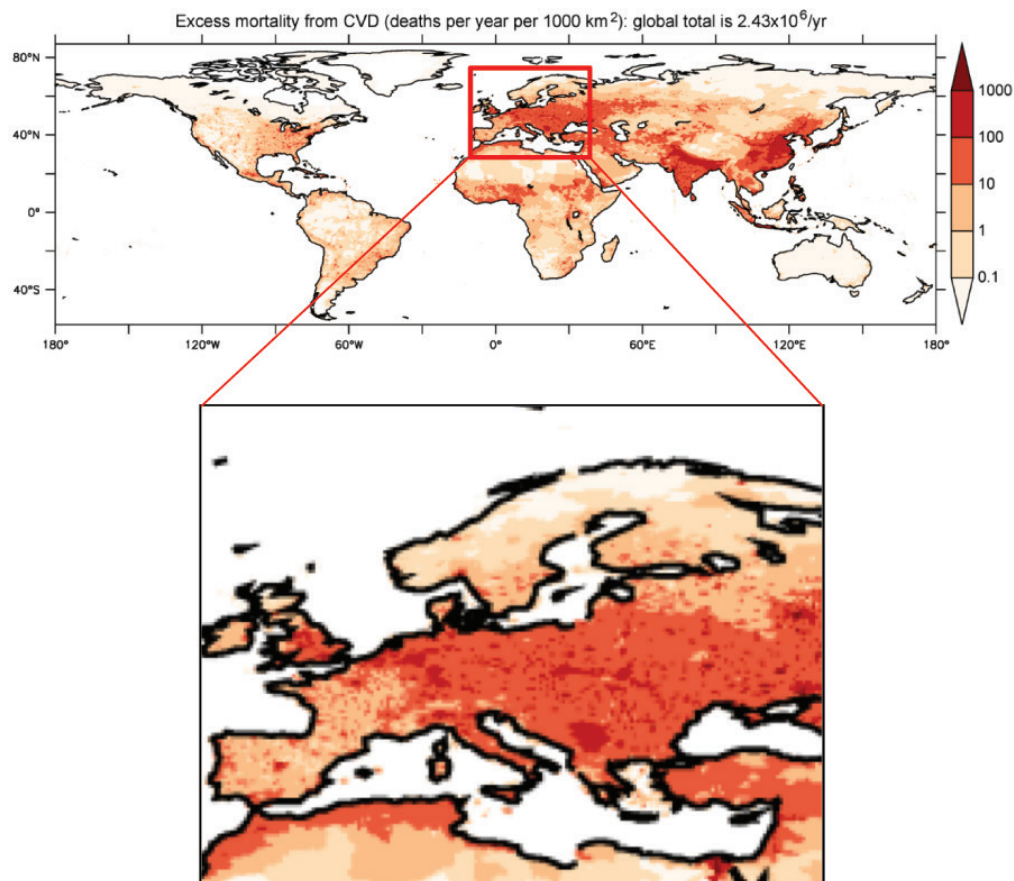**Figure 3. Estimates of excess deaths from cardiovascular disease induced by $PM_{2.5}$ in the year 2015.**
Adopted from Münzel *et al.*, *Eur Heart J* 2018 (Munzel *et al.*, 2018a) with permission of the publisher. Copyright © 2018, Oxford University Press. The figure represents an update of data from 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.*, 2018a). 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/m³) 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/m³, respectively (Munzel *et al.*, 2018a). Indeed, there are only 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
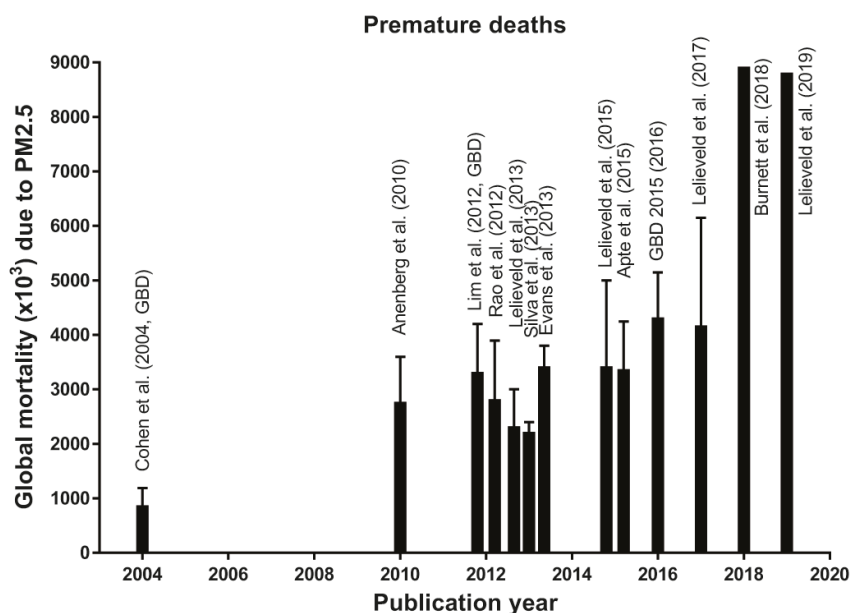

Figure 4. Literature estimates of global premature mortality attributed to outdoor air pollution by fine particulate matter ($PM_{2.5}$). GBD, Global Burden of Disease study. Redrawn and updated from Shiraiwa *et al.*, *Environ Sci Technol* 2017 (Shiraiwa *et al.*, 2017) with permission. Copyright © 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 $PM_{2.5}$ 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 sharpest increases in the cities of south and east Asia."

There is also emerging evidence for a causal association between $PM_{2.5}$ 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 lacks 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 6 Mio DALYs (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 & Foraster, 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) L_{den}[1], approximately 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) L_{Aeq}[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 & Foraster, 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, and/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,

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[1]Day-evening-night level. It is a descriptor of noise level based on energy equivalent noise level (L_{eq}) over a whole day with a penalty of 10 dB(A) for night time noise (22:00–7:00) and an additional penalty of 5 dB(A) for evening noise (i.e. 19:00–23:00).
[2]L_{Aeq} is the A-weighted equivalent continuous sound level in decibels measured over a stated period of time. Most community and industrial noise measurements are A-weighted so the L_{Aeq} descriptor is therefore widely used.

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 $\mu g/m^3$) (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
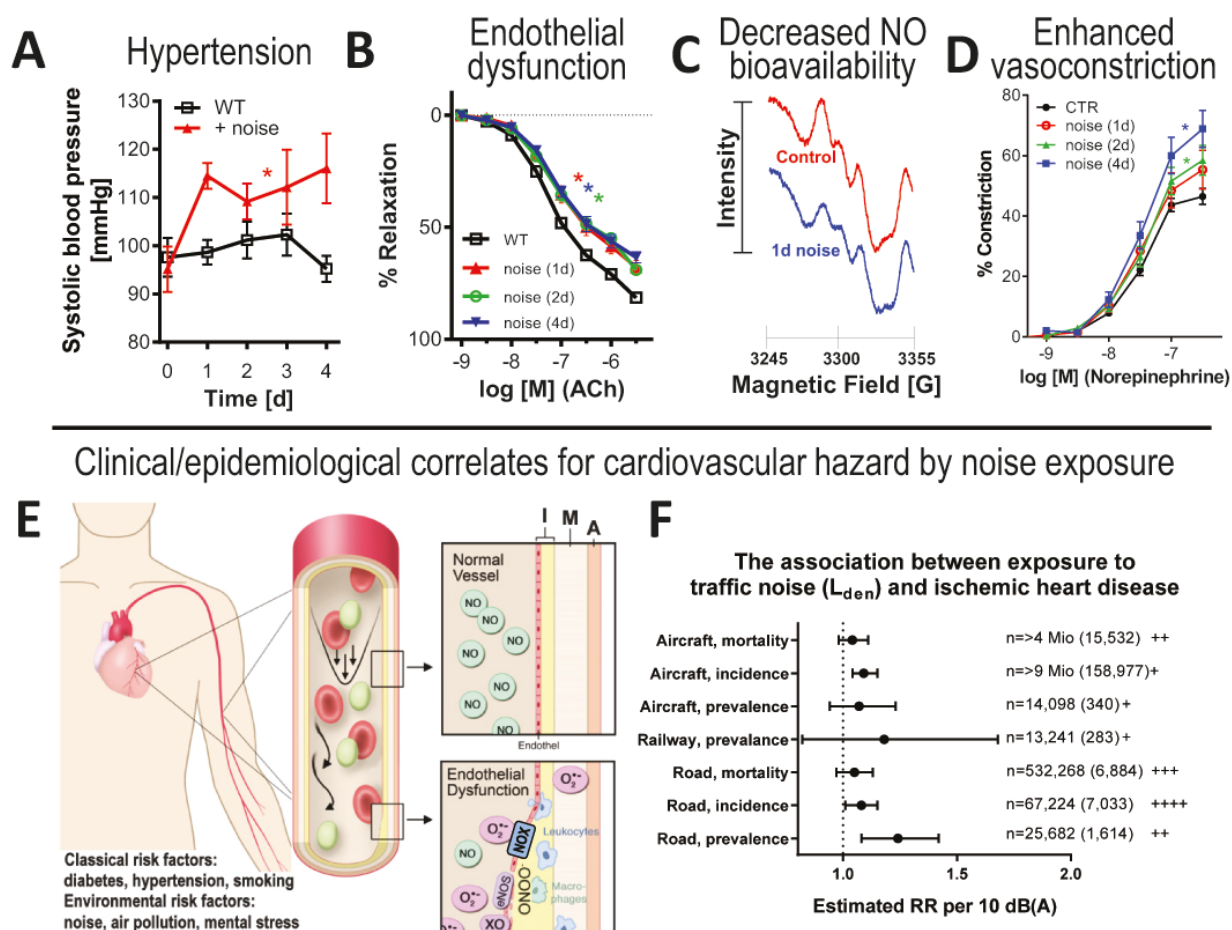

Figure 5. Summary of the results on vascular functional parameters of our noise mouse model with clinical/epidemiological correlates.
Aircraft noise exposure increases systolic blood pressure (measured by tail cuff plethysmography) (**A**), impairs endothelial function (measured by isometric tension method) (**B**), reduces vascular NO levels (measured with EPR as described (Kleschyov & Munzel, 2002)) (**C**) and causes enhanced sensitivity to vasoconstrictors (measured by isometric tension method) (**D**). 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. (**E**) Physiology and pathophysiology in the intact and damaged vasculature with direct effects of vascular oxidative stress and infiltration of macrophages/leukocytes. NO, nitric oxide; XO, xanthine oxidase; I, intima; M, media; A, adventitia. NOX, NADPH oxidase. Modified from (Munzel *et al.*, 2018b). With permission of the publisher. Copyright © 2018, Mary Ann Liebert, Inc. (**F**) Clinical correlate of noise-induced vascular dysfunction in our mouse studies as represented by hazard ratio with 95% confidence intervals for the risk of ischemic heart disease in response to different transportation noise exposures. L_{den}, day–evening–night noise level; quality level of evidence: + very low, ++ low, +++ moderate, ++++ high. Generated from tabular data of the actual WHO Environmental Noise Guidelines, Kempen *et al.*, *Int J Environm Res Pub Health* 2018 (Kempen, Casas, Pershagen & Foraster, 2018). This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (CC BY 4.0).

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
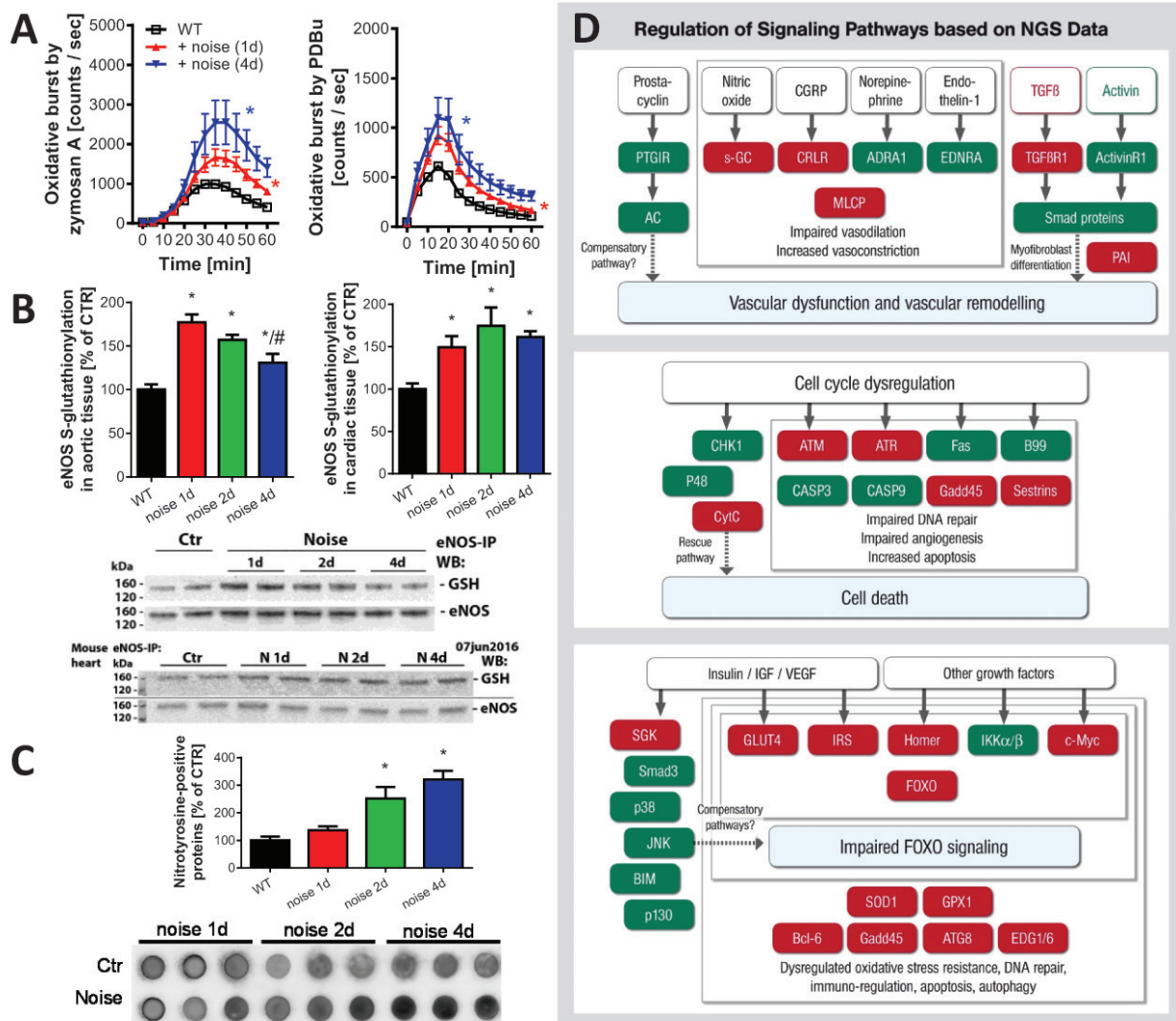

Figure 6. Summary of the results on vascular oxidative stress and dysregulated gene expression of our recently established noise mouse model.
Aircraft noise exposure increases whole blood oxidative burst upon stimulation with zymosan A and the phorbol ester PDBu (measured by L-012 dependent chemiluminescence, 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**). Nitrotyrosine-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; CGRP, 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; CytC, 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, intracellular 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 plethys-mography and endothelial dysfunction was observed after 1, 2 and 4 days of noise exposure using the iso-metric 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 re-vealed by applying the isometric tension method (Fig. 5C and 5D). These adverse hemodynamic and vascu-lar effects induced by transportation noise exposure in mice can be mechanistically explained by data of hu-man studies: impaired endothelial function (measured by flow-mediated dilation) is based on oxidative inacti-vation 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 mac-rophages (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 pro-teins) (Fig. 6A–C). Of note, with our subsequent stud-ies we revealed that noise-induced vascular and cerebral damage is prevented by *Nox2* knockout 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 signif-icantly up- or down-regulated in response to noise expo-sure (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 *Sacs, Nbeal1, PTPN4* and *NR4A3* 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 path-way, adrenergic signal transduction, focal adhesion, cell cycle control, apoptosis and kinase mediated growth and proliferation signaling centred around the Foxo tran-scription factors herein as well as in insulin and calcineu-rin signaling pathways (Fig. 6D). Subsequent studies ap-plying Illumina RNAseq to different tissues of aircraft noise exposed mice revealed substantial dysregulation of the circadian clock (Kroller-Schon *et al.*, 2018a). The mo-lecular mechanisms of vascular dysfunction in response to around-the-clock and nighttime aircraft noise were therefore strikingly similar to mechanisms by which tra-ditional cardiovascular risk factors such as diabetes (Hink *et al.*, 2001), hypertension (Mollnau *et al.*, 2002) and hy-percholesterolemia (Oelze *et al.*, 2000) induce endothelial dysfunction suggesting that noise will substantially accel-erate the process of atherosclerosis if cardiovascular risk factors are already present but also may contribute to cognitive impairment, mental disease and neurodegenera-tion by noise-dependent bonfire mechanisms.

As a limitation of the animal experimental studies we would like to mention that specific frequency com-ponents of traffic noise exert differentially pronounced health effects in human subjects (Chang *et al.*, 2014; Liu, Young, Yu, Bao & Chang, 2016) and, accordingly, trans-lation 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 pres-ence 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 air-craft noise as well as particular silent passages) may be of importance as well. Most importantly, the noise per-ception itself may be quite different in mice and men. Whereas human subjects show strong annoyance reac-tions in response to noise exposure during the day (e.g. due to interruption of cognitive activity and communi-cation), the detrimental effects of noise in mice may be mainly mediated by sleep deprivation when exposed dur-ing 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 chil-dren 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) (Collabora-tors, 2016). By contrast, DALYs resulting from pollu-tion-related disease are highly concentrated among in-fants 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 associ-ated changes of the external and internal exposome. Therefore, the EWAS approach would be dedicated to the life-long measurement of these exposures and ex-posomic changes. Since most deaths and DALYs due to pollution are observed in late life (high age) and ear-ly life (probably prenatal, neonatal and early childhood) these age groups obviously represent populations with increased vulnerability and higher risk for environmen-tal adverse health effects. Accordingly, these popula-tions require specific protective legislation by decision makers but also represent study cohorts of special in-terest for exposomic studies since the dynamic pro-cess 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 pol-lution 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) chil-dren are exposed to higher doses (have maybe larger uptake/weight ratio than adults), 3) detrimental fetal re-programming – i.e. what happened during pregnancy – plays an important role or 4) prenatal and early-life de-velopmental 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-
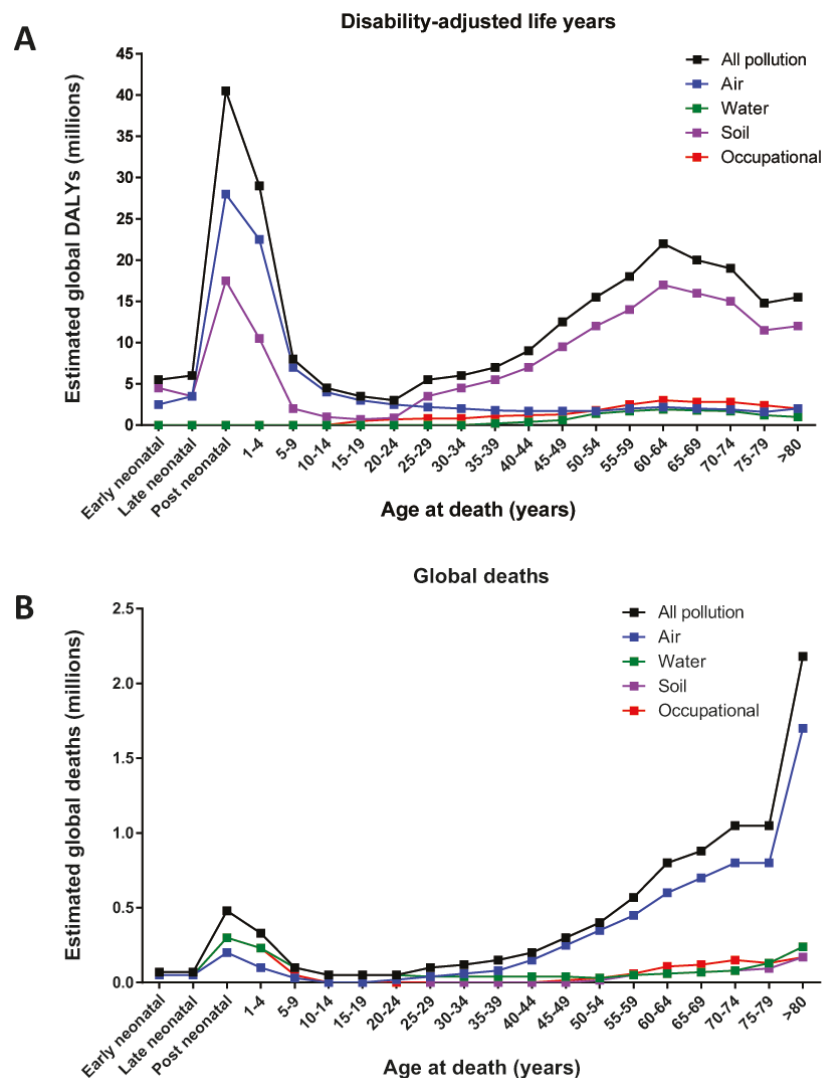
Figure 7. Estimated global deaths (A) and DALYs (B) by different pollution risk factors and age at death in 2015.
Redrawn from GBD Study *Lancet* 2016 (Collaborators, 2016). This article is available under the terms of the Creative Commons Attribution License (CC BY).

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.
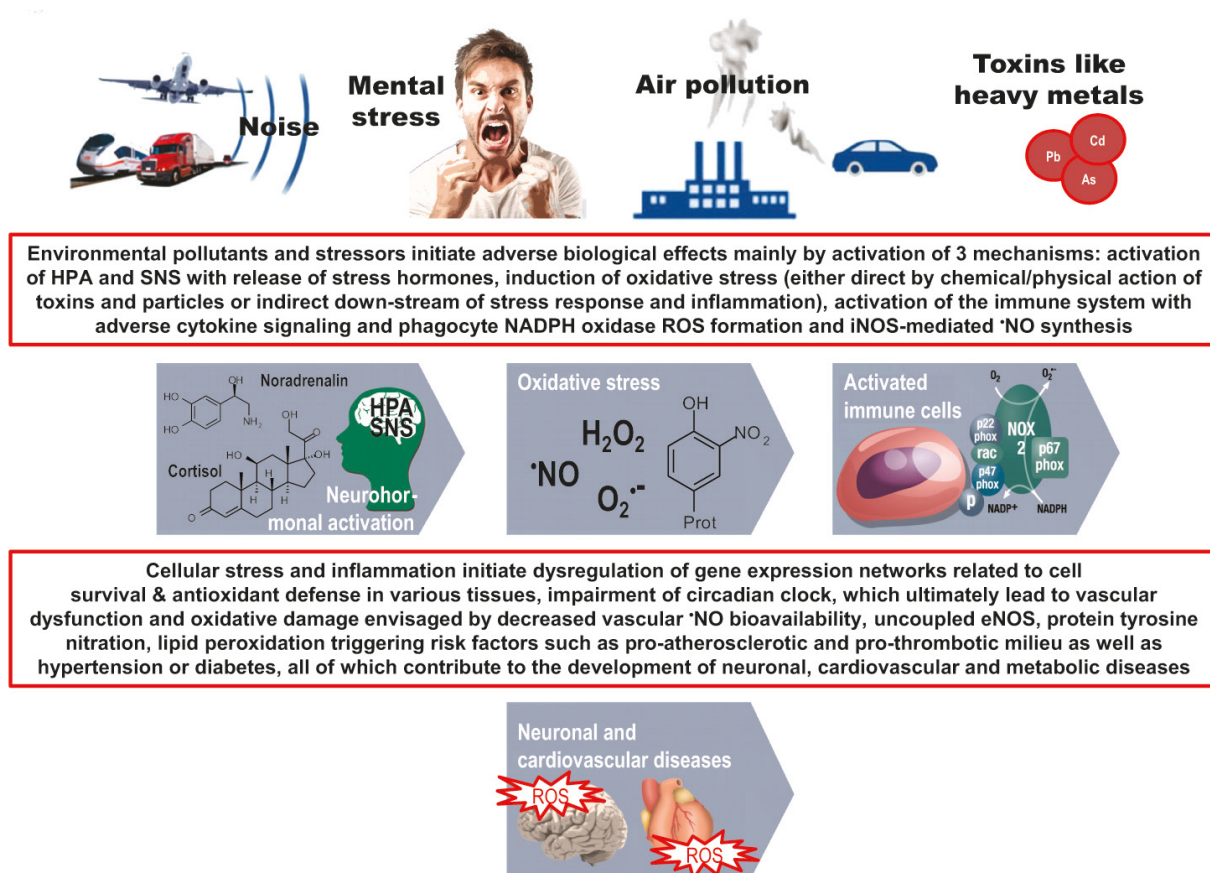
Figure 8. Unifying concept to explain the adverse effects of the environmental (and life style) risk factors air pollution, noise exposure, mental stress and environmental toxins such as heavy metals.
Almost all environmental stressors cause a primary stress reaction that is mediated either by the hypothalamic-pituitary-adrenal (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 (Munzel & Daiber, 2018) and modified from Daiber *et al.*, *Biofactors* 2019 (Daiber *et al.*, 2019) with permission. © 2019 International Union of Biochemistry and Molecular Biology.

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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